STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title: A Phase 3 Randomized, Double-Blind, Multi-Dose, Placebo and Naproxen-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-1611
Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AA	Adjudicated Arthropathy
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
CI	Confidence Interval
DA	Destructive Arthropathy
DMC	Data Monitoring Committee
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
mFAS	Modified full analysis set
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
OMERACT-OARSI	Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative and The Outcome Measure in Rheumatology
PCSV	Potentially clinically significant value

PDID	Protocol deviation identification number
PGA-OA	Patient Global Assessment - Osteoarthritis
PK	Pharmacokinetic
PPS	Per protocol set
prn	Pro re nata
PRO	Patient Reported Outcomes
PT	Preferred term
Q4W	Every 4 (weeks)
Q8W	Every 8 (weeks)
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RPOA	Rapidly Progressive Ostoearthritis
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 Universities Osteoarthritis Index

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R475-OA-1611 study as stipulated in Protocol Amendment 8 Global.

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 naproxen-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 naproxen, which is a member 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 52 weeks (with the option to continue for an additional 52 weeks of treatment) to fasinumab, naproxen, 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 with placebo, when administered for up to 16 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:

1. To evaluate the efficacy of fasinumab compared with naproxen, when administered for up to 16 weeks in patients with pain due to OA of the knee or hip
2. To evaluate the efficacy of fasinumab compared with placebo, when administered for up to 44 weeks in patients with pain due to OA of the knee or hip

3. To evaluate the safety and tolerability of fasinumab compared with naproxen, when administered for up to 16 weeks in patients with pain due to OA of the knee or hip
4. To evaluate the safety and tolerability of fasinumab compared with naproxen, when administered for up to 52 weeks in patients with pain due to OA of the knee or hip
5. To evaluate the safety and tolerability of fasinumab compared with naproxen, when administered for up to 104 weeks in patients with pain due to OA of the knee or hip
6. To evaluate the pharmacokinetic (PK) profile of fasinumab administered to patients with pain due to OA of the knee or hip for up to 52 weeks
7. To evaluate the PK profile of fasinumab administered to patients with pain due to OA of the knee or hip for up to 104 weeks
8. To evaluate the immunogenicity of fasinumab administered to patients with pain due to OA of the knee or hip for up to 52 weeks
9. To evaluate the immunogenicity of fasinumab administered to patients with pain due to OA of the knee or hip for up to 104 weeks
10. To evaluate the efficacy of fasinumab compared with naproxen, when administered for up to 44 weeks in patients with pain due to OA of the knee or hip

Additionally, the following are exploratory objectives:

- To evaluate additional patient reported outcome (PRO) measures in patients with pain due to OA of the knee or hip treated for up to 44 weeks with fasinumab, compared with placebo or naproxen.
- To evaluate the WOMAC pain and physical function subscale scores as well as additional PRO measures in patients with pain due to OA of the knee or hip treated for an additional 52 weeks with fasinumab, compared with naproxen pro re nata (prn).
- To evaluate the use of rescue medication in patients with pain due to OA of the knee of hip treated for up to 44 weeks with fasinumab, compared with placebo or naproxen.
- To evaluate the use of rescue medication in patients with pain due to OA of the knee of hip treated for an additional 52 weeks with fasinumab, compared with naproxen prn.

1.2.3. Modifications from the Statistical Section in the Final Protocol

There are no modifications from what is defined and specified in the statistical section of the final protocol.

1.2.4. Revision History for SAP Amendments

This is the second version of the SAP based on Protocol Amendment 8 Global. The original version was approved and dated 23APR2020 based on Protocol Amendment 7 Global. This version includes an additional analysis population in Section 3, the Modified Full Analysis Set (mFAS). Due to regional irregularities noted in a parallel phase 3 study that became fully

apparent only after unblinding that study, and the concern that the same irregularities would be present in data from similar sites in this study, the primary and secondary efficacy analysis will be performed on a modified Full Analysis Set that excludes patients in the randomization stratum from the region of concern. Analyses using the FAS will also be provided.

Wording was added to Section 2.2 to quantify how the power was impacted by changing the primary analysis population from the FAS to the mFAS.

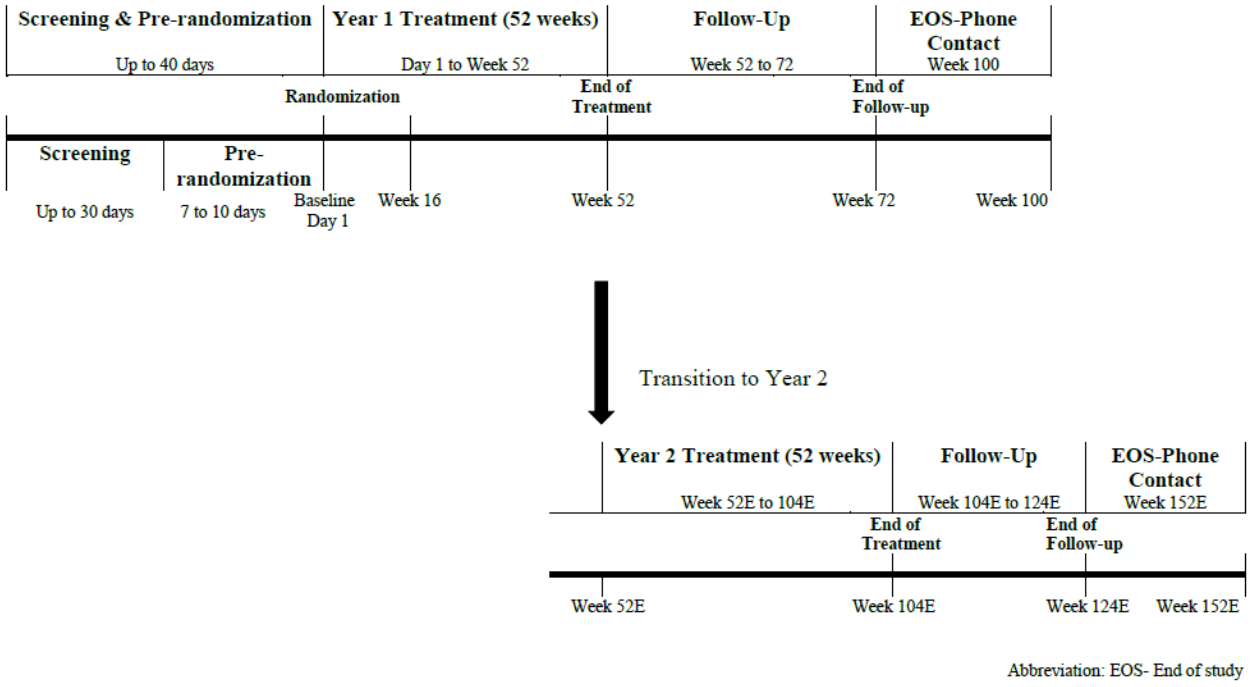
The method used to address imputed values that are implausible (Section 5.7.1) was also updated.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

The study consists of a screening period of up to 30 days, followed by a 7 to 10-day pre-randomization period. All randomized patients in this study will participate in Year 1, a 52-week randomized, double-blind, placebo- and naproxen-controlled treatment period. At the end of the 52-week treatment period, eligible patients have the option to continue for another 52-week double-blind naproxen-controlled treatment period called Year 2, followed by a 20-week follow-up period. Patients who do not consent, or are ineligible, for Year 2 will continue in a 20-week follow-up period. Patients are contacted by phone approximately 52 weeks after their last subcutaneous (SC) dose of study drug (Figure 1).

Figure 1: Study Flow Diagram



Abbreviation: EOS- End of study

Prior to Protocol R475-OA-1611 Amendment 4 Global, patients were randomized 3:3:3:3:1 to receive one of the following treatment regimens:

- Fasinumab 1 mg Q4W - Fasinumab 1 mg SC Q4W and naproxen-matching placebo oral, twice daily
- Fasinumab 3 mg Q4W - Fasinumab 3 mg SC Q4W and naproxen-matching placebo oral, twice daily
- Fasinumab 6 mg Q8W - Fasinumab 6 mg SC Q8W (patients received placebo injections at the study visits where study drug was not administered) and naproxen-matching placebo oral, twice daily

- Naproxen - Fasinumab-matching placebo SC Q4W and naproxen 500 mg oral, twice daily
- Placebo - Fasinumab-matching placebo SC Q4W and naproxen-matching placebo oral, twice daily

A total of 285 patients were enrolled in the fasinumab 3 mg SC Q4W and fasinumab 6 mg SC Q8W groups. However, dosing in these patients was discontinued, as recommended by the independent Data Monitoring Committee (DMC)in April 2018.

Post Protocol R475-OA-1611 Amendment 5 Global approximately 2,560 patients were planned to be randomized 3:3:3:1 to receive:

- Fasinumab 1 mg Q4W - Fasinumab 1 mg SC Q4W and naproxen-matching placebo oral, twice daily
- Fasinumab 1 mg Q8W - Fasinumab 1 mg SC Q8W (patients received placebo injections at the study visits where study drug was not administered) and naproxen-matching placebo oral, twice daily
- Naproxen - Fasinumab-matching placebo SC Q4W and naproxen 500 mg oral, twice daily
- Placebo - Fasinumab-matching placebo SC Q4W and naproxen-matching placebo oral, twice daily

Randomization was 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 (Europe, North America, and Rest of the World [South Africa]).

Protocol R475-OA-1611 Amendment 6 provided patients the option to continue in the study and receive treatment for an additional year (Year 2). The treatment arm the patients were assigned in Year 2 was determined by the treatment arm they were randomized to in Year 1 according to the following rules:

- Patients randomized to receive Placebo or Naproxen in Year 1 will be assigned to receive Naproxen prn during Year 2
- Patients randomized to received Fasinumab 1 mg Q4W in Year 1 will be assigned to remain on this dose for Year 2
- Patients randomized to received Fasinumab 1 mg Q8W in Year 1 will be assigned to remain on this dose for Year 2

2.2. Sample Size and Power Considerations

In this study, approximately 2560 patients were planned to be randomized to fasinumab 1 mg SC Q4W (840), fasinumab 1 mg SC Q8W (600), naproxen (840), or placebo (280) (see Section 5.1.3 of the protocol). This sample size was expected to provide adequate power for the comparisons between fasinumab and naproxen at week 16 for the WOMAC pain and physical function scores and the Patient Global Assessment - Osteoarthritis (PGA-OA) score and provide long term data for safety assessment.

The sample size was based on results of the WOMAC pain and physical function subscale scores and the PGA from the R475-PN-1227 study. The calculation of sample size assumed a 2-sided alpha level of 0.025 and a 15% dropout rate up to week 16 and a 30% dropout rate up to week 52. Enrollment of 840 patients in the fasinumab 1 mg Q4W group and 280 patients in the placebo group would have provided at least 99% power to detect an effect size of 0.46 in the WOMAC pain and physical function subscale scores (i.e., an absolute treatment difference of 1.1 between fasinumab and placebo and a standard deviation [SD] of 2.4 at week 16 and 52 for the full analysis set [FAS]). This sample size would have provided 99 % power to detect an effect size of 0.36 in PGA for an absolute treatment difference of 0.4 with a SD of 1.1 at week 16, and 98% power at week 52 for the FAS.

For the fasinumab 1 mg Q8W group, the 600 patients would have been compared to the approximately 200 patients in the placebo group who were enrolled after Protocol R475-OA-1611 Amendment 5 Global was implemented. For such comparisons, 2-sided alpha level of 0.025 and a 15% dropout rate up to week 16 and a 30% dropout rate up to week 52 were assumed. Additionally, the effect size for such comparisons were assumed to be 80% of the effect size for the comparison between fasinumab 1 mg Q4W group and the placebo group. Under these assumptions, enrollment of 600 patients in the fasinumab 1 mg Q8W group and 200 patients from the placebo group would have provided 97% power to detect an effect size of 0.368 (=0.46*80%) in the WOMAC pain and physical function subscale scores at week 16 and 93% power at week 52. This sample size would have provided 84% power to detect an effect size of 0.288 (=0.36*80%) in PGA at week 16, and 75% power at week 52 for the full analysis set (FAS).

The sample size calculation was also based on previously reported results of the WOMAC pain subscale and physical function subscale and the PGA for naproxen (Ekman 2014) (Schnitzer 2015). Assuming a 2-sided alpha level of 0.025 and a 15% dropout rate up to week 16 and a 30% dropout rate up to week 52, an enrollment of 840 patients in the fasinumab 1 mg Q4W group and the naproxen group would have provided at least 97% power to detect an effect size of 0.22 in the WOMAC pain subscale (i.e., an absolute treatment difference of 0.51 with a SD of 2.3) at week 16, and 92% power at week 52 for FAS. This sample size would have provide 98% 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) at week 16, and 96% power at week 52 for FAS. This sample size would have provided 87% power to detect an effect size of 0.18 in PGA at week 16 between fasinumab 1 mg Q4W and naproxen for the FAS.

While the number of patients randomized was based on the sample size calculations in the protocol, the analyses of the primary and secondary efficacy endpoints will be performed at levels of significance as specified in Section 5.7.4 of this document which differs than the initial assumptions used above.

Due to regional irregularities noted in a parallel phase 3 study, the population for the primary and secondary efficacy analyses was changed in Protocol Amendment 8 Global to be performed on a modified Full Analysis Set (mFAS) that excludes patients in the randomization stratum for that region. Based on the number of patients randomized and the testing stragefy specified in Section 5.7.4 it is estimated that this mFAS will provide:

- 99.9% power to detect a statistically significant difference between the 1 mg Q4W group and the placebo group in the WOMAC pain and physical function subscales at Week 16 using an alpha level of 0.05.
- 42% and 46% power to detect a statistically significant difference between the 1 mg Q8W group and the placebo group in WOMAC pain and physical function subscales, respectively, at Week16 using an alpha level of 0.01.
- 99.9% power to detect a statistically significant difference between the 1 mg Q4W group and the naproxen group in the WOMAC pain and physical function subscales at Week 16 using an alpha level of 0.04.

As the analysis for Year 2 will be descriptive only, a targeted sample size based on power considerations was not implemented for Year 2.

2.3. Study Plan

Study assessments and procedures are presented by study period and visit in Section 10.2 Table 3 and Table 4. A schedule for follow-up on JR surgery during the study is presented in Section 10.2 Table 5.

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 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 and patient reported outcome endpoints for Year 1 will be analyzed using the FAS including patients randomized to fasinumab 1 mg Q4W, fasinumab 1 mg Q8W, naproxen and placebo. For the analyses of fasinumab 1 mg Q8W group comparing to the control groups, only patients concurrently randomized (i.e. after Protocol R475-OA-1611 Amendment 5 Global was implemented) will be included.

3.2. The Modified Full Analysis Set (mFAS)

Due to regional irregularities noted in a parallel phase 3 study that became fully apparent only after unblinding that study, and the concern that the same irregularities would be present in data from similar sites from the same region in this study, the primary and secondary efficacy analyses will be performed on a modified Full Analysis Set (mFAS). This mFAS is comprised of the FAS excluding patients from the region of concern (Rest of the World stratum). Efficacy and patient reported outcome endpoints will be analyzed using the mFAS including patients randomized to fasinumab 1 mg Q4W, fasinumab 1 mg Q8W, naproxen and placebo. For the analysis of fasinumab 1 mg Q8W group comparing to the control groups, only the subset of patients concurrently randomized (ie, after Protocol R475-OA-1611 Amendment 5 Global was implemented) will be included.

3.3. The Per Protocol Set (PPS)

The per protocol set (PPS) includes all randomized patients from the mFAS who received all protocol required doses during the 16-week treatment period for the week 16 analysis and who do not have to be excluded due to relevant protocol violations. 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 protocol deviation identification number (PDID). For the analysis of fasinumab 1 mg Q8W group comparing to the control groups, only the subset of patients concurrently randomized (i.e. after Protocol R475-OA-1611 Amendment 5 Global was implemented) will be included.

A PPS using the entire FAS is defined analogously to above and will be used for performing sensitivity analysis on the entire FAS.

3.4. The Safety Analysis Sets (SAF)

The Year 1 safety analysis set (SAF – Year 1) 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 for Year 1 will be analyzed using the

SAF – Year 1 including patients randomized to fasinumab 1 mg Q4W, fasinumab 1 mg Q8W, naproxen, and placebo.

The Year 2 safety analysis set (SAF – Year 2) includes all patients who received at least 1 dose of the Year 2 study drug; it is based on the treatment received during Year 2 (as treated). Treatment compliance/administration, all clinical efficacy and safety variables and all patient reported outcomes from Year 2 will be analyzed using the SAF – Year 2.

The following rules will be used to define the actual treatment a patient received:

- Patients randomized to either the placebo or naproxen arm who receive at least one dose of active fasinumab during Year X will be considered as treated with fasinumab 1 mg Q8W and classified in the fasinumab 1 mg Q8W treatment arm for the purpose of analysis using the SAF – Year X, where X = 1 or 2.
- Patients randomized to the placebo arm who have not received any active fasinumab injections but were ever dispensed active naproxen during Year 1 will be considered as treated with naproxen and classified in the naproxen treatment arm for the purpose of analysis using the SAF – Year 1.
- For patients randomized to either the fasinumab 1 mg Q8W or Q4W arms, as treated is defined to be as randomized and they will be classified in the treatment arm they were randomized to for the purpose of the analysis using the SAF – Year X, where X = 1 or 2, with the following exceptions:
  - In Year 1, if a patient receives no doses of active naproxen or fasinumab, then the patient will be considered as treated with placebo and classified in the placebo treatment arm for the purpose of analysis using the SAF – Year 1.
  - In Year 1, if a patient receives no doses of fasinumab but were ever dispensed any active dose of naproxen, then the patient will be considered as treated with naproxen and classified in the naproxen treatment arm for the purpose of analysis using the SAF – Year 1.
  - In Year 2, if a patient receives no doses of fasinumab, then the patient will be considered as treated with naproxen prn and classified in the naproxen prn treatment arm for the purpose of analysis using the SAF – Year 2.

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 set includes all treated patients that had at least 1 non-missing drug concentration result following the first dose of study drug. 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 (as treated).

3.8. The Neutralizing Antibody (NAb) Set

The neutralizing antibody (NAb) analysis set includes all patients who received any study drug and who are negative in the fasinumab ADA assay or with at least one non-missing result in the fasinumab NAb assay following the 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 (as treated).

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline variables will be summarized:

- Age at screening (year)
- Age range (< 65, 65-74, ≥ 75 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino: Yes, No, Not Reported, and Unknown)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) calculated from weight and height
- Geographic Region (Europe, North America and Rest of World)
- Index Joint (Knee or Hip) per IWRS
- Kellgren-Lawrence score (2, 3, 4) per IWRS for the 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 Medication and Procedures

For patients who only participate in Year 1, Medications/Procedures will be recorded from the day of informed consent until either the Early Termination/JR Pre-operative Visit or End of Follow-up Clinic Visit at Week 72, which ever is applicable for each patient. For patients who continue into Year 2, Medications/Procedures will be recorded from the day of informed consent for Year 2 until the Early Termination E/JR Pre-operative Visit E or End of Follow-up Clinic Visit at Week 124E, which ever is applicable for each patient.

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.

Year 1 Concomitant medications/procedures are defined as medications/procedures starting prior to or during the Year 1 On-Treatment Period (as defined in Section 5) and ending during or after the Year 1 On-Treatment Period. *Year 2 Concomitant medications/procedures* are defined analogously.

For patients who do not continue into the Year 2, *Year 1 Post-Treatment medications/procedures* are medications/procedures starting after the Year 1 On-Treatment Period.

For patients who do continue into the Year 2, *Year 2 Post-Treatment medications/procedures* are medications/procedures starting after the Year 2 On-Treatment Period.

4.4. Prohibited Medication During Study

Patients will be required to discontinue all non-study pain medication (oral or topical; except up to 150 mg/day of aspirin/5-aminosalicylic acid [5-ASA], which is permitted for cardiac prophylaxis, per local guidelines) and opioid analgesic medications, starting at the pre-randomization visit and through the Year 1 and Year 2 Treatment Periods.

Opioid analgesic medications (including tramadol) are prohibited during the Year 1 and Year 2 Treatment Periods. Patients will be directed not to take concomitant medications that contain NSAIDs (oral or topical, except up to 150 mg/day of aspirin/5-ASA, which is permitted for cardiac prophylaxis) until at least 16 weeks after the last SC study drug injection. A list of medications containing NSAIDs will be provided in the study reference manual and a reference card given to the patients.

Other excluded medications during the Year 1 and Year 2 Treatment Periods 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 section 7.7.2 of the protocol for permitted muscle relaxants)
- Corticosteroids (topical, intranasal, and inhaled formulations are permitted), adenocorticotropic hormone
- Cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus

- Azathioprine, sulfasalazine, hydroxycholoroquine
- IL-6 or IL-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 list of concomitant medications taken during the Year 1 and Year 2 Treatment Periods will be reviewed by the study team to determine if any medication falls under one of the above categories. If a concomitant medication is adjudicated to be prohibited, a protocol deviation will be recorded.

The following variables will be summarized for prohibited medications:

- Number and percentage of patients using at least one prohibited medication during the Year 1 and Year 2 Treatment Periods separately.
- Number and percentage of patients using at least one prohibited medication during the Year 1 and Year 2 Follow-up Periods separately.
- Number and percentage of patients with at least one prohibited NSAID use during the Year 1 and Year 2 Treatment Periods separately.
- Number and percentage of patients with at least one prohibited NSAID use during the Year 1 and Year 2 Follow-up Periods separately.
- Number of days patients used prohibited medications during the Year 1 and Year 2 Treatment Periods separately.
- Number of days patients used prohibited NSAID medications during the Year 1 and Year 2 Treatment Periods separately.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variables

The co-primary efficacy variables in the study are:

1. Change in the WOMAC pain subscale scores from baseline to week 16 in patients treated with fasinumab compared with that of patients treated with placebo.
2. Change in the WOMAC physical function subscale scores from baseline to week 16 in patients treated with fasinumab compared with that of patients treated with placebo.

4.5.2. Secondary Efficacy Variables

The key secondary efficacy variables in the study are:

1. Change from baseline in the Patient Global Assessment (PGA) scores from baseline to week 16 in patients treated with fasinumab compared with that of patients treated with placebo
2. Percentage of patients treated with fasinumab, compared with that of patients treated with placebo, who had a response at week 16, with response defined as an improvement by ≥ 30% in the WOMAC pain subscale scores
3. Change in WOMAC pain subscale scores from baseline to week 16 in patients treated with fasinumab, compared with that of patients treated with naproxen
4. Change in WOMAC physical function subscale scores from baseline to week 16 in patients treated with fasinumab, compared with that of patients treated with naproxen
5. Change in WOMAC pain subscale scores from baseline to week 44 in patients treated with fasinumab, compared with that of patients treated with placebo
6. Change in WOMAC physical function subscale scores from baseline to week 44 in patients treated with fasinumab, compared with that of patients treated with placebo
7. Change in the PGA scores from baseline to week 44 in patients treated with fasinumab compared with that of patients treated with placebo
8. Change in the PGA scores from baseline to week 16 in patients treated with fasinumab compared with that of patients treated with naproxen
9. Change in WOMAC pain subscale scores from baseline to week 44 in patients treated with fasinumab, compared with that of patients treated with naproxen
10. Change in WOMAC physical function subscale scores from baseline to week 44 in patients treated with fasinumab, compared with that of patients treated with naproxen
11. Percentage of patients treated with fasinumab, compared with that of patients treated with naproxen, who had a response at week 16, with response defined as an improvement by ≥ 30% in the WOMAC pain subscale scores
12. Change in WOMAC pain subscale scores from baseline to the average score across Weeks 4, 8, 12 and 16, in patients treated with fasinumab compared with that of patients treated with placebo
13. Change in WOMAC physical function subscale scores from baseline to the average score across Weeks 4, 8, 12 and 16, in patients treated with fasinumab compared with that of patients treated with placebo
14. Change in WOMAC pain subscale scores from baseline to the average score across Weeks 36, 40 and 44, in patients treated with fasinumab compared with that of patients treated with placebo
15. Change in WOMAC physical function subscale scores from baseline to the average score across Weeks 36, 40 and 44, in patients treated with fasinumab compared with that of patients treated with placebo

4.5.3. Exploratory Variables

The exploratory endpoints in the study are

1. Change from baseline to week 16 and 44 in patient-reported outcome measures in patients with pain due to OA of the knee or hip treated with fasinumab compared to placebo
2. Change from baseline to week 16 and 44 in patient-reported outcome measures in patients with pain due to OA of the knee or hip treated with fasinumab compared to naproxen
3. The proportion of patients taking rescue medication, number of days on rescue medication, and weekly average use of rescue medication from baseline to week 16 and 44 in patients with pain due to OA of the knee or hip treated with fasinumab compared to placebo
4. The proportion of patients taking rescue medication, number of days on rescue medication, and weekly average use of rescue medication from baseline to week 16 and 44 in patients with pain due to OA of the knee or hip treated with fasinumab compared to naproxen
5. Percentage of patients treated with fasinumab, compared with that of patients treated with placebo, who had improvements of ≥ 50% and ≥ 70% in the WOMAC pain subscale scores at week 16 and 44
6. Percentage of patients treated with fasinumab, compared with that of patients treated with placebo, who had improvements of ≥ 30%, ≥ 50% and ≥ 70% in the WOMAC pain subscale scores at week 16 and 44
7. Percentage of patients treated with fasinumab, compared with that of patients treated with placebo who met the OMERACT-OARSI criterion at week 16 and 44
8. Change from baseline at all visits from week 52E and 104E of the WOMAC pain and physical function subscale scores in patients with pain due to OA of the knee or hip treated with fasinumab compared to naproxen prn
9. Change from baseline at all visits from week 52E and 104E in patient-reported outcome measures in patients with pain due to OA of the knee or hip treated with fasinumab compared to naproxen prn
10. The proportion of patients taking rescue medication, number of days on rescue medication, and weekly average use of rescue medication from week 52E to week 104E in patients with pain due to OA of the knee or hip treated with fasinumab compared to placebo
11. The proportion of patients taking rescue medication, number of days on rescue medication, and weekly average use of rescue medication from week 52E to week 104E in patients with pain due to OA of the knee or hip treated with fasinumab compared to naproxen

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 then at each visit until the end of the study. 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, Version 20 or 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 additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the 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 independent 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 cardiologist) selected using eCRF specific tick boxes on the AE page and corresponding Supplemental AE page indicating it was confirmed by a specialist.
- Peripheral sensory AEs that require a neurology or other specialty consultation, collected using an eCRF specific tick box on the AE page.
- Joint replacement surgery (refer to Section 9.6.1.4 in the protocol for when to report as an AESI) selected using an 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 Time and Events (Section 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 Section 10.3 for PCSV definitions).

4.6.4. Vital Signs

The following vital signs parameters will be collected according to the Schedule of Time and 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 Section 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, respectively

  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, respectively

  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 Time and Events in Section 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 clinically significant or abnormal clinically 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 Section 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 Time and Events in Section 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 domains will be described as normal or abnormal (clinically significant, or not clinically significant) with the exception of the carpal tunnel evaluation which will be described as present/absent.

4.6.8. Other Safety Variables

Exploratory safety endpoints include:

- Survey of Autonomic Symptoms questionnaire:
  - Potential events of sympathetic nervous system dysfunction are monitored throughout the study via the survey of autonomic symptoms. The survey asks if patients have a symptom, to what extent they are bothered by it. The extent to which symptoms are bothersome are described in 5 categories (not at all, a little, some, moderate, a lot).
  - Summaries will include the number and proportion of patients presenting with symptoms at scheduled timepoints by degree of bothersomeness. Change from baseline in the degree of bothersomeness of each symptom represented will also

be presented at scheduled timepoints. Change from baseline in the degree of bothersomeness will be described as better, same or worse.

- Joint Pain Questionnaire:
  - Number of subjects with significantly worse joint pain in any joint at each scheduled visit
  - Number of subjects with significantly worse joint pain by joint at each scheduled visit
- Joint space width for the 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 with 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 each of the collection times specified in Table 3 and Table 4 of the Schedule of Time and Events in Section 10.2.

4.8. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and NAb status at each time-point/visit. Serum samples for ADA will be collected at the clinic visits specified in Section 10.2. Samples positive in the fasinumab ADA assay will be further characterized for ADA titers and for the presence of NAb against fasinumab.

4.9. Quality-of-Life Variables

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

- 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, and 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.

4.10. Health Economic Variables

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

- HealthCare Resource Utilization (HCRU) including total and type of usage and hospitalizations.
- Change from baseline by visit in the WPAI-OA item and subscores 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 variables captured at multiple visits will be analyzed by the following observations periods:

- The Pre-Treatment Period is defined as the time from signing the ICF to before the first dose of study drug in Year 1.
- The Year 1 On-Treatment Period is defined as the day from first dose of Year 1 study drug through the day of last Year 1 SC dose + 4 weeks for those patients not proceeding into Year 2, or up to the first dose of Year 2 study drug for those patients proceeding into Year 2. Summaries for the Year 1 On-Treatment Period will be based on the SAF – Year 1.
- The Year 1 Post-Treatment Period is defined from the end of the Year 1 On-Treatment Period to the Week 72/Early Termination Visit for those patients not proceeding into Year 2. Summaries for the Year 1 Post-Treatment Period will be based on the SAF – Year 1.
- The Year 2 On-Treatment Period is defined as the day from first dose of Year 2 study drug through the day of last Year 2 SC dose + 4 weeks for those patients proceeding into Year 2. Summaries for the Year 2 On-Treatment Period will be based on the SAF – Year 2.
- The Year 1 and 2 On-Treatment Period is defined as day from first dose of Year 1 study drug through the day of last SC dose + 4 weeks. Summaries for the Year 1 and 2 On-Treatment Period will be based on both the SAF – Year 1 and SAF-Year 2.
- The Year 2 Post-Treatment Period is defined from the end of the Year 2 On-Treatment Period to the Week 124E/Early Termination E Visit for those patients proceeding into Year 2. Summaries for the Year 2 Post-Treatment Period will be based on the SAF – Year 2.

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 mFAS, FAS, SAF – Year 1 and SAF – Year 2.

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 – Year 1. 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. The same summaries will be also be supplied based on the SAF – Year 2.

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 – Year 1 and the SAF – Year 2 separately.
- All concomitant medications taken during the Year 1 On-Treatment Period will be summarized by treatment group based on the SAF – Year 1. Similarly, all concomitant medications taken during the Year 2 On-Treatment Period will be summarized by treatment group based on the SAF – Year 2.
- All Post-treatment medications taken during the Year 1 Post-Treatment period will be summarized by treatment group based on the subset of patients in the SAF – Year 1 who do not continue into Year 2. For patients who continue into Year 2, all concomitant medications taken during the Year 2 Post-Treatment period will be summarized by treatment group based on the SAF – Year 2.

5.4. 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. The following will be provided:

- All prohibited medications taken during the Pre-Treatment Period will be summarized by treatment group and overall, based on the SAF – Year 1 and SAF – Year 2 separately.
- All prohibited medications taken during the Year 1 Treatment and Follow-up Periods will be summarized by treatment group based on the SAF – Year 1. An analogous analysis will be performed for Year 2 Treatment and Follow-up Periods based on the SAF – Year 2.
- All prohibited NSAID medications taken during the Year 1 Treatment and Follow-up Periods will be summarized by treatment group based on the SAF – Year 1. An analogous analysis will be performed for Year 2 Treatment and Follow-up Periods based on the SAF – Year 2.

- The total number of days using prohibited NSAIDs during the Year 1 Treatment and Follow-up Periods (before AA for patients with AA) will be summarized by treatment group based on the SAF – Year 1. An analogous analysis will be performed for the Year 2 Treatment and Follow-up Periods based on the SAF – Year 2.
- The number of days from the last dose of study drug in Year 1 to the first NSAID dose will be summarized in the subset of patients in the SAF – Year 1 who do not continue into Year 2. Similarly, the number of days from the last dose of study drug in Year 2 to the first NSAID dose will be summarized based on the SAF – Year 2.

5.5. Subject Disposition

In addition to the summaries in the following subsections, the following will be provided:

- The total number of screened patients: defined as having signed the ICF
- The total number of randomized patients (defined in the protocol as having received a randomization number).
- The total number of patients in each analysis set.
- A listing of patients treated but not randomized, patients randomized but not treated and patients randomized but not treated as randomized.
- A listing of disposition for all patients.
- A listings of screening failures and reasons for screen failing.
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation.
- A listing of patients who withdrew from the study, along with reasons for study withdrawal.

5.5.1. Screening Disposition

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

- Screened patients.
- Patients randomized.
- 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.

5.5.2. Year 1 Treatment and Study Disposition

In the summaries below, percentages will be calculated using the number of patients in the mFAS as the denominator. Summaries will present the frequencies (and percentages as applicable) by treatment group for the following:

- Patients randomized. 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 the Year 1 Treatment Period.
- Patients who completed study treatment during the Year 1 Treatment Period.
- Patients who discontinued treatment during the Year 1 Treatment Period separated out by reasons for treatment discontinuation.
- Patients who enrolled in Year 2 (defined as having passed all the Inclusion/Exclusion criterion for Year 2 and signed the ICF form for Year 2).
- Patients who entered the Year 1 Follow-up Period.
- Patients who completed the Year 1 Follow-up Period.
- Patients who withdrew from the study during the Year 1 Treatment Period separated out by reasons for study withdrawal.

The same summary described above will also be provided based on the FAS.

5.5.3. Year 2 Disposition

In the summaries below, percentages will be calculated using the number of patients in the SAF – Year 2 as the denominator. Summaries will present the frequencies (and percentages as applicable) by treatment group for the following:

- Patients enrolled and treated in Year 2. The treatment groups reflected in this row are based on the treatment received in Year 2 (see Section 3.4).
- Patients who completed the Year 2 Treatment Period.
- Patients who completed study treatment during the Year 2 Treatment Period.
- Patients who discontinued treatment during the Year 2 Treatment Period separated out by reason for treatment discontinuation.
- Patients who entered the Year 2 Follow-up Period.
- Patients who completed the Year 2 Follow-up Period.
- Patients who withdrew from the study during the Year 2 Treatment Period separated out by reason for study withdrawal.

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 (see Section 5.8) 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 with descriptive statistics for the Year 1 and Year 2 Treatment Periods separately based on the SAF – Year 1 and SAF – Year 2 respectively.

The total number of SC injections will be summarized by treatment groups with descriptive statistics for the Year 1 and Year 2 Treatment Periods based on the SAF – Year 1 and SAF – Year 2 respectively. A summary of the number (and percentage) of patients categorized by the number of SC injections received will also be included.

Oral Study Drug

Overall treatment compliance to oral 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 for Year 1 up to treatment discontinuation of the Year 1 Treatment Period. It is calculated according to the following formula based on the Naproxen/Placebo Dispensing/Accountability eCRF:

$$\frac{\sum_{all\ treatment\ visits}(Number\ of\ pills\ dispensed - Number\ of\ pills\ returned)}{(date\ of\ last\ dose\ of\ oral\ study\ drug - date\ of\ first\ dose\ of\ oral\ study\ drug + 1) * 2}\ x100$$

Overall treatment compliance to oral study drug during the Year 1 Treatment Period will be summarized descriptively by treatment group based on the SAF – Year 1.

Since the oral study drug for Year 2 is naproxen prn, treatment compliance for oral study drug during the Year 2 Treatment Period is not applicable and will not be summarized.

5.6.2. Exposure to Investigational Products

The duration of SC study drug exposure during the Year 1 and Year 2 Treatment Periods is calculated as:

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

The duration of oral study drug exposure during the Year 1 and Year 2 Treatment Periods is calculated as:

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

The durations of SC and oral study drug exposures will be summarized by treatment group using descriptive statistics for the Year 1 and Year 2 Treatment Periods separately based on the SAF – Year 1 and SAF – Year 2 respectively.

The number and percentage of patients exposed to SC/oral study drug will be presented by specific time interval for each treatment group for the Year 1 and Year 2 Treatment Periods separately based on the SAF – Year 1 and SAF – Year 2 respectively. The time intervalss of interest are specified as:

- For Year 1 Treatment Period: ≥ 1 day, ≥ 29 days, ≥ 57 days, ≥ 85 days, ≥ 113 days, ≥ 141 days, ≥ 169 days, ≥ 197 days, ≥ 225 days, ≥ 253 days, ≥ 281 days, ≥ 309 days, ≥ 337 days, ≥ 365 days.
- For Year 2 Treatment Period: ≥ 365 day, ≥ 393 days, ≥ 421 days, ≥ 449 days, ≥ 477 days, ≥ 505 days, ≥ 533 days, ≥ 561 days, ≥ 589 days, ≥ 617 days, ≥ 645 days, ≥ 673 days, ≥ 701 days, ≥ 729 days.

5.6.3. Length of Study Observation

The length of study observation is calculated as:

= (Date of the last study visit [up to the end of the follow-up clinic visit, including post-op joint replacement follow-up visit 2] – date of the first study drug administration in Year 1) + 1

The total length of study participation is calculated as:

= (Date of the last scheduled study contact [up to the end of study phone call] – date of the first study drug administration in Year 1) + 1

The lengths of study observation and participation will be summarized by treatment group using descriptive statistics based on the SAF – Year 1 and SAF – Year 2 separately.

The number and percentage of patients with length of study observation/participation within specific time intervals will be presented by treatment group based on the SAF – Year 1 and SAF – Year 2 separately. The time intervals of interest are specified as:

- For Year 1: ≥ 1 day, ≥ 29 days, ≥ 57 days, ≥ 85 days, ≥ 113 days, ≥ 141 days, ≥ 169 days, ≥ 197 days, ≥ 225 days, ≥ 253 days, ≥ 281 days, ≥ 309 days, ≥ 337 days, ≥ 365 days ≥ 393 days, ≥ 505 days, ≥ 701 days.
- For Year 2: ≥ 365 days ≥ 393 days, ≥ 421 days, ≥ 449 days, ≥ 477 days, ≥ 505 days, ≥ 533 , ≥ 561 days, ≥ 589 days, ≥ 617 days, ≥ 645 days, ≥ 673 days, ≥ 701 days, ≥ 729 days, ≥ 757 days, ≥ 869 days, ≥ 1065 days.

5.7. Analyses of Efficacy Variables

Unless stated otherwise, all efficacy analyses will be based on the mFAS using the Year 1 baseline value. Confidence intervals will be constructed with level of confidence equal to 95%. Models including stratifying variables will utilize the value of these variables as captured in the IWRS system.

5.7.1. Analysis of Primary Efficacy Variables

The co-primary efficacy variables are:

1. Change in the WOMAC pain subscale scores from baseline to week 16
2. Change in the WOMAC physical function subscale score from baseline to week 16

The following hypotheses will be tested:

- $H_{1,1}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC pain or physical function subscale at week 16 versus there is treatment difference in WOMAC pain and physical function subscale score at week 16
- $H_{2,1}$: There is no treatment difference between fasinumab 1 mg Q8W and placebo in WOMAC pain or physical function subscale at week 16 versus there is treatment difference in WOMAC pain and physical function subscale score at week 16

For $H_{1,1}$, the estimand is the difference in means between the fasinumab 1 mg Q4W dose and placebo in the change from baseline to week 16 in the WOMAC pain and physical function scores in the mFAS, regardless of whether or not rescue medication or prohibited medication had been taken. Any data collected after discontinuing treatment in Year 1 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 mFAS. For patients who permanently discontinued treatment due to lack of efficacy, death or AEs, their missing WOMAC subscale scores after discontinuation will be imputed with values centered at the mean baseline WOMAC subscale score of the treatment group that patient was randomized to. For patients who discontinued treatment due to other reasons (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 [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 52 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 4751611. If a randomly imputed score is imputed outside the range of the WOMAC subscale score of 0-10, then the algorithm will continue to randomly impute scores until one within the range of 0-10 is obtained.
- 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 4751611 and adjustment for covariates including treatment groups, randomization strata (K-L category [2 to 3, or 4], index joint [knee, hip], and geographical region [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 addressed in the same manner as in step 1.

- 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).

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 [Europe, North America]), treatment, visit, and treatment-by-visit interaction as fixed effects. The MMRM will be fitted using the MIXED procedure in Statistical Analysis System (SAS) with an unstructured covariance matrix to model the within-patient errors. The denominator degrees of freedom will be estimated using Kenward-Roger's approximation. In the event a model cannot be 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 16, 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 $H_{1,1}$ will be rejected when the p-values corresponding to the difference in change from baseline to week 16 between fasinumab 1 mg Q4W and placebo is less than the available α_0 (see Section 5.7.4) for both the WOMAC pain subscale score and physical function subscale score.

Since the fasinumab 1 mg Q8W treatment arm was not included in the study prior to protocol amendment 5, the estimand and analysis method for testing $H_{2,1}$ will mimic that used for $H_{1,1}$ with the exception that only the subset of patients in the mFAS who were randomized post amendment 5 will be utilized in the statistical analysis.

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 and placebo in the change from baseline to week 16 in the WOMAC pain and physical function scores in the mFAS, regardless of study treatment discontinuation prior to week 52 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 52 will be used in this sensitivity analyses. Missing WOMAC subscale scores up to week 52 will be imputed with the same approach used in the primary analysis.

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 52 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 4751611. If a randomly imputed score is imputed outside the range of the WOMAC subscale score of 0-10, then the algorithm will continue to randomly impute scores until one within the range of 0-10 is obtained.
- 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 4751611 and adjustment for covariates including treatment groups, randomization strata strata (K-L category [2 to 3, or 4], index joint [knee, hip], and geographical region [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 addressed in the same manner as in step 1.
- Step 3: For missing data because of permanent study treatment discontinuation due to adverse events, death or lack of efficacy, δ will be added to the imputed values ($\delta = 0$ corresponds to the MAR assumption).

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 [Europe, North America]), treatment, visit, and treatment-by-visit interaction as fixed effects. 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 0.025 or 0.05. Results will be then summarized using summary tables and graphs.

Per Protocol Set Analysis

Sensitivity analyses based on the PPS will be performed using the 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

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 [Europe, North America]
- Age group [< 65, 65-74, ≥ 75 years]
- Sex [Male, Female]
- Weight group [< median baseline weight, ≥ median baseline weight kg]
- BMI group [≤ median baseline BMI, > median baseline BMI]
- Flare status [Flare, Non-Flare] where 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 subgroup-by-treatment interaction will be supplied. Forest plots for the subgroup analyses will also be provided.

5.7.3. Analysis of Secondary Efficacy Variables

The key secondary variables defined in the study protocol are:

1. Change in the Patient Global Assessment (PGA) scores from baseline to week 16
2. Percentage of patients who had a response at week 16, with response defined as an improvement by ≥30% in the WOMAC pain subscale scores
3. Change in WOMAC pain subscale scores from baseline to week 44
4. Change in WOMAC physical function subscale scores from baseline to week 44
5. Change in the PGA scores from baseline to week 44
6. Change in WOMAC pain subscale scores from baseline to the average score across Weeks 4, 8, 12 and 16

7. Change in WOMAC physical function subscale from baseline to the average score across Weeks 4, 8, 12 and 16
8. Change in WOMAC pain subscale scores from baseline to the average score across Weeks 36, 40 and 44
9. Change in WOMAC physical function subscale scores from baseline to the average score across Weeks 36, 40 and 44

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

- $H_{1,2}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in Patient Global Assessment score at week 16 versus there is treatment difference in Patient Global Assessment score at week 16
- $H_{1,3}$: 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 16 versus there is treatment difference in proportion of patients with ≥30% improvement in WOMAC pain at week 16
- $H_{1,4}$: There is no treatment difference between fasinumab 1 mg Q4W and naproxen in WOMAC pain subscale scores at week 16 versus there is a treatment difference in the WOMAC pain subscale scores at week 16
- $H_{1,5}$: There is no treatment difference between fasinumab 1 mg Q4W and naproxen in WOMAC physical function subscale scores at week 16 versus there is a treatment difference in the WOMAC physical function subscale scores at week 16
- $H_{1,6}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC pain subscale scores at week 44 versus there is treatment difference in WOMAC pain subscale scores at week 44
- $H_{1,7}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC physical function subscale scores at week 44 versus there is treatment difference in WOMAC physical function subscale scores at week 44
- $H_{1,8}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in Patient Global Assessment score at week 44 versus there is treatment difference in Patient Global Assessment score at week 44
- $H_{1,9}$: There is no treatment difference between fasinumab 1 mg Q4W and naproxen in Patient Global Assessment score at week 16 versus there is treatment difference in Patient Global Assessment score at week 16
- $H_{1,10}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in the WOMAC pain subscale scores averaged across Weeks 4, 8, 12 and 16 versus there is treatment difference in the WOMAC pain subscale scores averaged across Weeks 4, 8, 12 and 16
- $H_{1,11}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in the WOMAC physical function subscale scores averaged across Weeks 4, 8, 12 and

16 versus there is treatment difference in the WOMAC physical function subscale scores averaged across Weeks 4, 8, 12 and 16

- $H_{1,12}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in the WOMAC pain subscale scores averaged across Weeks 36, 40 and 44 versus there is treatment difference in the WOMAC pain subscale scores averaged across Weeks 36, 40 and 44
- $H_{1,13}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in the WOMAC physical function subscale scores averaged across Weeks 36, 40 and 44 versus there is treatment difference in the WOMAC physical function subscale scores averaged across Weeks 36, 40 and 44
- $H_{1,14}$: There is no treatment difference between fasinumab 1 mg Q4W and naproxen in WOMAC pain subscale scores at week 44 versus there is treatment difference in WOMAC pain subscale scores at week 44
- $H_{1,15}$: There is no treatment difference between fasinumab 1 mg Q4W and naproxen in WOMAC physical function subscale scores at week 44 versus there is treatment difference in WOMAC physical function subscale scores at week 44
- $H_{1,16}$: There is no treatment difference between fasinumab 1 mg Q4W and naproxen in the proportion of patients with ≥30% improvement in the WOMAC pain subscale scores at week 16 versus there is treatment difference in proportion of patients with ≥30% improvement in WOMAC pain at week 16
- $H_{2,2}$: There is no treatment difference between fasinumab 1 mg Q8W and placebo in Patient Global Assessment score at week 16 versus there is treatment difference in Patient Global Assessment score at week 16
- $H_{2,3}$: There is no treatment difference between fasinumab 1 mg Q8W and placebo in the proportion of patients with ≥30% improvement in the WOMAC pain subscale scores at week 16 versus there is treatment difference in proportion of patients with ≥30% improvement in WOMAC pain at week 16
- $H_{2,4}$: There is no treatment difference between fasinumab 1 mg Q8W and naproxen in WOMAC pain subscale scores at week 16 versus there is a treatment difference in the WOMAC pain subscale scores at week 16
- $H_{2,5}$: There is no treatment difference between fasinumab 1 mg Q8W and naproxen in WOMAC physical function subscale scores at week 16 versus there is a treatment difference in the WOMAC physical function subscale scores at week 16
- $H_{2,6}$: There is no treatment difference between fasinumab 1 mg Q8W and placebo in WOMAC pain subscale scores at week 44 versus there is treatment difference in WOMAC pain subscale scores at week 44
- $H_{2,7}$: There is no treatment difference between fasinumab 1 mg Q8W and placebo in WOMAC physical function subscale scores at week 44 versus there is treatment difference in WOMAC physical function subscale scores at week 44

- $H_{2,8}$: There is no treatment difference between fasinumab 1 mg Q8W and placebo in Patient Global Assessment score at week 44 versus there is treatment difference in Patient Global Assessment score at week 44
- $H_{2,9}$: There is no treatment difference between fasinumab 1 mg Q8W and naproxen in Patient Global Assessment score at week 16 versus there is treatment difference in Patient Global Assessment score at week 16
- $H_{2,10}$: There is no treatment difference between fasinumab 1 mg Q8W and placebo in the WOMAC pain subscale scores averaged across Weeks 4, 8, 12 and 16 versus there is treatment difference in the WOMAC pain subscale scores averaged across Weeks 4, 8, 12 and 16
- $H_{2,11}$: There is no treatment difference between fasinumab 1 mg Q8W and placebo in the WOMAC physical function subscale scores averaged across Weeks 4, 8, 12 and 16 versus there is treatment difference in the WOMAC physical function subscale scores averaged across Weeks 4, 8, 12 and 16
- $H_{2,12}$: There is no treatment difference between fasinumab 1 mg Q8W and placebo in the WOMAC pain subscale scores averaged across Weeks 36, 40 and 44 versus there is treatment difference in the WOMAC pain subscale scores averaged across Weeks 36, 40 and 44
- $H_{2,13}$: There is no treatment difference between fasinumab 1 mg Q8W and placebo in the WOMAC physical function subscale scores averaged across Weeks 36, 40 and 44 versus there is treatment difference in the WOMAC physical function subscale scores averaged across Weeks 36, 40 and 44

The hypotheses $H_{1,4}$, $H_{1,5}$, $H_{1,6}$, $H_{1,7}$, $H_{1,14}$ and $H_{1,15}$ can be tested within the same analysis method used to test $H_{1,1}$ as described in Section 5.7.1. Similarly, $H_{2,4}$, $H_{2,5}$, $H_{2,6}$ and $H_{2,7}$ can be tested within the same analysis methods used to test $H_{2,1}$ as described in Section 5.7.1. Additionally, the treatment policy analysis, per-protocol analysis and subgroup analyses described in Section 5.7.1 for the primary endpoint can also be utilized for the hypotheses mentioned in this paragraph.

To test $H_{1,2}$, $H_{1,8}$ and $H_{1,9}$, a method analogous to that used to test $H_{1,1}$ in Section 5.7.1 can be utilized, replacing the respective WOMAC subscale score with the PGA score. Likewise, $H_{2,2}$, $H_{2,8}$ and $H_{2,9}$ can be tested using a method analogous to that used to test $H_{2,1}$ in Section 5.7.1, replacing the respective WOMAC subscale score with the PGA score and only using the subset of patients in the mFAS randomized after protocol amendment 5 for the analyses. The multiple imputation algorithm will be modified to resample values outside the range of the PGA score (0-5) in a manner similar to the primary analysis.

To test $H_{1,3}$ and $H_{1,16}$, 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 [Europe, North America]) will be used with missing data considered as non-response. The same method can be utilized to test $H_{2,3}$, however, only basing the analysis on the subset of patients in the mFAS who were randomized post protocol amendment 5.

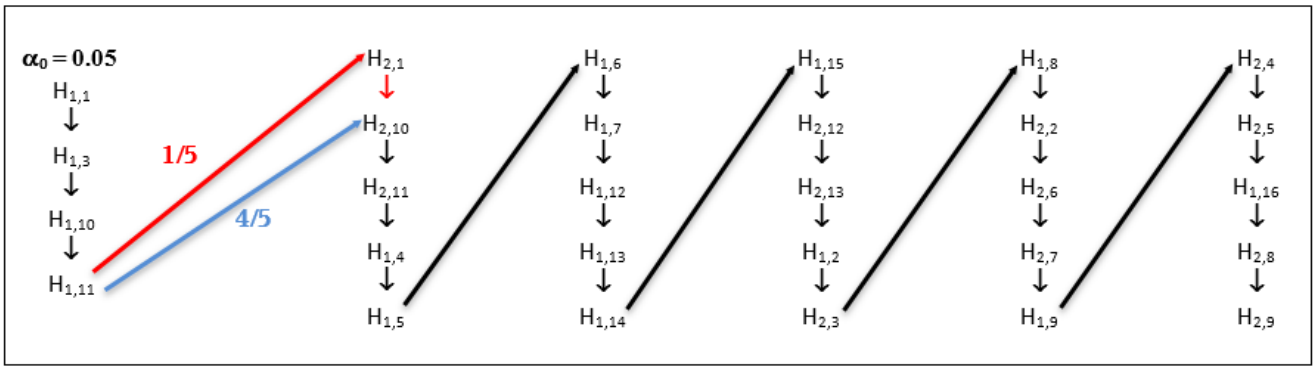
To test hypothesis $H_{1,10}$, $H_{1,11}$, $H_{1,12}$ and $H_{1,13}$, the same multiple imputation method used to test $H_{1,1}$ in Section 5.7.1 will be utilized. However, the analysis model for the average of the WOMAC subscale scores across multiple visits will instead be an ANCOVA model with terms 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]) and treatment. Hypothesis $H_{2,10}$, $H_{2,11}$, $H_{2,12}$ and $H_{2,13}$ will be tested via an analogous method using only the subset of patients in the mFAS randomized after protocol amendment 5 for the analyses.

5.7.4. Adjustment for Multiple Comparisons

To control the overall Type I Error of the clinical trial at 5%, the graphical testing procedure (Bretz 2009) will be applied. The order the hypothesis will be tested is provided in the schematic representation of the multiple testing procedure below (Figure 2).

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.

Figure 2: Hypothesis Testing Procedure



5.7.5. Analysis of Other Efficacy Variables

As additional sensitivity analyses, the following efficacy endpoints will be analyzed using the same method as was used for hypotheses $H_{1,1}$, and $H_{2,1}$:

- Change in WOMAC pain subscale scores from baseline to week 48
- Change in WOMAC physical function subscale scores from baseline to week 48
- Change in WOMAC pain subscale scores from baseline to week 52
- Change in WOMAC physical function subscale scores from baseline to week 52

The same analysis used for hypotheses $H_{1,3}$, $H_{1,16}$, and $H_{2,3}$ will be used to analyze the following additional efficacy endpoints:

- The number and percentage of patients with an improvement of ≥ 50% from baseline in the WOMAC pain subscale scores at weeks 16, 44, 52
- The number and percentage of patients with an improvement of ≥ 70% from baseline in the WOMAC pain subscale scores at week 16, 44, 52
- The number and percentage of patients with an improvement of ≥ 30% from baseline in the WOMAC physical function subscale scores at week 16, 44, 52
- The number and percentage of patients with an improvement of ≥ 50% from baseline in the WOMAC physical function subscale scores at week 16, 44, 52
- The number and percentage of patients with an improvement of ≥ 70% from baseline in the WOMAC physical function subscale scores at week 16, 44, 52
- The number and percentage of patients meeting the OMERACT-OARSI criterion at week 16, 44, 52

Cumulative distribution of percent change from baseline to Week 16 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.

Walking Index Joint Pain Questionnaire

Analysis of the WIJPNRS pain scale will be on the weekly averages. 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 [North America, Europe]), treatment, week (weeks 1, 2, …, 52), 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 – Year 1 and SAF – Year 2. Analogous analysis will be performed for both the Year 1 On-Treatment Period and Year 2 On-Treatment Period based on the SAF – Year 1 and SAF – Year 2 respectively.

For patients taking rescue medication, descriptive statistics of the number of days patients took rescue medications will be presented by treatment group during both the Year 1 On-Treatment Period and Year 2 On-Treatment Period based on the SAF – Year 1 and SAF – Year 2 respectively.

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

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

Descriptive statistics of the weekly average usage of rescue medications will be presented by treatment group for both the Year 1 On-Treatment Period and Year 2 On-Treatment Period based on the SAF – Year 1 and SAF- Year 2 respectively..

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 [North America, Europe]), 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 doses and placebo and naproxen, 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.

Data from Year 2

The following endpoints were collected in Year 2:

- WOMAC
- EQ-5D-5L
- WPAI-OA
- Rescue Medication Usage

Summary statistics for the above variables will be presented by treatment group for each visit in Year 2 based on the SAF – Year 2. For numeric endpoints, the raw, change from Year 1 baseline value and change from Year 2 baseline values will be summarized. No models will be fit to the data, nor will any statistical analysis be performed comparing treatment arms or statistics derived from statistical models.

5.7.7. FAS Analysis

All analyses of the co-primary, secondary, exploratory and PRO endpoints specified in Section 5.7.1, Section 5.7.2, Section 5.7.3, Section 5.7.5 and Section 5.7.6 will also be performed using the FAS. For analyses utilizing the stratification variable geographic region, the strata included will be: North America, Europe and Rest of World.

5.8. Analysis of Safety Data

The analysis of safety and tolerability will be performed on the SAF – Year 1 and SAF – Year 2, 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 JRs identified at the End of Study Phone Calls), or abnormalities is between the first dose of Year 1 study drug dose up to the end of the Follow-Up Period (either the week 72/Early Termination for those patients not proceeding into Year 2, the week 124E/Early Termination E for those patients proceeding into Year 2 or the Post-Op Joint Replacement Follow-up Visit 2). Any study drug-related SAEs occurring between the end of Follow-Up Period 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.

All safety analyses will be performed on Year 1 and Year 2 using the following common rules:

- The Year 1 baseline value will be used for all analyses of the Year 1 On-Treatment, Year 1 and 2 On-Treatment and Year 1 Post-Treatment Periods.
- The Year 2 baseline value will be used for all analyses of the Year 2 On-Treatment and Year 2 Post-Treatment Periods.

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.

Pre-treatment AEs are defined as AEs that developed or worsened during the Pre-Treatment Period.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the On-Treatment Periods.

Post-treatment AEs are defined as AEs that developed or worsened more than 4 weeks after the last dose of SC study drug.

The focus of adverse event reporting in the clinical study report will be on TEAEs.

For details on handling missing data and partial dates, see Section 6.4.

Summaries of all TEAEs in each treatment group will include:

- Overview of TEAEs, summarizing number of events and number and percentage of patients within the specified category:
  - Total number of TEAEs
  - Total number of serious TEAEs
  - Total number of treatment-emergent AESIs
  - Patients with any TEAEs
  - Patients with any serious TEAEs
  - Patients with any treatment-emergent AESIs
  - Patients with any TEAEs leading to permanent discontinuation from study drug

  - Patients with any TEAEs leading to withdrawal from the 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 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
- All Serious TEAEs by SOC and PT
- Post-treatment Serious AEs by SOC and PT
- All serious AEs by SOC and PT
- All non-serious TEAEs by SOC and PT
- Post-treatment non-serious AEs by SOC and PT
- All non-serious AEs by SOC and PT
- All AEs 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 above TEAE analyses will be performed for the Year 1 On-Treatment Period, Year 2 On-Treatment Period, Year 1 and 2 On-Treatment Period, Year 1 Post-Treatment Period and Year 2 Post-Treatment Period using the corresponding analyses sets specified in Section 5.

The following listings will be included:

- AEs leading to death
- TEAEs leading to permanent discontinuation from study drug (not applicable to post-treatment AEs)
- TEAEs leading to withdrawal from study
- Patients with Serious TEAEs
- AESIs
- Deaths
- All Cause 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. The PCSV laboratory summaries will be constructed for both Year 1 and Year 2 On-Treatment Periods.

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

- Adjudicated Arthropathy category 1 (Presence of AA: patients without / with AA)
- Adjudicated Arthropathy category 2 (Subtype of AA: patients without AA, patients with RPOA-1, and patients with other AA subtype except RPOA-1)
- Destructive Arthropathy category (Presence of DA: patients without AA, patients with non-DA AA, patients with DA)

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

For alkaline phosphatase, plots of means of the observed change from baseline over time will be presented by treatment group, overall and by subgroup.

Lab data collected during the Pre-Treatment Period 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 PCSV laboratory summaries will be constructed for both Year 1 and Year 2 On-Treatment Periods

The incidence of orthostatic hypotension, separated out by the specific criteria leading to an orthostatic hypotension diagnosis, will also be summarized by treatment group.

The above vital sign summaries will be constructed for the Year 1 and 2, Treatment and Follow-up Periods. Vital sign data collected during the Pre-Treatment Period 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.

The above ECG summaries will be presented for both On-Treatment Periods.

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 study. Similarly, summaries will be presented for neurological exam findings. These summaries will be constructed for the Treatment and Follow-up Periods, for both Year 1 and 2.

5.8.7. Analysis of Other Safety Variables

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

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.

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.

All-cause Joint Replacements

The number and percentage of patients with all-cause joint replacements will be presented by treatment group for the, Treatment and Follow-up Periods both Year 1 and Year 2. 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.

The time to JR is calculated as:

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

Plots of the Kaplan Meier curves by treatment group (as randomized to in Year 1) of time to JR will be presented based on the SAF – Year 1. 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 serum concentrations of functional fasinumab will be presented by nominal time point and dose. Concentrations below the LLOQ of the bioanalytical assay will be set to zero when calculating means.

Plots of individual concentrations over time will be presented by actual day (linear and log scales). Plots of mean and/or median serum concentrations of fasinumab will be presented by nominal time (linear and log scales). For linear-scaled plots, concentrations below the LLOQ will be set to zero; for log-scaled plots, concentrations below the LLOQ will be imputed as LLOQ/2.

Relationships between concentrations of fasinumab and efficacy endpoints, safety endpoints, and/or biomarkers may be evaluated, as appropriate.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of ADA Data

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

ADA response categories

- ADA Negative, defined as ADA negative response at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as a positive response in the ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient:

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

Titer categories (Maximum titer values)

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative patients (pre-existing immunoreactivity or negative in the fasinumab ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive patients by treatment groups and ADA titer categories
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients by treatment groups and ADA titer categories

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

5.10.2. 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 Exposure

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

5.10.3.2. Immunogenicity and Safety and Efficacy

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

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

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

- ADA positive patients, that is patients with treatment-emergent or treatment-boosted response.
- ADA negative patients, that is patients with pre-existing immunoreactivity or negative in the ADA assay at all time points.
- Patients with persistent treatment-emergent ADA response.
- 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

The following baselines will be used for both the efficacy and safety analyses.

- The Year 1 baseline value is defined as the last available value before randomization.
- The Year 2 baseline value is defined as the last available value after the last dose of Year 1 treatment but before the first dose of Year 2 treatment.

6.2. Data Handling Convention for Efficacy Variables

6.2.1. Handling of Missing Efficacy Data due to COVID-19 Public Health Measures

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 Data

Orthostatic Hypotension data

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

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

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

Patient reported outcomes data

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

6.4. Data Handling Conventions for Missing Data

Rules for handling missing data for primary and secondary efficacy variables are described in Section 5.7.1 and Section Section 5.7.3.

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 be 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 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 on 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, End-of-Treatment (EOT), and End-of-Study (EOS)/Early Termination (ET) 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 Section 10.2 Schedule of Time and Events. The following visit windows will be used to map the unscheduled visits, EOT and EOS /ET visits and eCOA assessments based on the study day:

Table 1: Year 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 1	8	[2, 11]
4	Week 2	15	[12, 22]
5	Week 4	29	[23, 43]
6	Week 8	57	[44, 71]
7	Week 12	85	[72, 99]
8	Week 16	113	[100, 127]
9	Week 20	141	[128, 155]
10	Week 24	169	[156, 183]
11	Week 28	197	[184, 211]
12	Week 32	225	[212, 239]
13	Week 36	253	[240, 267]
14	Week 40	281	[268, 295]
15	Week 44	309	[296, 323]

Visit Number	Visit Name	Targeted Study Days[a]	Analysis Window in Study Days
16	Week 48	337	[324, 351]
17	Week 52	365	[352, 393]
18	Week 56	393	[394, 463]
19	Week 72	505	[464, 603]
Phone 2	Week 100	701	≥ 604

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

Table 2: Year 2 Analysis Windows

Visit Number	Visit Name	Targeted Study Days[a]	Analysis Window in Study Days
17E	Week 52E	365E	[352, 379]
18E	Week 56E	393E	[380, 407]
19E	Week 60E	421E	[408, 435]
20E	Week 64E	449E	[436, 463]
21E	Week 68E	477E	[464, 491]
22E	Week 72E	505E	[492, 519]
23E	Week 76E	533E	[520, 547]
24E	Week 80E	561E	[548, 575]
25E	Week 84E	589E	[576, 603]
26E	Week 88E	617E	[604, 631]
27E	Week 92E	645E	[632, 659]
28E	Week 96E	673E	[660, 687]
29E	Week 100E	701E	[688, 715]
30E	Week 104E	729E	[716, 743]
31E	Week 108E	757E	[744, 813]
32E	Week 124E	869E	[814, 967]
Phone 2E	Week 152E	1065E	≥ 968

[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: Bulgaria, Denmark, France, Germany, Hungary, Italy, Lithuania, Poland, Romania, Russia, Spain, Ukraine, United Kingdom
- North America: United States
- Rest of World: South Africa

6.8. Statistical Technical Issues

Not applicable.

7. INTERIM ANALYSIS

No interim analysis of efficacy data from Year 1 will be conducted prior to collection of all data necessary for the the primary and secondary analysis.

A first-step analysis of all available efficacy and safety data for Year 1 and select analysis of available Year 2 safety data will be performed when all data for Year 1 Treatment Period (baseline through week 52) have been collected and validated for all randomized patients.

Another analysis will be performed for regulatory purposes on the remaining Year 1 WOMAC and PRO assessments and safety data (collected during the Year 1 follow-up period) and any Year 2 efficacy and safety data available at the time of the data cut-off for the second analysis.

Additional analyses of other efficacy and safety data may be performed for regulatory purposes as needed.

Individuals unblinded to patient-level data for the first-step or any subsequent analyses will no longer be involved in the day-to-day conduct of the ongoing study. Patient-level results will not be released to any site-facing personnel or anyone who is directly involved in the conduct of the study.

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*	*mFAS, FAS, PPS*	*Change from baseline at Week 16 in the WOMAC pain subscale scores* *&* *Change from baseline at Week 16 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 16 in the WOMAC pain subscale scores* *&* *Change from baseline at Week 16 in the WOMAC physical function subscale scores*
Secondary Endpoints						
Change from baseline in WOMAC pain subscale scores	*mFAS, FAS, PPS*	*Change from baseline at Week 44 in the WOMAC pain subscale scores*	*MMRM with multiple imputation*	*Sensitivity Analyses:* *- Treatment Policy Estimand* *- Analysis using the PPS*	*Subgroups: K-L Category, Index Joint, Region, Age Group, Sex, Weight, BMI Group.*	*Change from baseline at all other visits in the WOMAC pain subscale scores*
Change from baseline in WOMAC physical function subscale scores	*mFAS, FAS, PPS*	*Change from baseline at Week 44 in the WOMAC physical function subscale scores*	*MMRM with multiple imputation*	*Sensitivity Analyses:* *- Treatment Policy Estimand* *- Analysis using the PPS*	*Subgroups: K-L Category, Index Joint, Region, Age Group, Sex, Weight, BMI Group.*	*Change from baseline at all other visits in the WOMAC physical function subscale scores*

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Change from baseline in WOMAC pain subscale scores averaged across multiple timepoints	*mFAS, FAS*	*Change from baseline in WOMAC pain subscale scores averaged across Weeks 4, 8, 12 and 16*	*ANCOVA with multiple imputation*			*Change from baseline in WOMAC pain subscale scores averaged across Weeks 36,40 and 44*
Change from baseline in WOMAC physical function subscale scores averaged across multiple timepoints	*mFAS, FAS*	*Change from baseline in WOMAC physical function subscale scores averaged across Weeks 4, 8, 12 and 16*	*ANCOVA with multiple imputation*			*Change from baseline in WOMAC physical function subscale scores averaged across Weeks 36,40 and 44*
Change from baseline in PGA scores	*mFAS, FAS*	*Change from baseline at Week 44 in the WOMAC physical function subscale scores*	*MMRM with multiple imputation*			*Change from baseline at all other visits in PGA scores*
Proportion of patients with ≥ 30% improvement in WOMAC pain subscale	*mFAS, FAS*	*Proportion of patients with ≥ 30% improvement in WOMAC pain subscale at Week 16*	*CMH Test*			*NA*

Safety Analyses:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Treatment Emergent Adverse Events	*SAF – Year 1 & SAF – Year 2*	*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 Serious Adverse Events	*SAF – Year 1 & SAF – Year 2*	*Percent of patients by system organ class and preferred term*	*Descriptive Statistics*	*No*	*No*	*NA*
Treatment-related Treatment Emergent Adverse Events	*SAF – Year 1 & SAF – Year 2*	*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 – Year 1 & SAF – Year 2*	*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 – Year 1 & SAF – Year 2*	*Percent of patients by system organ class and preferred term*	*Descriptive Statistics*	*No*	*No*	*No*
Treatment Emergent Non-Serious Adverse Events	*SAF – Year 1 & SAF – Year 2*	*Percent of patients by system organ class and preferred term*	*Descriptive Statistics*	*No*	*No*	*No*
Clinical Laboratory Measurements	*SAF – Year 1 & SAF – Year 2*	*Actual and Change from baseline values*	*Descriptive Statistics*	*PCVS Analysis*	*No*	*No*
Vital Sign Measurements	*SAF – Year 1 & SAF – Year 2*	*Actual and Change from baseline values*	*Descriptive Statistics*	*PCVS Analysis*	*No*	*Incidence of Orthostatic Hypotension*
12-Lead ECGs	*SAF – Year 1 & SAF – Year 2*	*Actual and Change from baseline values*	*Descriptive Statistics*	*PCVS Analysis*	*No*	*Shift Table Analysis*

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Physical & Neurological Exams	*SAF – Year 1 & SAF – Year 2*	*Number of patients with new-onset abnormal examination findings*	*Descriptive Statistics*	*NA*	*No*	*No*
Survey of Autonomic Symptoms	*SAF – Year 1 & SAF – Year 2*	*Number of patients reporting the presence of each symptom/health problem*	*Descriptive Statistics*	*Number of Symptoms Reported* *Total Symptom Impact Score*	*No*	*No*
Adjudicated Arthropathy	*SAF – Year 1 & SAF – Year 2*	*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*	*No*
Joint Replacements	*SAF – Year 1 & SAF – Year 2*	*Number of patients with joint replacements*	*Descriptive Statistics*	*Time to JR*	*No*	*No*

10.2. Schedule of Time and Events

Table 3: Schedule of Events for Year 1

(To be followed by all Year 1 and Year 2 study participants through week 52. Patients participating in Year 1 only will follow this table for weeks 52 through 100. Patients who participate in Year 2 will follow Table 2 starting at week 52E after completing the week 52 visit in Table 1).

	Screen	Pre-Random	Year 1 Treatment (52 weeks)											
Study Week			**Baseline**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**
Study Day	**Up to 30 days**	**7 to 10 days**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**
Visit Window (days)				**±1**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Phone 1**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**
Screening/Baseline:														
Inclusion/Exclusion[2]	X	X	X											
Informed consent	X													
Genomics sub-study informed consent[3]	X													
Medical history	X													
Medication history	X													
Demographics	X													
Height	X													
Diary instructions		X	X											
Training on pain reporting/patient education brochures[4]	X	X												
Randomization			X											
Treatment														
SC study drug injection[5]			X			X	X	X	X	X	X	X	X	X
Dispense acetaminophen/paracetamol		X	X			X	X	X	X	X	X	X	X	X
Acetaminophen/paracetamol accountability			X		X	X	X	X	X	X	X	X	X	X
Dispense oral study drug			X			X	X	X	X	X	X	X	X	X
Oral study drug accountability						X	X	X	X	X	X	X	X	X

	Screen	Pre-Random	Year 1 Treatment (52 weeks)											
Study Week			**Baseline**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**
Study Day	**Up to 30 days**	**7 to 10 days**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**
Visit Window (days)				**±1**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Phone 1**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**
Recording of rescue medication use in diary[6]		X	X	X	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
Patient-Completed Assessments/Efficacy[23]:														
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	X	X	X
SF-36			X			X	X		X		X			
EQ-5D-5L			X			X	X		X		X			
HCRU	X							X			X			X
WPAI-OA			X			X	X		X					
TSQM	X					X	X		X					
Peripheral or central pain			X											
Safety:														
Weight	X										X			
Vital signs[9]	X		X		X	X	X	X	X	X	X	X	X	X
Physical examination	X										X		X	
Orthostatic blood pressure assessment[9,10]	X	X	X		X	X	X	X	X	X	X	X	X	X
Joint pain questionnaire[23]	X		X		X	X	X	X	X	X	X	X	X	X
Survey of autonomic symptoms[23]	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-BRIEF	X-BRIEF	X-BRIEF	X-BRIEF	X-BRIEF
Adverse events	----------→													
Injection site evaluation			X			X	X	X	X	X	X	X	X	X
Electrocardiogram	X													

	Screen	Pre-Random	Year 1 Treatment (52 weeks)											
Study Week			**Baseline**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**
Study Day	**Up to 30 days**	**7 to 10 days**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**
Visit Window (days)				**±1**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Phone 1**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**
Bilateral x-rays (knee, hip, shoulder)	X[11]								X					
MRI[12]	X													
Event-triggered imaging[13]				X	X	X	X	X	X	X	X	X	X	X
Pre-op questionnaire (JR follow-up)[14]														
Laboratory Testing:														
Hematology[15]	X						X		X		X			
Blood chemistry[15]	X						X		X		X			
ESR	X													
HbA1c[15]	X													
FSH and estradiol[15, 16]	X													
Pregnancy test (for WOCBP)[17]	X-Serum		X-Urine			X-Urine	X-Urine	X-Urine	X-Urine	X-Urine	X-Urine	X-Urine	X-Urine	X-Urine
Urinalysis and urine electrolytes[15]	X								X		X			
Urine drug test[15]	X													
PK, Antibody, and Research Sampling:														
PK sample[18]			X			X	X		X				X	
ADA sample[18]			X						X				X	
hs-CRP sample[18,19]			X			X			X					X
Research serum/plasma sample[18, 19]			X			X			X					X
Genomic sub-study sample (optional)[20]			X											

	Year 1 Treatment (52 weeks)					Follow-up			End of Study Phone Call
Study Week	**Week 40**	**Week 44**	**Week 48**	**EOT[24]/ Week 52**	**Early Termination /JR Pre-operative[1]**	**Week 56**	**Week 72**	**Early Termination /JR Pre-operative[1]**	**Week 100**
Study Day	**281**	**309**	**337**	**365**		**393**	**505**		**701**
Visit window (days)	±7	±7	±7	±7		±7	±7		±7
Visit Number	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**		**Visit 18**	**Visit 19**		**Phone 2**
Screening/Baseline:									
Inclusion/Exclusion[2]									
Informed consent									
Genomics sub-study informed consent[3]									
Medical history									
Medication history									
Demographics									
Height									
Diary instructions									
Training on pain reporting/patient education brochures[4]									
Randomization									
Treatment:									
SC study drug injection[5]	X	X	X						
Dispense acetaminophen/paracetamol	X	X	X						
Acetaminophen/paracetamol accountability	X	X	X	X	X				
Dispense oral study drug	X	X	X						
Oral study drug accountability	X	X	X	X	X				
Recording of rescue medication use in diary[6]	X	X	X	X	X				

	Year 1 Treatment (52 weeks)					Follow-up			End of Study Phone Call
Study Week	**Week 40**	**Week 44**	**Week 48**	**EOT[24]/ Week 52**	**Early Termination /JR Pre-operative[1]**	**Week 56**	**Week 72**	**Early Termination /JR Pre-operative[1]**	**Week 100**
Study Day	**281**	**309**	**337**	**365**		**393**	**505**		**701**
Visit window (days)	±7	±7	±7	±7		±7	±7		±7
Visit Number	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**		**Visit 18**	**Visit 19**		**Phone 2**
Concomitant therapies (medications and procedures)	X	X	X	X	X	X	X	X	
Patient-Completed Assessments/Efficacy: [23]									
WOMAC[7]	X	X	X	X	X	X	X	X	
PGA	X	X	X	X	X	X	X	X	
NRS[8]	X	X	X	X	X				
SF-36	X			X	X		X	X	
EQ-5D-5L	X			X	X		X	X	
HCRU				X	X				
WPAI-OA	X			X	X				
TSQM	X			X	X				
Safety:									
Weight				X	X		X	X	
Vital signs[9]	X	X	X	X	X	X	X	X	
Physical examination				X	X		X	X	
Orthostatic blood pressure and heart rate assessment[9,10]	X	X	X	X	X	X	X	X	
Joint pain questionnaire[23]	X	X	X	X	X	X	X	X	
Survey of autonomic symptoms[23]	X	X	X	X	X	X	X	X	
Neurologic examination	X-BRIEF	X-BRIEF	X-BRIEF	X-FULL	X-FULL	X-BRIEF	X-FULL	X-FULL	
Adverse events	----------→								
Injection site evaluation	X	X	X						
Electrocardiogram				X	X				
Bilateral x-rays (knee, hip, shoulder)				X	X		X	X	
Event-triggered imaging[13]	X	X	X	X	X	X	X	X	
Pre-op questionnaire (JR follow-up)[14]					X			X	

	Year 1 Treatment (52 weeks)					Follow-up			End of Study Phone Call
Study Week	**Week 40**	**Week 44**	**Week 48**	**EOT[24]/ Week 52**	**Early Termination /JR Pre-operative[1]**	**Week 56**	**Week 72**	**Early Termination /JR Pre-operative[1]**	**Week 100**
Study Day	**281**	**309**	**337**	**365**		**393**	**505**		**701**
Visit window (days)	±7	±7	±7	±7		±7	±7		±7
Visit Number	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**		**Visit 18**	**Visit 19**		**Phone 2**
End of study phone contact[21]									X
MRI of affected joint(s) for AA patients only[22]									X
Laboratory Testing:									
Hematology[15]				X	X		X	X	
Blood chemistry[15]				X	X		X	X	
Pregnancy test (for WOCBP)[17]	X-Urine	X-Urine	X-Urine	X – Urine	X-Urine	X-Urine	X-Urine	X-Urine	
Urinalysis and urine electrolytes[15]				X	X		X	X	
PK, Antibody, and Research Sampling:									
PK sample[18]				X	X	X	X	X	
ADA sample[18]				X	X		X	X	
Hs-CRP samples[18,19]				X	X		X	X	
Research serum/plasma sample[18, 19]				X	X		X	X	
Genomic sub-study sample (optional)[20]									

ADA: Anti-drug antibody
EOT: End of Treatment
EQ-5D-5L: EuroQoL 5 Dimensions 5 Level Questionnaire
ESR: Erythrocyte sedimentation rate
FSH: Follicle stimulating hormone
HbA1c: Glycated hemoglobin
HCRU: Healthcare Resource Utilization
hs-CRP: High-sensitivity C-reactive protein
JR: Joint replacement
MRI: Magnetic resonance imaging
NRS: Numeric Rating Scale
PGA: Patient Global Assessment
PK: Pharmacokinetic
SC: Subcutaneous
SF-36: 36-item Short Form Survey
TSQM: Treatment Satisfaction Questionnaire for Medication
WOCBP: Women of child-bearing potential
WOMAC: Western Ontario and McMaster Osteoarthritis Index
WPAI-OA: Work Productivity and Activity Impairment-Osteoarthritis

Footnotes for the Schedule of Events Table 3 (Year 1)

1. Patients who discontinue study drug before week 52 will be encouraged to follow the visit schedule through the remainder of the study. If a patient chooses to end study participation, he/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 administered after all laboratory, PK, ADA and research samples have been collected and all study related activities have been performed. Patients will be observed in the clinic for approximately 1 hour after SC study drug is administered.
6. Use of study-provided rescue medication will be recorded daily in patient diaries. Acetaminophen/paracetamol use will be reported from pre-randomization visit to week 52.
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 the 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 52. Walking index joint pain NRS score will be recorded by the patient at the site at the week 52 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. An MRI will be performed on the index and contralateral joints at screening for all patients. In addition, an MRI will be performed on any knee or hip with a K-L of ≥3.
13. Imaging (X-ray and possible 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.
14. In the event that a patient must undergo JR surgery during the study, the patient must complete the pre-operative study visit (early termination assessments, as applicable) and the procedures outlined in the schedule of events for JR follow-up (Table 5). This will include a Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements. The pre-operative visit must be completed before the JR surgery. Pre-operative images will be submitted to the adjudication committee for review.
15. Samples will be analyzed by the central laboratory and results evaluated by the investigator.
16. Assessment of follicle-stimulating hormone (FSH) and estradiol levels are only to be performed if assessment of postmenopausal status is required (ie, for female patients ≤59 years of age).
17. 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 drug. If the serum pregnancy test is positive, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 8.2.3.11 in the protocol).
18. 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.
19. Research samples should be collected after an overnight (minimum 8 hours) fast.
20. Only for patients who provide written informed consent for the optional genomics sub-study. The sample should be collected at the baseline visit but may be collected at any subsequent visit during the study.
21. The purpose of this phone contact is to ask the patient if they have had or are scheduled (or on a waiting list) to have a JR. Pre-operative images should be submitted to the central reader for adjudication, if available.
22. If the affected joint has undergone JR an X-ray may be substituted from an MRI.

23. Patient-reported outcome measures should be completed first at a study visit, prior to any clinical assessments and procedures (eg, blood draws, ECGs, study drug administration).
24. Patients who end treatment early but agree to follow/continue to attend regular study visits do not complete the assessments associated with EOT/week 52 at the time they end treatment. Instead, they complete assessments associated with the study visit they are attending at the time they end treatment early.

Table 4: Schedule of Events for Year 2

(Only to be followed by patients who participate in Year 2 after they have completed through week 52 [ie, the week 52 visit] in Year 1).

	Year 2 Treatment (52 weeks)													
Study Week	**Week 52E[17]**	**Week 56E**	**Week 60E**	**Week 64E**	**Week 68E**	**Week 72E**	**Week 76E**	**Week 80E**	**Week 84E**	**Week 88E**	**Week 92E**	**Week 96E**	**Week 100E**	**EOT[15] Week 104E**
Study Day	**365E**	**393E**	**421E**	**449E**	**477E**	**505E**	**533E**	**561E**	**589E**	**617E**	**645E**	**673E**	**701E**	**729E**
Visit Window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Visit Number	**Visit 17E**	**Visit 18E**	**Visit 19E**	**Visit 20E**	**Visit 21E**	**Visit 22E**	**Visit 23E**	**Visit 24E**	**Visit 25E**	**Visit 26E**	**Visit 27E**	**Visit 28E**	**Visit 29E**	**Visit 30E**
Screening/Baseline:														
Inclusion/Exclusion	X													
Informed consent	X													
Treatment														
SC study drug injection[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense acetaminophen/paracetamol	X	X	X	X	X	X	X	X	X	X	X	X	X	
Acetaminophen/paracetamol accountability		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense oral study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	
Oral study drug accountability		X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of rescue medication use in diary[3]		X	X	X	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
Patient-Completed Assessments/Efficacy[4]														
WOMAC[5]				X			X			X				X
EQ-5D-5L				X			X			X				X
WPAI-OA				X			X			X				X
Safety:														
Weight							X							X
Vital signs[6]		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination							X		X					X

	Year 2 Treatment (52 weeks)													
Study Week	**Week 52E[17]**	**Week 56E**	**Week 60E**	**Week 64E**	**Week 68E**	**Week 72E**	**Week 76E**	**Week 80E**	**Week 84E**	**Week 88E**	**Week 92E**	**Week 96E**	**Week 100E**	**EOT[15] Week 104E**
Study Day	**365E**	**393E**	**421E**	**449E**	**477E**	**505E**	**533E**	**561E**	**589E**	**617E**	**645E**	**673E**	**701E**	**729E**
Visit Window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Visit Number	**Visit 17E**	**Visit 18E**	**Visit 19E**	**Visit 20E**	**Visit 21E**	**Visit 22E**	**Visit 23E**	**Visit 24E**	**Visit 25E**	**Visit 26E**	**Visit 27E**	**Visit 28E**	**Visit 29E**	**Visit 30E**
Orthostatic blood pressure and heart rate assessment[6,7]		X	X	X	X	X	X	X	X	X	X	X	X	X
Joint pain questionnaire[4]		X	X	X	X	X	X	X	X	X	X	X	X	X
Survey of autonomic symptoms[4]		X	X	X	X	X	X	X	X	X	X	X	X	X
Neurologic examination		X-BRIEF	X-BRIEF	X-BRIEF	X-BRIEF	X-BRIEF	X-BRIEF	X-BRIEF	X-BRIEF	X-BRIEF	X-BRIEF	X-BRIEF	X-BRIEF	X-FULL
Adverse events	----------→													
Injection site evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram														X
Bilateral x-rays (knee, hip, shoulder)							X							X
Event-triggered imaging[8]		X	X	X	X	X	X	X	X	X	X	X	X	X
Pre-op questionnaire (JR follow-up)[9]														
Laboratory Testing:														
Hematology[10]							X							X
Blood chemistry[10]							X							X
Pregnancy test (for WOCBP)[11]		X-Urine	X-Urine	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[10]								X						X
PK, Antibody, and Research Sampling:														
PK sample[12]							X							X
ADA sample[12]							X							X
hs-CRP sample[12,13]				X			X			X				X
Research serum/plasma sample[12, 13]				X			X			X				X

	Year 2 Treatment (52 weeks)	Follow-up			End of Study Phone Call
Study Week	**Early Termination/ JR Preoperative E[1]**	**Week 108E**	**Week 124E**	**Early Termination/ JR Preoperative E[1]**	**Week 152E**
Study Day		**757E**	**869E**		**1065E**
Visit Window (days)		**±7**	**±7**		**±7**
Visit Number		**Visit 31E**	**Visit 32E**		**Phone 2E**
Screening/Baseline:					
Inclusion/Exclusion					
Informed consent					
Treatment					
SC study drug injection[2]					
Dispense acetaminophen/paracetamol					
Acetaminophen/paracetamol accountability	X				
Dispense oral study drug					
Oral study drug accountability	X				
Recording of rescue medication use in diary[3]	X				
Concomitant therapies (medications and procedures)	X	X	X	X	
Patient-Completed Assessments/Efficacy[4]					
WOMAC[5]	X	X	X	X	
EQ-5D-5L	X				
WPAI-OA	X				
Safety:					
Weight	X		X	X	
Vital signs[6]	X	X	X	X	
Physical examination	X		X	X	
Orthostatic blood pressure and heart rate assessment[6,7]	X	X	X	X	
Joint pain questionnaire[4]	X	X	X	X	
Survey of autonomic symptoms[4]	X	X	X	X	
Neurologic examination	X-FULL	X-BRIEF	X-FULL	X-FULL	
Adverse events	----------→				
Injection site evaluation					
Electrocardiogram	X				
Bilateral x-rays (knee, hip, shoulder)	X		X	X	
Event-triggered imaging[8]	X	X	X	X	

	Year 2 Treatment (52 weeks)	Follow-up			End of Study Phone Call
Study Week	**Early Termination/ JR Preoperative E[1]**	**Week 108E**	**Week 124E**	**Early Termination/ JR Preoperative E[1]**	**Week 152E**
Study Day		**757E**	**869E**		**1065E**
Visit Window (days)		**±7**	**±7**		**±7**
Visit Number		**Visit 31E**	**Visit 32E**		**Phone 2E**
Pre-op questionnaire (JR follow-up)[9]	X			X	
End of study phone contact[14]					X
MRI of affected joint(s) for AA patients only[16]					X
Laboratory Testing:					
Hematology[10]	X		X	X	
Blood chemistry[10]	X		X	X	
Pregnancy test (for WOCBP)[11]	X-Urine	X-Urine	X-Urine	X-Urine	
Urinalysis and urine electrolytes[10]	X		X	X	
PK, Antibody, and Research Sampling:					
PK sample[12]	X	X		X	
ADA sample[12]	X		X	X	
hs-CRP sample[12,13]	X		X	X	
Research serum/plasma sample[12,13]	X		X	X	

ADA: Anti-drug antibody
EOT: End of Treatment
EQ-5D-5L: EuroQoL 5 Dimensions 5 Level Questionnaire
hs-CRP: High-sensitivity C-reactive protein
JR: Joint replacement
MRI: Magnetic resonance imaging
PK: Pharmacokinetic
SC: Subcutaneous
WOCBP: Women of child-bearing potential
WPAI-OA: Work Productivity and Activity Impairment-Osteoarthritis

Footnotes for the Schedule of Events Table 4 (Year 2)

1. Patients who discontinue study drug before week 104 will be encouraged to follow the visit schedule through the remainder of the study. If a patient chooses to end study participation, he/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. Subcutaneous study drug administration will be the last procedure at each dosing visit and will be administered after all laboratory, PK, ADA, and research samples have been collected and all study related activities have been performed. Patients will be observed in the clinic for approximately 1 hour after SC study drug is administered.

3. Use of study-provided rescue medication will be recorded daily in patient diaries. Acetaminophen/paracetamol use will be reported from pre-randomization visit to week 104.
4. Patient-reported outcome measures should be completed prior to any clinical assessments (eg, blood draws, ECGs, study drug administration).
5. The WOMAC Full Survey will be completed for the index joint.
6. If the pulse is less than 45 bpm, an ECG with rhythm strip will be obtained to confirm the heart rate and rhythm.
7. 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.
8. Imaging (X-ray and possible 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.
9. In the event that a patient must undergo JR surgery during the study, the patient must complete the pre-operative study visit (early termination assessments, as applicable) and the procedures outlined in the schedule of events for JR follow-up (Table 5). This will include a Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements. The pre-operative visit must be completed before the JR surgery. Pre-operative images will be submitted to the adjudication committee for review.
10. Samples will be analyzed by the central laboratory and results evaluated by the investigator.
11. In the event of a positive urine pregnancy test result, the patient should have a serum pregnancy test with a negative result in order to continue study drug. If the serum pregnancy test is positive, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 8.2.3.11 in the protocol).
12. 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.
13. Research samples should be collected after an overnight (minimum 8 hours) fast.
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 should be submitted to the central reader for adjudication, if available.

15. Patients who end treatment early but agree to follow/continue to attend regular study visits do not complete the assessments associated with EOT/week 104E at the time they end treatment. Instead, they complete assessments associated with the study visit they are attending at the time they end treatment early.
16. If the affected joint has undergone JR, an X-ray may be substituted for an MRI.
17. The week 52E Year 2 visit should occur on the same day as the week 52 Year 1 visit, but could occur at any time during the visit window.

Table 5: Follow-Up Period for Patients Undergoing Joint Replacement Surgery on Study

	Post-Operative	Long-Term
	Follow-up Visit 1 4 weeks after joint replacement surgery	**Follow-up Visit 2** 20 weeks after joint replacement surgery
Follow-up Study Day (Visit Window)[1]	**Follow-up Day 29 (±5)**	**Follow-up Day 140 (±7)**
Treatment:		
Concomitant medications and therapy	X	X
Safety:		
Adverse events	----------→	
Vital signs	X	X
Orthostatic blood pressure[2]	X	X
Physical examination with joint exam	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 the Schedule of Events Table 5 (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 followinga report of clinically significant worsening or exacerbation of pain in the 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

Parameter	PCSV	Comments
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin <=35% Total Bilirubin or Total Bilirubin <=1.5 ULN) at baseline	Conjugated bilirubin dosed on a case-by-case basis.
ALT/AST and Total Bilirubin	(ALT >3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN) (AST >3 ULN and TBILI>2 ULN) and baseline (AST <=3 ULN or TBILI <=2 ULN) (ALT >3 ULN and TBILI>1.5 ULN) and baseline (ALT <=3 ULN or TBILI <=1.5 ULN) (AST >3 ULN and TBILI>1.5 ULN) and baseline (AST <=3 ULN or TBILI <=1.5 ULN)	FDA DILI Guidance July 2009.
ALT/AST and Total Bilirubin and ALP	(ALT >3 ULN and TBILI>2 ULN and ALP < 2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN or ALP >=2 ULN) (AST>3 ULN and TBILI>2 ULN and ALP < 2 ULN) and baseline (AST <=3 ULN or TBILI <=2 ULN or ALP >=2 ULN)	FDA DILI Guidance July 2009.

Parameter	PCSV	Comments
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
Chloride - Hypochloremia - Hyperchloremia	 <80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium - Hyponatremia - Hypernatremia	 ≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria

Parameter	PCSV	Comments
Potassium - Hypokalemia - Hyperkalemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	 FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
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.

Parameter	PCSV	Comments
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison - Principles of internal Medicine 17th Ed., 2008.
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).

Parameter	PCSV	Comments
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.

Parameter	PCSV	Comments
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	
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

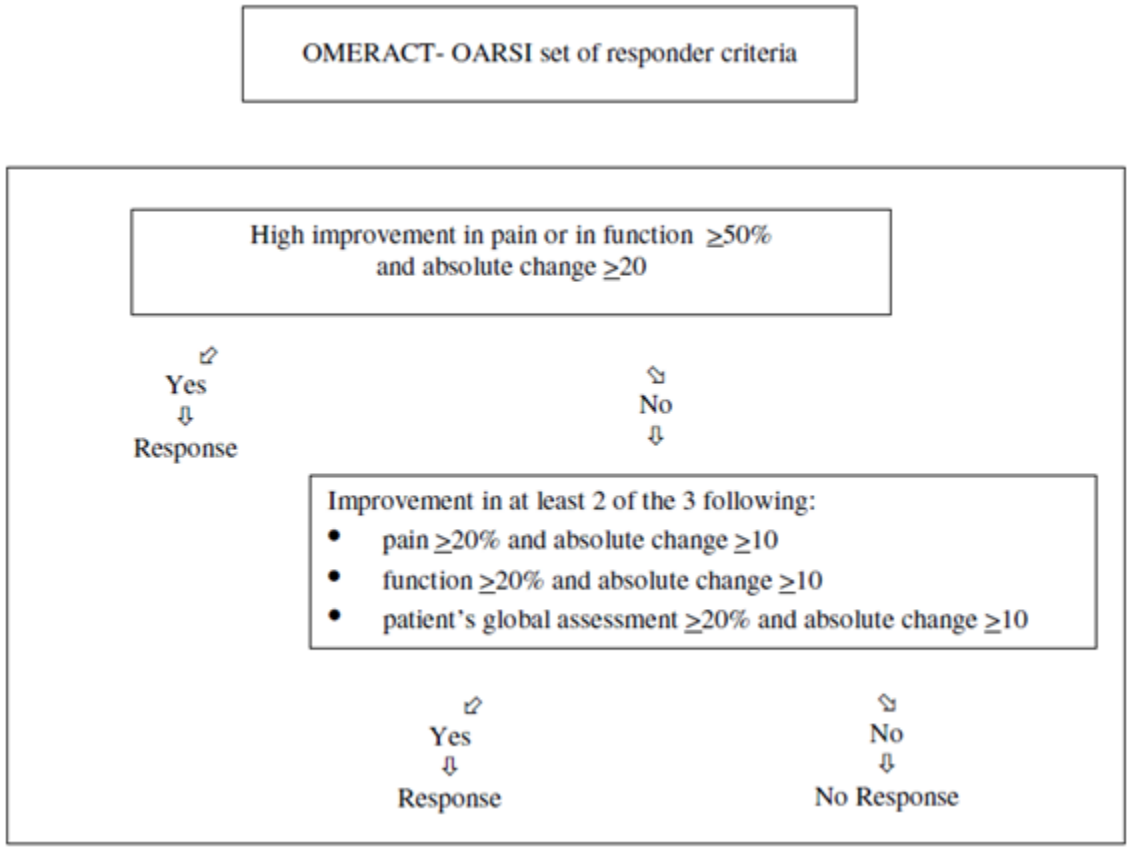
Patients in violation of any of the following Inclusion/Exclusion Criterion will be excluded from the Per-Protocol Set.

- Inclusion Criterion 4: A clinical diagnosis of OA of the knee or hip based on the American College of Rheumatology criteria with radiologic evidence of OA (K-L score ≥2 for the index joint) at the screening visit, with the following definitions:
  - The index joint is defined as the joint with OA under evaluation for this study
  - A joint previously treated with JR surgery cannot be the index joint
  - A joint previously surgically modified within the past year cannot be the index joint (with the exception of cruciate ligament reconstruction surgery, patellar fracture repair surgery, or meniscal repair)
  - If a patient has a K-L score of ≥2 at more than 1 knee or hip joint, the index joint is the joint with the greatest WOMAC pain subscore at the screening visit
  - If 2 or more knee or hip joints have a K-L score of ≥2 and the same WOMAC pain subscore, the index joint is the joint with the greater K-L score
  - If 2 or more joints have a K-L score of ≥2, the same WOMAC pain subscores, and the same K-L scores, then the investigator may choose 1 of these joints as the index joint
- Inclusion Criterion 5: Moderate-to-severe pain in the index joint defined as a WOMAC average pain subscale score of ≥4 at both the screening and randomization visits
- Inclusion Criterion 7: A history of at least 12 weeks of analgesics use for pain due to OA of the knee or hip, as defined by:
  - a) Inadequate pain relief from acetaminophen/paracetamol AND
  - Intolerance to or inadequate pain relief from opioid or tramadol therapy, unwillingness to take opioid or tramadol therapy for a medically acceptable reason, or lack of access to an opioid or to tramadol
- Exclusion Criterion 10: History of naproxen intolerance, or existence of a medical condition that is high risk for naproxen-associated complications (eg, high risk of gastrointestinal bleed, previous ulcer, condition requiring use of anti-coagulants or anti-platelet therapy, or acute coronary syndrome)

Additionally, patient who experience any of the Protocol Deviations listed below will be excluded from the Per-Protocol Set.

PDID	Description of Protocol Deviation
3.01	Baseline visit not performed
3.24	Screening visit was not performed
5.14	WOMAC patient assessment was not administered at Week 16 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 Set of Responder Criteria



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

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