IND: Number: 103245
EudraCT: 2016-005020-29

Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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:	Fasinumab
Study Name:	FACT OA1
Clinical Phase:	3
Protocol Number:	R475-OA-1611
Protocol Version:	R475-OA-1611 Amendment 9 Global
Amendment 9 Global Date of Issue	*See appended electronic signature page*
Amendment 8 Global Date of Issue	01 Jul 2020
Amendment 7 Global Date of Issue	23 Apr 2020
Amendment 6 Global Admin Date of Issue:	18 Jun 2019
Amendment 6 Global Date of Issue:	05 Mar 2019
Amendment 5 Global Date of Issue:	11 Jul 2018
Amendment 4 Global Date of Issue:	24 May 2018
Amendment 3 Global Date of Issue:	27 Apr 2018
Amendment 2VHP Date of Issue:	20 Oct 2017
Amendment 1VHP Date of Issue:	07 Oct 2017
Amendment 1 Date of Issue:	26 Sep 2017
Original Date of Issue:	27 Mar 2017
Scientific/Medical Monitor:	[redacted] Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

[redacted]

AMENDMENT HISTORY

Amendment 9 Global

Description of Change	Brief Rationale	Section # and Name
The purpose of this amendment is to permanently discontinue all patients in the Year 2 Treatment Period from study drug and to complete the End of Treatment study visit for impacted patients. These patients will be encouraged to complete all remaining study visits and procedures in the follow-up period and the end of study phone call.	On 11August 2020, the independent Data Monitoring Committee (DMC) for the fasinumab phase 2/3 program recommended termination of the program. The recommendation was based on a review of the totality of evidence, including the emerging unblinded data. Based on the independent DMC recommendation, the sponsor discontinued dosing with fasinumab as of 17 August 2020. The only patients impacted were the patients participating in the optional Year 2 portion of the R475-OA-1611 study. These patients will be encouraged to enter the safety follow-up period for Year 2.	Protocol Synopsis: Study Design Section 1.1 Background Section 1.2 Summary of Risks and Benefits to Patients Participating in this Study Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 5.1 Study Description and Duration Section 7.3.2.1 Reasons for Permanent Discontinuation of Study Drug

Amendment 8 Global

Description of Change	Brief Rationale	Section # and Name
Modification to the primary and secondary efficacy analysis set	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 analyses will be performed on a modified full analysis set that excludes the randomization stratum for the region of concern. Analyses of the FAS population will also be provided.	Protocol Synopsis: Statistical Plan List of Abbreviations and Definitions of Terms Section 10.2 Justification of FAS and mFAS Sample Size Section 10.3.2 Modified Full Analysis Set Section 10.3.3 Per Protocol Set Section 10.4.3.1 Primary Efficacy Analysis Section 10.4.3.2 Secondary Efficacy Analysis

Amendment 7 Global

Description of Change	Brief Rationale	Section # and Name
Added a statement to address the impact of the COVID-19 pandemic.	To explain the plan for ensuring continuity of clinical study activities and study oversight activities during the coronavirus	Section 1.2 Summary of Risks and Benefits to Patients Participating in this Study Section 8.1 Schedule of Events

	disease 2019 (COVID-19) public health emergency.	
Year 2 to stop enrollment.	The objective of the Year 2 Extension is to collect safety data on patients chronically exposed to fasinumab over a 2-year period. The on-going COVID-19 pandemic is currently limiting patient travel to sites for the receipt of study drug. Therefore, these patients will not be chronically exposed to fasinumab and, consequently, we are stopping enrollment of new patients into Year 2.	Protocol Synopsis: Study Design Section 3.2.1 Rationale for Study Design Section 5.1 Study Description and Duration Section 6.2.3 Inclusion Criteria for Year 2
Secondary efficacy objectives and endpoints at week 52 have been changed to week 44.	Due to the COVID-19 pandemic and its associated impact on limiting patient travel and site operations, it is likely that the missing data for the week 52 efficacy endpoint will exceed the original assumptions as described in Section 10.2. Transitioning to week 44 was chosen because the number of patients having completed the week 44 visit is estimated to be the best option to provide the most robust/complete data set for secondary efficacy analyses.	Protocol Synopsis: Objectives Protocol Synopsis: Endpoints Section 2.2 Secondary Objectives Section 4.2.2 Secondary Endpoints
Addition of secondary and exploratory endpoints and their associated objectives and analyses.	To align with the statistical analysis described in detail in the statistical analysis plan.	Protocol Synopsis: Objectives Protocol Synopsis: Endpoints Protocol Synopsis: Statistical Plan Section 2.2 Secondary Objectives Section 2.3 Exploratory Objectives Section 4.2.2 Secondary Endpoints Section 4.2.3 Exploratory Endpoints Section 5.2 Planned Interim Analysis Section 10.1 Statistical Hypotheses Section 10.3 Analysis Sets Section 10.3.1 Full Analysis Set Section 10.3.2 Per-Protocol Set Section 10.3.3 Safety Analysis Set Section 10.3.4 Urgent Safety Measure Set Section 10.3.5 Pharmacokinetic Analysis Set Section 10.3.6 Anti-drug Antibody Analysis Set Section 10.3.7 The Neutralizing Antibody Set Section 10.4.3.1 Primary Efficacy Analysis

		Section 10.4.3.2 Secondary Efficacy Analysis Section 10.4.4 Safety Analysis Section 10.4.4.1 Adverse Events Section 10.4.4.2 Other Safety Section 10.4.4.3 Treatment Exposure Section 10.4.4.4 Treatment Compliance Section 10.5 Interim Analysis

Amendment 6 Global Admin

Change and Rationale	Sections Changed
This is a non-substantial amendment to add collection of concomitant therapies (medications and procedures) during the follow-up period of Year 2 and at the early-termination visit for Year 2. Collection of this information was inadvertently omitted from the previous amendment.	Table 2 Schedule of Events for Year 2

Amendment 6 Global

Changes and Rationale	Sections Changed
Main Change:	
The study design has been modified to include a second year of treatment with fasinumab or naproxen. The purpose of this modification is to obtain longer-term safety data to further elucidate the safety profile of fasinumab. The initial 52-week treatment period is referred to as Year 1 and the second 52-week treatment period is referred to as Year 2. At the end of the 52-week treatment period of Year 1, patients who are eligible and willing to participate in Year 2 will continue in the study for a second 52-week treatment period and will then enter the 20-week follow up period. Patients who are ineligible for Year 2, or are eligible but unwilling to enter Year 2, will enter directly into the 20-week follow-up period at the completion of Year 1.	Clinical Study Protocol Synopsis: Objectives, Study Design, Study Duration, Treatments, Endpoints, Procedures and Assessments, Statistical Plan Section 2.2 Secondary Objectives Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 4.3.1 Safety Endpoints for Year 1 (All randomized and Treatment Patients) Section 4.3.2 Safety Endpoints for Year 2 (All Randomized and Treated Patients Proceeding into Year 2) (added) Section 5.1 Study Description and Duration Figure 1 Study Flow Diagram Section 5.1.1 Screening and Pre-Randomization Section 5.1.3 Randomization Section 5.1.4 Treatment Period for Year 1 Section 5.1.5 Treatment Period for Year 2 (added) Section 5.1.6 Follow-up Period Section 5.1.7 End of Study Phone Contact Section 5.2 Planned Interim Analysis Section 6.2.1 Inclusion Criteria for Year 1 Section 6.2.2 Exclusion Criteria for Year 1 Section 6.2.3 Inclusion Criteria for Year 2 (added) Section 6.2.4 Exclusion Criteria for Year 2 (added) Section 7.1 Investigational and Reference Treatments Section 7.2 Rescue Treatment(s) Section 7.5 Method of Treatment Assignment Section 7.7.1 Prohibited Medications Section 7.7.2 Permitted Medications and Procedures Table 1 Schedule of Events for Year 1 Table 2 Schedule of Events for Year 2 (added) Section 8.1.2 Footnotes for Schedule of Events Table 2 (Year 2) (added) Section 8.1.4 Early Termination Visit Section 8.2.2.1 Western Ontario and McMaster Universities Osteoarthritis Index Section 8.2.2.4 EuroQoL 5 Dimensions 5 Level Questionnaire

Changes and Rationale	Sections Changed
	Section 8.2.2.7 Work Productivity and Activity Impairment Section 8.2.3.1 Vital Signs Section 8.2.3.2 Physical Examination Section 8.2.3.3 Electrocardiogram Section 8.2.3.4 Assessment of Orthostatic Blood Pressure and Heart Rate Section 8.2.3.5 Joint Pain Questionnaire Section 8.2.3.6 Survey of Autonomic Symptoms Section 8.2.3.7 Neurologic Examination Section 8.2.3.8 Imaging Section 8.2.3.11 Laboratory Testing Section 8.2.3.12 Injection Site Evaluations Section 8.2.4.1 Drug Concentration Measurements and Samples Section 8.2.4.2 Anti-Drug Antibody Measurements and Samples Section 8.2.5.1 Biomarkers Section 9.4.1 Adverse Events Section 9.4.2 Serious Adverse Events Section 10.3.3 Safety Analysis Set Section 10.4.3.2 Secondary Efficacy Analysis Section 10.4.4 Safety Analysis Section 10.4.4.1 Adverse Events Section 10.4.4.2 Other Safety Section 10.4.4.3 Treatment Exposure Section 10.4.4.4 Treatment Compliance Section 10.5 Interim Analysis

Changes and Rationale	Sections Changed
All Other Changes:	
Site locations were added to the Synopsis.	Clinical Study Protocol Synopsis: Site Locations
A time frame was defined for the Year 1 safety endpoints.	Clinical Study Protocol Synopsis: Endpoints Section 4.3.1 Safety Endpoints for Year 1 (All Randomized and Treated Patients)
Text was updated to align with current best practices (ie, updated protocol template text).	Section 4.5 Anti-Drug Antibody Variables Section 10.4.6 Analysis of Immunogenicity Section 14.5 Clinical Study Data Transparency (added)
It has been clarified that patient-reported outcome measures should be completed before any clinical assessments.	Table 1 Schedule of Events for Year 1 Section 8.1.1 Footnotes for Schedule of Events Table 1 (Year 1), footnote #23 Section 8.2.2 Efficacy Procedures Section 8.2.3.5 Joint Pain Questionnaire Section 8.2.3.6 Survey of Autonomic Symptoms
The scale used to assess the WOMAC index has been revised to the numerical rating scale (previously incorrectly cited as the Likert scale).	Section 8.2.2.1 Western Ontario and McMaster Universities Osteoarthritis Index
A footnote has been added to the Schedule of Events tables to clarify that patients who discontinue study drug 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 1 Schedule of Events for Year 1 Section 8.1.1 Footnotes for Schedule of Events Table 1 (Year 1), footnote #24
Other minor edits have been made to clarify text or correct minor errors.	Clinical Study Protocol Synopsis: Population - Sample Size List of Abbreviations and Definitions of Terms Section 7.3.2 Study Drug Discontinuation Table 1 Schedule of Events for Year 1 continued (missing study day numbers have been added) Section 8.1.1 Footnotes for Schedule of Events Table 1 (Year 1), footnotes #1, #17 Section 8.2.3.11 Laboratory Testing Section 10.3.4 Per-Protocol Set Section 10.3.5 Pharmacokinetic Analysis Set Section 10.3.6 Anti-Drug Antibody Analysis Set

Amendment 5 Global

The purpose of this amendment is to update the exclusion criteria to improve patient safety and to include an additional fasinumab dose group of 1 mg every 8 weeks (Q8W). Additional changes were made to ensure consistency across the fasinumab program, improve clarity, and to make minor corrections. The following table outlines the changes made to the protocol and the affected sections:

Changes and Rationale	Sections Changed
Main changes to improve patient safety:	
The exclusion criterion #22 regarding adverse cardiac events within the past 12 months prior to the screening visit has been updated to exclude patients with a *history* of adverse cardiac events. In addition, acute coronary syndrome has been removed from this criterion because this is covered by exclusion criterion #10.	Section 6.2.2 Exclusion Criteria, #22
In exclusion criterion #10 regarding history of naproxen intolerance or existence of a medical condition that is high risk for naproxen-associated complications, the general statement regarding the use of concomitant medications for which naproxen is contraindicated has been removed. Specific medications that are not to be taken concomitantly with naproxen are listed in the Prohibited Medications section. In addition, patients with conditions requiring use of antiplatelet therapy have been added to this criterion.	Section 6.2.2 Exclusion Criteria, #10
A new exclusion criterion has been added to exclude patients at the highest risk of renal complications due to non-steroidal anti-inflammatory drug (NSAID) use, as follows: 'Patients taking concomitant ACE inhibitors/ARBs and diuretics, or presence of an estimated glomerular filtration rate (GFR) <30 mL/minute/1.73m^{2}'	Section 6.2.2 Exclusion Criteria, #40
The reasons for permanent discontinuation of study drug have been updated to ensure that patients enrolled under an earlier version of the protocol are immediately discontinued from study drug and moved to the follow-up period if they meet either of the updated exclusion criteria #22 and #40 described above, or are taking the newly added prohibited medications described above (combination therapy of diuretics with either an ACE inhibitor or ARB).	Section 7.3.2.1 Reasons for Permanent Discontinuation of Study Drug

Changes and Rationale	Sections Changed
All other changes:	
A fasinumab 1 mg Q8W dose group has been added and the randomization ratio and statistical analysis have been updated accordingly. Additional changes have been made to the statistical analysis methods to be consistent across fasinumab program.	Clinical Study Protocol Synopsis: Study Design, Population, Treatments, Statistical Plan. Section 3.2.2 Rationale for Dose Selection Section 5.1.3 Randomization Section 6.1 Number of Patients Planned Section 7.1 Investigational and Reference Treatments Section 7.5 Method of Treatment Assignment Section 10.1 Statistical Hypothesis Section 10.2 Justification of Sample Size Section 10.3.1 Efficacy Analysis Set Section 10.3.3 Safety Analysis Set Section 10.4.3.1 Primary Efficacy Analysis
Clarified that fasinumab and fasinumab-matching placebo are referred to as 'SC study drug' and that naproxen and naproxen-matching placebo are referred to as 'oral study drug'.	Throughout the document
The rescue medication (acetaminophen/paracetamol) text has been updated to be consistent across the fasinumab program: • Clarified that acetaminophen/paracetamol may be taken for inadequate pain relief for osteoarthritis (OA) and for other acceptable reasons (eg, headache, fever); • Added text to clarify the dosing instructions; • Added text to caution against consumption of alcoholic beverages while on acetaminophen/paracetamol	Clinical Study Protocol Synopsis: Rescue Treatment Section 7.2 Rescue Medication Section 7.7.2 Permitted Medications and Procedures
The section on Prohibited Medications has been updated: • To include methotrexate, which should be used with caution in patients taking NSAIDs and because methotrexate clearance can be decreased with concurrent NSAIDs, leading to potential increases in methotrexate levels; • To include anticoagulants and antiplatelet therapy (eg, warfarin, heparins, factor Xa inhibitors, thrombin inhibitors, aspirin/5-aminosalicylic acid (aspirin/5-ASA) >150 mg daily, clopidogrel), which should be used with caution in patients taking NSAIDs; • To include recreational use of marijuana in addition to medical marijuana, as both have the potential to impact efficacy assessments;	Section 7.7.1 Prohibited Medications

Changes and Rationale	Sections Changed
• To include combination therapy of diuretics with either an ACE inhibitor or ARB; • To clarify that cyclobenzaprine, carisoprodol, orphenadrine and tizanidine are muscle relaxants • To make minor corrections	
Text has been added or updated to align with current Regeneron best practices	Section 7.4.2 Local Injection Site Reactions (Section added) Section 7.5.2 Emergency Unblinding Section 12.1 Monitoring of Study Sites
Changes have been made to the Schedule of Events table and footnotes for clarity, to make minor corrections and for consistency across the fasinumab program: • Concomitant medication collection has been added to the screening and pre-randomization visits • Added a separate row to the Schedule of Events table for high-sensitivity C-reactive protein (hs-CRP) • Event-triggered imaging has been added at the week 1 phone visit • Removed the footnote from the erythrocyte sedimentation rate (ESR) row of the Schedule of Events table that states the ESR sample will be analyzed by the central laboratory (ESR samples will be analyzed locally using kits provided by the central lab, see row below) • Clarified in footnote #4 that patients will review a "Participating in a Research Study: What You Need to Know" brochure and a "Reporting Your Pain' brochure at the screening and pre-randomization visits • Corrected a typo in footnote #5 • Clarified that walking index joint pain NRS scores are recorded by the patient using their diary and not onsite at the pre-randomization visit in footnote #8	Table 1: Schedule of Events Section 8.1.1 Footnotes for Schedule of Events Table, footnote #4 Section 8.1.1 Footnotes for Schedule of Events Table, footnote #5 Section 8.1.1 Footnotes for Schedule of Events Table, footnote #8 Section 8.1.1 Footnotes for Schedule of Events Table, footnote #18
Corrected the text describing the Healthcare Resource Utilization Questionnaire to state that the sites (not the patients) will complete the questionnaire.	Section 8.2.2.6 Healthcare Resource Utilization Questionnaire
The Laboratory Testing text has been corrected to state that ESR testing will be performed at the site using kits provided by the central laboratory. Drugs included in the urine drug test have been listed.	Section 8.2.3.11 Laboratory Testing

Changes and Rationale	Sections Changed
The section on treatment compliance has been updated to include a description of how compliance will be calculated for the oral study drug.	Section 10.4.4.4 Treatment Compliance
The study Scientific/Medical Monitor has been changed from [redacted] to [redacted]	Title page
Minor edits or additions have been made to the text throughout the document for clarity, to delete redundant text, to make minor corrections, and to ensure consistency across the fasinumab program.	List of Abbreviations and Definitions of Terms Clinical Study Protocol Synopsis: Study Design, Procedures and Assessments, Endpoints Section 1.1 Background Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 4.3.1 Safety Endpoints Section 5.1 Study Design Section 5.1.1 Screening and Pre-Randomization Section 5.1.2 Rescreening Section 5.1.7 End of Study Phone Contact (Week 100) Section 6.2.1 Inclusion Criteria, #6 Section 6.2.1 Inclusion Criteria, #8 Section 6.2.1 Inclusion Criteria, #9 Section 6.2.2 Exclusion Criteria, #29 Section 7.1 Investigational and Reference Treatments Section 7.3.2.1 Reasons for Permanent Discontinuation of Study Drug Section 7.3.2.2 Reasons for Temporary Discontinuation of Study Drug Section 7.6.1 Packaging, Labeling and Storage Section 7.6.2 Supply and Disposition of Treatments Section 7.7 Concomitant Medications and Procedures Section 8.1.4 Early Termination Visit Section 8.2.2.1 Western Ontario and McMaster Universities Osteoarthritis Index Section 8.2.1.8 Instructions for Use of Diary (section added) Section 8.2.1.9 Patient Education Brochures (section added) Section 8.2.2.3 Walking Index Joint Pain Numeric Rating Score Section 8.2.2.7 Work Productivity and Activity Impairment Section 8.2.2.8 Treatment Satisfaction Questionnaire for Medication Section 8.2.3.10 Procedures to be Performed Only in the Event of a Joint Replacement Surgery Section 8.2.3.11 Laboratory Testing

Changes and Rationale	Sections Changed
	Section 8.2.4.1 Drug Concentration Measurements and Samples Section 8.2.5 Research Samples Section 8.2.5.1 Biomarkers Section 8.2.5.2 Future Biomedical Research Section 9.4.3 Other Events that Required Accelerated Reporting Section 9.6.1.1 Adjudicated Arthropathy Section 9.6.1.3 Peripheral Sensory Adverse Events Section 11.2 Electronic Systems Section 12.1 Monitoring of Study Sites

Amendment 4 Global

The primary purpose of this amendment was to incorporate an urgent safety measure, which requires discontinuing the 3 mg every 4 weeks (Q4W) and 6 mg every 8 weeks (Q8W) dose regimens. The recommendation by the independent Data Monitoring Committee (DMC) to discontinue these dose regimens was made following a review of unblinded data from an ongoing study in the fasinumab phase 3 osteoarthritis program (R475-PN-1523) and was based on an imbalance in clinically relevant adverse events including time to total joint replacement, peripheral edema, arthralgia and a trend towards early fractures in the 6 mg Q8W group. Based on the independent DMC review, study of lower dose levels (eg, 1 mg Q4W) may continue to be evaluated in this population. With this amendment, patients randomized to the 3 mg Q4W or 6 mg Q8W dose regimens will be permanently discontinued from study drug but encouraged to otherwise complete all remaining study visits and study procedures in the follow up period and the end of study phone call.

Amendment 3 Global (obsolete)

The primary purpose of this amendment was to update the exclusion criteria to improve patient safety. Additional changes were made to ensure consistency across the fasinumab program, improve clarity and to make minor corrections. This amendment was not implemented.

Amendment 2VHP

The purpose of this amendment was to incorporate health authority feedback, ensure consistency across the program, improve clarity, remove redundant text and correct typos. These changes brought Amendment 2VHP in line with Amendment 1.

Amendment 1VHP

The purpose of this amendment was to incorporate health authority feedback.

Amendment 1

The purpose of this amendment was to incorporate health authority feedback, ensure consistency across the program, improve clarity, remove redundant text and correct typos.

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CLINICAL STUDY PROTOCOL SYNOPSIS

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
Site Location(s)	Multiple sites in Bulgaria, Denmark, Germany, Hungary, Lithuania, Poland, Romania, Russia, South Africa, Spain, Ukraine, UK, and USA.
Principal Investigator	To be determined
Objectives	**Primary Objective** 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 osteoarthritis (OA) of the knee or hip. **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 assess 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 assess 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 assess 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

	Exploratory Objectives To evaluate additional patient reported outcome 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 patient reported outcome (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 or 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.
Study Design	This study is a randomized, double-blind, placebo- and naproxen-controlled study designed to evaluate the efficacy and safety of fasinumab in patients with OA of the knee or hip who have a history of inadequate pain relief with acetaminophen/paracetamol and a history of intolerance to or inadequate pain relief with opioids (or are unwilling to take opioids or have lack of access to opioids). All randomized patients in this study will participate in Year 1, which is intended to provide efficacy and safety data for OA patients exposed for up to 52 weeks to fasinumab, a non-steroidal anti-inflammatory drug (NSAID) comparator (naproxen), or placebo. At the end of the 52-week treatment period of Year 1, patients who are eligible and willing to participate in Year 2 will continue in the study for a second 52-week treatment period and will then enter the 20-week follow-up period. Note: As of 26 March 2020, all enrollment into Year 2 has been terminated due to the COVID-19 pandemic. Any patients currently enrolled in Year 2 are to remain in the study. Patients who are ineligible for Year 2, or are eligible but unwilling to enter Year 2, will enter directly into the 20-week follow-up period at the completion of Year 1. Year 2 is intended to provide safety data for OA patients exposed to fasinumab or naproxen for up to 104 weeks (52 weeks in Year 1 and a further 52 weeks in Year 2). Note that no patients will receive placebo only in Year 2 (see Treatment Period for Year 2 below). Efficacy will be assessed during Year 2 to monitor the risk-benefit profile of fasinumab but, as Year 2 is not powered for a formal efficacy analysis, efficacy results will be summarized descriptively. The overall study period for patients in Year 1 who do not participate in Year 2 will be up to approximately 105 weeks including screening and pre-randomization. For these patients, the study consists of a screening period of up to 30 days, a 7 to 10 day pre-randomization/washout period (7 days with a +3 day window), a 52-week treatment period, a 20-week follow-up period, and an end of study phone contact at 52 weeks following the last subcutaneous (SC) dose of study drug. Eligible patients who choose to participate in Year 2 will receive treatment for a total of 104 weeks and will then enter a 20-week follow-up period, followed by the final phone call approximately 52 weeks after the last dose of SC study drug.

Note: As of 17August 2020, all patients on treatment have been permanently discontinued from study drug and will complete the End of Treatment visit. This impacts only patients in the Year 2 treatment period as treatment in Year 1 has ended. All patients will be encouraged to complete all remaining study visits and procedures in the follow-up period and the end of study phone call.

Screening and Pre-Randomization

At the screening visit, patients will consent to all study assessments planned for Year 1 and will be informed that they could potentially continue in the study for the second year if eligible. Eligibility and consent for Year 2 will be conducted at the end of Year 1. Approximately 4 weeks prior to randomization, patients will undergo screening procedures, including X-ray of the shoulders, hips, and knees, and magnetic resonance imaging (MRI) of the index and contralateral joints must be performed and assessed by the central imaging vendor. In addition, any knee or hip joint with a Kellgren-Lawrence (K-L) score of ≥3 will have MRI completed during the screening period. During the screening period, all patients will continue to take their current treatment regimen for OA pain, which must include use of an oral NSAID on a regular basis, defined as approximately 4 days per week over the last 4 weeks.

Patients eligible for the study will complete a 7 to 10 day pre-randomization period, during which patients will discontinue and/or undergo a washout of their standard-of-care pain medications for OA. All pain medications, except for the study-provided rescue medication (acetaminophen/paracetamol), will be discontinued.

Randomization

At the baseline visit of Year 1, patients will be randomized 3:3:3:1 to the following treatment groups as follows:

- Fasinumab 1 mg SC once every 4 weeks (Q4W) and naproxen-matching placebo oral, twice daily
- Fasinumab 1 mg SC once every 8 weeks (Q8W) and naproxen-matching placebo oral, twice daily
- Fasinumab-matching placebo SC Q4W and naproxen 500 mg oral, twice daily
- Fasinumab-matching placebo, SC, Q4W and naproxen-matching placebo oral, twice daily

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

Treatment Period for Year 1 (Baseline to Week 52)

During the treatment period of Year 1 (day 1 through week 52), patients will be permitted to use only acetaminophen/paracetamol as rescue medication. Patients will record their use of acetaminophen/paracetamol in a diary.

The study visits during the treatment period will include 1 phone visit on day 8 (±1 day).

Safety and efficacy assessments will be performed and potential events of adjudicated arthropathy (AA) and sympathetic nervous system dysfunction will be monitored.

At the end of the treatment period, patients who are eligible and willing to participate in Year 2 will continue in the study for a second 52-week treatment period. Patients who are ineligible for Year 2, or are eligible but unwilling to enter Year 2, will enter directly into the 20-week follow-up period.

Treatment Period for Year 2 (Week 52E to Week 104E)

Study weeks during Year 2 will be denoted with an E to represent study weeks during the extension (eg, week 52E) and to differentiate them from study weeks with the same numbers in the follow-up period for patients who only participate in Year 1.

Eligible patients who choose to participate in Year 2 will not be re-randomized at week 52. Patients will receive treatment based on the treatment they received in Year 1, as shown below.

Year 1	Year 2
Fasinumab 1 mg SC Q4W and naproxen-matching placebo oral, twice daily	Fasinumab 1 mg SC Q4W and naproxen-matching placebo oral, prn*
Fasinumab 1 mg SC Q8W (patients will receive placebo injections at the study visits where study drug is not administered) and naproxen-matching placebo oral, twice daily	Fasinumab 1 mg SC Q8W (patients will receive placebo injections at the study visits where study drug is not administered) and naproxen-matching placebo oral, prn*
Fasinumab-matching placebo SC Q4W and naproxen 500 mg oral, twice daily	Fasinumab-matching placebo SC Q4W and naproxen 500 mg oral, prn*
Fasinumab-matching placebo SC Q4W and naproxen-matching placebo oral, twice daily	Fasinumab-matching placebo SC Q4W and naproxen 500 mg oral, prn*

*The maximum naproxen dose (or naproxen placebo dose) allowed will be no more than the amount allowed during Year 1 (ie, 500 mg twice daily or 1 capsule of placebo twice daily).

Naproxen (and naproxen-matching placebo) will be administered as needed (ie, prn) in Year 2 instead of twice daily as in Year 1, due to the known safety profile associated with chronic NSAID use.

A fasinumab-matching placebo/naproxen-matching placebo group will not be included in Year 2 so as not to have patients who are experiencing moderate-to-severe pain due to their OA go for an entire 2-year period with only rescue medication of acetaminophen/paracetamol available to them for pain control. Patients who were randomized to fasinumab-matching placebo/naproxen-matching placebo in Year 1 will be switched to fasinumab-matching placebo/naproxen 500 mg prn for the second year of treatment to ensure they have access to some form of pain medication in addition to acetaminophen/paracetamol.

During the treatment period of Year 2 (week 52E through week 104E), rescue medication (acetaminophen/paracetamol) will continue to be permitted for all patients and use will be recorded in a diary.

Safety and efficacy assessments will continue through Year 2.

	Follow-up At the end of the treatment period (week 52 for patients participating in Year 1 only, or week 104E for patients participating in Year 1 and Year 2), follow-up of patients will continue for an additional 20 weeks. Safety and efficacy assessments will be performed similarly to those of the treatment period. If a patient must undergo joint replacement surgery during the study, he or she will be asked to complete pre-operative imaging and to undergo post-surgery follow-up. A phone contact questionnaire will be conducted approximately 52 weeks after administration of the last SC dose of study drug to document patient status with regard to joint replacement surgery (if patient underwent, is scheduled for, or is on a wait list for joint replacement surgery). Patients who had an AA will have an MRI performed of the affected joint(s).
Study Duration	The duration of the study for patients who participate in Year 1 only is up to approximately 105 weeks, including the screening and pre-randomization periods. The duration of the study for patients who participate in Year 1 and Year 2 is up to approximately 157 weeks, including the screening and pre-randomization periods. Patients who discontinue study drug will be requested to return for all scheduled study visits and to complete all planned assessments, including phone contacts.
Population	
Sample Size:	Enrollment of approximately 2845 patients is planned for this study, which includes a total of 285 patients who were enrolled in the fasinumab 3 mg SC Q4W and 6 mg SC Q8W groups under earlier versions of the protocol before dosing was discontinued due to the urgent safety measure, and a total of approximately 2560 patients who will be randomized to fasinumab 1 mg SC Q4W, 1 mg SC Q8W, naproxen, and placebo. Approximately 840 patients will be randomized to the fasinumab 1 mg SC Q4W group, 840 patients to the naproxen-only group, and 280 patients to the placebo group. An estimated 600 patients will be randomized to the fasinumab 1 mg Q8W group.
Target Population:	Men and women who are at least 18 years of age at the time of study entry with a clinical diagnosis at the screening visit of OA of the knee or hip, based on the American College of Rheumatology criteria, and with radiologic evidence of OA (K-L score ≥2) at the index joint.
Treatments	
SC Study Drug **Dose/Route/Schedule:**	Fasinumab 1 mg SC Q4W, 1 mg SC Q8W (patients will receive placebo injections at study visits where study drug is not administered) (Year 1 and Year 2)
Oral Study Drug **Dose/Route/Schedule:**	Naproxen 500 mg oral twice daily (Year 1) or 500 mg oral prn (Year 2) (the maximum naproxen dose allowed will be no more than the amount allowed during Year 1 [ie, 500 mg twice daily]).

SC Study Drug Placebo Route/Schedule:	Fasinumab placebo SC Q4W (Year 1 and Year 2)
Oral Study Drug Placebo Route/Schedule:	Naproxen placebo Oral, twice daily (Year 1) or oral prn (Year 2)
	At the baseline visit of Year 1, patients will be randomized 3:3:3:1 to receive 1 of the following treatment regimens under amendment 5 global: • Fasinumab 1 mg SC Q4W and naproxen-matching placebo oral, twice daily • Fasinumab 1 mg SC Q8W (patients will receive placebo injections at the study visits where study drug is not administered) and naproxen-matching placebo oral, twice daily • Fasinumab-matching placebo SC Q4W and naproxen 500 mg oral, twice daily • Fasinumab-matching placebo SC Q4W and naproxen-matching placebo oral, twice daily Prior to amendment 5 global, patients were randomized 3:3:3:3:1 to receive one of the following treatment regimens: • Fasinumab 1 mg SC Q4W and naproxen-matching placebo oral, twice daily • Fasinumab 3 mg SC Q4W and naproxen-matching placebo oral, twice daily • 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 • Fasinumab-matching placebo SC Q4W and naproxen 500 mg oral, twice daily • Fasinumab-matching placebo SC Q4W and naproxen-matching placebo oral, twice daily
Rescue Treatment:	During the Year 1 and Year 2 treatment periods, acetaminophen/paracetamol will be the only study-provided rescue medication. In the event that pain relief for OA pain is inadequate, or in the event of other pain (eg, headache) or fever, 1 to 2 tablets/capsules of acetaminophen/paracetamol may be taken no less than 4 hours apart as needed according to local standard of care. The maximum daily dose during the treatment and follow-up periods is 2500 mg (500 mg x 5 tablets/capsules) in countries where 500 mg strength tablets/capsules are available, or 2600 mg (325 mg x 8 tablets/capsules) in countries where 325 mg strength tablets/capsules are available.

Endpoints

Primary:	The co-primary endpoints are: 1. Change in the Western Ontario and McMaster Universities Osteoarthritis Index (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.

Secondary: The key secondary endpoints of the study are:

1. Change 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

Safety:

Safety endpoints for Year 1 (all randomized and treated patients)

Safety endpoints for Year 1 (through week 52) will include:

- Incidence of adjudicated arthropathy (AA) (as confirmed by independent adjudication)
- Incidence of destructive arthropathy (DA) (as confirmed by independent adjudication)
- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of sympathetic nervous system dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist)
- Incidence of peripheral sensory AEs that require a neurology or other specialty consultation
- Incidence of all-cause joint replacements (JRs)

The incidence of JRs at the telephone survey 52 weeks after the last dose of study drug (week 100) will also be evaluated.

Safety endpoints for Year 2 (all randomized and treated patients proceeding into Year 2)

The safety endpoints listed above for Year 1 will be evaluated for Year 2 from the first dose of study drug given in Year 2 through week 104E (end of treatment), as well as for the periods of Year 1 and Year 2 from day 1 through week 104E.

The incidence of JRs at the telephone survey approximately 52 weeks after the last dose of study drug (week 152E) will also be evaluated.

Procedures and Assessments

At the screening visit, patients will provide informed consent, medical history, and medication history. Determination of the K-L score of the knee or hip will be performed to establish a diagnosis of OA based on the American College of Rheumatology criteria using a K-L score cutoff of ≥2. Patients will be assessed for childbearing potential and complete a self-reported assessment of peripheral or central pain.

Efficacy in Year 1 will be assessed by the change from baseline in the WOMAC pain and physical function subscale scores, the PGA, the Numeric Rating Scale of the average walking index joint pain, the EuroQoL 5 Dimensions 5 Level Questionnaire, the 36-item Short Form Survey, the Healthcare Resource Utilization Questionnaire, the Work Productivity and Activity Impairment-Osteoarthritis questionnaire, and the Treatment Satisfaction Questionnaire for Medication. The WOMAC total and stiffness scores will also be evaluated. Efficacy in Year 2 will be assessed by the change from baseline in the WOMAC pain and physical function subscale scores, the EuroQoL 5 Dimensions 5 Level Questionnaire and the Work Productivity and Activity Impairment-Osteoarthritis questionnaire.

Safety assessments will be performed at each study visit and upon occurrence of any joint adverse events (AEs). Potential events of AA will be monitored via clinical signs and symptoms of worsening joint pain during the study and adjudication of pre-operative imaging for patients who

	undergo joint replacement during the conduct of the study. Potential events of sympathetic nervous system dysfunction will be monitored throughout the study through physical examination, AE reporting, assessment of orthostatic hypotension, and the Survey of Autonomic Symptoms. After the end-of-study visit and approximately 52 weeks after administration of the last dose of SC study drug, a phone contact questionnaire will be conducted to document patient status with regard to JR surgery (if patient underwent, is scheduled for, or is on a wait list for JR surgery). Patients who had an AA will have an MRI performed of the affected joint(s).
Statistical Plan	**Statistical Hypothesis** There are 29 hypotheses for the primary and key secondary endpoints. The primary endpoint comparison of study drug with placebo for the WOMAC pain and physical function subscale scores will be declared superior only if the comparisons are significant for both WOMAC pain and physical function subscale scores. A graphical testing procedure will be applied to control for multiplicity and to maintain study-wise Type I error rate at a two-sided 0.05 level for the hypotheses ($H_{1,i}$, i=1,…,16 for fasinumab 1 mg Q4W, and $H_{2,i}$, i=1,…,13 for fasinumab 1 mg Q8W) for the primary and key secondary endpoints. If a hypothesis is rejected, the alpha level for that hypothesis will be reallocated to other hypotheses according to the pre-specified procedure. **Justification of FAS and mFAS Sample Size** The planned sample size was expected to provide adequate power for the comparisons between fasinumab doses and naproxen at week 16 for the WOMAC pain and physical function scores and the PGA score and provide long term data for safety assessment. The sample size for the full analysis set (FAS) population 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 at week 16 and week 52. 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 standard deviation (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 in the FAS population were to be compared to approximately 200 patients in the placebo group who were enrolled under amendment 5 global. For such comparisons, 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, were assumed. Additionally, the effect size for such comparisons was 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 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. 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 at week 16 and 93% power at week 52 for the FAS. This sample size would have provided 98% power to detect an effect size of 0.24 in WOMAC physical function subscale (ie, absolute treatment difference of 0.50 with a SD of 2.1) at week 16 and 96% power at week 52 for the 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.

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 population for the primary and secondary efficacy analyses was changed in Protocol Amendment 8 to be based on a modified full analysis set (mFAS) that excludes the randomization stratum for that region. Based on the assumptions above, it is estimated that this mFAS will provide:

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

Statistical Methods

Baseline demographic disease characteristics, including medical history and exposure to study drug, will be summarized by treatment group using descriptive statistics. Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

The primary efficacy variables will be analyzed using multiple imputation approach with a mixed-effect model for repeated measure (MMRM) based on the mFAS with adjustment for missing data due to lack of efficacy, death or AEs assuming the WOMAC scores would on average return to baseline values. The imputed data for patients discontinued from the study treatment due to lack of efficacy, death or AEs will be centered at the mean baseline value. The missing data for patients who discontinued treatment due to other reasons will be imputed under missing-at-random assumption. Sensitivity analysis using tipping point approach with multiple imputation will be performed to assess the robustness of the results due to treatment discontinuation.

	For analysis of continuous secondary endpoints at fixed timepoints (ie, week 16 and week 44), the analysis method will be the same as that used for the primary efficacy endpoints. For the analysis of secondary endpoints involving the averaging over several visits, analysis will be performed using a multiple imputation approach with an ANCOVA model based on the mFAS with adjustment for missing data performed in the same manner as was done for the primary endpoint. For analysis of secondary endpoints that are categorical variables, eg, proportions of patients with ≥30% improvement in the WOMAC pain subscale scores at week 16, the Cochran Mantel Haenszel approach will be used based on the mFAS, stratifying by the randomization strata. For Year 2 analysis, the efficacy and patient-reported outcome (PRO) endpoints collected will be summarized descriptively. The summary of safety results will be presented for Year 1, Year 2, and the combined treatment period of Year 1 and Year 2. Safety data including TEAEs and treatment emergent adverse events of special interest, vital signs, physical exams, laboratory tests, electrocardiograms, and anti-drug antibody formation will be listed and summarized by treatment group.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5-ASA	5-aminosalicylic acid
AA	Adjudicated arthropathy
ACE	Angiotensin-converting enzyme
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ARB	Angiotensin receptor blocker
bpm	Beats per minute
BUN	Blood urea nitrogen
C_{max}	Maximal concentration
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
C_{trough}	Trough concentrations
CTCAE	Common Terminology Criteria for Adverse Events
DA	Destructive arthropathy
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EQ-5D-5L	EuroQoL 5 Dimensions 5 Level Questionnaire
ESR	Erythrocyte sedimentation rate
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
HbA1c	Hemoglobin A1c

HCRU	Healthcare Resource Utilization
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation
INR	International normalized ratio
IRB	Institutional Review Board
IVRS	Interactive voice response system
IWRS	Interactive web response system
JR	Joint replacement
K-L	Kellgren-Lawrence
IV	Intravenous
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MMRM	Mixed-effect Model for Repeated Measures
MRI	Magnetic Resonance Imaging
NAb	Neutralizing antibody
NGF	Nerve growth factor
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
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
PGA	Patient Global Assessment
PK	Pharmacokinetic
PPS	Per protocol set
prn	Pro re nata
PRO	Patient-reported outcome
PT	Preferred term
QRS	Complex of Q, R, and S waves on an electrocardiogram
Q4W	Every 4 weeks
Q8W	Every 8 weeks

RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation
SF-36	36-item Short Form Survey
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TJR	Total joint replacement
TrkA	Tyrosine kinase type 1
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
USMS	Urgent Safety Measure Set
WBC	White blood cell
WOCBP	Woman of child-bearing potential
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WPAI-OA	Work Productivity and Activity Impairment-Osteoarthritis

1. INTRODUCTION

1.1. Background

Chronic musculoskeletal pain affects a large portion of the global population. A significant cause of chronic musculoskeletal pain is due to osteoarthritis (OA). Osteoarthritis is a progressive, chronic disease caused by the breakdown and loss of cartilage of the joints, which leads to pain in the hips, knees, hands, feet, and spine. It is characterized by focal areas of loss of articular cartilage in synovial joints accompanied by subchondral bone changes, osteophyte formation at the joint margins, thickening of the joint capsule and mild synovitis. Symptoms and disability increase with increasing age. The prevalence of OA in patients aged 65 and older is 60% in men and 70% in women, and continually rising (Sarzi-Puttini 2005).

Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment in patients with mild-to-moderate OA. The efficacy of NSAIDs is well-documented, albeit modest, but their use is associated with a number of risks (Bingham 2007) (Bjordal 2004) (Makarowski 2002) (Silverstein 2000). The risks associated with long-term therapy with NSAIDs, in particular, have been well-characterized and include gastrointestinal (GI) bleeding and increased risk of cardiovascular events (Lanas 2011) (Trelle 2011). Non-steroidal anti-inflammatory drugs have limited efficacy in many OA patients; those with advanced OA typically try several NSAIDs and must often move to other therapies such as opioids.

Treatment guidelines for OA suggest that opioids may be used in OA only if management with NSAIDs is ineffective, intolerable, or otherwise contraindicated. However, the use of opioids is limited by central nervous system effects, nausea and vomiting, constipation, and potential for abuse and dependence. In addition, opioid use may be associated with both acute and chronic side effects, including drowsiness, dizziness, gastrointestinal intolerability, motor imbalance, respiratory depression, and even death. Opioid use must be closely monitored in patients who are vulnerable or are potentially vulnerable to abuse or addiction. Moreover, there is no evidence to support superiority of opioids over other available pain medications. While the efficacy of opioids in treating pain over a short duration is supported by research data, long-term efficacy has not been evaluated.

Thus, there remains an unmet medical need for alternative treatment options to opioids that have a more effective analgesic effect, particularly since there are a significant number of patients who are intolerant to or do not get adequate pain relief from the currently available treatment options. Inadequate pain relief has a profound impact on the quality of life for millions of people worldwide with an associated substantial cost to society, including healthcare cost (Salmon 2016) and loss of productivity (Dibonaventura 2011).

Neurotrophins are a family of peptide growth factors that play a role in the development, differentiation, survival and death of neuronal and non-neuronal cells (Chao 2006). Nerve growth factor (NGF) was the first neurotrophin to be identified, and its role in the development and survival of both peripheral and central neurons during the development of the nervous system is well characterized (Crowley 1994) (Smeyne 1994). In the adult, NGF is not required as a survival factor but acts as a pain mediator that sensitizes neurons (Pezet 2006). Nerve growth factor activity is mediated through 2 different membrane-bound receptors, the high-affinity tyrosine kinase type 1 (TrkA) and the low-affinity p75 neurotrophin receptors.

By acting upstream of several relevant molecular pathways, the NGF/TrkA system appears to play a major role in the control of pain. Administration of NGF has been shown to provoke pain in both rodents (Lewin 1994) and humans (McArthur 2000), while NGF antagonists have been shown to prevent hyperalgesia and allodynia in animal models of neuropathic and chronic inflammatory pain (Ramer 1999). Humans with mutations in TrkA (hereditary sensory and autonomic neuropathy IV) or NGF (hereditary sensory and autonomic neuropathy V) have been identified with a loss of deep pain perception (Einarsdottir 2004) (Indo 1996). In addition, NGF is known to be elevated in the synovial fluid of patients with rheumatoid arthritis and other types of arthritis (Aloe 1992) (Halliday 1998), and to be up-regulated in injured and inflamed tissues in conditions such as cystitis, prostatitis, and chronic headache (Lowe 1997) (Miller 2002) (Sarchielli 2001).

Fasinumab (also known as REGN475) is a fully-human high-affinity monoclonal antibody directed against NGF. By selectively blocking NGF, fasinumab has the potential to be effective in modulating NGF-associated pain without some of the adverse side effects of other analgesic medications, such as opioids and NSAIDs. Following an evaluation of the safety and tolerability of the antibody in a single-ascending-dose first-in-human study (study R475-PN-0817), a proof-of-concept study evaluating the effect of fasinumab on pain in 217 patients with OA of the knee was completed (study R475-PN-0901, see current version of the Fasinumab Investigator's Brochure). Three intravenous (IV) doses of fasinumab were evaluated (0.03, 0.1, 0.3 mg/kg every 8 weeks [Q8W]). All three doses, compared with placebo, were associated with statistically significant improvement in pain as evaluated by walking knee pain, the Western Ontario and McMaster Osteoarthritis Index (WOMAC), and the Patient's Global Impression of Change questionnaire. Additionally, the R475-PN-1227 study in patients with OA revealed significant efficacy in the WOMAC pain subscale score for each of the doses of fasinumab evaluated (1 mg, 3 mg, 6 mg, and 9 mg given every 4 weeks [Q4W]) compared with placebo (see current version of the Investigator's Brochure). Results from recent clinical studies with other anti-NGF antibodies, tanezumab (Pfizer) and fulranumab (Janssen), also support the role of NGF in pain modulation in patients with pain due to OA of the knee and hip (Brown 2012) (Hefti 2006) (Lane 2010) and in patients with chronic low back pain (Katz 2011) (Kivitz 2013).

In all clinical studies completed to date, fasinumab was generally well tolerated. Arthralgia, joint swelling, peripheral edema, hypoesthesia, and myalgia were more frequently reported in fasinumab-treated patients than in placebo-treated patients. In neurological evaluations, abnormalities in vibration sense were more frequent in the fasinumab patients than in the placebo patients. These adverse events (AEs) or physical examination abnormalities associated with fasinumab were generally mild to moderate in intensity and were transient (see current version of the Investigator's Brochure).

Data from studies of tanezumab and fulranumab demonstrated these molecules were associated with an increased risk of destructive arthropathy (DA), a unique clinical form of rapidly progressive arthropathy over and above that seen in the normal progression of osteoarthritis. Analyses of the tanezumab data by its sponsor, defined by anatomic pathological criteria on specimens obtained on joint replacement (JR), revealed that the risk of DA increases with tanezumab dose and is further increased with the concomitant use of chronic NSAIDs (>90 days) (Lane 2010). Most cases of DA occurred in joints with a documented history of OA.

Based on the potential risk of DA identified in tanezumab and fulranumab, the US Food and Drug Administration (FDA) placed this class of anti-NGF antibodies on clinical hold in 2010. Following a review of anti-NGF antibody clinical data in March 2012, the FDA determined that clinical studies of anti-NGF therapies could resume if mitigation strategies are implemented to minimize the risk of DA. To address concerns about potential events of DA, a risk-mitigation approach is also being implemented for all fasinumab studies, as outlined in Section 9.6.1.1. This approach includes sensitive, prospective, and rigorous radiologic screening and monitoring for select changes in joint structure. The patients who develop these changes, which are referred to throughout this document as adjudicated arthropathy (AA), are required to discontinue study therapy.

Since the removal of the FDA clinical hold, Regeneron has conducted or initiated several clinical trials of fasinumab. In all clinical studies to date, fasinumab was associated with a low rate of discontinuations due to adverse events. Patients treated with fasinumab generally had more frequent events than did placebo-treated patients of arthralgia, joint swelling, peripheral edema, altered peripheral sensation (eg, paresthesia, dysesthesia), and myalgia.

In 2012, studies of other anti-NGF monoclonal antibodies (mAbs) identified adverse changes in the sympathetic nervous system of mature animals of several species (rat and non-human primate). These effects include a reversible decrease in neuron volume. To date, no statistically significant or consistent effects of fasinumab on the sympathetic nervous system have been detected in animal studies with up to 6-months of treatment. Nonetheless, based on the potential risk of sympathetic nervous system toxicity associated with these other anti-NGF mAbs in animal studies, a risk mitigation approach is being implemented for all fasinumab studies, as outlined in Section 9.6.1.2.

In the phase 2/3 study of fasinumab in patients with pain due to OA of the knee or hip (R475-PN-1227), 26 AA events occurred in 24 patients. There was an increase in AA events that appeared to be related to greater fasinumab dose. Although these events were milder than the severe DA events presented at the 2012 FDA Arthritis Advisory Committee, in consideration of the lack of an observed dose response for efficacy in OA, the benefit-risk ratio was deemed unfavorable for the fasinumab 6 mg Q4W and 9 mg Q4W doses in patients with OA, in comparison to the other fasinumab doses that were studied (ie, 1 mg Q4W and 3 mg Q4W). The dose regimens that were being evaluated in the phase 3 studies for OA pain in the knee or hip included 1 mg Q8W, 1 mg Q4W, 3 mg Q4W, and 6 mg Q8W. In April 2018, the independent Data Monitoring Committee (DMC) recommended discontinuing 6 mg Q8W and 3 mg Q4W (expected to have similar exposure to 6 mg Q8W) based on a review of unblinded data in an ongoing study in the fasinumab phase 3 OA program (R475-PN-1523). Subsequently, a small Regeneron team reviewed the data and agreed with this recommendation. The DMC noted imbalances in clinically relevant adverse events including time to total joint replacement, peripheral edema, arthralgia and a trend towards early fractures. The phase 3 program for OA pain in the hip or knee continued to evaluate fasinumab 1 mg with the highest dose regimen of 1 mg Q4W. In August 2020, the independent DMC recommended termination of the fasinumab program. The recommendation was based on a review of the totality of evidence, including the emerging unblinded data. Based on the independent DMC recommendation, the sponsor has discontinued dosing with fasinumab. At the time of this recommendation and amendment, the only patients to be impacted are the patients participating in the optional Year 2 portion of the R475-OA-1611 study. These patients will be encouraged to enter the Year 2 safety follow-up period.

Fasinumab is currently being evaluated in a phase 3 trial (R475-PN-1523) designed to assess the long-term safety and efficacy of multiple doses of fasinumab in patients with OA. The phase 3 study described here, R475-OA-1611, is designed to compare the efficacy and safety of fasinumab with those of placebo and of naproxen, a standard-of-care NSAID for moderate-to-severe pain due to OA.

Additional background information on fasinumab and the development program may be found in the current version of the Investigator's Brochure.

1.2. Summary of Risks and Benefits to Patients Participating in this Study

As discussed above in Section 1.1, there are potential risks and benefits to patients participating in the study. Please refer to the Investigator's Brochure and informed consent form (ICF) for additional detailed information and analysis of the potential risks and benefits associated with fasinumab administration. Pain due to OA is a condition that results in significant morbidity and disability as well as marked loss of productivity. There is a significant unmet medical need for treatments with this condition. In Study R475-OA-1611, patients with pain due to OA will be randomized to fasinumab, naproxen or placebo; each of these treatment groups presents potential benefits and risks to patients as described below.

- Fasinumab

Fasinumab represents a potentially effective therapy that may be beneficial to patients who do not achieve adequate pain relief, are unable to tolerate existing therapies, or have absolute or relative contraindications to existing therapies for OA pain of the hip or knee. Previous fasinumab study (R475-PN-1227) results have further confirmed earlier efficacy observations and demonstrate that fasinumab provides significant pain relief compared to placebo in OA patients across all doses administered. Some common side effects seen in patients treated with fasinumab are joint-related events such as joint pain, joint/limb swelling, joint damage, new or worsening OA and occurrence of joint replacement surgery, and upper respiratory tract infection. The joint damage that has been observed usually occurred in a knee or hip and sometimes in multiple joints. The joint damage occurred with or without increased joint pain and, at times, was more rapid and more severe than what is normally seen with OA. Some patients treated with fasinumab who develop this joint damage have had a higher chance of undergoing joint replacement surgery. In addition, this higher risk of joint replacement surgery has also been noted in fasinumab-treated patients who did not develop joint damage. Further, this joint damage occurred more frequently in patients who received NSAIDs along with drugs of the group of anti-NGF and, therefore, concomitant administration of fasinumab and NSAIDs, apart from low dose aspirin, is prohibited in this study. Other adverse effects that have been seen in patients taking fasinumab include a risk of bone fracture and altered peripheral sensation, including hypoesthesia and paraesthesia. Some patients had pain, numbness, or tingling in their wrist/hand and found to have carpal tunnel syndrome, which was sometimes treated with a surgical procedure. Finally, events associated with sympathetic nervous system dysfunction are being closely monitored due to findings from animal studies, although to date, this hasn't been observed in patients treated with fasinumab.

Throughout the entire fasinumab clinical development program, the potential risks noted above are being mitigated by implementing close monitoring of patients via extensive clinical and radiologic assessments. These mitigation activities are described in detail in Section 9.6.1.

Based on review of the totality of evidence from ongoing data across the fasinumab program as of August 2020, the independent DMC recommended that the fasinumab program be stopped. The Sponsor has discontinued dosing with fasinumab. The only patients impacted were the patients participating in the optional Year 2 portion of the R475-OA-1611 study. The Sponsor believes it is important to continue off-treatment follow-up for all active patients in the study to complete safety follow-up. This safety follow-up is important to understand the benefit/risk for fasinumab.

- Naproxen

The benefits and risks of naproxen, an NSAID, at the recommended dosage are well documented. NSAIDs are efficacious and are the mainstay of treatment in patients with mild-to-moderate OA. The most frequently reported side effects of naproxen include cardiovascular events (eg, edema), gastrointestinal symptoms (eg, abdominal pain, nausea, and constipation), dermatological events (pruritus, skin eruptions), central nervous system (headache, dizziness, drowsiness) and dyspnea. Additional side effects include abnormal renal function, anemia, anaphylactoid reactions, gastrointestinal bleeding, hyper- and hypoglycemia, and renal failure.

The overall benefit risk profile for naproxen is favorable.

- Placebo

The main potential risks associated with placebo are the lack of, or inadequate pain relief. Measures taken to minimize the risks associated with placebo use are as follows:

- Availability of rescue medication (acetaminophen/paracetamol).
- Patients can withdraw from the study at any time if pain persists despite the use of acetaminophen/paracetamol at the recommended dosage.

Please refer to Section 3.2 for additional information on the rationale for including a placebo group.

Patient Considerations in Response to COVID-19

Measures to account for the COVID-19 pandemic that minimize the risks to the patients in the study as well as healthcare providers have been put in place (see Section 8.1 for details).

2. STUDY OBJECTIVES

2.1. Primary Objective

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.

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 assess 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 assess 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 assess 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

2.3. Exploratory Objectives

To evaluate additional patient reported outcome 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 patient reported outcome (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 or 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.

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Based on results from previous clinical studies of fasinumab in patients with OA, fasinumab is expected to provide effective pain relief based on an improvement in the WOMAC pain sub-scale score and improved functionality based on the WOMAC physical function sub-scale.

3.2. Rationale

3.2.1. Rationale for Study Design

The present study is a randomized, double-blind, placebo- and naproxen-controlled study 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 take opioids) for OA pain management.

The target study population was chosen because they currently have unmet medical needs with respect to incomplete pain control, despite the availability of NSAIDs. The study will be conducted with appropriate eligibility criteria to exclude patients who may be at risk for events of joint damage and sympathetic nervous system effects.

Year 1

All randomized patients in this study will participate in Year 1, which is intended to provide efficacy and safety data for OA patients exposed for up to 52 weeks to fasinumab, an NSAID comparator (naproxen), or placebo. At the end of the 52-week treatment period of Year 1, patients who are eligible and willing to participate in a second 52-week treatment period will enter Year 2 (see below). Patients who are ineligible for Year 2, or are eligible but unwilling to enter Year 2, will enter directly into a 20-week follow-up period at the completion of Year 1 and thereby only participate in the Year 1 portion of the study.

At the screening visit, patients will consent to all study assessments planned for Year 1 and will be informed that they could potentially continue in the study for the second year if eligible. Eligibility and consent for Year 2 will be conducted at the end of Year 1. Note: As of 26 March 2020, enrollment into Year 2 has been terminated due to the COVID-19 pandemic and, therefore, Year 1 patients reaching week 52 will move directly into the Year 1 follow-up period.

This study will enroll patients who have failed or are intolerant to opioids and have inadequate pain relief from acetaminophen/paracetamol. As there are currently a limited number of therapeutic options available for these patients, enrollment of this study population supports equipoise with respect to randomization of patients to fasinumab or to placebo.

The patients will be stratified by the affected index joint (hip or knee), by Kellgren-Lawrence (K-L) score (2 to 3, or 4), and by geographic region to enable analysis of efficacy and safety (as defined in Section 5.1). The K-L stratification scheme is used here to ensure that there is an equal distribution of patients with the most severe OA at baseline across the dosing groups.

The inclusion of a placebo treatment group in Year 1 is important to accurately determine the efficacy of fasinumab. Non-steroidal anti-inflammatory drugs are the most common medications used to treat pain due to OA. Therefore, comparison of fasinumab to the NSAIDs treatment group will aid in determining the efficacy of fasinumab compared to a frequently used and effective standard of care class of medications for OA, but that have associated clinically significant AEs. As naproxen is a commonly used and highly effective NSAID (Ong 2007), it has been selected as the comparator drug for this study.

Inclusion of both the placebo group and the active treatment comparator group in Year 1 will be important to accurately estimate the risk of AEs, including the AEs of special interest of

adjudicated arthropathy, sympathetic nervous system dysfunction, and altered peripheral sensation. Specific questionnaires and physical examinations will be employed to monitor for these AEs of special interest. All patients included in the study will have regular study visits and receive diagnostic procedures (ie, X-rays, magnetic resonance imaging [MRI]) to evaluate their ongoing OA. Adverse event monitoring will be ongoing throughout the trial. Patients and investigators can choose to end participation at any time.

Acetaminophen/paracetamol will be made available as rescue treatment for any patient as appropriate. Therefore, the use of a placebo group is justified, as placebo-treated patients will not be placed at significant risk.

Year 2

Year 2 is intended to provide safety data for OA patients exposed to fasinumab or naproxen for up to 104 weeks (52 weeks in Year 1 and a further 52 weeks in Year 2). Efficacy during Year 2 will be assessed via WOMAC to monitor the risk-benefit profile of fasinumab. However, since Year 2 of the study is not powered for formal efficacy assessments, efficacy results will be summarized descriptively. Eligible patients must consent to participate in Year 2 at the end of their Year 1 participation. As of 26 March 2020, enrollment into Year 2 has been terminated due to the COVID-19 pandemic and therefore enrollment for any patients still eligible to enroll into Year 2 as of this date is no longer an available option. All patients currently enrolled into Year 2 as of this date are to remain in the study. As of 17 August 2020, all patients on treatment have been permanently discontinued from study drug and will complete the End of Treatment visit. This impacts only patients in the Year 2 treatment period as treatment in Year 1 has ended. All patients will be encouraged to complete all remaining study visits and procedures in the follow-up period and the end of study phone call.

Patients who were randomized to fasinumab in Year 1 will continue treatment with the same fasinumab dose regimen in Year 2. Patients who were randomized to a fixed dose of naproxen in Year 1 will receive naproxen pro re nata (prn) in Year 2. To maintain the study blind, patients on fasinumab will receive naproxen-matching placebo prn and patients on naproxen will receive fasinumab-matching placebo Q4W.

A fasinumab-matching placebo/naproxen-matching placebo group will not be included in Year 2 so as not to have patients who are experiencing moderate-to-severe pain due to their OA go for an entire 2-year period with only rescue medication of acetaminophen/paracetamol available to them for pain control. Patients who were randomized to fasinumab-matching placebo/naproxen-matching placebo in Year 1 will be switched to naproxen prn (and fasinumab-matching placebo Q4W) for the second year of treatment to ensure they have access to some form of pain medication in addition to acetaminophen/paracetamol.

As in Year 1, all patients in Year 2 will have regular study visits and receive diagnostic procedures (ie, X-rays, MRI) to evaluate their ongoing OA. Adverse event monitoring will be ongoing throughout the trial. Patients and investigators can choose to end participation at any time.

Acetaminophen/paracetamol will be made available as rescue treatment during Year 2 for any patient as appropriate.

3.2.2. Rationale for Dose Selection

Previous versions of this protocol randomized patients to receive fixed-dose, subcutaneous (SC) injections of 1 mg of fasinumab Q4W, 3 mg fasinumab Q4W, 6 mg fasinumab Q8W (with alternating placebo injections at the monthly visits where fasinumab will not be given, to maintain the blind), naproxen active comparator, or matching placebo. Based on April 2018 recommendations from the independent DMC for this study that reviewed unblinded data from a different ongoing phase 3 study of fasinumab (R475-PN-1523), the decision was made to discontinue further evaluation of fasinumab at 3 mg Q4W or 6 mg Q8W in the phase 3 program. This recommendation was based on an imbalance in clinically relevant adverse events including time to total joint replacement, peripheral edema, arthralgia and a trend towards fractures. Under amendment 4 global, all patients previously randomized to 3 mg Q4W or 6 mg Q8W under an earlier version of the protocol were discontinued from study drug, but encouraged to otherwise continue all protocol visits and study procedures in the follow-up period and the end of study phone call. Based on the independent DMC review, study of lower dose levels (eg,1 mg Q4W) may continue to be evaluated in the OA population. Given the discontinuation of the 3 mg and 6 mg doses, greater exposure to the fasinumab 1 mg dose is required to increase the size of the fasinumab safety database for potentially clinically relevant doses. Under this amendment, exposure to the fasinumab 1 mg dose will be increased by continuing to enroll patients into the 1 mg Q4W group as planned, and adding a 1 mg Q8W group to increase exposure to the 1 mg dose and to replicate the efficacy profile of this dose regimen, which was first evaluated in R475-PN-1523.

Clinical trial data, including PK data, that support selection of these fasinumab doses include those from the phase 1 studies in healthy volunteers (R475-PN-0817 and TDU-11480), the R475-PN-0901 phase 2 proof-of-concept study in patients with pain due to OA of the knee, the R475-PN-1227 phase 2/3 study in patients with OA of the hip or knee, the R475-PN-0908 single-dose, proof-of concept study in patients with sciatic pain.

Single subcutaneous (SC) doses of fasinumab of up to 30 mg were well-tolerated in healthy male and female subjects in the TDU-11480 study. All single IV doses of fasinumab in the R475-PN-0817 study in healthy male and female subjects were generally well tolerated at all but the highest IV dose (1 mg/kg). The occurrence of neurosensory AEs, which were transient and non-severe, led to the decision to refrain from escalating above the 1 mg/kg IV dose and instead, to expand enrollment of the 1 mg/kg IV cohort.

In the R475-PN-0901 phase 2 proof-of-concept study of fasinumab in patients with pain due to OA of the knee, multiple IV doses of up to 0.3 mg/kg administered Q8W demonstrated efficacy with regard to pain relief and were well tolerated in Caucasian subjects. All 3 doses of fasinumab (0.03 mg/kg, 0.1 mg/kg, and 0.3 mg/kg IV Q8W) were associated with greater improvement compared with placebo in walking index knee pain, standardized total WOMAC score, WOMAC subscales (pain, function, and stiffness) and Patient's Global Impression of Change. However, it was noted that pain relief had the slowest onset with the lowest (0.03 mg/kg) dose.

In the R475-PN-1227 phase 2 study of fasinumab in patients with pain due to OA of the hip or knee, all SC doses (1 mg, 3 mg, 6 mg, and 9 mg Q4W) demonstrated efficacy in pain relief and physical function measures, based upon WOMAC pain and physical function scales assessed after 16 weeks of treatment. Considering the relative lack of an observed dose response for efficacy and increased risk of AA with both the 9 mg and 6 mg Q4W doses, the latter doses are no longer

being studied for the treatment of pain due to OA. Neuromuscular AEs, such as arthralgia and paresthesia, were reported more frequently in fasinumab treated patients than in placebo-treated patients, though these events were typically mild or moderate in intensity. The efficacy and safety data from the 1 mg and 3 mg Q4W dose regimens in R475-PN-1227 supported the previous dose selection of 1 mg and 3 mg Q4W and 6 mg Q8W for the present study. Now, with the removal of the 3 mg Q4W and 6 mg Q8W dose regimens due to emerging safety information, the 1 mg Q4W dose regimen will continue to be evaluated in this study and is deemed to have a favorable benefit-risk profile. The addition of the 1 mg Q8W dose regimen will aid in the determination of a minimally efficacious dose. Note, with this amendment all dose regimens of study drug have been discontinued.

All randomized patients in Year 1 will receive orally administered naproxen (500 mg twice daily) or matching placebo. The 500 mg twice daily naproxen dose is a standard, approved dose for pain associated with OA.

All patients who choose to enter Year 2 will take 500 mg naproxen as needed (ie, prn), which is considered standard-of-care for pain associated with OA, or naproxen-matching placebo prn. The prn dosing schedule was chosen considering the known safety profile associated with chronic NSAID use. In general, the lowest effective dose should be used for the shortest duration taking into consideration the patient's medical history, concomitant medications, comorbidities, and age. The maximum dose allowed will be no more than the amount allowed during Year 1 (ie, 500 mg twice daily).

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc.), disease characteristics including medical and surgical history, and medication history for each patient.

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The co-primary endpoints 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.

4.2.2. Secondary Endpoints

The key secondary endpoints of the study are:

1. Change 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

4.2.3. Exploratory Endpoints

The exploratory endpoints in the study are:

1. Change from baseline to weeks 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 weeks 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 weeks 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 weeks 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 weeks 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 weeks 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 weeks 16 and 44
8. Descriptive analyses of the change from baseline at all visits from weeks 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. Descriptive analyses of the change from baseline at all visits from weeks 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 weeks 52E to 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 weeks 52E to 104E in patients with pain due to OA of the knee or hip treated with fasinumab compared to naproxen

4.3. Safety Endpoints

4.3.1. Safety Endpoints for Year 1 (All Randomized and Treated Patients)

Safety endpoints for Year 1 (through week 52) will include:

- Incidence of AA (as confirmed by independent adjudication)
- Incidence of DA (as confirmed by independent adjudication)
- Incidence of TEAEs
- Incidence of sympathetic nervous system dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist)

- Incidence of peripheral sensory AEs that require a neurology or other specialty consultation
- Incidence of all-cause JRs

The incidence of JRs at the telephone survey 52 weeks after the last dose of study drug (week 100) will also be evaluated.

4.3.2. Safety Endpoints for Year 2 (All Randomized and Treated Patients Proceeding into Year 2)

The safety endpoints listed above in Section 4.3.1 will be evaluated for Year 2 from the first dose of study drug given in Year 2 through week 104E (end of treatment), as well as for the periods of Year 1 and 2 from day 1 through week 104E.

The incidence of JRs at the telephone survey 52 weeks after the last dose of study drug (week 152E) will also be evaluated.

4.4. Pharmacokinetic Variables

The PK variables will consist of fasinumab concentrations in samples collected at time points specified in Table 1 and Table 2.

4.5. Anti-Drug Antibody Variables

Anti-drug antibody (ADA) variables include ADA status (positive or negative), titer, neutralizing antibody (NAb) status, and time point/visit. Samples in this study will be collected at the clinical visits specified in Table 1 and Table 2.

5. STUDY DESIGN

5.1. Study Description and Duration

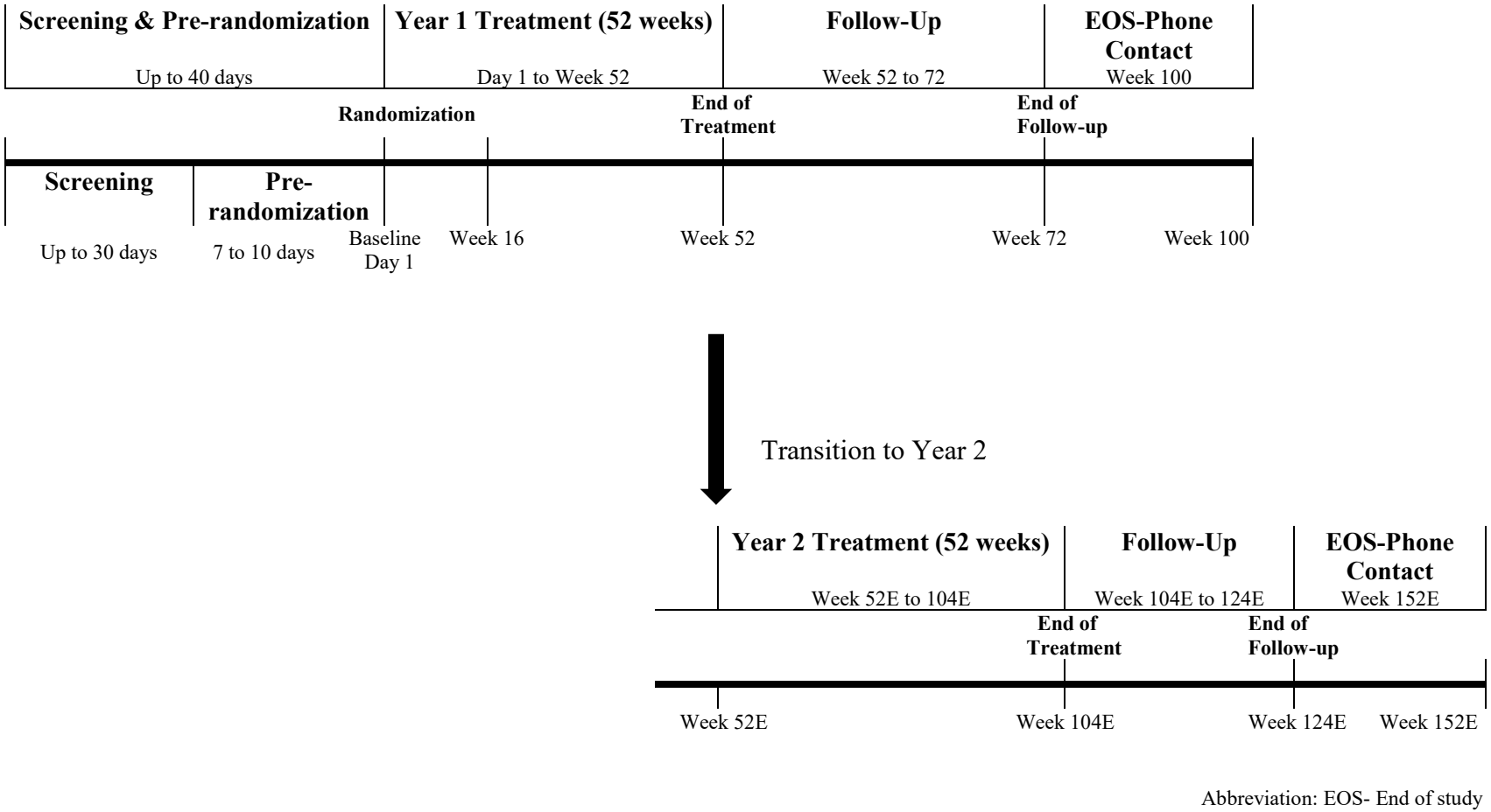
This study is a randomized, double-blind, placebo- and naproxen-controlled study designed to evaluate the efficacy and safety of fasinumab in patients with OA of the knee or hip who have a history of inadequate pain relief with acetaminophen/paracetamol and a history of intolerance to or inadequate pain relief from opioids (or are unwilling to take opioids or have lack of access to opioids).

The overall study period for patients in Year 1 who do not participate in Year 2 will be up to approximately 105 weeks including screening and pre-randomization. For these patients, the study consists of a screening period of up to 30 days, a 7 to 10-day pre-randomization/washout period (7 days with a +3 day window), a 52-week treatment period, a 20-week follow-up period, and a final phone call approximately 52 weeks after the last dose of SC study drug (Figure 1). At the end of the Year 1 treatment period, eligible patients can choose to consent to Year 2 and undergo a second year of treatment instead of entering the 20-week follow-up period. Note: As of 26 March 2020, all enrollment into Year 2 has been terminated due to the COVID-19 pandemic. Any patients currently enrolled in Year 2 are to remain in the study. Patients who participate in Year 2 will receive treatment for a total of 104 weeks and will then enter a 20-week follow-up period followed

by the final phone call approximately 52 weeks after the last dose of SC study drug (Figure 1). Note: As of 17 August 2020, all patients on treatment have been permanently discontinued from study drug and will complete the End of Treatment visit. This impacts only patients in the Year 2 treatment period as treatment in Year 1 has ended. All patients will be encouraged to complete all remaining study visits and procedures in the follow-up period and the end of study phone call.

Study weeks during Year 2 will be denoted with an E to represent study weeks during the extension (eg, week 52E) and to differentiate them from study weeks with the same numbers in the follow-up period for patients who only participate in Year 1.

Figure 1: Study Flow Diagram



Abbreviation: EOS- End of study

5.1.1. Screening and Pre-Randomization

At the screening visit, patients will consent to all study assessments planned for Year 1 and will be informed that they could potentially continue in the study for a second year if they meet eligibility requirements for Year 2. Eligibility and consent for Year 2 will be conducted at the end of Year 1.

Prior to randomization, patients will undergo screening procedures, including X-ray of the shoulders, hips, and knees. Magnetic resonance imaging of the index and contralateral joints must be performed at screening and the results assessed by the central imaging vendor. In addition, an MRI will be performed on any knee or hip joint with a K-L score of ≥3. Randomization visits cannot occur until there is confirmation from the central imaging vendor that there are no exclusionary findings on the X-rays and any required MRIs. During the screening period, all patients will continue to take their current treatment regimen for OA pain, which must include use of an oral NSAID on a regular basis, defined as approximately 4 days per week over the last 4 weeks.

Patients eligible for the study will complete a pre-randomization period, during which all pain medication, except for the study-provided rescue medication (acetaminophen/paracetamol), will be discontinued. The pre-randomization visit will be 7 to 10 days (7 days with a +3 day window) before the randomization visit. Patients will discontinue and/or undergo a washout of, their standard-of-care pain medications for OA during the pre-randomization period. As needed, patients may take acetaminophen/paracetamol for pain relief according to the regional standard-of-care (see Section 7.2 for details). Acetaminophen/paracetamol must not be taken within 24 hours prior to the randomization visit.

5.1.2. Rescreening

Re-testing During Screening or Pre-randomization

An assessment that fails to meet eligibility criteria may be repeated once within the screening or pre-randomization period when approved by the Sponsor or designated Medical Monitor under either of the following conditions: 1) the failure is believed by the investigator to be due to a condition that would resolve or could be treated, or 2) a laboratory value minimally exceeds the cut-off value and is not clinically relevant. Only the assessments that did not meet the eligibility criteria require repetition, if done within the screening period or pre-randomization period. Patients may not repeat any assessments if they do not meet the WOMAC criteria or have orthostatic hypotension (defined in Section 8.2.3.4) during the screening or pre-randomization visit.

Rescreening Due to Screen Failure

Rescreening can be completed for patients who fail to meet the screening visit window requirements or who are unable to complete all imaging assessments within the specified screening period. Patients who are rescreened after the pre-randomization window must be declared screen failures, be registered in the IVRS as a new patient with a new identification number, and then repeat all screening procedures, with the exception of imaging assessments. Any imaging assessments would need to be repeated only if they were taken more than 60 days from completion of the previous screening X-rays and MRI assessments. Patients cannot rescreen if they have

screen failed due to not meeting the WOMAC criteria or have orthostatic hypotension (defined in Section 8.2.3.4) during the screening or pre-randomization visit.

5.1.3. Randomization

Enrollment of approximately 2845 patients is planned for this study, which includes a total of 285 patients who were enrolled in the fasinumab 3 mg SC Q4W and 6 mg SC Q8W groups under earlier versions of the protocol before dosing was discontinued due to the urgent safety measure, and a total of approximately 2560 patients who will be randomized to fasinumab 1 mg SC Q4W, 1 mg SC Q8W, naproxen, and placebo.

At the baseline visit of Year 1, patients will be randomized 3:3:3:1 to the following treatment groups as follows:

- Fasinumab 1 mg SC Q4W
- Fasinumab 1 mg SC Q8W
- Naproxen 500 mg oral, twice daily
- Placebo

Prior to amendment 5 global, it is estimated that approximately 560 patients were randomized as follows: 240 patients to the fasinumab 1 mg SC Q4W group, 240 patients to the naproxen-only group and 80 patients to the placebo group. Under amendment 5 global, a further 2000 patients were planned to be randomized as follows: 600 patients to the fasinumab 1 mg SC Q4W group, 600 patients to the naproxen-only group, 200 patients to the placebo group, and 600 patients to the newly added fasinumab 1 mg SC Q8W group. Thus, overall, this study will enroll approximately 2560 patients as follows: 840 patients to the fasinumab 1 mg SC Q4W group, 600 patients to the 1 mg SC Q8W group, 840 patients to the naproxen group, and 280 patients to the placebo group.

Prior to amendment 5 global, approximately 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 DMC in April 2018.

Patients will receive treatment as described in Section 7.1. Randomization will be stratified according to the affected index joint (hip or knee), the K-L score (2 to 3 or 4) at the screening visit, and geographical region.

Eligible patients who choose to participate in Year 2 will not be re-randomized at week 52. See Section 7.1 for treatment assignments in Year 2.

5.1.4. Treatment Period for Year 1

During the treatment period (day 1 through week 52), patients will be permitted to use only acetaminophen/paracetamol as rescue medication. The study visits during the treatment period will include 1 phone visit on day 8 (±1 day). Patients will record their use of acetaminophen/paracetamol in a diary. Patients should discontinue use of acetaminophen/ paracetamol at least 24 hours prior to the start of each study visit in order to minimize the confounding effects of the rescue medication on efficacy measurements.

Efficacy will be assessed by the change from baseline in the WOMAC pain and physical function subscale scores, the PGA, the 36-item Short Form Survey (SF-36), the EuroQoL 5 Dimensions 5 Level Questionnaire (EQ-5D-5L), the Numeric Rating Scale (NRS) of the average walking index joint pain, the Work Productivity and Activity Impairment-Osteoarthritis (WPAI-OA), the Healthcare Resource Utilization (HCRU) questionnaire, and the Treatment Satisfaction Questionnaire for Medication (TSQM). The WOMAC total and stiffness scores will also be evaluated.

Safety assessments will be performed at each study visit during treatment period, as outlined in Table 1.

At the end of the treatment period, patients will either enter the 20-week follow-up period or will be offered by their investigator to enter Year 2, if eligible.

5.1.5. Treatment Period for Year 2

During the treatment period of Year 2 (week 52E through week 104E), patients will be permitted to use only acetaminophen/paracetamol as rescue medication. Patients will record their use of acetaminophen/paracetamol in a diary. Patients should discontinue use of acetaminophen/ paracetamol at least 24 hours prior to the start of each study visit in order to minimize the confounding effects of the rescue medication on efficacy measurements.

Efficacy will be assessed by the change from baseline in the WOMAC pain and physical function subscale scores, the EQ-5D-5L and the WPAI-OA. The WOMAC total and stiffness scores will also be evaluated.

Safety assessments will be performed at each study visit during treatment period, as outlined in Table 2.

5.1.6. Follow-Up Period

At the end of the treatment period (week 52 for patients participating in Year 1 only, or week 104E for patients participating in Year 1 and Year 2), follow-up of patients will continue for an additional 20 weeks. Safety and efficacy assessments will be performed according to the schedule outlined in Table 1 (for patients participating in Year 1 only) or Table 2 (for patients participating in Year 1 and Year 2).

If a patient must undergo JR surgery during the study, he or she will be asked to complete pre-operative imaging and to undergo post-surgery follow-up as outlined in Table 3.

5.1.7. End of Study Phone Contact

The end of study phone contact will be at week 100 for patients participating in Year 1 only or week 152E for patients participating in Year 1 and Year 2.

A phone contact questionnaire will be conducted at approximately 52 weeks after administration of the last dose of fasinumab or fasinumab-matching placebo to document patient status with regard to JR surgery (if patient underwent, is scheduled for, or is on a wait list for JR surgery). Patients who had an AA will have an MRI performed of the affected joint(s). If the affected joint has undergone JR an X-ray may be substituted for an MRI.

5.1.8. Study Stopping Rules

An independent Data Monitoring Committee (DMC) will monitor unblinded data on an ongoing basis to assess the risk/benefit profile of fasinumab. Based on these reviews, in the context of the totality of evidence, if the DMC has significant concerns at any time regarding a meaningful imbalance between treatment groups in joint-related AEs, sympathetic nervous system dysfunction, neurosensory disturbances, or any other safety issues, the DMC may make a recommendation to temporarily halt, alter, or terminate:

- individual dose groups within the study or across studies
- the full study (screening, randomization, dosing of study drug)
- the fasinumab program

for additional review and communication to regulatory authorities. Based on the outcome of the review and discussions with the appropriate regulatory authorities, the study may be suspended, restarted, or terminated.

Formal program wide statistical study stopping criteria for clinical studies involving fasinumab may be added to the DMC charter as deemed necessary by the sponsor, DMC and/or Health Authorities.

5.1.9. End of Study Definition

The end of study is defined as the last phone contact of the last patient in this study.

5.2. Planned Interim Analysis

No interim analysis of efficacy data from Year 1 will be conducted prior to collection of all data necessary for 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 (see Section 10.5 for statistical details of this analysis).

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 of the 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.

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

An independent DMC will meet periodically to review unblinded data as the study progresses, and based on the findings, will make recommendations to the sponsor about the conduct of the study. The DMC will comprise independent statistical and medical experts. Further details will be defined in the DMC charter. Additional safety monitoring will occur on an ongoing basis by the Regeneron Safety Team.

5.3.2. Arthropathy Adjudication Committee

An independent, expert, blinded adjudication committee, composed of radiologists, will adjudicate all potential joint AEs of AA (defined in Section 9.6.1.1) as well as pre-operative images in patients undergoing JR.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Enrollment of approximately 2845 patients is planned for this study (see Section 5.1.3).

6.2. Study Population

Eligible patients for this study consist of men and women who are at least 18 years of age at the time of study entry with a clinical diagnosis at the screening visit of OA of the knee or hip, based on the American College of Rheumatology criteria, and with radiologic evidence of OA (K-L score ≥2) at the index joint.

6.2.1. Inclusion Criteria for Year 1

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Male and female patients, at least 18 years of age, at screening
2. Provide signed informed consent
3. Body mass index ≤39 at screening visit
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

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
6. Willing to discontinue current pain medications and to adhere to study requirements for rescue treatments (acetaminophen/paracetamol to be taken as needed with a maximum daily dose of 2500 mg [countries where 500 mg strength tablets/capsules are available] or 2600 mg [countries where 325 mg strength tablets/capsules are available])
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
    b. 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
8. Currently using a stable dose of NSAID, defined as using oral NSAIDs at regularly prescribed doses for approximately 4 days per week over the last 4 weeks (patients who are screen failures prior to the randomization visit but who met the NSAID use criterion at screening would still meet this criterion if they are eligible for rescreening)
9. Willing to continue a stable dose of oral NSAID during the screening period, defined as using NSAIDs for approximately 4 days per week
10. Willing to discontinue glucosamine sulfate and chondroitin sulfate treatments during the initial 16 weeks of treatment
11. Stable treatment with glucosamine sulfate and chondroitin sulfate treatments must be stopped during the pre-randomization period
12. Consent to allow all radiographs and medical/surgical/hospitalization records of care received elsewhere prior to and during the study period to be shared with the investigator
13. Willing to maintain current activity and exercise levels throughout the study
14. Willing and able to comply with clinic visits and study-related procedures and willing to provide follow-up information related to any JR surgery that occurs within the period of time covered by their intended participation in the study
15. Able to understand and complete study-related questionnaires

6.2.2. Exclusion Criteria for Year 1

A patient who meets any of the following criteria will be excluded from the study:

1. Non-compliance with the NRS recording during the pre-randomization period (4 or more consecutive missed diary entries)
2. History or presence at the screening visit of non-OA inflammatory joint disease (eg, rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudo-gout, gout, spondyloarthropathy, polymyalgia rheumatica, joint infections within the past 5 years), Paget's disease of the spine, pelvis or femur, neuropathic disorders, multiple sclerosis, fibromyalgia, tumors or infections of the spinal cord, or renal osteodystrophy
3. History or presence on imaging of arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressive OA type 1 or type 2), stress fracture, recent stress fracture, neuropathic joint arthropathy, hip dislocation (prosthetic hip dislocation is eligible), knee dislocation (patella dislocation is eligible), congenital hip dysplasia with degenerative joint disease, extensive subchondral cysts, evidence of bone fragmentation or collapse, or primary metastatic tumor with the exception of chondromas or pathologic fractures during the screening period
4. Trauma to the index joint within 3 months prior to the screening visit
5. Signs or symptoms of carpal tunnel syndrome within 6 months of screening visit
6. Patient is not a candidate for MRI
7. Is scheduled for a JR surgery to be performed during the study period or who would be unwilling or unable to undergo JR surgery if one eventually became necessary
8. History or presence at the screening visit of autonomic neuropathy, diabetic neuropathy, or other peripheral neuropathy, including reflex sympathetic dystrophy
9. History or diagnosis of chronic autonomic failure syndrome including pure autonomic failure, multiple system atrophy (Shy-Drager syndrome)
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)
11. Known allergy or sensitivity to doxycycline or related compounds, or monoclonal antibodies
12. Poorly controlled diabetes (defined as any single value of hemoglobin A1c [HbA1c] >9.0%) at the screening visit
13. Known history of human immunodeficiency virus infection
14. Known history of ocular herpes simplex virus, herpes simplex virus pneumonia, or herpes simplex virus encephalitis
15. History of sickle cell disease, including sickle cell anemia and β-thalassemia

16. Confirmed elevated screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 times the upper limit of normal (ULN)
17. Resting heart rate of <50 beats per minute (bpm) or >100 bpm (by vital sign assessment or as captured during electrocardiogram [ECG] assessment) at the screening or randomization visits
18. History or presence of 2nd or 3rd degree heart block, 1st degree heart block with abnormal QRS complex, or bifascicular block by ECG assessment at the screening visit
19. History or presence of orthostatic hypotension, as defined in Section 8.2.3.4, at the screening, pre-randomization, or randomization visits
20. History of poorly controlled hypertension, as defined by:
    a. Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg at the screening visit
    b. Systolic blood pressure of 160 mm Hg to 179 mm Hg or diastolic blood pressure of 100 mm Hg to 109 mm Hg at the screening visit, AND a history of end-organ damage (including history of left ventricular hypertrophy, heart failure, angina, myocardial infraction, stroke, transient ischemic attack, peripheral arterial disease and moderate to advanced retinopathy [hemorrhages or exudates, papilledema])
21. Congestive heart failure with NY Heart Classification of stage III or IV (Dolgin 1994)
22. History of peripheral vascular disease, transient ischemic attack, cerebrovascular accident, myocardial infarction, unstable angina, or documented atherosclerotic cardiovascular disease
23. Significant concomitant illness including, but not limited to, psychiatric, cardiac, renal, hepatic, neurological, endocrinological, metabolic, or lymphatic disease that, in the opinion of the investigator, would adversely affect the patient's participation in the study
24. New major illness diagnosed within 2 months prior to the screening visit
25. Known history of infection with hepatitis B virus. Patients with a history of hepatitis B are eligible if there is documentation of a negative test for hepatitis B surface antigen and a positive test for antibodies to the hepatitis B virus surface antigen
26. Known history of infection with the hepatitis C virus. Patients with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test
27. History or presence of malignancy within the last 5 years prior to screening, except patients who have been treated successfully with no recurrence for >1 year of basal cell or squamous cell carcinoma of the skin or in-situ cervical cancer
28. History of hospital admission for depression or suicide attempt within 5 years or active, severe major depression at screening
29. Use of systemic, eg, IV, oral or intramuscular corticosteroids within 30 days prior to the screening visit. Intra-articular corticosteroids in the index joint within 12 weeks prior to the screening visit, or to any other joint within 30 days prior to the screening visit (topical, intra-nasal, and inhaled corticosteroids are permitted)

30. Use of a monoamine reuptake inhibitor, tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors for treatment of pain within 4 weeks prior to the screening visit
31. Has positive urine drug test results during screening (eg, amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates), unless in the opinion of the investigator, the positive test results may be due to the patient's current permitted medications.
32. History of (within 5 years prior to the screening visit) or current alcoholism, alcohol abuse, substance abuse, or abuse of prescription pain medication
33. History of cannabis use for the treatment of pain within the past 6 months prior to the screening visit
34. Ongoing participation in a clinical research study evaluating another investigational drug or having received another investigational product within 30 days or 5 half-lives of the screening visit, whichever is longer
35. Exposure to an anti-NGF antibody prior to the screening visit or known sensitivity or intolerance to anti-NGF antibodies or participation in a clinical trial evaluating anti-NGF antibodies
36. Member of the clinical site study team and/or his/her immediate family
37. Pregnant or breastfeeding women
38. Women of childbearing potential who have a positive pregnancy test result or do not have their pregnancy test result at baseline
39. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to start of the first treatment, during the study, and for at least 20 weeks after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence[†‡].

    * Postmenopausal women must be amenorrheic for at least 12 months (without an alternative medical cause) in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented complete hysterectomy or tubal ligation.

    † Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

    ‡ Periodic abstinence (calendar, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method

(LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

40. Patients taking concomitant angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and diuretics, or presence of an estimated glomerular filtration rate (GFR) <30 mL/minute/1.73m^{2*}

    * GFR is calculated using the Modification of Diet in Renal Disease Study (MDRD) equation, as follows:

      GFR = 175 x (Standardized SCr)-1.154 x (age)-0.203 (x 0.742 if female) x (1.212 if African American)

      GFR is expressed in mL/min/1.73m2

      SCr is serum creatinine expressed in mg/dL

      Age is expressed in years

Note: 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.

6.2.3. Inclusion Criteria for Year 2

Note: Any Year 1 patient attending their week 52 visit on or after 26 March 2020 will no longer have the option to enroll into Year 2.

1. Completed the treatment period of Year 1
2. Did not permanently discontinue study drug during Year 1
3. Received no less than 10 of the 13 planned doses of SC study drug during the treatment period of Year 1
4. Provide informed consent for Year 2
5. Willing to continue to maintain current activity and exercise levels throughout Year 2
6. Willing and able to comply with clinic visits and study-related procedures and willing to provide follow-up information related to any JR surgery that occurs within the period of time covered by their intended participation in the study

6.2.4. Exclusion Criteria for Year 2

Women of childbearing potential who are unwilling to continue to practice highly effective contraception during the study, and for at least 20 weeks after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence[†‡].

† Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study

treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

‡ Periodic abstinence (calendar, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

6.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 8.1.4.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.3.2.

6.4. Replacement of Patients

Patients prematurely withdrawn from the study or study drug will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Study drug in this study includes fasinumab, naproxen, and their matching placebo. Fasinumab and its matching placebo are SC study drug. Naproxen and its matching placebo are oral study drug.

Fasinumab drug product is supplied for this study in the following concentrations:

- Fasinumab 2 mg/mL: Each 1 mL single use pre-filled syringe delivers 0.5 mL of a 2 mg/mL solution (1 mg dose) of study drug
- Fasinumab-matching placebo: Each 1 mL single use pre-filled syringe delivers 0.5 mL of placebo solution

Naproxen 500 mg capsules and naproxen-matching placebo capsules will be provided by the sponsor.

Year 1

At the baseline visit of Year 1, patients will be randomized 3:3:3:1 to receive 1 of the following treatment regimens:

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

All patients will receive SC injections of fasinumab or fasinumab-matching placebo. All SC injections will be in the abdomen, thigh, or upper arm. Patients will be observed in the clinic for approximately 1 hour after study drug is administered. Patients randomized to earlier versions of the protocol with 3 mg Q4W or 6 mg Q8W fasinumab were discontinued from study drug for the remainder of the study and moved directly into the follow-up period.

Naproxen 500 mg or naproxen-matching placebo will be administered orally, twice daily. A proton pump inhibitor or other gastric protective medication may be prescribed if deemed medically necessary by the investigator or sub-investigator.

Doses of SC study drug must be given within ±7 days from the scheduled dose date. If the window is missed, the SC dose of fasinumab or fasinumab-matching placebo should not be administered, however the oral dose of naproxen or naproxen-matching placebo will be dispensed. The next SC dose of fasinumab or fasinumab-matching placebo should be administered at the next scheduled dosing date.

Detailed instructions for study drug dose administration are provided in the pharmacy manual.

Year 2

During Year 2, patients will receive one of the following treatment regimens based on the treatment they received during Year 1:

Year 1	Year 2
Fasinumab 1 mg SC Q4W and naproxen-matching placebo oral, twice daily	Fasinumab 1 mg SC Q4W and naproxen-matching placebo oral, prn*
Fasinumab 1 mg SC Q8W (patients will receive placebo injections at the study visits where study drug is not administered) and naproxen-matching placebo oral, twice daily	Fasinumab 1 mg SC Q8W (patients will receive placebo injections at the study visits where study drug is not administered) and naproxen-matching placebo oral, prn*
Fasinumab-matching placebo SC Q4W and naproxen 500 mg oral, twice daily	Fasinumab-matching placebo SC Q4W and naproxen 500 mg oral, prn*
Fasinumab-matching placebo SC Q4W and naproxen-matching placebo oral, twice daily	Fasinumab-matching placebo SC Q4W and naproxen 500 mg oral, prn*

*The maximum naproxen dose (or naproxen placebo dose) allowed will be no more than the amount allowed during Year 1 (ie, 500 mg twice daily or 1 capsule of placebo twice daily).

Administration of SC study drug will be performed as stated above for Year 1.

Naproxen 500 mg or naproxen-matching placebo will be administered prn. A proton pump inhibitor or other gastric protective medication may be prescribed if deemed medically necessary by the investigator or sub-investigator.

7.2. Rescue Treatment(s)

During the Year 1 and Year 2 treatment periods, acetaminophen/paracetamol will be the only study-provided rescue medication. In the event that pain relief for OA pain is inadequate, or in the event of other pain (eg, headache) or fever, 1 to 2 tablets/capsules of acetaminophen/paracetamol may be taken no less than 4 hours apart, as needed, according to local standard of care. The maximum daily dose during the treatment and follow-up periods is 2500 mg (500 mg x 5 tablets/capsules) in countries where 500 mg strength tablets/capsules are available, or 2600 mg (325 mg x 8 tablets/capsules) in countries where 325 mg strength tablets/capsules are available (eg, North America). Where 500 mg strength tablets/capsules are available, the highest individual single dose is 1 gram. Where 325 mg tablets/capsules are available, the highest individual single dose is 650 mg.

In order to prevent severe liver damage, patients should be cautioned to avoid consumption of alcoholic beverages while on acetaminophen/paracetamol. Patients should also be cautioned not to take rescue medication at intervals of fewer than 4 hours and to take no more than the maximum allowable single dose (1 to 2 tablets/capsules) or maximum allowable total daily dose.

Acetaminophen/paracetamol must not be taken within 24 hours prior to scheduled study visits during the Year 1 and Year 2 treatment periods in order to minimize the confounding effects of rescue medication on efficacy assessments. Use of acetaminophen/paracetamol as study-provided rescue medication during the Year 1 and Year 2 treatment periods will be reported daily by patients using e-diaries. During the Year 1 and Year 2 treatment periods, the acetaminophen/paracetamol will be sourced by the study sites and dispensed to the patient at each visit where SC study drug is administered. Acetaminophen/paracetamol accountability will be conducted at each study visit, starting at the baseline visit and continuing through the end of the treatment period.

During the 20-week follow-up period, acetaminophen/paracetamol will not be provided by the sites to the patients. If acetaminophen/paracetamol is used, dosing instructions will be the same as during the treatment period including the maximum allowed daily dose. Use of acetaminophen/paracetamol will be captured as a concomitant medication.

7.3. Dose Modification and Study Treatment Discontinuation Rules

7.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

7.3.2. Study Drug Discontinuation

Study drug may be temporarily or permanently discontinued due to medical need, as determined by the investigator or the Sponsor and according to the study stopping rules (Section 5.1.8).

Patients who permanently discontinue from study drug will be encouraged to remain in the study and to complete all study procedures and assessments including completion of the diary, the only exception being not receiving study drug (oral and SC). Patients must continue to adhere to the prohibited medication list as per Section 7.7.1. Patients who agree and thus do not withdraw from the study will be asked to return to the clinic for all remaining study visits per Table 1.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete early termination study assessments, per Table 1.

Patients who discontinue from study drug prior to study completion due to an AA (see Section 9.6.1.1) should return to the clinic for all remaining study visits per the visit schedule.

In the event that a patient must undergo JR surgery during the treatment or follow-up periods, he/she will be discontinued from study drug and asked to return to the study site for a pre-operative visit and for follow-up safety evaluations (as described in Section 8.2.3.10) 4 and 20 weeks after surgery. Pre-operative imaging (X-ray and MRI) will be obtained and submitted to the independent adjudication committee for review to ensure that an AA event is not in occurrence. Instructions for the submission process are provided in the study manual.

7.3.2.1. Reasons for Permanent Discontinuation of Study Drug

As of 17 August 2020, all patients in the Year 2 Treatment Period must be immediately discontinued from study drug, undergo all End of Treatment visit assessments, and move directly into the 20-week safety follow-up period.

Prior to 17 August 2020, study drug dosing was to be permanently stopped in the event of any of the following:

- A patient who is currently enrolled under an earlier version of this protocol must be immediately discontinued from study drug, undergo all end of treatment visit assessments, and move directly into the 20-week safety follow-up period under this version of the protocol, if they meet any of the following conditions that were excluded after re-evaluating the safety profile of NSAIDs:
  - They have a known medical history (at any time) of peripheral vascular disease, transient ischemic attack, cerebrovascular accident, myocardial infarction, unstable angina, or documented atherosclerotic cardiovascular disease; or
  - They have a known GFR <30 mL/minute/1.73m^2 or,
  - They are currently taking combination therapy of a diuretic with either an ACE inhibitor or ARB (Note: Patients may remain in the study if they are willing and able to change their antihypertensive regimen such that they are no longer on a combination of a diuretic with either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
- A patient who was randomized under an earlier version of the protocol to 3 mg Q4W or 6 mg Q8W fasinumab
- A patient developing clinically significant peripheral sensory or motor neurologic events confirmed by a neurologist's examination and graded by the neurologist as at

least moderate peripheral neuropathy limiting activities of daily living (ADL), ie, grade ≥2 according to Common Terminology Criteria for Adverse Events (CTCAE) v.4; study sites should use CTCAE v.4 criteria throughout the study for consistency

- Evidence of pregnancy
- A patient developing new or worsening signs and symptoms indicative of carpal tunnel syndrome
- Continued non-compliance with protocol-defined maximum acetaminophen/ paracetamol use (with a maximum daily dose of 2500 mg [countries where 500 mg strength tablets / capsules are available] or 2600 mg [countries where 325 mg strength tablets / capsules are available]) during the treatment and follow-up periods, after appropriate counseling
- Continued non-compliance with the protocol, including usage of NSAIDs that are not permitted in the study, after appropriate counseling
- Joint replacement surgery
- AESIs of:
  - Adjudicated arthropathy, as described in Section 9.6.1.1.
  - Sympathetic nervous system dysfunction, as described in Section 9.6.1.2.
- Hepatotoxicity. Study drug should be discontinued if the following are observed:
  - Total bilirubin (TBL) >2x ULN or international normalized ratio (INR) >1.5, and
  - ALT or AST >3x ULN, and
  - No other cause for 1 and 2 is readily apparent

Other causes of ALT, AST, and TBL elevations may include alcoholic hepatitis, autoimmune hepatitis, non-alcoholic hepatitis, heritable diseases (Gilbert's Syndrome), heart failure, and viral hepatitis.

NOTE: Study drug may be withheld in patients who do not meet criteria for permanently discontinuing study drug, until an alternative cause for drug-induced liver injury can be determined. The patient may be re-challenged if an alternative cause for elevated liver function tests is found and the liver function tests return to baseline, but only after discussion with the sponsor.

- Systemic hypersensitivity reaction deemed by the investigator to be related to study drug
- Gastrointestinal bleeding, acute coronary syndrome
- Any other medical need, as determined by the investigator
- Sponsor decision
- Patient decision

7.3.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug may be temporarily discontinued due to medical need, as determined by the investigator. Subcutaneous study drug (fasinumab or fasinumab-matching placebo) will be temporarily withheld while awaiting imaging adjudication for worsening joint pain or when routine imaging suggests adjudicated arthropathy and prompts the need for additional imaging (see Section 9.6.1.1), or for patients who are determined to have orthostatic hypotension or determined to have new or worsening symptoms suggestive of sympathetic nervous system dysfunction while awaiting evaluation by a specialist (see Section 9.6.1.2). Patients may continue to take naproxen or naproxen-matching placebo during this time. Subcutaneous study drug (fasinumab or fasinumab-matching placebo) should not be re-started until the next study visit unless imaging/evaluation results are available within the current visit window. If oral study drug is temporarily discontinued by the investigator, patients may continue to take SC study drug during this time.

7.4. Management of Acute Reactions

7.4.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use for injections performed at the study site. All injection reactions must be reported as AEs (as defined in Section 9.3.1) and graded using the grading scales as instructed in Section 9.5.1.

Acute systemic reactions following injection of study drug SC should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

7.4.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 9.5.1.

7.5. Method of Treatment Assignment

At the baseline visit of Year 1, patients will be randomized in a 3:3:3:1 ratio to receive fasinumab (1 mg SC Q4W, 1 mg SC Q8W), naproxen, or placebo according to a central randomization scheme provided by an interactive voice response system (IVRS) / interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified according to the affected index joint (hip or knee), the K-L score (2 to 3 or 4) at the screening visit, and geographical region.

Prior to Amendment 5 global, patients were randomized 3:3:3:3:1 to receive fasinumab (1 mg Q4W, 3 mg Q4W, 6 mg Q8W), naproxen, or placebo.

Patients participating in Year 2 will receive treatment as described in Section 7.1. No re-randomization will occur at the time of entry into Year 2.

7.5.1. Blinding

Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron study medical director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

Blinded study drug kits coded with a drug numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Anti-drug antibody results will not be communicated to the sites before the end of the study, and the sponsor operational team will not have access to results associated with patient identification until after the final database lock.

No study personnel involved in the day-to-day conduct of the study will have access to unblinded data before the database is locked for this study.

7.5.2. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy).

If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment
- Only the affected patient will be unblinded
- The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient
- The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

7.5.3. Unblinding for Regulatory Reporting Purposes

Treatment assignments for certain patients may be unblinded to Pharmacovigilance and Risk Management personnel for the purpose of regulatory reporting of suspected serious adverse reactions (SUSARs).

7.6. Treatment Logistics and Accountability

7.6.1. Packaging, Labeling, and Storage

A drug numbering system will be used to label blinded study drug. Lists linking drug numbers with product lot numbers will be maintained by the groups (or companies) responsible for study

drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Subcutaneous study drug will be stored at the site at a temperature of 2°C to 8°C while oral study drug will be stored at 20°C to 25°C; storage instructions will be provided in the pharmacy manual.

7.6.2. Supply and Disposition of Treatments

Subcutaneous and oral study drugs will be shipped to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, study drug will be destroyed or returned to the sponsor or designee. Refer to the pharmacy manual for instructions.

7.6.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study drug that is:

- dispensed to each patient,
- returned from each patient (if applicable), or
- returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

7.6.4. Treatment Compliance

All study drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

7.7. Concomitant Medications and Procedures

Any treatment administered and/or procedures performed from screening to the end of the follow-up period will be considered concomitant medication and/or procedures, respectively. This includes medications and/or procedures that were started before the study and are ongoing during the study.

7.7.1. Prohibited Medications

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 (eg, 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 for permitted muscle relaxants)
- Corticosteroids (topical, intranasal, and inhaled formulations are permitted), adrenocorticotropic hormone
- Cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus
- Azathioprine, sulfasalazine, hydroxychloroquine
- 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

7.7.2. Permitted Medications and Procedures

Patients receiving chronic medication therapy must be on a stable dose of such medication for at least the 30 days prior to the screening visit. Monoamine reuptake inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors are permitted for non-pain-related treatment. Patients must be on therapy for at least 8 consecutive weeks and on a stable dose for at least 4 weeks prior to the screening visit and throughout the planned duration of the patient's participation in the study.

Low-dose aspirin/5-ASA (up to 150 mg/day) for cardiac prophylaxis is also permitted. Acetaminophen/paracetamol taken acutely for treatment of non-OA pain is also permitted; however, the total daily dosage limits cannot be exceeded, regardless of the reason for acetaminophen/paracetamol use. During the pre-randomization and the Year 1 and Year 2 treatment periods, acetaminophen/paracetamol use will be captured in the diary; use for relief of pain other than pain due to OA will be reported in the diary as "other". During the screening and

follow-up periods, acetaminophen/paracetamol taken for any reason will be reported as concomitant medication. Topical steroids are also permitted.

Muscle relaxants, such as Skelaxin® (metaxalone) and others, are permitted. Prohibited muscle relaxants are listed in Section 7.7.1.

Physical therapies (such as transcutaneous electrical nerve stimulation and acupuncture) are permitted during the trial, provided that patients have been on a stable regimen for at least 4 weeks prior to entering into the trial and that they expect to maintain this regimen during the trial.

Joint replacement is a permitted procedure during the study.

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1, Table 2 and Table 3.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Table 1: 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 and heart rate 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**											

ADA: Anti-drug antibody
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

Table 1: Schedule of Events Year 1 (continued)

(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).

	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

8.1.1. Footnotes for the Schedule of Events Table 1 (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 3). 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).
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 2: 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**

Table 2: Schedule of Events for Year 2 (continued)

	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**	

	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**
Event-triggered imaging[8]	**X**	**X**	**X**	**X**	
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

8.1.2. Footnotes for the Schedule of Events Table 2 (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 3). 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).
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. Samples should be collected prior to SC study drug administration on SC study drug dosing days.

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 3: 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

8.1.3. Footnotes for Table 3 - Follow-up Period for Patients Undergoing Joint Replacement Surgery

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

8.1.4. Early Termination Visit

Patients who are permanently withdrawn from study drug early should be encouraged to continue in the study and complete all other study assessments without receiving study drug. If a patient decides to completely withdraw consent from the study, every attempt should be made to have the patient complete an early termination visit (as outlined in Table 1 or Table 2, as applicable). 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.

8.1.5. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

8.2. Study Procedures

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed at the screening visit for the sole purpose of determining study eligibility or characterizing the baseline population:

8.2.1.1. Informed Consent

All patients must sign and date the Institutional Review Board (IRB)/ Ethics Committee (EC)-approved written ICF before any study procedures are performed, per Section 14.2.

8.2.1.2. Medical History

The investigator or designee will take a complete medical history that includes information on concurrent medical conditions and the severity for each condition that has not resolved.

8.2.1.3. Medication History

The investigator or designee will record information on a patient's medication history, including any history of intolerance to naproxen.

8.2.1.4. Demographics

A patient's demographic characteristics will be recorded, including age, height, weight, gender, race, and ethnicity.

8.2.1.5. Determination of Osteoarthritis

Diagnosis of OA of the knee or hip will be based on the American College of Rheumatology criteria with radiologic evidence of OA (K-L score ≥2)

In addition, diagnosis of OA of the hip and knee will use the following criteria:

Hip

The American College of Rheumatology clinical and radiographic criteria for the diagnosis of OA of the hip (Altman 1991) should be used to confirm a diagnosis of OA of the hip, as applicable, at screening. The criteria consist of the following combinations:

- Hip pain, and
- At least 2 of the following 3 features:
  - Erythrocyte sedimentation rate (ESR) <20 mm/hour
  - Radiographic femoral or acetabular osteophytes
  - Radiographic joint space narrowing (superior, axial, and/or medial)

Additional information is provided in the study reference manual.

Knee

The American College of Rheumatology clinical and radiographic criteria for the diagnosis of OA of the knee (Altman 1986) should be used to confirm a diagnosis of OA of the knee, as applicable, at screening. The criteria consist of the following combinations:

- Knee pain
- Osteophytes on radiograph
- At least 1 of the following 3 features:
  - Age >50 years
  - Stiffness <30 minutes
  - Crepitus

Additional information is provided in the study reference manual.

8.2.1.6. Assessment of Childbearing Potential

Each female patient should be evaluated for childbearing potential.

Women will be considered to be of childbearing potential unless they are postmenopausal, or have had a tubal ligation, a bilateral oophorectomy, bilateral salpingectomy, or complete hysterectomy.

For women ≥60 years of age, postmenopausal is defined as at least 12 continuous months of spontaneous amenorrhea. In women ≤59 years of age, postmenopausal is defined as at least 12 continuous months of spontaneous amenorrhea, with serum FSH levels >40 IU/L (>40 mIU/mL) and serum estradiol levels <5 ng/dL (<184 pmol/L) (Section 8.2.3.11).

8.2.1.7. Assessment of Peripheral or Central Pain

Patients will complete a self-reported survey to evaluate the peripheral versus central nature of their pain at time points indicated in Section 8.1.

A copy of the survey is provided in the study reference manual.

8.2.1.8. Instructions for Use of Diary

At the pre-randomization and baseline visits, patients will be instructed on the use of the NRS for scoring their walking index joint pain. Patients will be trained on the use of the diary to report their walking index joint pain NRS score and their daily acetaminophen/paracetamol use for OA and other non-OA-related reasons. Retraining should occur as needed throughout the conduct of the study.

8.2.1.9. Patient Education Brochures

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.

8.2.2. Efficacy Procedures

All the measures in this section are patient-reported outcome measures and should be completed before any clinical assessments.

8.2.2.1. Western Ontario and McMaster Universities Osteoarthritis Index

The WOMAC index is used to assess patients with OA of the hip or knee using 24 parameters, and reported using a numerical rating scale. This index can be used to monitor the course of a disease or to determine effectiveness of study drugs. Patients will complete the WOMAC Full Survey at the time points indicated in Table 1 and Table 2. If possible, the assessment should be administered and entered by the same person throughout the study.

A copy of WOMAC assessments will be provided in the study reference manual.

8.2.2.2. Patient Global Assessment of Osteoarthritis

The Patient Global Assessment of OA is a patient-rated assessment of their current disease state on a 5-point Likert scale (1 = very good; 2 = good; 3 = fair; 4 = poor; and 5 = very poor). Patients will complete the assessment scale at the time points indicated in Table 1.

A copy of the assessment is provided in the study reference manual.

8.2.2.3. Walking Index Joint Pain Numeric Rating Score

Walking index joint pain intensity (scored using the NRS) will be reported by the patient each day in his or her diary, starting during the pre-randomization period through week 52. Once initial eligibility criteria are confirmed during the screening period, the investigator or designee will review the NRS with the patient at the baseline visit.

A copy of the assessment is provided in the study reference manual.

8.2.2.4. EuroQoL 5 Dimensions 5 Level Questionnaire

The EQ-5D-5L is a standardized measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L, as a measure of health-related quality of life, defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Each dimension has 5 ordinal levels of severity: “no problems” (1), “slight problems” (2), “moderate problems” (3), “severe problems” (4), and “unable to” (5). Overall health state is defined as a 5-digit number. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, which ranges from <0 for states worse than dead to 1 (full health), anchoring dead at 0. Patients will complete the questionnaire at time points indicated in Table 1 and Table 2.

A copy of the assessment is provided in the study reference manual.

8.2.2.5. 36-Item Short Form Medical Outcomes Study Questionnaire Version 2

The SF-36 version 2 standard is a health status measure with a 4-week recall period. The SF-36 measures eight concepts: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health. Two summary measures of physical and mental health are constructed from the eight scales. Patients will complete the questionnaire at time points indicated in Table 1. Higher scores on the scales and summary measures indicate better health status.

A copy of the assessment is provided in the study reference manual

8.2.2.6. Healthcare Resource Utilization Questionnaire

The Healthcare Resource Utilization questionnaire is a tool designed to capture, over a preceding three-month period, healthcare utilization events that are not collected as part of the safety assessments in the current study. Examples of these types of events include a patient's use of walking aid, emergency room visits, and physician office visits. Sites will complete the questionnaire at time points indicated in Table 1. The overall healthcare resource use will be

computed based on responses to the healthcare resource utilization questionnaire as well as any hospital visits that are captured in the safety database.

A copy of the assessment is provided in the study reference manual.

8.2.2.7. Work Productivity and Activity Impairment

The work productivity and activity impairment-osteoarthritis questionnaire is a validated measure of impairments in work and daily activities (Reilly 1993) (Zhang 2010). Patients will complete the questionnaire at time points indicated in Table 1 and Table 2.

A copy of the assessment is provided in the study reference manual.

8.2.2.8. Treatment Satisfaction Questionnaire for Medication

The Treatment Satisfaction Questionnaire for Medication (TSQM) is a standardized instrument to assess patients' satisfaction with medication. The questionnaire provides scores on 4 domains - side effects, effectiveness, convenience, and global satisfaction. Patients will complete the TSQM at time points indicated in Table 1.

A copy of the assessment is provided in the study reference manual.

8.2.3. Safety Procedures

8.2.3.1. Vital Signs

Vital signs, including body temperature and respiratory rate, will be collected predose at time points according to Table 1 and Table 2. Blood pressure and heart rate will be collected as part of the orthostatic hypotension assessments. If at any visit after the randomization visit the pulse is less than 45 bpm, an ECG with rhythm strip will be obtained to confirm the heart rate and rhythm.

8.2.3.2. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 1 and Table 2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history. Measurements of patient height and weight should be recorded at the time points indicated in Table 1 and Table 2.

8.2.3.3. Electrocardiogram

A standard 12-lead ECG will be performed at the time points indicated in Table 1 and Table 2, with the patient in the supine position for approximately 5 minutes and prior to blood samples being drawn. Heart rate will be recorded from the ventricular rate, and the PR, QRS, and the QT and QTc intervals will be recorded. The ECG data will be read by a central reading center. Detailed procedures will be provided in a separate manual provided by the central reading center.

8.2.3.4. Assessment of Orthostatic Blood Pressure and Heart Rate

An assessment of orthostatic blood pressure will be conducted at the time points indicated in Table 1 and Table 2. The assessments should be conducted as per the instructions in the study manual. 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

If the initial assessment for orthostatic hypotension is consistent with the above definition, the supine and standing blood pressures and/or pulse should be repeated as outlined above, up to 2 more times.

8.2.3.5. Joint Pain Questionnaire

A joint pain questionnaire will be completed by the patient at the time points indicated in Table 1 and Table 2. For each knee, hip, and shoulder joint, the patient will be prompted to indicate if he or she has experienced pain. A patient report of having experienced pain will serve as a tool to prompt further evaluations as deemed necessary by the investigator.

Joint Pain Questionnaire is a patient-reported outcome measure and should be completed along with other patient-reported outcome measures but before any clinical assessments.

A copy of the assessment is provided in the study reference manual.

8.2.3.6. Survey of Autonomic Symptoms

Signs and symptoms of autonomic dysfunction will be assessed by the investigator at time points indicated in Table 1 and Table 2. If possible, the assessment should be completed by the same person throughout the study. A patient report of having experienced symptoms of autonomic dysfunction will serve as a tool to prompt further evaluations as deemed necessary by the investigator.

Survey of Autonomic Symptoms is a patient-reported outcome measure and should be completed along with other patient-reported outcome measures but before any clinical assessments.

A copy of the survey is provided in the study reference manual.

8.2.3.7. Neurologic Examination

A full or a brief neurological examination will be performed at the time points indicated in Table 1 and Table 2. Neurological findings at baseline that are not exclusionary should be recorded in the medical history. Findings at subsequent visits will be assessed by the investigator to determine if these should be recorded as an AE.

The neurological examination will cover the following domains: motor, sensory, cranial nerves, reflexes, and coordination/balance and assessment for presence/absence of signs of carpal tunnel syndrome and may be conducted by any clinician at the site qualified to do so. Whenever possible, the same clinician who conducts the baseline neurological examination should continue to conduct the examinations on a given patient. The investigator may refer patients with persistent or worsening neurologic symptoms for a neurologic consultation, if clinically indicated. Additional neurologic assessments will include nerve conduction studies and other tests as deemed clinically necessary in the judgement of the neurologist.

Complete guidance on how to conduct the full and the brief neurologic examination is provided in the study reference manual.

8.2.3.8. Imaging

Radiographs of the large joints (knees, hips, and shoulders) will be taken using a standard approach at the time points indicated in Table 1 and Table 2. An MRI of the index and contralateral joints must be performed at screening. MRIs will also be performed on any hip or knee joint with a K-L score of ≥3. Radiographs and an MRI must be performed on any joint following a report of clinically significant worsening or exacerbation of pain in that joint. An X-ray and an MRI should also be performed pre-operatively if a patient is to have a JR during the study. Event based and pre-operative images will be submitted for adjudication. Detailed procedures will be provided in a separate manual provided by the central imaging center. Radiograph or MRI will be sent to a central reader, where the images will be digitized.

Radiographs

Weight-bearing (standing) posterior-anterior radiographs of both knees in the semi-flexed position, and anterior-posterior radiographs of both hips and both shoulders, will be conducted at these visits. Additional instructions for positioning of joints are provided in the study reference manual.

Radiographs of the knees, hips, and shoulders will be sent to a central reader and evaluated to confirm no evidence of AA such as rapidly progressive osteoarthritis type 1 or 2, subchondral insufficiency fracture, or osteonecrosis.

MRI

During screening, MRIs of the index and contralateral joints as well as joints with a K-L score ≥3 will be sent to a central reader to confirm that there is no evidence of an exclusionary features. Confirmation that there are no exclusionary findings on MRI must be received before a patient can be randomized. An MRI of any joint will be considered if radiographs taken after randomization suggest the presence of an abnormal process inconsistent with normal progression of OA, as determined by the investigator or central reader.

At the end of study phone contact, patients who had an AA will have an MRI performed of the affected joint(s). If the affect joint has undergone JR an X-ray may be substituted for an MRI.

Refer to the supplemental imaging manuals for data collection and management procedures.

8.2.3.9. End of Study Phone Contact

An end of study phone contact will be conducted at 52 weeks following the last dose of SC study drug. Patients will be asked whether they underwent JR surgery following the last in-clinic visit of the follow-up period or whether they are scheduled (or on a waiting list) for JR surgery. Patients who had JR surgery will also be asked to submit pre-operative imaging (X-ray and MRI, if available) for adjudication. Patients who had an AA will have an MRI performed of the affected joint(s). If the affected joint has undergone JR an X-ray may be substituted for an MRI.

8.2.3.10. Procedures to be Performed Only in the Event of a Joint Replacement Surgery

In the event that a patient must undergo JR surgery during the treatment or follow-up periods, the patient will be discontinued from study drug and asked to return for a pre-operative visit. The pre-operative visit should be completed before JR surgery if possible and pre-operative images will be submitted to the adjudication committee for review. Following the JR surgery, the patient will complete follow-up safety evaluations at 4 weeks, and 20 weeks after surgery (Table 3).

In the event that the pre-operative visit is not performed, standard-of-care pre-operative images of the joint with JR must be obtained and submitted to the central imaging vendor's adjudication committee for review. Imaging of all other joints per the pre-operative visit procedures will be done post-operatively at the first JR follow-up study visit (4 weeks after surgery) if not done before surgery.

All available medical history/information for patients who undergo JR surgery must be collected, including the results of histopathologic examination.

Full details of these assessments are provided in the study reference manual.

Knee Society Score

The Knee Society Score is an investigator-completed questionnaire that is used to objectively measure a patient's ability to function before and after total knee arthroplasty (Insall 1989). If possible, the assessment should be completed by the same person throughout the study.

Harris Hip Score

The Harris Hip Score is an investigator-completed questionnaire that is used to objectively measure a patient's ability to function before and after total hip arthroplasty (Harris 1969). If possible, the assessment should be completed by the same person throughout the study.

8.2.3.11. Laboratory Testing

The central laboratory will analyze all screening and on-study laboratory samples for blood chemistry, hematology, HbA1c, urine analysis, urine drug tests, and serum pregnancy tests. Urine pregnancy and ESR testing will be done at the site using kits provided by the central laboratory.

Regeneron or its designee will be responsible for fasinumab PK, anti-fasinumab antibody, biomarker development, and pharmacogenetic sample assessments; the central laboratory will ship the samples to Regeneron or a specialty laboratory depending on the assessment.

All samples will be collected before SC study drug administration. Missed tests should be reported in the source documents and in the eCRF, as appropriate. Central laboratory kits will be provided for sample collection and shipment. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at time points according to Table 1 and Table 2.

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Phosphorus
Chloride	Blood urea nitrogen (BUN)	Uric acid
Carbon dioxide	Aspartate aminotransferase (AST)	Creatine phosphokinase (CPK)
Calcium	Alanine aminotransferase (ALT)	
Glucose	Alkaline phosphatase (ALP)	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Urine Electrolytes

Creatinine
Phosphorus

Other Laboratory Tests

Serum and urine samples for pregnancy testing will be collected from women of childbearing potential (as defined in Section 8.2.1.6) at time points according to Table 1 and Table 2. At each study visit during the treatment period, urine pregnancy testing will be done before the study drug is administered. 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 Table 1 and Table 2).

To assess postmenopausal status for women ≤59 years of age, serum samples to test for FSH levels and estradiol levels will be collected for analysis at the central laboratory according to Section 8.2.1.6.

Samples will be collected for HbA1c and ESR testing at time points according to Table 1.

Urine drug testing will be performed at screening and includes amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.

Blood samples for fasinumab PK and ADA assessment (Section 8.2.4) will also be collected.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or an authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study drug or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.4.5. Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

8.2.3.12. Injection Site Evaluations

An injection site evaluation should be conducted following the injection at each doing visit, according to Table 1 and Table 2.

8.2.4. Pharmacokinetic and Anti-Drug Antibody Procedures

8.2.4.1. Drug Concentration Measurements and Samples

Samples for fasinumab concentration will be collected at time points listed in Table 1 and Table 2.

Any unused samples may be used for exploratory biomarker research.

8.2.4.2. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 1 and Table 2.

Any unused samples may be used for exploratory biomarker research.

8.2.5. Research Samples

8.2.5.1. Biomarkers

Serum and plasma samples will be collected at time points according to Table 1 and Table 2. These samples may be used to measure biomarkers related to inflammation, collagen, and bone turnover, OA pain and NGF, and may include CTX-I, osteocalcin, hs-CRP, and matrix metalloprotein -generated collagen fragments (CIM, C3M). Samples may be used to study other

markers of collagen and bone turnover, OA and pain. If necessary, samples may also be used to identify markers associated with AEs.

8.2.5.2. Future Biomedical Research

Unused research samples, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research of OA and other diseases. No additional samples will be collected for future biomedical research. After 15 years, any remaining samples will be destroyed.

8.2.5.3. Genomics Sub-study - Optional

Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF before collection of the samples. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study. Samples for DNA extraction should be collected on day 1/baseline (predose), but may be collected at any study visit.

DNA samples for the genomics sub-study will be de-identified as defined by the International Council for Harmonisation (ICH) guideline E15. Sub-study samples will be stored for up to 15 years after the final date of the database lock and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with collagen and bone turnover, OA, pain, and response to fasinumab. In addition, associations between genomic variants and prognosis or progression of OA as well as other diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug or other diseases. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, and DNA copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period.

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the IRB/EC all unanticipated problems involving risks to patient. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, regardless of assessed causality.

9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, IRBs/ECs as appropriate, and to the investigators.

Any AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected. Any worsening of or new onset of symptoms related to OA, which occurs

during the screening/washout period prior to study drug administration will be considered expected.

In addition, the sponsor will report in an expedited manner all SAEs that are expected and at least reasonably related to the study drug to the health authorities, according to local regulations.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and IRBs/ECs as appropriate.

9.3. Definitions

9.3.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug, which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease, which is temporally associated with the use of a study drug, whether or not it is considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

9.3.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above. Examples of these include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

9.3.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 9.4.3).

Adverse events of special interest are described in Section 9.4.3.

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the patient completes the follow-up period, ie, week 72/early termination for those patients not proceeding into Year 2, or week 124E/early termination for those patients proceeding into Year 2. Refer to the study reference manual for the procedures to be followed.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manual for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE after the patient completes the follow-up period, ie, week 72/early termination for those patients not proceeding into Year 2, or week 124E/early termination for those patients proceeding into Year 2, the following will apply:

- SAE with an onset within 30 days of the end of the follow-up period - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of follow-up period - only SAEs deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.
- SAE reported by the patient at the end of the study phone call and deemed by the investigator to be drug related will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study subject during the study or within 20 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study subject and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest: All AESI, serious and non-serious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting per Section 9.4. Monitoring of AESIs is described in Section 9.6.1. Events considered AESIs are:

- Adjudicated arthropathy (as confirmed by adjudication)
- Joint replacement surgery (refer to Section 9.6.1.4 for when to report as an AESI)
- Sympathetic nervous system dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist)
- Peripheral sensory AEs that require a neurology or other specialty consultation

Refer to the study manual for the procedures to be followed.

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the study reference manual for the procedures to be followed.

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

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

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

9.4.6. Follow-up

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

The severity of AEs will be graded according to the following scale:

- **Mild:** Does not interfere in a significant manner with the patient normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade:

- **Mild**: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity.
- **Moderate**: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity.
- **Severe**: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis.

9.5.2. Evaluation of Causality

9.5.2.1. Relationship of Adverse Events to Study Drug

The relationship of AEs to study drug will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug.

Related: There is a reasonable possibility that the event may have been caused by the study drug.

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by the study drug?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- do not reappear or worsen when dosing with study drug is resumed

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug
- resolve or improve after discontinuation of study drug
- reappear or worsen when dosing with study drug
- are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

9.5.2.2. Relationship of Adverse Events to Study Conduct

The relationship of AEs to study conduct will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by study conduct?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by study conduct.

Related: There is a reasonable possibility that the event may have been caused by study conduct.

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by the study conduct?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the course of the study.
- do not reappear or worsen when dosing with study participation is resumed

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the course of the study.
- resolve or improve after discontinuation from study participation.
- reappear or worsen when study participation is resumed

9.6. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

9.6.1. Monitoring Adverse Events of Special Interest

9.6.1.1. Adjudicated Arthropathy

Adjudicated arthropathy is an umbrella term that encompasses the following conditions:

- Rapidly progressive OA type 1 and 2
- Subchondral insufficiency fractures
- Primary osteonecrosis

In addition, AAs will be evaluated to determine if they meet the criteria for destructive arthropathy.

Potential events of AA will be monitored via clinical signs and symptoms of worsening joint pain during the course of the study (eg, by applying adverse experiences, the joint pain questionnaire and imaging) as well as scheduled imaging and pre-operative imaging, if a patient requires a joint replacement during the study.

Clinically significant worsening of joint pain during the course of this study is characterized as a worsening of pain in any joint that occurs in spite of treatment with analgesics, is in the opinion of the investigator inconsistent with the normal progression of OA, and is at least 2 weeks duration (or less than 2 weeks if deemed clinically significant at the discretion of the investigator).

If a patient reports an increase in pain as described above, study drug administration will be withheld while imaging of the affected joint, as well as any additional imaging deemed appropriate to understand the cause of the worsening pain, is performed (Section 8.2.3.8). A decision to perform imaging after patient reporting of worsening joint pain will be documented in the respective case report form (CRF) page. Images, along with any other radiographic evaluation, will be submitted to the adjudication committee for review (Section 5.3.2). The investigator may consider aspiration of synovial fluid for further analysis such as cell count and crystal analysis.

If routine imaging suggests the presence of one of the types of AA, study drug administration will be withheld. Any additional imaging deemed appropriate will be obtained. The images, along with results of any other radiographic evaluation, will be submitted to the Adjudication Committee for review (Section 5.3.2).

If the adjudication does not confirm the presence of AA, according to the adjudication criteria, study drug may be restarted.

Study drug dosing will be terminated for patients with findings that suggest AA, and the patients will be referred for orthopedic consultation. If presence of AA is confirmed by the adjudication committee, the case must be reported as an AESI (Section 9.3.3 and Section 9.4.3).

Any patient whose study drug is discontinued due to an AA should be encouraged to return to the clinic for all remaining study visits. Prior to the scheduled JR, the patient should complete the pre-operative study visit (Section 8.2.3.10) and, after the JR, should complete the week 4 and week 20 post-operative study visits (Table 3). Pre-operative images, along with any other radiographic evaluation will be submitted to the Adjudication Committee for review (Section 5.3.2).

Details of data collection for adjudication of events will be provided in the adjudication charter.

9.6.1.2. Sympathetic Nervous System Dysfunction

Sympathetic nervous system dysfunction will be monitored throughout the study through physical examination, AE reporting, assessment of orthostatic hypotension, and the Survey of Autonomic Symptoms (Section 8.2.3.6). New onset or worsening of signs and symptoms of autonomic dysfunction will be evaluated by the investigator. Sympathetic nervous system dysfunction will only be diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist.

In cases where new or worsening symptoms consistent with sympathetic nervous system dysfunction are moderate to severe or are clinically significant and do not resolve or return to baseline in 2 weeks (or less at the discretion of the investigator), study drug will be withheld and the patient will be referred to a specialist. If the evaluation by the appropriate specialist does not suggest sympathetic nervous system dysfunction, study drug may be restarted. If the specialist's evaluation does reveal sympathetic nervous system dysfunction then study drug will be permanently discontinued and the case reported as an AESI (Section 9.4.3).

Orthostatic hypotension may be a manifestation of sympathetic nervous system dysfunction. If a patient is determined to have orthostatic hypotension, study drug should be withheld and the AE should be entered in the electronic CRF (eCRF.). The following procedures should be followed:

- If the patient is symptomatic and a clinical explanation for orthostatic hypotension is identified (such as a new medication or dehydration due to exercise or illness or excessive heat exposure), study drug will be withheld, and the patient should return to the study site for an unscheduled visit in 1 to 10 days for an unscheduled assessment of orthostatic hypotension.
  - If the orthostatic hypotension has resolved, study drug may be restarted.
  - If the orthostatic hypotension has not resolved, then study drug will be withheld, and the patient will be referred to a specialist (neurologist or a cardiologist) for evaluation of sympathetic nervous system dysfunction.
  - If the specialist's evaluation does not reveal new onset sympathetic nervous system dysfunction, including symptoms of bradycardia (lightheadedness), orthostatic hypotension (lightheadedness on standing), syncope, absence of sweating in conditions where sweating would be expected, or if the specialist's evaluation identifies an alternative cause, such as initiation of a new medication known to cause orthostasis, then study drug may be given at the next visit.
  - If the specialist's evaluation does reveal sympathetic nervous system dysfunction, then study drug will be permanently discontinued and the case reported as an AESI (Section 9.4.3).
- If the patient has asymptomatic orthostatic hypotension, study drug will be withheld, and the patient should return to the study site for an unscheduled visit in 1 to 10 days for an unscheduled assessment of orthostatic hypotension.
  - If the unscheduled assessment does not reveal orthostatic hypotension then study drug may be continued.

- If the unscheduled assessment demonstrates orthostatic hypotension then study drug will continue to be withheld until the patient has been evaluated by a specialist (neurologist or a cardiologist) for evidence of sympathetic nervous system dysfunction.
- If the specialist's evaluation does not reveal new sympathetic nervous system dysfunction including symptoms of bradycardia (lightheadedness), orthostatic hypotension (lightheadedness on standing), syncope, absence of sweating in conditions where sweating would be expected, or if the specialist's evaluation identifies an alternative cause such as initiation of a new medication known to cause orthostasis, then study drug may be restarted.
- If the specialist's evaluation does reveal sympathetic nervous system dysfunction then study drug will be permanently discontinued and the case reported as an AESI (Section 9.4.3).

9.6.1.3. Peripheral Sensory Adverse Events

Altered peripheral sensation (eg, paraesthesia and hypoaesthesia) is an important identified risk with fasinumab (see Investigator's Brochure) and other anti-NGF compounds. Any peripheral sensory AE that, per the investigator's judgment, requires a neurology or other specialty consultation must be reported as an AESI. If any peripheral sensory event persists for 2 months the patient must be referred for a neurology or other specialty consultation and the event must be reported as an AESI (Section 9.4.3).

9.6.1.4. Joint Replacement Surgery

An end of study phone contact will be conducted at 52 weeks following the last dose of study drug to evaluate the number of patients who have undergone or are scheduled for JR surgery as described in Section 8.2.3.9. Any elective JR surgery planned before completion of the ICF would be part of the exclusion criteria and would not be considered an AE.

After signing of the ICF, report JR surgery as an AESI if the JR surgery is an elective event that is not associated with a new/worsening AE.

Do not report JR surgery as an AE/AESI if the JR surgery is for the treatment of a new or worsening AE. In this case, the new or worsening AE should be the reported AE/AESI term.

9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure or this protocol, and has a reasonable suspected causal relationship to the medicinal/study drug).

10. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make

changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 1.

10.1. Statistical Hypothesis

There are 29 hypotheses for the primary and key secondary endpoints. The primary treatment comparison for the WOMAC pain and physical function subscale scores is declared superior only if the comparisons are significant for both WOMAC pain and physical function subscale scores. The graphical testing procedure (Bretz 2009) will be applied to control for multiplicity and to maintain study-wise Type I error rate at two-sided 0.05 level for the two sets of hypotheses ($H_{1,i}$, i=1,…,16 for fasinumab 1 mg Q4W, and $H_{2,i}$, i=1,…,13 for fasinumab 1 mg Q8W) for the primary and key secondary endpoints. If a hypothesis is rejected, the alpha level for that hypothesis will be reallocated to other hypothesis according to a pre-specified procedure. The testing will stop when no hypothesis can be rejected at any step. Details will be provided a priori in the SAP.

- $H_{1,1}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC pain or physical function subscale scores at week 16 versus there is treatment difference in WOMAC pain and physical function subscale scores at week 16
- $H_{1,2}$: 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 the WOMAC pain subscale scores at week 16 versus there is treatment difference in WOMAC pain subscale scores at week 16
- $H_{1,5}$: There is no treatment difference between fasinumab 1 mg Q4W and naproxen in the WOMAC physical function subscale scores at week 16 versus there is treatment difference in 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
- $H_{2,1}$: There is no treatment difference between fasinumab 1 mg Q8W and placebo in WOMAC pain or physical function subscale scores at week 16 versus there is treatment difference in WOMAC pain and physical function subscale scores 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 the WOMAC pain subscale scores at week 16 versus there is treatment difference in WOMAC pain subscale scores at week 16
- $H_{2,5}$: There is no treatment difference between fasinumab 1 mg Q8W and naproxen in the WOMAC physical function subscale scores at week 16 versus there is treatment difference in 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

10.2. Justification of FAS and mFAS Sample Sizes

In this study, approximately 2560 patients were 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). 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 PGA score and provide long term data for safety assessment.

The sample size for the full analysis set (FAS) population 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 (ie, 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 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 an 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 in the FAS population were to be compared to approximately 200 patients in the placebo group who were enrolled after 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 was 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 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 (ie, an absolute treatment difference of 0.51 with an SD of 2.3) at week 16, and 92% power at week 52 for FAS. This sample size would have provided 98% power to detect an effect size of 0.24 in WOMAC physical function subscale (ie, absolute treatment difference of 0.50 with an 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.

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 population for the primary and secondary efficacy analyses was changed in Protocol Amendment 8 to be based on a modified full analysis set (mFAS) that excludes the randomization stratum for that region. Based on the assumptions above, it is estimated that this mFAS will provide:

- 99.9% power to detect a significant difference between the 1 mg Q4W group and the placebo group in the WOMAC pain and physical function subscales at an alpha level of 0.05

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

10.3. Analysis Sets

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:

10.3.1. Full Analysis Set

The FAS includes all randomized patients excluding patients affected by the urgent safety measure in May 2018 (ie, 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 (ie, after Protocol R475-OA-1611 Amendment 5 Global was implemented) will be included.

10.3.2. Modified Full Analysis Set

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 an 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.

10.3.3. 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. A list of protocol violations which lead to exclusion from the PPS and corresponding protocol deviation identification number (PDID) will be included in the SAP. For the analysis of fasinumab 1 mg Q8W group comparing to the control groups, only patients concurrently randomized (ie, after Protocol R475-OA-1611 Amendment 5 Global was implemented) will be included.

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

10.3.4. Safety Analysis Set

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 and all clinical safety variables for Year 2 will be analyzed using this SAF – Year 2.

10.3.5. Urgent Safety Measure Set

The urgent safety measure set (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.

10.3.6. Pharmacokinetic Analysis Set

The PK analysis set includes all treated patients who 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).

10.3.7. Anti-Drug Antibody Analysis Set

The ADA analysis set includes all treated 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).

10.3.8. The Neutralizing Antibody Set

The NAb analysis set includes all patients who received any study drug and who are negative in the fasinumab ADA assay or with at least 1 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).

10.4. Statistical Methods

10.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF

- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

Baseline demographic, disease characteristics including medical history, and exposure to study drug will be summarized descriptively by treatment group using descriptive statistics. Continuous variables will be summarized with mean, median, SD, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Details of the statistical methods will be provided in the SAP.

10.4.3. Efficacy Analyses

10.4.3.1. Primary Efficacy Analysis

The primary efficacy variables will be analyzed using multiple imputation approach with a mixed-effect model for repeated measure (MMRM) based on the mFAS with adjustment for missing data due to lack of efficacy, death or AEs assuming the WOMAC scores would on average return to baseline values. A monotone missing data structure will be achieved using the MCMC option of PROC MI. Data collected after discontinuing treatment up to week 16 will not be used in the primary efficacy analysis, but used in a treatment policy sensitivity analysis. Multiple imputation for the remaining data will be based on the monotone missing data structure of the change from baseline scores using the regression imputation option in PROC MI. The missing data for patients who discontinued treatment due to other reasons will be imputed under missing-at-random assumption. The imputed data for patients discontinued from the study treatment due to lack of efficacy, death or AEs will be centered at the mean baseline value.

Missing data will be imputed 50 times to generate 50 complete data sets. Each imputed data set will be analyzed using the MMRM with terms for baseline 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 [North America, Europe]), treatment, visit, and treatment-by-visit interaction. The MMRM will be performed using the MIXED procedure in Statistical Analysis System (SAS) with an unstructured covariance matrix to model the within-patient errors. Denominator degrees of freedom will be estimated using Kenward-Roger's approximation. The results from the 50 analyses will be combined using Rubin's formulae (PROC MIANALYZE). The least-squares mean estimates for the mean change from baseline to week 16, as well as the differences of the estimates between fasinumab and placebo, and between fasinumab and naproxen, with their corresponding standard errors, p values and associated 95% confidence intervals, will be provided.

Sensitivity analysis of the treatment policy estimand for the co-primary endpoints will be performed using similar analysis method as the primary efficacy analysis including data collected after discontinuing treatment up to week 16. 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). After each imputation, a fasinumab patient's imputed data will subtract δ from the imputed score at each corresponding time point. By progressively increasing δ, the sensitivity analysis will explore the tipping point, ie, the δ value when the p-value for a treatment comparison is above 0.05. Additional analyses will be performed for the primary and secondary endpoints using the FAS. Additional sensitivity analysis will be performed for the primary and select secondary endpoints using the PPS.

10.4.3.2. Secondary Efficacy Analysis

For analysis of continuous secondary endpoints at fixed timepoints (ie, week 16 and week 44), the analysis method will be the same as that used for the primary variables. For the analysis of secondary endpoints involving the averaging over several visits (see endpoints 12 to 15 in Section 4.2.2), analysis will be performed using a multiple imputation approach with an ANCOVA model based on the mFAS with adjustment for missing data performed in the same manner as was done for the primary endpoint. For analysis of categorical variables in secondary endpoints, eg, proportions of patients with ≥30% improvement in the WOMAC pain subscale scores at week 16, the Cochran Mantel Haenszel approach will be used based on the mFAS, stratifiying by the randomization strata (K-L category [2 to 3, or 4], index joint [knee, hip], and geographical region [North America, Europe]). Missing data will be considered as non-response.

For Year 2 analysis, the efficacy and PRO endpoints collected will be summarized descriptively.

10.4.4. Safety Analysis

The summary of safety results will be presented for Year 1, Year 2, and the combined Year 1 and Year 2 treatment periods.

Safety data including TEAEs and treatment emergent AESIs, vital signs, physical exams, laboratory tests, ECGs, and ADA formation will be listed and summarized by treatment group.

Thresholds for potentially clinically significant values (PCSVs) in laboratory parameters and vital signs will be defined by the sponsor and be in effect at the time of final SAP approval.

The time interval to detect any AEs, including AESIs (except JRs identified at the End of Study Phone Calls) is between the first dose of Year 1 study drug injection and the end of 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), as well as study drug-related SAEs occurring between the end of Follow-up Period and the End of Study.

For safety variables, the following observation periods are defined:

- The Pretreatment 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 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 study drug dose + 4 weeks for those patients proceeding into Year 2. Summaries for the Year 2 Post-Treatment Period will be based on the SAF – Year 2.
- The Combined 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 Combined On-Treatment Period will be based on the SAF – Year 1.
- 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.

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

- 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.

10.4.4.1. Adverse Events

Definitions

The Year 1 and Year 2 TEAEs are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the respective on-treatment periods.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed. The focus of adverse event reporting in the clinical study report will be on TEAEs. Post-treatment AEs and all AEs during the study will be summarized similarly as TEAEs.

For the Year 1, Year 2, and Combined On-Treatment Periods, summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

- Treatment-emergent AESIs (defined with a PT or a pre-specified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group similarly to TEAEs.

In addition, AESIs will be reported according to the adjudicated diagnosis. Imaging data related to AA including change from baseline in joint space width will be summarized.

10.4.4.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics for the Year 1, Year 2, the Combined On-Treatment Periods and the Post-treatment periods.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics for the Year 1, Year 2, the Combined On-Treatment Periods and the Post-treatment periods.

Potentially clinically significant value at any post-randomization time point will be summarized for each clinical laboratory test.

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

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

10.4.4.3. Treatment Exposure

Because of the half-life of the biologic being studied, the duration of SC study drug exposure for the Year 1 and Year 2 On-Treatment Periods will be presented by treatment group and calculated as:

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

The number and percentage of patients exposed to SC study drug will be presented by specific time intervals for each treatment group for the Year 1 and Year 2 On-Treatment Periods respectively. The time intervals of interest will be specified in the SAP.

10.4.4.4. Treatment Compliance

Overall treatment compliance to SC study drug injection is defined as the actual number of SC injections compared to the expected number of SC injections during the on-treatment period up to treatment discontinuation, for the Year 1 and Year 2 On-Treatment Periods respectively. It is calculated according to the following formula:

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

The total number of actual doses of fasinumab will be summarized for the Year 1 and Year 2 On-Treatment Periods respectively.

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 for Year 1. It is calculated according to the following formula:

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

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

10.4.5. Analysis of Drug Concentration Data

Summaries of serum concentrations of functional fasinumab will be presented by nominal time point and dose. Plots of individual concentration over time will be presented by actual day (linear and log scales). Plots of mean or median concentrations of functional fasinumab will be presented by nominal day (linear and log scales).

No formal statistical analysis will be performed.

10.4.6. Analysis of Immunogenicity

Immunogenicity will be characterized by the ADA response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 9-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative
- Treatment-boosted ADA response, defined as any post-dose positive ADA assay response that is 9-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA Titer values
  - Low (titer <1,000)
  - Moderate (1,000≤titer ≤10,000)
  - High (titer >10,000)
- NAb status - samples testing positive in the ADA assay will also be tested in the NAb assay and reported as positive or negative.

Listings of ADA positivity, ADA titers, and NAb positivity presented by patient, time point, and dose group will be provided. Incidence of treatment-emergent ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level for each of the main 52-week treatment and long-term safety extension studies respectively.

The influence of ADAs on drug concentrations will be evaluated. Assessment of impact of ADAs on safety and efficacy may be provided.

10.5. Interim Analysis

The first-step analysis will consist of the primary and secondary efficacy analyses and will be conducted as soon as all patients have been randomized and all data for Year 1 (baseline through week 52) have been collected and validated. This will consist of the analyses of the primary and secondary efficacy endpoints at week 16 and/or week 44. Safety analysis will also be performed on the safety data for Year 1 and select safety data for Year 2.

No alpha adjustment is necessary, as the efficacy analyses for Year 1 will be the final primary and secondary efficacy analysis for efficacy and the efficacy analyses for Year 2 will only be descriptive and exploratory. The results of the analysis for Year 1 will not be used to change the conduct of the ongoing Year 2 period in any aspect.

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 interim analysis.

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

As the primary and secondary efficacy analyses will have been completed in the first-step analysis, no adjustments due to multiplicity will be necessary for any subsequent analysis of the data.

Individuals unblinded to patient-level data for the first-step or any of the 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.

10.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

General rules for handling missing data:

- Rules for handling missing data for efficacy assessments due to missing individual item data will follow each questionnaire's instrument manual.
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study drug, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study drug date, then the start date by the study drug intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the CRF assessment recorded by the investigator.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with non-protocol-specified clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

10.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history, surgical history) will be done using internationally recognized and accepted dictionaries.

The eCRF data for this study will be collected with an electronic data capture (EDC) tool, Rave Medidata.

11.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS / IWRS system – randomization and study drug supply
- Rave Medidata EDC system – clinical data capture
- SAS
- A pharmacovigilance and clinical safety software system – collection and reporting of SAEs and AESIs
- Electronic Clinical Outcome Assessment systems – collect patient-reported outcome or patient clinical assessment results

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, CRO monitor) will visit each site prior to enrollment of the first patient, and periodically during the study.

The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version as well as any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on eCRF within the EDC system by trained site personnel. All required CRFs must be completed for each patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

13. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit

- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB or EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

14.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB or EC. A copy of the IRB- or EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new

information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

14.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by their patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

14.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB or EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB or EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB or EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB- or EC-approval letter with a current list of the IRB or EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB or EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

14.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB- or EC-approved amendment Where required per local legislation, regulatory authority approval will also be sought.

16. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

16.1. Premature Termination of the Study

The sponsor has the right to terminate the study or dosing in the study, prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

16.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB or EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed by the investigator. This signed declaration accompanies each set of patient final eCRF that will be provided to the sponsor.

17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant

regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

18. DATA QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are summarized.

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 11.1).

Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 12.1, Section 12.2, Section 13).

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 12.1).

All patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient final CRF (Section 12.3, Section 17.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 12.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 17.2).

19. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

20. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

21. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

22. REFERENCES

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23. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, entitled "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," dated as noted in the appended signature page, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board or Ethics Committee. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Scientific/Medical Monitor, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the conduct of the study.

Study 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

Protocol Number: R475-OA-1611

Protocol Version: R475-OA-1611 Amendment 9 Global

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00122598 v1.0

ESig Approval	[redacted]-2020 17:34:47 GMT+0000
ESig Approval	[redacted]-2020 17:41:18 GMT+0000
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Signature Page for VV-RIM-00122598 v1.0 Approved