IND: Number: 103245
EudraCT: 2015-003783-36

Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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

Compound	Fasinumab
Study Name	FACT LTS & OA
Clinical Phase:	3
Protocol Number:	R475-PN-1523
Protocol Version:	R475-PN-1523 Amendment 9
Amendment 9 Date of Issue	*See appended electronic signature page*
Amendment 8 Date of Issue	11 Jul 2018
Amendment 7 Date of Issue	24 May 2018
Amendment 6 Date of Issue:	02 Oct 2017
Amendment 5 Global Date of Issue:	16 Mar 2017
Amendment 4 EU Date of Issue	12 Jan 2017
Amendment 4 Date of Issue:	25 Aug 2016
Amendment 3 Date of Issue	20 June 2016
Amendment 2 Date of Issue:	25 January 2016
Amendment 1 Date of Issue:	11 December 2015
Original Date of Issue:	21 October 2015
Scientific/Medical Monitor:	Marcela Vergara, MD Director, Clinical Sciences Tolga Baykal, MD, PhD Senior Director, Clinical Sciences Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

AMENDMENT HISTORY

Amendment 9

The purpose of this non-substantial amendment is to update the text regarding the interim analysis so that the protocol and the statistical analysis plan are aligned. Additional minor edits have been made as outlined in the table below.

Change and Rationale	Sections Changed
The text describing the interim analysis has been edited so that the text in the protocol and the statistical analysis plan are aligned.	Section 3.2 Planned Interim Analysis Section 9.5.6 Interim Analysis
The additional (blinded) medical monitor has been listed on the title page.	Title page
The formatting error in the footnotes to Table 1 has been corrected (ie, a missing footnote number has been added and subsequent footnotes have been re-numbered).	Table 1 Schedule of Events – Screening through Week 16 Visit, Footnote 8 (missing number added), Footnote 9, Footnote 10, Footnote 11, Footnote 12, Footnote 13, Footnote 14 (renumbered).
Text has been added to align with current best practices (ie, updated protocol template text).	Section 13.5 Clinical Study Data Transparency
Additional minor edits have been made for clarity.	Clinical Study Protocol Synopsis: Treatment Section 1.3.2 Rationale for Dose Selection Section 5.1 Investigational and Reference Treatments Section 5.5 Method of Treatment Assignment

Amendment 8

The primary purpose of this amendment is to gain greater safety exposure to the fasinumab 1 mg dose in the main safety study. Patients will be enrolled into the main study and randomized to fasinumab 1 mg every 8 weeks (Q8W), 1 mg every 4 weeks (Q4W) or placebo. This will increase the size of the fasinumab safety database for potentially clinically relevant doses and, thus, will contribute to the overall fasinumab safety assessment. Minor edits and corrections have also been made. The following table outlines the changes made to the protocol and the affected sections:

Change and Rationale	Sections Changed
Text has been updated to state that patients will be enrolled into the main study and randomized in a 3:3:1 ratio to fasinumab 1 mg Q8W, 1 mg Q4W or placebo.	Clinical Study Protocol Synopsis: Treatments, Statistical Plan Section 1.3.2 Rationale for Dose Selection Section 3.1 Study Description and Duration Section 5.1 Investigational and Reference Treatments Section 5.5 Method of Treatment Assignment
The primary objective and primary endpoint have been updated to summarize all safety data rather than referring to a particular AE, SAE or AESI as a primary or secondary endpoint. The secondary objective and secondary endpoints have been removed. The exploratory endpoint 'Incidence of and time to cases meeting pre-specified criteria for needing joint replacement' has been removed.	Clinical Study Protocol Synopsis: Objectives, Endpoints Section 2.1 Primary Objective Section 8.2 Primary Endpoint Section 8.3 Exploratory Endpoints
Minor edits, additions or deletions have been made to the text for clarity, to make minor corrections and to ensure consistency across the fasinumab program.	Clinical Study Protocol Synopsis: Treatments, PK and ADA Variables List of Abbreviations and Definitions of Terms Section 1.1 Background Section 4.2.2 Additional inclusion criteria for Sub-Study Patients Only (mis-numbering has been corrected) Section 5.5 Method of Treatment Assignment Table 1 Schedule of Events – Screening through Week 16 Visit (abbreviations) Table 2 Schedule of Events – Week 20 Visit through Week 52 Visit (abbreviations) Table 3 Schedule of Additional Events – Only for Patients Participating in the Efficacy Sub-Study (Screening through Week 16 Visit) (abbreviations) Section 6.3.1.4 Western Ontario and McMaster Universities Osteoarthritis Index Section 6.3.3 Western Ontario and McMaster Universities Osteoarthritis Index Section 7.4.3 Other Events that Require Accelerated Reporting Section 7.6.1.1 Adjudicated Arthropathy Section 7.6.1.3 Peripheral Sensory Adverse Events Section 8.5 Pharmacokinetic Variables Section 8.6 Anti-Drug Antibody Variables Section 9.2 Determination of Sample Size Section 9.5.3 Safety Analysis Section 10.2 Electronic Systems

Amendment 7

The primary purpose of this amendment is 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 this ongoing study 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 6

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

Amendment 5 global

The primary purpose of this amendment is to improve detections of risks and benefits as follows:

- Remove from the global version of the protocol the eligibility for treatment from patients who were treated under earlier versions of the protocol with the 6 mg every 4 weeks (Q4W) or 9 mg Q4W dosing regimen. This change was incorporated previously into a local version of the protocol, R475-PN-1523.04EU
- Update the doses, dosing schedule, and the rationale for dose selection for the main study (1 mg Q4W, 3 mg Q4W, and 6 mg Q8W) and sub-study (1 mg Q8W, 1 mg Q4W, 3 mg Q4W, and 6 mg Q8W)
- Add an end of study phone contact at 52 weeks following the last dose of study drug to determine whether a joint replacement (JR) was performed or is scheduled (or the patient is on a waiting list)
- Update the number of patients enrolled and the randomization allocation
- Update the language that refers to stopping guidelines for a dose arm, the study or the program
- Clarify the safety objectives and update the associated endpoints and statistical methods
- Simplify the efficacy sub-study objective and update the associated endpoints and statistical methods
- Change the magnetic resonance imaging (MRI) requirement at screening to also include the index and contralateral joint
- Add an end of study definition
- Add text to describe the interim analysis

- Update the exclusion criterion regarding contraception to align with Regeneron protocol template language
- Add additional inclusion and exclusion criteria for the efficacy sub-study
- Reduce the time that patients in the efficacy sub-study are required to discontinue use of paracetamol/acetaminophen from 48 hours to 24 hours prior to the start of the study visits.
- Add additional reasons for permanent discontinuation of study drug
- Change the permitted aspirin dose for cardiac prophylaxis from up to 100 mg to up to 150 mg per local guidelines
- Add that an MRI may be requested by the imaging vendor after review of a patient's x-rays
- Add a PK sample collection at week 32, week 60 (12 weeks following the last dose of study drug) and the early termination visit during the follow-up period
- Add an ADA sample collection at week 32 and the early termination visit during the follow-up period
- Add blood pressure measurement for the assessment of orthostatic hypotension at the pre-randomization visit for patients in the efficacy sub-study, and follow-up visit 1 and follow-up visit 2 for patients who undergo joint replacement surgery, and add orthostatic blood pressure to the list of vital signs summarized for descriptive statistics
- Add urinary drug test to the screening and week 16 visit for patients in the efficacy sub-study
- Reduce the number of electrocardiograms (ECG) performed from week 20 to week 52 (Treatment period 2)
- Add joint replacement surgery to the list of AESIs
- Update the PK and ADA variables, update the definition of the PK and ADA analysis sets, and update the analysis of PK data

In addition, the study name, FACT LTS&OA, has been added to the protocol title page, and minor edits have been made to improve clarity and remove redundancy.

Amendment 4 EU: 12 Jan 2017

The purpose of this amendment is to:

- Remove eligibility for treatment from patients who were treated under earlier versions of the protocol with the 6 mg every 4 weeks (Q4W) or 9 mg Q4W dosing regimen.
- Update the Rationale for Dose Selection
- Make minor edits and clarifications

Amendment 4: 25 Aug 2016

The purpose of this amendment is to update the laboratory and urine collection timepoints in the protocol and to add the collection of serum creatinine, urine creatinine, urine phosphorous, and urinalyses. These tests have been added to better monitor patient safety during the trial.

Amendment 3: 20 June 2016

Purpose:

The purpose of this amendment is to update the protocol and to provide clarifications. The changes to the protocol in this amendment are listed below:

- Update the dose selection for the study to 6 mg Q8 weeks.
- Update the randomization ratio for the study to 2:1 for the main portion of the study and 1:1 for efficacy sub-study.
- Replace the terminology "Onset of Efficacy Sub-Study" with "Efficacy Sub-study."
- A risk-benefit assessment has been incorporated, and includes a placebo arm justification in the rationale for study design.
- Inclusion criterion 7 was updated to include that unwillingness to take opioids must be due to a medically acceptable reason.
- Added the following inclusion criteria specific for the efficacy sub-study
  - Willing to discontinue glucosamine sulfate and chondroitin sulfate treatments during the initial 16 weeks of treatment.
  - Stable treatment with glucosamine sulfate and chondroitin sulfate treatments must be stopped during the pre-randomization period.
- Update the permitted therapy section to include physical therapies provided that patients were on a stable regimen prior to entering into the trial and provided that they anticipate they will maintain this regimen during the trial, if possible.
- Updated the prohibited therapy to include glucosamine and chondroitin sulfate during treatment period 1 and to include all IL-1 inhibitors including diacerein during treatment periods 1 and 2
- Added chemistry and hematology safety labs at week 16 and week 32 at the request of the Voluntary Harmonization Procedure (VHP) process.
- Added Phosphorous to the serum chemistry panel.
- Bilateral radiographs of the knee, hip, and shoulder were added to the week 4 and week 20 visits following total joint replacement (JR).
- Added a section defining a suspected unexpected serious adverse reaction (SUSAR) and SUSAR reporting.
- Additional text was added to indicate that all substantial protocol amendments will be approved by the competent authorities before changes are implemented according to national regulations.

- Corrected text for response rate endpoints in Section 2.4 and 8.4 to indicate that the endpoints are percentages of responders.
- Updated multiple testing procedure in Section 9.1, sample size determination in Section 9.2 and efficacy analysis in Section 9.5.2 corresponding to the dose change.

Amendment 2: 25 January 2016

Purpose:

The purpose of this amendment is to update the protocol and to provide clarifications. The changes to the protocol in this amendment are listed below:

- Clarify that study medication will be withheld if a patient is determined to have orthostatic hypotension and added directions related to the assessment of sympathetic nervous system dysfunction
- Add that new signs and symptoms indicative of carpal tunnel syndrome will be a reason for permanent discontinuation of study drug.
- Add that continued noncompliance with protocol-defined maximum acetaminophen/paracetamol use (>2500 mg in Europe or >2600 mg in non-European countries) after appropriate counseling will be a reason for permanent discontinuation of study drug.
- Revise the notification requirement for emergency unblinding from "The investigator should notify Regeneron and/or designee before unblinding the patient, whenever possible" to "The investigator should promptly document and explain to the sponsor any premature unblinding."
- Clarify that the maximum dose of paracetamol/acetaminophen to be used as rescue medication was decreased from 3 g to 2500 mg in Europe or 2600 mg in non-European countries
- Include a multiplicity adjustment for analysis of the endpoints to be studied in the sub-study.
- Add that corresponding baseline scores for the primary analysis variables for sub-study patients will be analyzed.
- Update Exclusion Criterion #20 to clarify that a transient ischemic attack (TIA) or cerebrovascular accident are exclusionary if they have occurred within 12 months of screening or myocardial infarctions or acute coronary syndromes are exclusionary if they have occurred within 6 months of screening.
- Remove Exclusion Criterion #26 as it was redundant; alcoholism is exclusionary in a subsequent criterion.
- Add the word "average" to Inclusion Criterion #5 to clarify the criterion to read 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
- Add that Hyaluronic Acid Intra-articular Injections are prohibited during period 1 of the study.

- Remove "Clinic Visit 4-weeks post last dose" column from Table 4 as it was a duplicate of the "End of Treatment Visit" column in Table 2

Amendment 1: 11 December 2015

Purpose:

The purpose of this amendment is to incorporate changes requested by the Food and Drug Administration (FDA) as follows:

- Edit to clearly indicate that participation in the onset of pain relief sub-study is in addition to participation in the main study
- Update imaging language to state that radiographs and/or MRI will or must (rather than may or should) be performed on any joint following report of a clinically significant worsening or exacerbation of pain in that joint
- Add a definition of destructive arthropathy and delete the sentence stating that no significant treatment emergent adverse events (TEAEs) related to autonomic dysfunction have been reported
- Add follow-up clinic visits 4 and 12 weeks after the last dose of study drug and a phone call 8 weeks after the last dose of study drug
- Update study stopping rules to state that the Independent Data Monitoring Committee (IDMC) may recommend temporarily halting the study for additional review and communication to regulatory authorities if the IDMC has significant concerns regarding a meaningful imbalance in adverse events (AEs) including joint-related AEs, sympathetic nervous system dysfunction, or neurosensory disturbances
- Revise eligibility criteria to clarify that the same diagnostic criteria for osteoarthritis (OA) of the knee or hip will apply to all patients and not just to sub-study patients
- Add willingness to consider JR surgery if necessary as a new inclusion criterion
- Remove redundancy and consolidate exclusion criteria
- Add signs or symptoms of carpal tunnel syndrome within 6 months of screening as an exclusion criterion
- Add history or presence of reflex sympathetic dystrophy at the screening visit to exclusion criteria
- Add history or diagnosis of chronic autonomic failure syndrome including pure autonomic failure, multiple system atrophy (Shy-Drager Syndrome) as a new exclusion criterion
- Add confirmed elevated screening alanine aminotransaminase (ALT) or aspartate aminotransaminase (AST) ≥2.5 times the ULN as a new exclusion criterion
- Add an upper rate of >100 bpm to, and delete the pre-randomization period as a time point from the exclusion criterion for resting heart rate since most patients will not have an in-office visit (only sub-study patients have a pre-randomization visit)

- Add evaluation of the injection site as a safety assessment at baseline and weeks 4, 8, 12, 16, 20, 24, and at clinic visits between week 28 and the end of treatment
- Label the Schedule of Events from week 20 through week 52 as Table 2, and indicate that it applies for all patients
- Add assessment of orthostatic blood pressure for sub-study patients at weeks 1, 2, 4, 8, and 12 and delete at pre-randomization visit
- Add collection of medical history related to the JR surgery at the post-operative visit (follow-up visit 1) and the long-term visit (follow-up visit 2)
- Add rapidly progressive osteoarthritis type 1 or type 2, significant bone collapse and significant bone loss to exclusion criteria
- Add known history of ocular herpes simplex virus, herpes simplex virus pneumonia, or herpes simplex virus encephalitis as a new exclusion criterion
- Add clinically significant sensory and motor neurologic events grade ≥2 according to CTCAE as a reason for permanent discontinuation of study drug and add that study sites should use CTCAE v.4 criteria throughout the study for consistency
- Include carpal tunnel syndrome and state that neurological assessments will include nerve conduction studies and other tests as deemed clinically necessary in the judgement of the neurologist
- Add multiplicity adjustment strategy to Section 9.1 and clarify primary efficacy analysis method in Section 9.3.1 for the sub-study

The following changes were also made:

- Correct the EudraCT number
- Clarify that standard-of-care therapy permitted beginning at week 16 for inadequate pain relief for OA pain is limited to non- non-steroidal anti-inflammatory drugs (NSAIDs)
- Correct that patient participation in the study will be a minimum duration of 37 weeks and that maximum study duration is 77 weeks
- Decrease the maximum daily dose of paracetamol/acetaminophen permitted as rescue medication for OA pain from 4 g to 3 g
- Clarify that treatment with study drug would be stopped after all remaining patients randomized to fasinumab or placebo have completed the week 12 study visit
- Add the requirement for an MRI of the affected joint if screening radiographs are inconclusive for potential joint related findings, and before the pre-randomization visit for any knee or hip joint with a baseline K-L score ≥3
- Add that previous surgical modification of the index joint cannot have occurred within the past year
- Change the time period for the exclusion criteria from “baseline visits” to “randomization” to be consistent with other exclusion criteria

- Delete the pre-randomization period from the exclusion criterion for history or presence of orthostatic hypotension (only sub-study patients have a pre-randomization visit)
- Correct the additional exclusion criterion to state that ≥4 consecutive missed diary entries during the pre-randomization (not the randomization) period would make sub-study patients ineligible to participate in the study
- Update wording of exclusion criterion relating to alcohol, substance, or prescription pain medication abuse to keep consistent across the program
- Delete exclusion criterion for resting heart rate from section of additional exclusion criteria for sub-study patients only as it applies to all patients
- Clarify that use of other investigational agents, cyclosporine, azathioprine, tumor necrosis factor antagonists, corticosteroids (other than topical and inhaled formulations), tocilizumab, and abatacept are prohibited during treatment period 2 as well as during treatment period 1
- Change the caption of Table 1 to indicate that the Schedule of Events from screening through week 16 applies for all patients
- Delete assessment of vital signs and associated information at the pre-randomization visit for sub-study patients
- Delete collection of anti-drug antibody (ADA) sample at week 8
- Add a footnote to state that historical bilateral radiographs may be acceptable as outlined in the study imaging acquisition guidelines
- Clarify that an electrocardiogram (ECG) with rhythm strip will be obtained and sent to the central reader only if a patient's pulse is less than 45 bpm at any visit subsequent to randomization
- Add collection of a research serum/plasma sample at the end of treatment visit
- Update caption of Schedule of Events table to clarify that it applies only to patients who are also participating in the onset of pain relief sub-study
- Add collection of a PK/drug concentration sample, a research serum/plasma sample, and an ADA sample at the end of study visit
- Update language to reflect added visits at weeks 4 and 12, and phone call at week 8 during the follow-up period
- Add a section to indicate that injection site evaluation will be conducted following the injection at each dosing visit
- Remove sitting blood pressure from assessment of vital signs as it is a redundant procedure since both supine and standing measurements are part of the assessment of orthostatic blood pressure
- Add that all available medical history/information for patients who undergo JR surgery must be collected, including results of histopathologic examination

- Indicate that patients who agree to participate in the onset of pain relief sub-study will be required to sign a separate informed consent form (ICF)
- Edit section heading to clarify that efficacy procedures for sub-study patients are for the onset of pain relief sub-study
- Indicate that pulse should be measured per the instructions in the study manual.
- Clarify the definition of orthostatic hypotension and describe the assessment of orthostatic blood pressure
- Clarify that worsening of pain in any joint despite treatment with analgesics, that is inconsistent with the normal progression of OA and lasts at least 2 weeks will be considered as clinically significant independent of the investigator's opinion
- Describe sympathetic nervous system dysfunction and outline assessment and action to be taken with regard to study drug
- Make clarifications and administrative edits

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3 Randomized, Double-blind, Multi-Dose, Placebo-Controlled Study to Evaluate the Long-Term Safety and the Efficacy of Fasinumab in Patients with Pain Due to Osteoarthritis of the Knee or Hip
Site Locations	North America, Latin America, Europe, and Asia/Pacific/South Africa
Objectives	**Primary Objective**: To describe the safety and tolerability of fasinumab, including adverse events of special interest (AESIs), in patients with pain due to radiographically-confirmed OA of the knee of hip
Additional Objectives for the Efficacy Sub-study	The objective of the sub-study is to evaluate the efficacy of fasinumab compared with placebo when administered to patients with pain due to radiographically-confirmed OA of the knee or hip.
Study Design	The study consists of a screening period of up to 30 days (Screening Period), followed by a 7 to 10 day pre-randomization period (Pre-Randomization Period), a 16-week randomized, double-blind, placebo-controlled treatment period (Treatment Period 1), a 36-week, double-blind, placebo-controlled treatment period (Treatment Period 2) in which non-NSAID standard-of-care pain medications can also be used in the event of inadequate pain relief for OA pain, a 24-week follow-up period, and an end of study phone contact at 52 weeks following the last dose of study drug to determine whether a joint replacement (JR) has been conducted or is scheduled (or the patient is on a waiting list). A subset of patients will also participate in a 16-week sub-study to characterize the efficacy of fasinumab. Efficacy assessments will be performed during treatment period 1, which will be followed by the 36-week treatment period 2, and the 24-week follow-up period.
Study Duration	Total duration of participation will be up to 105 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:

Up to 7000 patients are planned to be randomized in this study. Enrollment may be less than 7000 depending on enrollment across all studies in the fasinumab program. Approximately 1000 of these patients will participate in the efficacy sub-study.

Target Population:

Eligible patients for this study will be men and women ≥18 years of age at the time of study entry with a clinical diagnosis of OA of the knee or hip based on the American College of Rheumatology criteria with radiologic evidence of OA (Kellgren-Lawrence [K-L] score ≥2) at the index joint at the screening visit, and WOMAC average pain subscale score of ≥4 at both the screening and randomization visits.

Eligibility for this study is also limited to patients who:

- have a history of inadequate pain relief from paracetamol/acetaminophen, and
- are intolerant or have a history of inadequate pain relief from at least 1 oral non-steroidal anti-inflammatory drug (NSAID), and
- are either intolerant or who have a history of inadequate pain relief from opioid therapy, who are unwilling to take opioid therapy due to a medically acceptable reason or who lack access to opioid therapy

Treatment

Study Drug Dose/Route/Schedule:

Randomized patients will receive fixed-dose, subcutaneous (SC) injections of fasinumab at 1 mg every 8 weeks (Q8W), 1 mg every 4 weeks (Q4W), or matching placebo Q4W from day 1 up to week 48. Patients randomized to 1 mg Q8W will have alternating placebo injections when study drug is not administered. Under amendment 8 and amendment 9, the patient allocation into the main safety study will be 3:3:1 to 1 mg Q8W, 1 mg Q4W or placebo Q4W.

Anyone previously randomized to 9 mg Q4W or 6 mg Q4W (or matching placebo) before amendment 3, or randomized to 6 mg Q8W or 3 mg Q4W under amendment 3 or subsequent amendments, will be discontinued from study drug and encouraged to complete all remaining study visits and study procedures in the follow up period and the end of study phone call.

There were no patients enrolled into the main safety study under amendment 5 or amendment 6. The patient allocation for the efficacy sub-study for all patients randomized to

	amendment 5 global or amendment 6 was 1:1:1:1:1 to 1 mg fasinumab Q8W, 1 mg fasinumab Q4W, 3 mg fasinumab Q4W, 6 mg fasinumab Q8W or matching placebo Q4W. Randomization was stratified by screening K-L score (2-3, 4) and by geographic region (North America, Latin America, Europe, or Asia/Pacific). For the sub-study, stratification was also by index joint. After the 16 week sub-study, patients will then continue in the main safety study, in which dosing will continue through week 48.
Rescue Treatment Route/Schedule:	Paracetamol/acetaminophen is the study-provided rescue medication for OA pain and may be taken as needed, with a maximum daily dose of 2500 mg in Europe and 2600 mg in non-European countries throughout the entire treatment period. Sub-study patients should discontinue use of paracetamol/acetaminophen 24 hours prior to the start of the randomization visit (baseline) and subsequent study visits with efficacy assessments. Beginning at week 16, patients may take non-NSAID standard-of-care therapy in the event of inadequate pain relief for OA pain. Though use of NSAIDs should generally be avoided, limited use is allowed for non-OA related pain or fever after week 16.
Endpoints	
Primary:	The primary endpoint is safety monitoring including adverse event (AE) incidence, serious adverse event (SAE) incidence, AESI incidence, changes in safety laboratory analyses, and incidence of anti-fasinumab antibody formation from baseline to week 52 (treatment period 1 and 2) and to week 72 (end of follow-up period).
Additional Endpoints for the Efficacy Sub-Study	
Primary:	In addition to the main study endpoints, the following co-primary endpoints will be evaluated for the efficacy sub-study: • Change from baseline to week 16 in the WOMAC pain subscale score • Change from baseline to week 16 in the WOMAC physical function subscale score

Secondary:	Key secondary efficacy endpoints for the sub-study are: • Change from baseline to week 16 in the Patient Global Assessment for OA score • The percentage of patients who had a response at week 16, with response defined as an improvement by ≥30% in WOMAC pain subscale scores
PK and ADA variables:	The pharmacokinetic (PK) variable is fasinumab concentrations in serum at specified sampling time points. The anti-drug antibody (ADA) variables include ADA status (positive or negative) and titer.
Procedures and Assessments	Physical examinations, medical history, concomitant medication assessment, vital signs, electrocardiograms (ECGs), imaging, laboratory assessment, neurologic evaluations, and orthostatic hypotension assessment will be performed and the joint pain questionnaire and autonomic nervous system survey will be administered to assess safety. Adverse events, SAEs, and concomitant medications will be assessed at each study visit. Samples to determine serum concentrations of functional fasinumab and anti-fasinumab antibodies will be collected at predetermined time points. Efficacy will be assessed in sub-study patients using the WOMAC sub scales, the Patient Global Assessment of OA, Numeric Rating Scale (NRS) average walking index joint pain, and use of rescue medication. Radiographs and/or magnetic resonance imaging (MRI) will be performed on any joint following a report of clinically significant worsening or exacerbation of pain in that joint. Potential events of adjudicated arthropathy (AA) and sympathetic nervous system dysfunction will be monitored during the course of the study. In the event that a patient must undergo JR surgery during the treatment or follow-up periods, they will be discontinued from study drug and asked to return to the study site for a preoperative visit, and for follow-up safety evaluations 4 and 20 weeks after surgery. Approximately 52 weeks after administration of the last study drug dose, 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	This study will contribute to the overall assessment of fasinumab safety in patients with pain associated with OA. Treatment-emergent adverse events (TEAEs) and treatment-emergent AESIs will be listed and summarized by treatment group. Differences in event rate for AESIs between fasinumab and placebo will be estimated using exact binomial confidence intervals. The sample size of the efficacy sub-study was selected to have a sufficient number of patients to allow treatment comparisons of sub-study primary efficacy endpoints. The effect size for WOMAC pain subscale score, WOMAC physical function subscale score and Patient Global Assessment were 0.46, 0.46, and 0.36, respectively as observed in the phase 2 study R475-PN-1227. Assuming a dropout rate of 15% at week 16, 200 patients per treatment arm, would provide at least 96% power to detect an effect size of 0.46 for WOMAC pain and physical function subscale scores based on a 2-sided test at the 0.0167 significance level. The sample size will provide at least 82% power to detect an effect size of 0.36 in Patient Global Assessment score. The primary efficacy variables will be analyzed using a multiple imputation approach with mixed-effect model for repeated measure (MMRM) based on the FAS with adjustment for missing data due to treatment discontinuation for the reasons of lack of efficacy or AEs assuming the WOMAC scores would on average return to baseline values. The missing data for patients who discontinued treatment due to lack of efficacy or AEs will be imputed with values centered at the mean baseline value of the treatment group that patients were randomized to. 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. Sensitivity analysis using tipping point approach with multiple imputation will also be performed to assess the robustness of the results due to treatment discontinuation. For analysis of continuous variables in secondary endpoints, the analysis method is the same as for the primary variables. For analysis of categorical variables in secondary endpoints (if identified later), the Cochran-Mantel-Haenszel approach stratified by the randomization strata will be used.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

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

1. INTRODUCTION AND RATIONALE

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 which is 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.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment in patients with mild-to-moderate OA. Their efficacy is well documented, although modest (Bjordal 2004), but their use is not without risk. Many patients with acute and chronic pain do not receive adequate pain relief despite the wide variety of analgesic medications that are currently available, either because the medications are not effective in all patients, or because their use is limited by toxicity or intolerability. The risks associated with long-term NSAID therapy have been well characterized and include gastrointestinal bleeding and increased risk of cardiovascular events. In some patients (eg, those with hypertension and pre-existing renal or gastrointestinal disease), the chronic use of NSAIDs may be contraindicated (see current version of the Investigator's Brochure). Guidelines suggest that opioids may be used in OA only if management with NSAIDs is ineffective, intolerable, or otherwise contraindicated. However, opioid use can be associated with both acute and chronic side effects. These include drowsiness, dizziness, gastrointestinal tolerability and motor imbalance, all of which can have serious consequences in older patients. There is data to support the efficacy of opioids in treating pain over a short duration; however, long-term efficacy has not been evaluated. Furthermore, there is no evidence to support superiority of opioids over other available pain medications. Additionally, opioids must be carefully used in patients vulnerable or potentially vulnerable to abuse or addiction. 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 and loss of productivity.

As a result, there remains an unmet medical need for alternative treatment options with more effective analgesia and/or with an improved side-effect profile. This is an important need 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.

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 (Smeyne 1994, Crowley 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 (Indo 1996, Einarsdottir 2004). 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 non-steroidal anti-inflammatory drugs (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 osteoarthritis (OA) of the knee was completed (study R475–PN-0901, see current version of the Investigator's Brochure). Three intravenous (IV) doses of fasinumab were evaluated (0.03, 0.1, 0.3 mg/kg every 8 weeks [Q8W]), all of which were associated with statistically significant improvement in pain compared with placebo when evaluated by walking knee pain, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the Patient's Global Impression of Change questionnaire. Additionally, an interim analysis of the R475-PN-1227 osteoarthritis study was conducted and 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 each given every 4 weeks [Q4W]) compared to placebo (data on file). 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 (Lane 2010, Hefti 2006, Brown 2010, Sanga 2011) and in patients with chronic low back pain (Kivitz 2013, Katz 2011).

In all clinical studies completed to date, fasinumab was generally well tolerated, although joint-related events have occurred more frequently in fasinumab-treated patients than in placebo-treated patients. Additionally, 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 fasinumab-treated patients than in placebo-treated patients. These adverse events (AEs) or physical examination abnormalities associated with fasinumab were generally mild to moderate in intensity and were transient in nature (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 OA. Analyses of the tanezumab data by its sponsor, defined by anatomic pathological criteria on specimens

obtained on joint replacement (JR), showed 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 with tanezumab and fulranumab, the US Food and Drug Administration (FDA) placed the class of anti-NGF antibodies on clinical hold in 2010. Following 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 being implemented for all fasinumab studies, as outlined in Section 7.6.1.1. This approach includes sensitive, prospective, and rigorous radiologic screening and monitoring for certain changes in joint structure. Patients who develop these changes, termed '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, non-clinical studies of the sponsors of other anti-NGF monoclonal antibodies identified adverse changes in the sympathetic nervous system of mature animals of several species (rat and non-human primate). These effects included 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. Based on the potential risk of sympathetic nervous system toxicity identified in non-clinical studies of other anti-NGF monoclonal antibodies, a risk-mitigation approach is being implemented for all fasinumab studies, as outlined in Section 7.6.1.2.

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). Accordingly, 6 mg Q4W and 9 mg Q4W were removed from the present study in an amendment issued in June 2016. 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 the present study. 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 will continue to evaluate fasinumab 1 mg with the highest dose regimen of 1 mg Q4W, which is supported by the independent DMC as having a favorable benefit-risk profile.

Osteoarthritis is a condition that results in significant morbidity and disability, as well as marked loss of productivity for those affected (see current version of the Investigator's Brochure). For those patients affected, fasinumab represents an effective anti-NGF therapy which has the potential to help those patients who do not achieve adequate pain relief, are unable to tolerate existing therapies, or have absolute or relative contraindications to existing therapies.

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-1523, patients with pain due to OA will be randomized to fasinumab 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 restricted 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 7.6.1.

Finally, the selected dose of fasinumab has been chosen to also contribute to the further maintenance of a favorable risk-benefit.

In summary, the overall benefit risk profile for fasinumab in this study 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 1.3 for additional information on the rationale for including a placebo group.

1.3. Rationale

1.3.1. Rationale for Study Design

The purpose of this randomized, double-blind, placebo-controlled study is to evaluate the long-term safety, tolerability, and the efficacy of fasinumab in patients with pain due to radiographically confirmed OA of the knee or hip who have a history of inadequate pain relief with paracetamol/acetaminophen, and a history of inadequate pain relief or intolerance to oral NSAIDs, and opioid therapy. During the initial 16 weeks of the trial, standard-of-care pain medications will be prohibited with the exception of paracetamol/acetaminophen, which will be provided as a rescue medication. Following the first 16 weeks, patients will be able to utilize standard-of-care pain medication including limited use NSAIDs (for non-OA pain or fever), as well as paracetamol/acetaminophen (Section 5.2.2), in addition to study drug. Therefore, this study will also provide safety data on the concomitant use of fasinumab with other analgesics, including limited use NSAIDs.

A subset of patients will participate in an efficacy sub-study, in addition to participation in the main long-term safety study. In the sub-study, efficacy parameters will be assessed over the 16 weeks following randomization.

Overall, this study will provide long-term safety data for up to 52 weeks of exposure to fasinumab or placebo to allow assessment of risk-benefit of fasinumab in patients with chronic pain due to knee or hip OA who have failed or who are intolerant of NSAIDs and opioids, and who have inadequate pain relief from acetaminophen. The study is being conducted with appropriate eligibility criteria to exclude patients who may be at risk for adjudicated arthropathy and sympathetic nervous system effects. In addition, specific questionnaires and physical exams are being employed to monitor for events of arthralgia, altered peripheral sensation, adjudicated arthropathy, and sympathetic nervous system effects.

In this study, a placebo arm is important to accurately estimate the risk of AEs, including AEs of special interest (AESI) (adjudicated arthropathy, sympathetic nervous system dysfunction, peripheral sensory AEs, and JR surgery). Since this study is enrolling patients who have failed or are intolerant to NSAIDs or opioids, and who have inadequate pain relief from paracetamol/acetaminophen, there are limited other therapeutic options available, supporting

equipoise with randomization to placebo. For all patients, rescue medication (paracetamol/acetaminophen) will be made available for breakthrough pain. In addition, following the initial 16 weeks of the trial, patients will be allowed to use other pain medications for OA pain, with the exception of NSAIDs. Limited NSAID use will be allowed to treat non-OA pain or fever after week 16.

Participation in the study provides additional benefits. All patients included in the study will have regular study visits and receive diagnostic procedures 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. Therefore, the use of a placebo arm is justified as placebo treated patients will not be placed at significant risk and will have access to rescue medication, as appropriate.

1.3.2. Rationale for Dose Selection

Previous versions of this protocol randomized patients to receive fixed-dose, subcutaneous (SC) injections of fasinumab at 6 mg Q8W (amendment 3 onwards in the main study) and 1 mg Q8W, 1 mg Q4W, 3 mg Q4W, 6 mg Q8W (amendment 5 in the efficacy sub-study), or matching placebo. The purpose of the 1 mg Q8W dose regimen is to aid in the determination of a minimally effective dose. An independent DMC recommended discontinuing 6 mg Q8W and 3 mg Q4W (expected to have similar exposure to 6 mg Q8W) following a review of unblinded data from this ongoing study. The recommendation 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 patients administered 6 mg Q4W (dose discontinued in amendment 3, issued on 20 June 2016) or 6 mg Q8W. Based on the independent DMC review, study of lower dose levels (eg,1 mg Q4W) may continue to be evaluated in this population. Under amendment 7, issued on 24 May 2018, all patients previously randomized to 3 mg Q4W or 6 mg Q8W under earlier versions of the protocol were discontinued from study drug but encouraged to complete all remaining study visits and study procedures in the follow-up period, and the end of study phone call. 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 amendment 8, issued on 11 Jul 2018, patients will be in a 3:3:1 ratio to fasinumab 1 mg Q8W, 1 mg Q4W or placebo. This randomization ratio was chosen based on the need to enroll more patients on the 1 mg dose regimens and the need to include placebo patients for blinding purposes.

Patients originally randomized to 6 mg Q4W or 9 mg Q4W were transitioned to 6 mg Q8W in amendment 3 (issued on 20 June 2016). These patients and patients on matching placebo were subsequently discontinued from study drug in amendment R475-PN-1523.04EU (issued on 12 January 2017) and amendment 5 global (issued on 16 March 2017), but encouraged to otherwise continue all protocol visits and complete all study procedures with the exception of receiving study drug. This decision was based on data from the phase 2/3 study, R475-PN-1227, which showed an increase in AA events that occurred more frequently at the highest doses evaluated (6 mg and 9 mg Q4W).

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

from the phase 2 study in patients with osteoarthritis of the hip or knee (R475-PN-1227), and the single-dose, proof-of-concept study in patients with sciatic pain (R475-PN-0908), as well as pharmacokinetics (PK).

Single subcutaneous (SC) doses of fasinumab of up to 30 mg were well tolerated in healthy male and female subjects (study TDU-11480). Single IV doses of up to 1 mg/kg were also studied in healthy male and female subjects (study R475-PN-0817). In this study, fasinumab was generally well tolerated at all but the highest IV dose (1 mg/kg). Neurosensory AEs, which were transient and not severe, led to expansion of the 1 mg/kg IV cohort and a decision to not dose-escalate beyond this level.

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 to 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, 6mg, 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. 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.

2. STUDY OBJECTIVES

2.1. Primary Objective

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

2.2. Exploratory Objectives

Other objectives of the study are:

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

2.3. Additional Objectives for the Efficacy Sub-Study

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

3. STUDY DESIGN

3.1. Study Description and Duration

This study will further characterize the safety profile of fasinumab including the incidence of AESIs and provide data on long-term exposure. A subset of approximately 1000 patients will also participate in a sub-study to characterize the efficacy of fasinumab. Participation in the sub-study will last for the first 16 weeks of this study; patients will then be rolled over into the long-term safety study.

The study consists of a screening period of up to 30 days (Screening Period), a 7 to 10 day pre-randomization period (Pre-Randomization Period), a 16-week randomized, double-blind, placebo-controlled treatment period (Treatment Period 1), a 36-week, double-blind, placebo-controlled treatment period (Treatment Period 2) in which non-NSAID standard-of-care pain medications can also be used in the event of inadequate pain relief for OA pain, a 24-week follow-up period with in-clinic visits (Follow-up Period), and an end of study phone contact at 52 weeks following the last dose of study drug to evaluate the number of patients who have undergone JR surgery, are scheduled for JR surgery, or on a waiting list for JR surgery (Figure 1).

- **Screening Period (up to 30 days before the pre-randomization period):** After informed consent has been signed, eligibility for enrollment will be determined based upon parameters assessed during the screening and pre-randomization periods. X-rays of the shoulders, hips and knees will be performed during the screening period. Magnetic resonance imaging (MRI) of the index and contralateral joint must be performed and assessed by the central reader. Any knee or hip joint with a K-L score of ≥3 will have an MRI completed during the screening period. Pre-randomization visits cannot occur until the MRIs of those joints have been completed and the central reader confirms that there are no exclusionary findings. During the screening period, all patients may continue to take their current treatment regimen for OA pain.
- **Pre-Randomization Period (7 to 10 days before the randomization/baseline visit [day 1]):** Patients who meet the initial eligibility criteria, as assessed in the screening period, may enter the pre-randomization period. An in-office pre-randomization visit will occur for patients enrolled in the sub-study while a phone visit will occur if patients are only in the safety portion of the trial without the sub-study. The pre-randomization phone call or visit occurs 7 to 10 days before the randomization visit. Patients will stop taking/washout of their standard-of-care pain medications for OA during the pre-randomization period. In the event of inadequate OA pain relief, patients may take paracetamol/acetaminophen according to local standard-of-care, with a maximum daily dose of 2500 mg in Europe and 2600 mg in countries outside of Europe. Sub-study patients should discontinue use of paracetamol/acetaminophen 24 hours prior to the start of the randomization visit (baseline).

  For any patient who had an MRI of any joint during screening, confirmation that there are no exclusionary findings on MRI must be received from the central reader before the patient can be randomized.

Treatment Period 1 (starts with day 1 and continues through week 16): The initial 16-week treatment period (treatment period 1) will begin at the randomization visit (baseline/day 1) and continue up to the week 16 visit. All patients will undergo baseline assessments at the day 1 visit and will be randomized to receive one of the ongoing study drug dose regimens (1 mg Q4W, 1 mg Q8W, or placebo). Patients randomized to 1 mg Q8W will receive alternating placebo injections at the monthly visits where active study medication will not be given to maintain the blind.

During treatment period 1, patients will be supplied with paracetamol/acetaminophen as the study-provided rescue medication. All patients will record rescue medication use in their diaries from the randomization visit through treatment period 1. All use of NSAIDs during treatment period 1, including oral or topical formulations, is prohibited (except up to 150 mg/day of aspirin/5-ASA, which is permitted for cardiac prophylaxis per local guidelines). Patients may be withdrawn from the study after appropriate counseling if they continue to use NSAIDs during treatment period 1.

Safety assessments will be performed at each study visit during treatment period 1, as outlined in Table 1. Potential events of adjudicated arthropathy will be monitored via clinical signs and symptoms of worsening joint pain during the study (eg, using the joint pain questionnaire and imaging). Potential events of sympathetic nervous system dysfunction will be monitored throughout the study through physical examination, AE reporting, assessment of orthostatic hypotension and via the Survey of Autonomic Symptoms.

Efficacy assessments will be performed for patients participating in the sub-study as outlined in Table 3. Sub-study patients should discontinue use of paracetamol/acetaminophen 24 hours prior to the start of study visits during treatment period 1 in order to minimize the confounding effects of the rescue medication on efficacy measurements.

- **Treatment Period 2 (starts with study drug administration at week 16 and continues through week 52):** Treatment period 2 begins at the week 16 visit and continues through the week 52 visit. Patients will continue to receive fasinumab 1 mg Q8W, 1 mg Q4W or placebo Q4W during this period. At the week 24 visit, X-rays of the hips, knees, and shoulders will be obtained. The last dose of study drug will be administered at week 48.

  During treatment period 2, patients may use non-NSAID standard-of-care pain treatment as rescue treatment and limited use of oral NSAIDs for non-OA related pain or fever.

  Non-steroidal anti-inflammatory drugs will be study-provided as tablets or capsules, and may be used for up to 10 days in an 8-week period, 30 days in a 6-month period, and 60 days in a 1-year period. Use of oral NSAIDs in excess of these amounts is prohibited. The daily dose should not exceed the recommended maximum daily dose per the product labeling. Topical NSAIDs are prohibited during treatment period 2. Patients may be withdrawn from the study after appropriate counseling if continued noncompliance with protocol-defined maximum NSAID use occurs.

Patients will continue to be supplied with paracetamol/acetaminophen during treatment period 2.

The use of paracetamol/acetaminophen and/or NSAIDs should be recorded daily by the patient in the patient's diary. All other pain medications will be obtained and used per local standard-of-care; their use will be reported as concomitant medication during regular study visits.

- **Follow-up Period (for 24 weeks after the last dose of study drug, up to week 72):** Patients will be followed for an additional 24 weeks following administration of the last dose of study drug. Patients who were discontinued from 3 mg Q4W or 6 mg Q8W fasinumab under amendment 7 were immediately entered into the follow-up period. Patients will have safety assessments performed at clinic visits, which will occur at 4 weeks, 12 weeks, and 24 weeks after the last dose of study drug. Additionally, a phone contact will be conducted at 8 weeks following the last dose of study drug to monitor for AEs and concomitant medications.

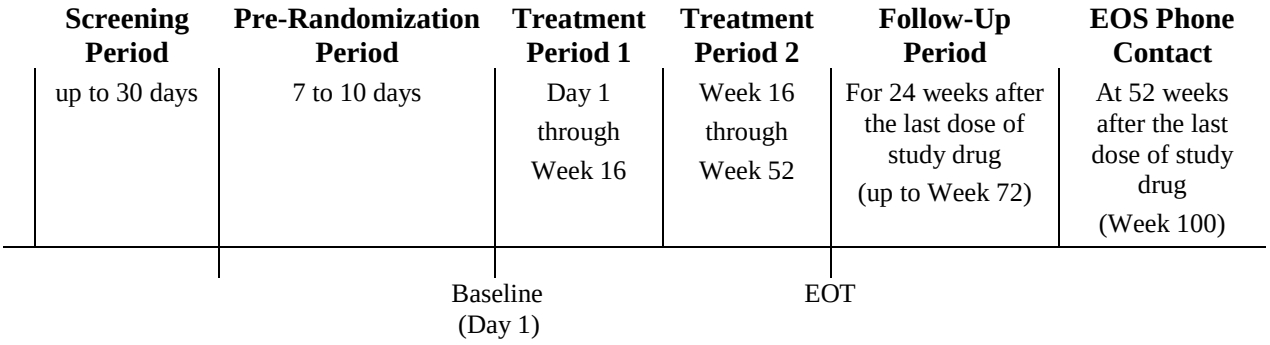
  During the follow-up period, patients must still only use the limited use amounts of NSAIDs for non-OA pain or fever. Patients may increase their dose of NSAIDs beyond the limit outlined for treatment period 2 starting 16 weeks after their last dose of study drug.

  All AEs will continue to be monitored during this period.

  If a patient must undergo JR surgery during the treatment or follow-up periods (up to week 24 after the last dose), then the patient will be asked to complete post-surgery follow-up assessments, as outlined in Table 5.

- **End of Study Phone Contact (week 100):** A phone contact questionnaire will be conducted at 52 weeks following the last dose of study drug to document patient status with regard to JR surgery (if a patient underwent JR, is scheduled to have JR surgery, or is on a waiting 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.

Figure 1: Study Flow Diagram



EOT: End of treatment; EOS: End of study

3.1.1. 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 the sponsor to temporarily halt, alter or terminate:

- individual dose arms 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.

3.1.2. End of Study Definition

The end of the study for this study is defined as the last telephone contact for the last patient.

3.2. Planned Interim Analysis

The week 72 primary safety analysis will be conducted when 72-week data, including 24-week follow-up data, are available for all randomized patients. Additional interim analysis of safety data may be performed for regulatory authority or internal decision-making purposes.

The primary efficacy analysis for the sub-study may be conducted when 16-week data are available for all randomized patients in the sub-study. No alpha adjustment is necessary, as the week 16 efficacy analysis will be the final primary analysis for efficacy. Patient-level results will not be disclosed to any site-facing personnel or to any personnel directly involved with the conduct of the study.

3.3. Study Committees

3.3.1. 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.

3.4. Adjudication of Arthropathy

All potential events of arthropathy will be adjudicated by an independent, blinded adjudication committee composed of radiologists. Further details will be defined in the Arthropathy Adjudication Charter.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients

Up to 7000 patients are planned to participate in this study (enrollment may be less than 7000 depending on enrollment across all studies in the fasinumab program). A subset of approximately 1000 patients will participate in the efficacy sub-study.

4.2. Study Population

Eligible patients for this study will be men and women ≥18 years of age with a history of pain due to OA of the knee or hip and inadequate pain relief or intolerance to current analgesic therapy.

4.2.1. Inclusion Criteria

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

1. Male or female ≥18 years of age at the screening visit
2. Provide signed informed consent
3. Body mass index ≤39
4. 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
    - The index joint is defined as the joint with OA under evaluation for this study
    - A joint previously treated with joint replacement surgery cannot be the index joint
    - A joint previously surgically modified within the past year cannot be the index joint
    - 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 (paracetamol/acetaminophen to be taken as needed with a maximum daily dose of 2500 mg in Europe and 2600 mg in countries outside of Europe and limited use of oral NSAIDs [see Section 5.2.2] during treatment period 2)

7. A history of 12 weeks of analgesic use for OA of the knee or hip as defined by:
   - Inadequate pain relief from paracetamol/acetaminophen, and
   - Intolerance or inadequate pain relief from at least 1 oral NSAID, and
   - Intolerance to or inadequate pain relief from opioid therapy, unwillingness to take opioid therapy for a medically acceptable reason, or lack of access to opioid therapy
8. History of regular use of analgesic medications for OA pain (defined as an average of 4 days per week over the 4 weeks prior to the screening visit), including NSAIDs, selective cyclooxygenase 2 inhibitors, opioids, paracetamol/acetaminophen, or combinations thereof
9. Willing to maintain current activity and exercise levels throughout the study
10. Willing and able to comply with clinic visits and study-related procedures, and willing to provide follow-up information related to any joint replacement surgery that occurs within the period of time covered by their intended participation in the study
11. Able to understand and complete study-related questionnaires
12. Willing to consider total JR surgery, if necessary

4.2.2. Additional Inclusion Criteria for Sub-Study Patients Only

1. Willing to discontinue glucosamine sulfate and chondroitin sulfate treatments during the initial 16 weeks of treatment
2. Stable treatment with glucosamine sulfate and chondroitin sulfate treatments must be stopped during the pre-randomization period.
3. Provide consent to allow all radiographs/other imaging and medical/surgical/hospitalization records for care received elsewhere during the study period to be shared with investigator

4.2.3. Exclusion Criteria

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

1. History or presence at the screening visit of non-OA inflammatory joint disease (eg, rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudogout, 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
2. History or presence on imaging of arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressive osteoarthritis 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
3. Signs or symptoms of carpal tunnel syndrome within 6 months of screening

4. Patient is not a candidate for MRI
5. Is scheduled for a joint replacement surgery to be performed during the study period
6. Systemic (ie, 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)
7. History or presence at the screening visit of autonomic neuropathy, diabetic neuropathy, or other peripheral neuropathy, including reflex sympathetic dystrophy
8. History or diagnosis of chronic autonomic failure syndrome including pure autonomic failure, multiple system atrophy (Shy-Drager syndrome)
9. Poorly controlled diabetes (defined as any single value of hemoglobin A1c [HbA1c] >9.0%) at the screening visit
10. Known history of human immunodeficiency virus infection
11. Known history of ocular herpes simplex virus, herpes simplex virus pneumonia, or herpes simplex virus encephalitis
12. History of sickle cell disease, including S-C disease and S-β thalassemia
13. Confirmed elevated screening alanine aminotransaminase (ALT) or aspartate aminotransaminase (AST) ≥2.5 times the ULN
14. Resting heart rate of <50 beats per minute (bpm) or >100 bpm (by vital sign assessment or as captured during ECG assessment) at the screening or randomization visits
15. History or presence of 2nd or 3rd degree heart block, 1st degree heart block with abnormal QRS, or bifascicular block by ECG assessment at the screening visit
16. History or presence of orthostatic hypotension, as defined in Section 6.3.4.6, at the screening or randomization visits
17. History of poorly controlled hypertension
    - Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg at the screening visit
    - 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 [TIA], peripheral arterial disease and moderate to advanced retinopathy [hemorrhages or exudates, papilledema])
18. Congestive heart failure with NY Heart Classification of stage III or IV
19. Transient ischemic attack (TIA) or cerebrovascular accident within the past 12 months prior to the screening visit, or myocardial infarction, or acute coronary syndromes within the past 6 months prior to the screening visit

20. 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
21. New major illness diagnosed within 2 months prior to the screening visit
22. 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.
23. Known history of infection with hepatitis C virus. Patients with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test.
24. 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
25. Known allergy or sensitivity to doxycycline or related compounds, or monoclonal antibodies
26. History of (within 5 years prior to the screening visit) current alcoholism, alcohol abuse, substance abuse, or abuse of prescription pain medication
27. History of cannabis use for the treatment of pain within the past 6 months prior to the screening visit
28. Ongoing participation in a clinical research study evaluating another investigational drug or having received another investigational product with 30 days or 5 half-lives of the screening visit, whichever is longer
29. 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
30. Member of the clinical site study team and/or his/her immediate family
31. Pregnant or breast-feeding women
32. Women of childbearing potential who have a positive pregnancy test result or do not have their pregnancy test result at baseline
33. 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; intrauterine hormone-releasing system; bilateral tubal ligation; vasectomized partner; and or sexual abstinence[†, ‡].

    * Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented 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, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

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.

4.2.4. Additional Exclusion Criteria for Sub-Study Patients Only

1. Four or more consecutive missed diary entries during the pre-randomization period
2. Trauma to the index joint within 3 months prior to the screening visit
3. 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
4. Presence of orthostatic hypotension at the pre-randomization visit
5. 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.
6. History of hospital admission for depression or suicide attempt within 5 years or active, severe major depression at screening

4.3. 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 sponsor have the right to withdraw a patient from the study in the event of an intercurrent illness, AE, treatment failure, protocol violation, cure, and for administrative, or other reasons. Patients may also be withdrawn from the study, after appropriate counseling, for continued noncompliance with protocol-defined maximum NSAID use.

An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who withdraw prematurely from the study will be asked to complete study assessments per Section 6.2.10.

4.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational and Reference Treatments

Under amendment 8 and amendment 9, patients will be enrolled into the main safety study and randomized to 1 of the following treatment arms:

- Fasinumab 1 mg SC Q8W (patients will receive placebo injections at the study visits where fasinumab is not administered)
- Fasinumab 1 mg SC Q4W
- Placebo SC Q4W

Prior to amendment 7 (urgent safety measure), patients were randomized to 6 mg Q8W or placebo in the main study (after amendment 3), and to the following treatment arms in the efficacy sub-study (amendment 5):

- Fasinumab 1 mg SC Q8W (included in the efficacy sub-study only; patients will receive placebo injections at the study visits where fasinumab is not administered)
- Fasinumab 1 mg SC Q4W
- Fasinumab 3 mg SC Q4W
- Fasinumab 6 mg SC Q8W (patients will receive placebo injections at the study visits where fasinumab is not administered)
- Placebo SC Q4W

Enrollment into the efficacy sub-study was completed prior to amendment 7.

All patients previously enrolled into the main study had completed treatment prior to amendment 7. Under amendment 7, patients randomized to 3 mg Q4W or 6 mg Q8W in the efficacy sub-study were discontinued from study drug for the remainder of the study. All patients who were discontinued from study drug immediately entered the follow-up period.

Patients originally randomized to earlier versions of the protocol (prior to amendment 3) with 9 mg Q4W, 6 mg Q4W, or placebo Q4W were discontinued from study drug for the remainder of the study under an amendment 4EU (issued on 12 January 2017) and amendment 5 global (issued on 16 March 2017).

All patients will receive SC injections Q4W from day 1 up to week 48. All SC injections will be in the abdomen, thigh, or upper arm. Study drug (fasinumab or placebo) will be administered at the study site after all study visit procedures have been completed. Patients will be observed in the clinic for approximately 1 hour after study drug is administered.

Instructions for study drug administration are provided in the pharmacy manual.

Doses of study drug must be given within ±7 days from the scheduled dose date. If the window is missed, the dose should not be administered. The next dose should be administered at the next scheduled dosing date.

5.2. Rescue Treatments

Rescue treatments will be provided to all patients according to Section 6.1.

5.2.1. Paracetamol/Acetaminophen - Weeks 1 through 16

Study-provided paracetamol/acetaminophen is the only allowable rescue treatment for OA pain during treatment period 1. In the event of inadequate relief for OA pain, paracetamol/acetaminophen may be taken as needed according to local standard-of-care, with a maximum daily dose of 2500 mg in Europe and countries with 500 mg tablets/capsules or 2600 mg in countries outside of Europe with 325 mg tablets/capsules. Sub-study patients should discontinue use of paracetamol/acetaminophen 24 hours prior to the start of the randomization visit (baseline) and prior to the start of scheduled study visits during treatment period 1 in order to minimize the confounding effects of the rescue medication on efficacy measurements.

The amount of paracetamol/acetaminophen used in the preceding 24 hours will be reported by patients from the randomization visit (day 1) using the patient diary. All patients will record rescue medication use starting at the randomization visit. Paracetamol/acetaminophen accountability will be conducted at each site visit starting at the week 4 visit. Paracetamol/acetaminophen will be sourced by the sites and reimbursed by the sponsor unless country-specific regulations and customs require a different approach.

Patients should be cautioned to avoid consumption of alcoholic beverages while taking paracetamol/acetaminophen and to take no more than the maximum daily allowable dose. For additional information regarding rescue medication, please refer to the study pharmacy manual.

5.2.2. Paracetamol/Acetaminophen and Non-Steroidal Anti-Inflammatory Drugs - Weeks >16

Study-provided paracetamol/acetaminophen is the only study-provided rescue treatment for OA pain during treatment period 2, with a maximum daily dose of 2500 mg in Europe and other countries where 500 mg strength tablets/capsules are available and 2600 mg in any countries outside of Europe where 325 mg strength tablets/capsules are available.

Beginning at week 16, patients may take non-NSAID standard-of-care therapy in addition to study drug, in the event of inadequate pain relief for OA pain. Patients may also use limited-use NSAIDs for non-OA related pain or fever after week 16.

Non-steroidal anti-inflammatory drugs will be provided as tablets or capsules. The daily dose of NSAIDs should not exceed the recommended maximum daily dose per the product labeling, and their use will be limited to:

- 10 days in an 8-week period
- 30 days in a 6-month period
- 60 days in a 1-year period

The amount of paracetamol/acetaminophen and NSAIDs used in the prior 24 hours will be reported by patients in their diary. Non-steroidal anti-inflammatory drug accountability will be conducted at the end of treatment visit. Non-steroidal anti-inflammatory drugs will be sourced by the sites and reimbursed by the sponsor unless country-specific regulations and customs

require a different approach. Use of all other NSAIDs, including other oral or topical formulations, is prohibited. After appropriate counseling, patients may be withdrawn from dosing for continued noncompliance with protocol-defined maximum NSAID use. During the follow-up period, patients may increase their dose of NSAIDs 16 weeks after their last dose of study drug. Additionally, patients who discontinue study medication during the treatment period should follow the protocol-specified NSAID requirements; however, the NSAID dose can be increased to standard of care doses 16 weeks after their last dose of study medication.

5.3. Dose Modification and Study Drug Discontinuation Rules

5.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

5.3.2. Study Drug Discontinuation

Study drug may be permanently or temporarily discontinued due to medical need, as determined by the investigator, medical monitor, or the sponsor and according to the study stopping rules (Section 3.1.1).

Patients who permanently discontinue from study drug will be asked to remain in the study and to return to the clinic for all remaining study visits, per the visit schedule. Once patients discontinue from study drug, they can restart standard-of-care medications for the treatment of their OA pain with the exception of NSAIDs. Non-steroidal anti-inflammatory drugs can be restarted for OA pain 16 weeks after the last dose of study drug.

Patients who opt to withdraw from the study will be asked to complete the early termination visit per Section 6.2.10.

Patients who discontinue from study drug early due to a clinically relevant joint event (see Section 7.6.1.1) 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, they 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 6.3.4.10) 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.

5.3.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- A patient being randomized under amendment 3 or a subsequent amendment and treated with the 3 mg Q4W or 6 mg Q8W dosing regimen
- A patient being randomized under an earlier version of the protocol before amendment 3 and treated with the 6 mg Q4W, 9 mg Q4W, or placebo Q4W dosing regimen
- A subject developing clinically significant sensory and 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, ie, grade ≥2 according to v.4 (CTCAE); 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 noncompliance with protocol-defined maximum NSAID use (see Section 4.3) after appropriate counseling
- Continued noncompliance with protocol-defined maximum acetaminophen/paracetamol use (with a maximum daily dose of 2500 mg in Europe and other countries where 500 mg strength tablets/capsules are available and 2600 mg in any countries outside of Europe where 325 mg strength tablets/capsules are available) after appropriate counseling
- JR Surgery
- AESI:
  - Adjudicated arthropathy, as described in Section 7.6.1.1
  - Sympathetic nervous system dysfunction , as described in Section 7.6.1.2
- Hepatotoxicity
  - Study drug should be discontinued if:
    a) Total bilirubin (TBL) >2x ULN or international normalized ratio (INR) >1.5 and
    b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x ULN and
    c) No other cause for a and b is readily apparent

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

  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 assessed as related to study medication
- Any other medical need, as determined by the investigator
- Sponsor decision
- Patient decision

5.3.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug may be temporarily discontinued due to medical need, as determined by the investigator. Study drug 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 (Section 7.6.1.1), 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 (Section 7.6.1.2). Study drug should not be re-started until the next study visit unless imaging/evaluation results are available within the current visit window.

5.4. Management of Acute Reactions

5.4.1. 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 7.4.1) and graded using the grading scales as instructed in Section 7.5.1.

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.

5.5. Method of Treatment Assignment

Under amendment 8 and amendment 9, patients will be randomized into the main safety study in a 3:3:1 ratio to receive fixed-dose, SC injections of fasinumab at 1 mg Q8W, 1 mg Q4W, or placebo. Patients randomized to 1 mg Q8W will receive alternating placebo injections at the monthly visits where active study drug will not be given to maintain the blind. Randomization will be performed according to a predetermined central randomization scheme generated by a Regeneron Statistician and provided to the study site personnel by the interactive voice response system (IVRS). Randomization in the study is stratified by baseline K-L score (2-3, 4) and geographic region (such as North America, Latin America, Europe, or Asia/Pacific/South Africa).

There were no patients enrolled into the main safety study under amendment 5 or amendment 6. The patient allocation for the efficacy sub-study for all patients randomized to amendment 5 global or amendment 6 was 1:1:1:1:1 to 1 mg of fasinumab Q8W, 1 mg of fasinumab Q4W, 3 mg of fasinumab Q4W, 6 mg of fasinumab Q8W, or matching placebo Q4W. Randomization was performed according to a predetermined central randomization scheme generated by a Regeneron Statistician and provided to the study site personnel by the IVRS. Randomization in the study was stratified by baseline K-L score (2-3, 4) and geographic region (such as North America, Latin America, Europe, or Asia/Pacific/South Africa). For the sub-study, stratification was also by index joint (knee, hip).

5.5.1. 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 medication 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 (ADA) 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.

5.5.2. 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 before unblinding the patient, whenever possible

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.

5.5.3. 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 unexpected serious adverse reactions (SUSARs).

5.6. Treatment Logistics and Accountability

5.6.1. Packaging, Labeling, and Storage

A medication numbering system will be used in labeling blinded investigational study drug. Lists linking medication 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.

Study drug (fasinumab and its placebo) will be refrigerated at the site at a temperature of 2°C to 8°C; refrigerator temperature will be logged daily. Storage instructions for study drug will be provided in the pharmacy manual.

5.6.2. Supply and Disposition of Treatments

Study drug (fasinumab and its placebo) will be shipped at a temperature of 2°C to 8°C to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (ie, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all used and unused study drug will be destroyed or returned to the sponsor or designee.

5.6.3. Treatment Accountability

All drug accountability records for blinded fasinumab and its placebo, and study-provided rescue medications must be kept current.

The investigator must be able to account for all used and unused study drug and rescue treatments. These records should contain the dates, quantity, and study drug:

- dispensed to each patient,
- returned from each patient (if applicable), and
- disposed of at the site 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.

5.6.4. Treatment Compliance

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

5.6.5. Patient Drug Accountability

Patients will be asked to bring in their study-provided supplies of paracetamol/acetaminophen to each study visit (starting at the week 4 visit through the week 52 visit), and remaining medication will be counted to calculate medication use and compliance.

Patients will be asked to bring in their study-provided supplies of NSAIDs to each visit starting at the week 20 visit until their end of treatment visit/early termination visit. Patients will also be instructed to report the daily use of these medications using their diary.

5.7. Concomitant Medications

Any treatment administered from screening until the end of the follow-up period or early termination is considered concomitant medication. This includes medications that were started prior to the study and are ongoing during the study. Prior to randomization, all paracetamol/acetaminophen will be recorded as a concomitant medication. Starting from the randomization visit, paracetamol/acetaminophen will be recorded as rescue medication in the patient diary.

5.7.1. Permitted Therapy

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 nonpain 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 (up to 150 mg per local guidelines) aspirin/5-ASA for cardiac prophylaxis is also permitted. Paracetamol/acetaminophen taken acutely for treatment of non-OA pain is also permitted. Paracetamol/acetaminophen taken for non-OA pain relief should be reported as concomitant medication. Other permitted medications are glucosamine, chondroitin sulfate and rescue treatments (discussed in Section 5.2). Topical steroids and topical non-NSAID analgesics are also permitted. During treatment period 2 and for 16 weeks after the last dose of study drug, NSAIDs for non-OA related pain or fever may be used for up to 10 days in an 8-week period, 30 days in a 6-month period, and 60 days in a 1-year period. The daily dose of NSAIDs should not exceed the recommended maximum daily dose per the product labeling. Muscle relaxants such as Skelaxin® (metaxalone) are permitted. Prohibited muscle relaxants are listed in Section 5.7.2.

Physical therapies (such as transcutaneous electrical nerve stimulation and acupuncture) are permitted during the trial provided that patients were on a stable regimen prior to entering into the trial and provided that they anticipate that they will maintain this regimen during the trial.

5.7.2. Prohibited Therapy

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

Opioid analgesic medications (including tramadol) are prohibited through week 16. 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) during treatment period 1. Patients may take non-NSAID standard-of-care therapy (see Section 5.2.2) in addition to study drug, in the event of inadequate pain relief for OA pain, starting after the week 16 visit (see Section 5.2.2). Though use of oral NSAIDs should generally be avoided, a limited use is allowed for non-OA related pain or fever after week 16. A list of medications containing NSAIDs will be provided in the study reference manual. The dose of oral NSAIDs may be

increased and topical NSAIDs may be used during the follow-up period, but no earlier than 16 weeks after the last dose of study drug.

Other excluded drugs during treatment period 1 are:

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

For sub-study only during treatment period 1:

- Glucosamine sulfate
- Chondroitin sulfate

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

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

6. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

6.1. Schedule of Events

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

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

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

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

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

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

1. HIV and/or hepatitis testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards
2. Only for patients who provide written informed consent for the optional genomics sub-study. The sample should be collected at the baseline visit, but may be collected at any subsequent visit during the study.
3. After the patient has otherwise met study eligibility criteria assessed during the screening period, an MRI must be performed before the pre-randomization phone call for the index and contralateral joint as well as any knee or hip joint that has a baseline K-L score ≥3. Confirmation from the central reader that there are no exclusionary findings on the MRI must be received before the patient can be randomized.
4. At the screening visit, the WOMAC pain sub-scale will be evaluated for both knees and both hip joints.
5. Study drug administration will be the last procedure at each dosing visit, and will be done after all laboratory samples have been collected and all study assessments and procedures are performed. Patients should be observed in the clinic for approximately 1 hour after administration of study drug for evidence of a hypersensitivity reaction.
6. Patients will be provided with a diary for recording their daily use of paracetamol/acetaminophen beginning on day 1 through the week 52 visit and their NSAID use from week 16 through week 52.

7. If the pulse is less than 45 bpm at any visit after the randomization visit, an ECG with rhythm strip will be obtained and sent to the central reader to confirm the heart rate and rhythm.
8. Imaging (X-ray and/or MRI) will be considered for worsening joint pain despite treatment with analgesics, which in the opinion of the investigator, is inconsistent with the normal progression of OA and lasts for at least 2 weeks (or less, at the discretion of the investigator). Additionally, pre-operative imaging for any JR should be submitted for adjudication, if possible.
9. In the event that a patient must undergo JR surgery during the treatment or follow-up periods, he or she will be discontinued from study drug and asked to return for a pre-operative visit, and for follow-up safety evaluations 4 weeks and 20 weeks after surgery (Table 5). The pre-operative visit should be completed before JR surgery if at all possible. Joint replacement questionnaires are Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements.
10. To be performed only if postmenopausal status has to be assessed for female patients ≤59 years of age.
11. In the event of a positive serum pregnancy test result, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 5.3.2).
12. In the event of a positive urine pregnancy test result, the patient should have a serum pregnancy test with a negative result in order to continue study participation. If the serum pregnancy test is positive, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 5.3.2).
13. PK, ADA, and research samples may also be drawn at any scheduled visit or unscheduled visit if a patient experiences a treatment-related safety TEAE.
14. Historical radiographs may be acceptable as outlined in the study imaging acquisition guidelines.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

F/U: Follow-up

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

6.2. Study Visit Descriptions

6.2.1. Screening Period (Up to 30 days)

Informed consent must be obtained prior to any screening procedures. After informed consent has been obtained, patients may be screened for eligibility. The screening window is 30 days from the time the informed consent has been signed. If the patient has not met screening eligibility criteria by the end of the 30-day screening window, the patient will be identified as a screen failure. Patients who screen fail may rescreen per Section 6.2.2. Laboratory assessments used to determine eligibility may be repeated during the screening period. The procedures outlined in the schedule of events should be completed during the screening period (Table 1).

When applicable, all pain assessments at the screening visits and subsequent visits should be completed prior to the physical examination. The patient reported outcomes assessments should be completed prior to all other efficacy assessments.

After the patient has otherwise met study eligibility criteria assessed during the screening period, an MRI will be performed prior to the pre-randomization phone call/visit for the index and contralateral joint and well as any knee or hip joint with a K-L score ≥3. Confirmation from the central reader that there are no exclusionary findings on MRI must be received before a patient can be randomized.

6.2.2. Rescreening

Patients who do not meet eligibility criteria may rescreen once and only after approval of the sponsor or designee. Rescreening may occur if it is believed by the investigator that the reason for screen failure was due to a condition that would resolve or could be treated, or a laboratory value that minimally exceeded the cut-off value and is not clinically relevant. Patients cannot rescreen if they have screen failed due to not meeting the WOMAC criteria or have orthostatic hypotension. 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 screen failed under amendment 3, 4 or 5 may rescreen under amendment 6 if they have not previously rescreened.

Only the assessments that did not meet eligibility criteria during the first screening are required to be repeated during the rescreen, if done within the screening period or pre-randomization period. Patients who are rescreened after the screening and pre-randomization windows end, must re-consent for study participation and repeat all screening procedures with the exception of imaging assessments. Any imaging assessments need to be repeated only if they were taken more than 60 days from when previous screening X-rays and MRI assessments were completed.

6.2.3. Pre-Randomization Period (7 to 10 days)

Following the screening period, patients will complete a 7 to 10 day pre-randomization period. Patients who are not participating in the sub-study will complete the pre-randomization visit as a telephone contact. Sub-study patients will return to the clinic for a pre-randomization visit 7 to 10 days before the randomization visit. During the pre-randomization period, all patients will be instructed to stop using their standard-of-care pain medications and to use only paracetamol/acetaminophen as rescue treatment. In addition, sub-study patients should

discontinue use of paracetamol/acetaminophen 24 hours prior to the start of the randomization visit (baseline).

6.2.4. Baseline/Randomization Visit (Day 1)

If a patient has met all screening eligibility criteria, study sites will complete the procedures as detailed in the schedule of events for the baseline visit. The patient-reported outcomes assessments at this and subsequent visits should be completed prior to all other assessments. During treatment period 1 (screening to week 16), patients will be observed in the clinic for approximately 1 hour for evidence of a hypersensitivity reaction following study drug administration. Paracetamol/acetaminophen will be provided to patients to be used as rescue treatment, taken as needed, according to local standards-of-care, to a maximum total dose of 2500 mg in Europe and 2600 mg in countries outside of Europe per day, starting on day 1. All use of NSAIDs, including oral or topical formulations, is prohibited. Patients will record their daily use of rescue treatment using a diary starting from the randomization visit through the end of treatment. All laboratory samples at this and subsequent visits must be collected and all study procedures must be performed before study drug is administered. At dosing study visits, urine pregnancy testing will be done and read 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 participation. If the serum pregnancy test is positive, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 5.3.2).

The date of the first dose of study drug is designated on day 1. All subsequent visits should be scheduled based on this date.

6.2.5. Week 1 through Week 16

Complete visits and assessments are outlined in the schedule of events (Table 1 and Table 3). For sub-study patients, the patient-reported outcomes should be completed prior to all other assessments. At dosing visits, all study procedures should be completed before administration of study drug. Patients who discontinue study drug should complete the end of treatment visit per the schedule of events and return for the remaining study visits, if possible. If patients are not able to continue study participation, they should return for an early termination visit, per the schedule of events. The amount of paracetamol/acetaminophen used in the preceding 24 hours will be reported by patients from the randomization visit (day 1) using the patient diary.

If patients proceed into treatment period 2, all patients, including sub-study patients, will continue to follow the same schedule of events.

6.2.6. Week 20 up to Week 52

Complete visits and assessments are outlined in the schedule of events (Table 2). Patients who discontinue study drug should complete the end of treatment visit per the schedule of events and return for the remaining study visits, if possible. If patients are not able to continue study participation, they should return for an early termination visit, per the schedule of events.

During this period, non-NSAID standard-of-care pain medications can be taken in the event of inadequate pain relief for OA pain, and limited use NSAIDs can be used for non-OA related pain

or fever, as defined in Section 5.2.2. All patients will report their use of rescue treatment and limited use NSAIDs in their diaries from week 16 through week 52.

6.2.7. Week 52 or End of Treatment Visit

Assessments for the end of treatment visit at week 52 are outlined in the schedule of events (Table 2).

If treatment is stopped for patients (for example, due to conditions in Section 3.1 or Section 5.3.2.1 being met or for other reasons per the patient or investigator), patients should complete the end of treatment/week 52 assessments at their next scheduled visit. Patients who discontinue study drug should be encouraged to continue participation in the study. All subsequent visits should be conducted according to the schedule of events and all procedures should be completed, except for study medication administration. Imaging does not need to be repeated at a routine visit if all radiographs were conducted within 30 days and submitted for central reading.

Although patients are encouraged to continue all scheduled clinic visits, if they refuse to do so but are willing to provide safety follow-up over the phone, pertinent safety data should be collected.

6.2.8. Week 52 through Week 72

Patients will be followed and will complete study visits and phone contacts through the end of the follow-up period 24 weeks after receiving the last dose of study drug.

6.2.9. Week 100

Patients will complete an end of study phone contact questionnaire at week 100 to record whether the patient has had a JR at any time following the last in-clinic visit of the follow-up period or is scheduled (or on a waiting list) to have 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.

6.2.10. Early Termination Visit (as Applicable)

Patients who do not want to remain in the study following discontinuation of study drug will be asked to return to the clinic as soon as possible for the early termination assessments, per the schedule of events. If a patient declines to return to the site for an early termination visit, he or she should be contacted by telephone to collect safety information.

6.2.11. Visits in the Event of Joint Replacement Surgery

In the event that a patient must undergo JR surgery during the treatment or follow-up periods, he or she will be discontinued from study drug and asked to return for a pre-operative visit, and for follow-up safety evaluations 4 weeks and 20 weeks after surgery. The pre-operative visit should be completed before JR surgery and pre-operative X-rays ± MRIs should be submitted to the central imaging vendor for adjudication, if at all possible.

6.2.12. 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.

6.3. Study Procedures

6.3.1. Procedures Performed Only at the Screening Visit, Pre-Randomization Visit, or Baseline/Randomization Visit

6.3.1.1. Informed Consent

All patients must sign and date an Institutional Review Board (IRB)-approved or Ethics Committee (EC)-approved informed consent form (ICF) before any study procedures are performed, per Section 13.2. Patients who agree to participate in the efficacy sub-study will be required to sign a separate ICF.

6.3.1.2. 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.

6.3.1.3. Medication History

The investigator or designee will query patients on the medication(s) they have taken for their OA (medication history), including information on their ability to tolerate the medication, and will record the information on an electronic case report form (e-CRF) for this purpose.

6.3.1.4. 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 scale. This index can be used to monitor the course of a disease or to determine effectiveness of medications. Patients will complete the WOMAC Pain Subscale at the time points indicated in Section 6.1. If possible, the assessment should be administered and the results entered by the same person at the screening and baseline visits.

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

6.3.1.5. 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
- They have had a tubal ligation, a bilateral oophorectomy, bilateral salpingectomy, or hysterectomy

In women >59 years of age, postmenopausal status is defined as at least 12 continuous months of spontaneous amenorrhea. In women ≤59 years of age, postmenopausal status is defined as at

least 12 continuous months of spontaneous amenorrhea, with serum follicle-stimulating hormone (FSH) levels >40 IU/L (>40 mIU/mL) and serum estradiol levels <5 ng/dL (<184 pmol/L).

6.3.2. Efficacy Procedures for the Efficacy Sub-Study Only

6.3.2.1. Walking Index Joint Pain

The patient's walking index joint pain Numerical Rating Scale (NRS) score, indicating the average daily index joint pain over the past 24 hours or weekly index joint pain, will be recorded by the site at the pre-randomization visit, and by the patient each day thereafter through week 16 in the patient diary.

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

6.3.2.2. Patient Global Assessment of Osteoarthritis

The Patient Global Assessment of OA is a patient-rated assessment of patient current disease state on a 5-point Likert scale (1 = very well; 2 = well; 3 = fair; 4 = poor; and 5 = very poor). Sub-study patients will complete the assessment scale at the time points indicated in Section 6.1.

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

6.3.3. 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 scale. This index can be used to monitor the course of a disease or to determine effectiveness of medications. Sub-study patients will complete the assessment scale at the time points indicated in Section 6.1. If possible, the assessment should be administered and the results entered by the same person throughout the study.

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

6.3.4. Safety Procedures

6.3.4.1. Physical Examination

Patients will have a thorough and complete physical examination including an examination of the knees, hips, and shoulders at the time points indicated in Section 6.1. 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 Section 6.1.

6.3.4.2. Vital Signs

Vital signs including temperature, and respiration will be collected at time points indicated in Section 6.1. At visits at which study drug is administered, vital signs should be measured before SC injection. 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.

6.3.4.3. Electrocardiogram

A standard 12-lead ECG will be performed at the time points indicated in Section 6.1 with the patient in the supine position for approximately 5 minutes and prior to blood samples being drawn. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT, QTc intervals 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.

6.3.4.4. Joint Pain Questionnaire

A joint pain questionnaire will be completed by the patient at the time points indicated in Section 6.1. For each knee, hip, and shoulder joint, the patient will be prompted to indicate if they have experienced pain.

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

6.3.4.5. Survey of Autonomic Symptoms

Signs and symptoms of autonomic dysfunction will be assessed by the investigator at time points indicated in Section 6.1. If possible, the assessment should be completed by the same person throughout the study.

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

6.3.4.6. Assessment of Orthostatic Hypotension and Heart Rate

A blood pressure for the assessment of orthostatic hypotension will be conducted at the time points indicated in Section 6.1. 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

OR

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

OR

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

OR

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

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.

6.3.4.7. Neurological Evaluation

A full or a brief neurological examination will be performed at the time points indicated in Section 6.1. 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.

6.3.4.8. Imaging

Radiographs of the large joints (knees, hips, and shoulders) will be taken using a standard approach at the time points indicated in Section 6.1. An MRI of the index, contralateral, and of any hip or knee joint with a K-L score of ≥3 will be completed at screening. In addition, radiographs and/or an MRI must be performed of any joint following a report of clinically significant worsening or exacerbation of pain in that joint. 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 adjudicated arthropathy such as RPOA type 1 or 2, subchondral insufficiency fracture, or osteonecrosis.

MRI

During screening, MRIs of the index, contralateral and of joints with a K-L score ≥3 will be sent to a central reader to confirm that there is no evidence of adjudicated arthropathy or other 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 affected 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.

6.3.4.9. End of Study Phone Contact

An end of study phone contact will be conducted at 52 weeks following the last dose of 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 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.

6.3.4.10. 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, he or she will be discontinued from study drug and asked to return for a pre-operative visit, and for follow-up safety evaluations 4 weeks and 20 weeks after surgery (see Table 5).

In the event that the pre-operative visit is not performed, standard-of-care pre-operative images of the joint with the JR must be obtained and submitted to the central imaging vendor. 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 post 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.

6.3.4.11. Laboratory Testing

The central laboratory will analyze all screening and on-study laboratory samples for blood chemistry, hematology, HbA1c, urine analysis, urine drug tests (sub-study patients only) and serum pregnancy tests. Urine pregnancy 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 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 Section 6.1.

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Creatinine	Glucose	Alkaline phosphatase
Phosphorous	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 Chemistries

Creatinine	Phosphorous

Other Laboratory Tests

Serum and urine samples for pregnancy testing will be collected from women of childbearing potential (as defined in Section 6.3.1.5) at time points according to Section 6.1. At dosing study visits, 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 participation. If the serum pregnancy test is positive, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 5.3.2).

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 6.1 and Section 6.3.1.5.

Samples will be collected for HbA1c and erythrocyte sedimentation rate testing at time points according to Section 6.1.

Blood samples for research (Section 6.3.6) will also be collected.

Urine samples for the urine drug test will be collected (from sub-study patients only) at time points according to Section 6.1.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or 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 medication 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 7.4.5.

6.3.4.12. Injection Site Evaluation

An injection site evaluation for local reactions should be conducted following the injection at each dosing visit, according to Section 6.1.

6.3.5. Pharmacokinetic and Antibody Procedures

6.3.5.1. Drug Concentration Measurements and Samples

Samples for drug concentration will be collected before administration of study drug at time points listed in Section 6.1. Detailed instructions for blood sample collection are included in the laboratory manual provided to study sites.

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.5.2. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected before administration of study drug at time points listed in Section 6.1. Detailed instructions for blood sample collection are included in the laboratory manual provided to study sites.

Any unused samples collected for ADA assessment may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.6. Research Samples

Serum and plasma samples will be collected at time points according to Section 6.1. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

6.3.6.1. Use and Storage of Research Samples (Serum and Plasma)

Research serum and plasma samples will be collected and stored, and may be used to measure biomarkers related to collagen and bone turnover, OA, pain and NGF, and may include C-telopeptide of type I collagen (CTX-I; a marker for breakdown of type I collagen found in bone), C-telopeptide of type II collagen (CTX-II), high-sensitivity C-reactive protein and matrix metalloproteinase-generated fragment of C-reactive protein. Samples may be used to study other markers of collagen and bone turnover, OA, pain and NGF. If necessary, the samples may also be used to identify markers associated with toxicity. All samples will be single coded to maintain patient confidentiality. The samples may be stored for up to 15 years.

6.3.6.2. Optional Genomics Sub-study

Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF prior to collection of the DNA sample. Blood for DNA extraction should be collected at the baseline visit, but may be collected at any study visit. Patients who choose not to enroll in the genomics sub-study are still eligible to enroll in the primary study.

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 may be stored and used for up to 15 years after the final date of the clinical study report.

DNA analyses may be performed to better understand genetic associations with collagen and bone turnover, OA, pain, and response to fasinumab. If indicated, genetic analyses may also be performed to identify markers associated with AEs. Analyses may include sequence determination and/or single nucleotide polymorphism (SNP) studies of candidate genes. Genome-wide studies, including (but not limited to) SNP analyses and/or genomic sequencing may also be performed.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Obligations of Investigator

The investigator must promptly report to the IRB/EC all unanticipated problems involving risks to patients. 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 causality.

7.2. 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, IECs/IRBs as appropriate, and to the investigators (in a blinded manner).

Any AE not listed as an expected event in the Reference Safety Information section of the Investigator's Brochure or in this protocol will be considered as unexpected. Any worsening of or new onset of symptoms related to OA that occur during the screening period prior to study drug administration will be considered expected.

In addition, the sponsor will report all other 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 IECs/IRB as appropriate.

7.3. Definitions

7.3.1. 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 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.

7.3.2. 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 1 of the other serious outcomes listed above (eg, 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).

7.3.3. Adverse Events of Special Interest

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

Adverse events of special interest are described in Section 7.4.3.

7.4. Recording and Reporting Adverse Events

7.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of the follow-up period (week 72). Refer to the study reference manual for the procedures to be followed.

Information on follow-up for AEs is provided in Section 7.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 7.4.5.

7.4.2. 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, the following will apply:

- SAE with an onset within 30 days of the end of follow-up period (week 72)/early termination visit - 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 (week 72)/early termination visit - 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 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.

7.4.3. Other Events that Require Accelerated Reporting

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), by telephone within 24 hours of identification, any pregnancy occurring in a female patient during the study or within 20 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn 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 7.4.2. Monitoring of AESIs is described in Section 7.6. Events considered to be AESIs are:

- Adjudicated arthropathy (as confirmed by adjudication)
- Sympathetic nervous system dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist)
- Peripheral sensory AEs that require a neurology or other specialty consultation
- JR surgery (refer to Section 7.6.1.4 for when to report as an AESI)
  - Patients should be counselled that if they require JR surgery during the trial, they should contact the site immediately and have pre-operative X-rays and MRI

completed of the joint that will be replaced. The pre-operative images must be submitted to the central imaging vendor for adjudication

7.4.4. 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.

7.4.5. 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 7.5.1.

7.4.6. 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.

7.5. Evaluation of Severity and Causality

7.5.1. Evaluation of Severity

Adverse events will be graded according to the following scale:

- **Mild:** Does not interfere in a significant manner with the subject's 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 subject.
- **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 subject hospitalized.

7.5.2. Evaluation of Causality

Relationship of AEs 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 adverse event 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

Relationship of AEs 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 adverse event 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

7.6. Safety Monitoring

The investigator will monitor the safety of study patients 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. The study monitor 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.

7.6.1. Monitoring Adverse Events of Special Interest

7.6.1.1. Adjudicated Arthropathy

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

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

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

Potential events of adjudicated arthropathy will be monitored via clinical signs and symptoms of worsening joint pain (joint pain questionnaire), AE monitoring, and routine imaging.

Clinically significant worsening of joint pain during the course of this study is defined as worsening of pain in any joint despite treatment with analgesics (see Section 5.2), which is inconsistent with the normal progression of OA and that lasts at least 2 weeks (or less at the discretion of the investigator).

If a patient reports an increase in joint pain, as described above, then study drug administration will be withheld. Imaging of the affected joint will be performed, as well as any additional imaging deemed appropriate to understand the cause of the worsening pain (Section 6.3.4.8). The decision to perform imaging after patient reports of worsening joint pain will be documented in the respective CRF page. Images, along with any other radiographic evaluation, will be submitted to the Adjudication Committee for review (Section 3.4). The investigator may consider aspiration of synovial fluid for further analysis such as cell count and crystal analysis.

If routine imaging suggests one of the forms of adjudicated arthropathy, then study drug administration will be withheld. Any additional imaging deemed appropriate will be obtained. Images, along with any other radiographic evaluation, will be submitted to the Adjudication Committee for review (Section 3.4).

If the adjudication does not confirm the case as adjudicated arthropathy according to the adjudication criteria, study drug may be restarted.

Patients with findings that suggest adjudicated arthropathy will have their dosing terminated and will be referred for orthopedic consultation, and once confirmed by the adjudication committee, the case must be reported as an AESI (Section 7.3.3 and Section 7.4.3).

Patients should be encouraged to return to the clinic for remaining study visits. Prior to the scheduled JR, the patient should complete the pre-operative study visit and week 4 and week 20 post-operative study visits (Section 6.2.11 and Section 6.3.4.10). Pre-operative images, along with any other radiographic evaluation will be submitted to the Adjudication Committee for review (Section 3.4).

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

7.6.1.2. 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 6.3.4.5). 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 7.4.3).

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 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 can 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 7.4.3).
- 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 can 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 7.4.3).

7.6.1.3. 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 7.4.3).

7.6.1.4. 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 6.3.4.9. 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.

7.7. Investigator Alert Notification

Regeneron or its 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, and has a reasonable suspected causal relationship to the medicinal/investigational product).

8. STUDY VARIABLES

8.1. Demographic and Baseline Characteristics

Standard demography will include patient variables (eg, age, race, weight, height, etc.), baseline characteristics (eg, K-L categories, geographical regions), medical and surgical history, medication history, WOMAC pain score (knee and hip), and bilateral radiograph (knee, hip, and shoulder) for each patient.

8.2. Primary Endpoint

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

8.3. Exploratory Endpoints

Other endpoints in the study are:

- The proportion of patients taking rescue medication, number of days on rescue medication, and weekly average usage of rescue medication
- The percent of patients using standard-of-care analgesic medication
- Time to JR decision
- Survey of Autonomic Symptom scores

8.4. Additional Endpoints for the Efficacy Sub-Study

In addition to the main long-term safety study endpoints, the following endpoints will be evaluated for the efficacy sub-study.

Co-Primary efficacy endpoints for the sub-study are:

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

Key secondary efficacy endpoints for the sub-study are:

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

Additional secondary efficacy endpoints may be evaluated and will be detailed in the statistical analysis plan (SAP).

8.5. Pharmacokinetic Variables

Pre-dose samples will be collected from patients in the sub-study. The PK variable is fasinumab concentrations in serum at specified sampling time points.

8.6. Anti-Drug Antibody Variables

Samples for ADA evaluation will be collected at baseline and at subsequent study visits. Anti-drug antibody variables include ADA status (positive or negative) and titer as follows:

- Treatment emergent - defined as any post-dose positive ADA response when baseline results are negative
- Treatment boosted - defined as any post-dose positive ADA response that is at least 9-fold over the baseline level when baseline is positive in the ADA assay
- Titer Values
- Titer category ▪ low (titer <1,000); moderate (1,000≤ titer ≤10,000); high (titer >10,000)
- Neutralizing ADA activity for samples positive in the ADA assay

9. STATISTICAL PLAN

This section provides the basis for the 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 8.

9.1. Statistical Hypothesis for the Sub-Study Population

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. Hence, there are 6 hypotheses to be tested between the primary and key secondary efficacy endpoints. A hierarchical testing procedure will be used to control the overall type I error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. The hierarchical testing order will be detailed in the SAP. The hypotheses to be tested are:

- H_{11}: There is no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC pain or physical function subscale scores at week 16 versus there is treatment difference in WOMAC pain and physical function subscale scores at week 16
- H_{12}: There is no treatment difference between fasinumab 1 mg Q4W and placebo in Patient Global Assessment score at week 16 versus there is treatment difference in Patient Global Assessment score at week 16
- H_{13}: There is no treatment difference between fasinumab 1 mg Q4W and placebo in the proportion of patients with ≥30% improvement in the WOMAC pain subscale scores at week 16 versus there is treatment difference in proportion of patients with ≥30% improvement in WOMAC pain at week 16
- H_{21}: There is no treatment difference between fasinumab 1 mg Q8W and placebo in WOMAC pain or physical function subscale scores at week 16 versus there is treatment difference in WOMAC pain and physical function subscale scores at week 16
- H_{22}: There is no treatment difference between fasinumab 1 mg Q8W and placebo in Patient Global Assessment score at week 16 versus there is treatment difference in Patient Global Assessment score at week 16
- H_{23}: There is no treatment difference between fasinumab 1 mg Q8W and placebo in the proportion of patients with ≥30% improvement in the WOMAC pain subscale scores at week 16 versus there is treatment difference in proportion of patients with ≥30% improvement in WOMAC pain at week 16

9.2. Determination of Sample Size

The sample size for this long-term safety study was selected according to regulatory requirements for sufficient patients with adequate treatment exposure. With approximately 1750 patients expected to be treated with placebo, a total of up to 7000 patients was planned to be randomized. This study will provide an adequate assessment of safety in patients with pain associated with OA. For example, based on Exact Binomial Testing, with approximately 5250 patients with pain associated with OA exposed to fasinumab, if the observed incidence rate is 1.0%, one can be 97.5% confident that the true incidence rate is not greater than 1.3% (Table 6).

Table 6: Observed Incidence Rate (n/N) and 95% CI (Based on Exact Binomial Test) (%)

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

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

9.3. Analysis Sets

9.3.1. Efficacy Analysis Sets

The full analysis set for the efficacy sub-study includes all randomized patients in the sub-study. Efficacy analyses will be based on the treatment allocated (as randomized). The full analysis set for the LTS study includes all randomized patients in the overall study. Patient disposition and baseline characteristics will be summarized based on the full analysis set of the LTS study.

9.3.2. Safety Analysis Set

The safety analysis set (SAF) for the entire study includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF for the entire study. The SAF for the sub-study includes all randomized patients in the sub-study who received any study drug; it is based on the treatment received (as treated). Selected safety analysis will be performed for the sub-study. Details will be provided in the SAP.

9.3.3. Per Protocol Set

The per protocol set (PPS) will include all randomized patients in the sub-study who do not have major protocol deviations through week 16. The PPS will be used to perform sensitivity analyses for the primary and selected secondary efficacy endpoints.

9.3.4. Pharmacokinetics Analysis Set

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

9.3.5. Anti-Drug Antibody Analysis Set

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

9.4. 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

9.5. Statistical Methods

9.5.1. Demography and Baseline Characteristics

Baseline demographic, disease characteristics, and exposure to study drug will be summarized descriptively by treatment group using descriptive statistics. Continuous variables will be summarized with mean, median, standard deviation (SD), minimum, and maximum. Categorical

variables will be summarized with frequency and percentage. Details of the statistical methods will be provided in the SAP.

9.5.2. Efficacy Analyses for the Sub-Study Population

9.5.2.1. Primary Efficacy Analysis

The primary efficacy variables will be analyzed using a multiple imputation approach with mixed-effect model for repeated measure (MMRM) based on the FAS with adjustment for missing data due to treatment discontinuation for the reasons of lack of efficacy or AEs assuming the WOMAC scores would on average return to baseline values. The missing data for patients who discontinued treatment due to lack of efficacy or AEs will be imputed with values centered at the mean baseline value of the treatment group that patients were randomized to. 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 primary efficacy variable (eg, WOMAC pain subscale score at baseline for the analysis of change from baseline in WOMAC pain subscale score), treatment, randomization strata, visit, and treatment-by-visit interaction. The MMRM will be performed using the MIXED procedure in the Statistical Analysis System (SAS) with an unstructured covariance matrix to model the within-patient errors. Denominator degrees of freedom will be estimated using Kenward-Roger's approximation. The results from the 50 analyses will be combined using Rubin's formulae (PROC MIANALYZE). The least-squares means estimates for the mean change from baseline to week 16, as well as the difference of the estimates between fasinumab and placebo, with the corresponding standard error, p-value and associated 95% confidence interval will be provided. Hypothesis testing will be performed as specified in Section 9.1 to control for multiplicity. 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

Additional sensitivity analysis using 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). Multiple imputation will be based on monotone missing data structure of the change from baseline score using regression option in PROC MI. Monotone missing data structure will be achieved using MCMC option of PROC MI. After each imputation, a fasinumab patient's imputed data will subtract k (e.g., 20%, 40%, 100%, …) times the treatment effect at each corresponding time point. By progressively increasing coefficient k, the sensitivity analysis will explore the tipping point, ie, the upper bound on the critical value of coefficient k at which conclusion from the primary analysis will be overturned ($p>0.05$). Additional sensitivity analyses will be performed the same way for the primary and selected secondary endpoints using the PPS.

9.5.2.2. Secondary Efficacy Analysis

For analysis of continuous variables in secondary endpoints, the analysis method is the same as for the primary variables. For analysis of categorical variables in secondary endpoints (if identified later), the Cochran-Mantel-Haenszel approach stratified by the randomization strata will be used with missing data considered as non-response.

9.5.3. Safety Analysis

The incidence rate is defined as the number of events divided by the duration of the overall observation period. The incidence rate will be summarized by treatment group along with 2-sided 95% confidence interval. The incidence rate differences and ratios between each fasinumab dose group and placebo will be computed and presented along with 2-sided 95% confidence intervals.

Change from baseline in joint space width of the index knee or hip will be summarized by treatment group. Time to event endpoints, such as time to JR decision, will be analyzed using the Kaplan-Meier approach.

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
- The on-treatment period is defined as the day of the first dose of study drug to 4 weeks after the day of the last dose of SC study drug.
- The follow-up period is defined as from the end of the on-treatment period up to 24 weeks post the last dose of study drug (week 72).

9.5.3.1. Adverse Events

Definitions

Treatment-emergent adverse events are defined as those that are not present at baseline or that represent the exacerbation of a preexisting condition during the on-treatment period.

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.

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 7.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

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.

Treatment-emergent AESIs will be listed and summarized by treatment group. Differences in event rate for AESIs between fasinumab and placebo will be estimated using exact binomial confidence intervals. Imaging data related to AA including change from baseline in joint space width will be summarized.

9.5.3.2. Other Safety

Vital Signs

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

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Potentially clinically significant values (PCSVs) will be summarized by treatment group.

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

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

9.5.3.3. Treatment Exposure

Days of treatment exposure during the study will be presented by treatment and calculated as:

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

The length of the observation period (days) will be presented by treatment group and calculated as:

- (Date of last study visit – date of first study drug administration) +1.

The number and percentage of patients randomized and exposed to double-blinded study drug will be presented by specific time periods for each treatment group.

The time periods of interest may consist of exposure intervals 0 - <12, 12 - <24, 24 - <52, and ≥52 weeks. In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, mean, SD, median, minimum and maximum.

A summary of the number of doses by treatment group will be provided.

9.5.3.4. Treatment Compliance

Treatment compliance with protocol-defined investigational product will be calculated as follows:

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

Treatment compliance will be presented by specific ranges for each treatment group. The ranges of interest may consist of 10 disjoint intervals with width of 10% such as 0% - <10%, 10% - <20%, 20% - <30%, etc., up to 90% - 100%.

9.5.4. Analysis of Pharmacokinetic Data

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

9.5.5. Descriptive Analysis of Anti-Drug Antibody Data

Listings of ADA positivity and titers presented by patient, time point, and dose group will be provided. Prevalence of treatment-emergent and treatment-boosted ADA response will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts.

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

9.5.6. Interim Analysis

The week 72 primary safety analysis will be conducted when 72-week data, including 24-week follow-up data, are available for all randomized patients. Additional interim analysis of safety data may be performed for regulatory authority or internal decision-making purposes.

The primary efficacy analysis for the sub-study may be conducted when 16-week data are available for all randomized patients in the sub-study. No alpha adjustment is necessary, as the week 16 efficacy analysis will be the final primary analysis for efficacy. Patient-level results will not be disclosed to any site-facing personnel or to any personnel directly involved with the conduct of the study.

Detailed interim analysis timing and analyses will be pre-specified in the SAP.

9.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

General rules for handling missing data:

- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations will be made for missing laboratory data, ECG data, vital signs data, or physical examination data.

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 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.

9.7. 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 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. 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 CRF data for this study will be collected with an electronic data capture (EDC) tool.

10.2. Electronic Systems

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

- IVRS – randomization
- Rave Medidata - EDC system
- Electronic diary may be used for patients in the sub-study to collect rescue medication usage and NRS scores
- Statistical Analysis System (SAS) – statistical review and analysis
- A pharmacovigilance and clinical safety software system (ARGUS – collection and reporting of SAEs and AESIs)
- Electronic Clinical Outcome Assessment systems – collect patient-reported outcome or patient clinical assessment results

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with ICH guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. 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.

11.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs by trained site personnel. A CRF must be completed for each and every 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 CRF page 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 system. For corrections made via data queries, a reason for any alteration must be provided.

12. 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/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.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. 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.

13.2. 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/EC. A copy of the IRB/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.

The principles of informed consent are described in ICH Guidelines for Good Clinical Practice.

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

13.3. 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 initials and a 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.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/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/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/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/EC approval letter with a current list of the IRB/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/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. 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.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF without an IRB/EC-approved amendment. All substantial protocol amendments will be approved by the competent authorities before changes are implemented according to national regulations. Some exceptions may apply in the event of urgent safety actions, in accordance with local regulatory procedures.

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

15.1. Premature Termination of the Study

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

15.2. 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/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.

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the sponsor with the final set of CRFs for each patient.

16.2. 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.

17. 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 10.1).

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 11.1, Section 11.2, Section 12).

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 11.1).

All patient data collected during the study will be recorded on paper or eCRF 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 11.3, Section 16.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 11.2).

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 16.2).

18. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

19. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

20. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

21. REFERENCES

Aloe L, Tuveri MA, Carcassi U, Levi-Montalcini R. Nerve growth factor in the synovial fluid of patients with chronic arthritis. Arthritis Rheum 1992;35:351-355.

Bjordal JM, Ljunggren AE, Klovning A, and Slørdal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomized placebo controlled trials. BMJ 2004;329(7478): 1317.

Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, West CR. Tanezumab reduces osteoarthritic knee pain: Results of a randomized, double-blind, placebo-controlled phase 3 trial. Ann Rheum Dis 2010;69 (Suppl 3):106.

Chao M, Rajagopal R, and Lee FS. Neurotrophin signaling in health and disease. ClinSci (Lond) 2006;110:167.

Crowley C, Spencer SD, Nishimura MC, Chen KS, Pitts-Meek S, Armanini MP, et al. Mice lacking nerve growth factor display perinatal loss of sensory and sympathetic neurons yet develop basal forebrain cholinergic neurons. Cell 1994;76:1001-11.

Einarsdottir E, Carlsson A, Minde J, Toolanen G, Svensson O, Solders G et al. A mutation in the nerve growth factor beta gene (NGFB) causes loss of pain perception. Human Molecular Genetics 2004;13:799–805.

Halliday DA, Zettler C, Rush RA, Scicchitano R, McNeil JD. Elevated nerve growth factor levels in the synovial fluid of patients with inflammatory joint disease. Neurochem Res 1998;23:919-22.

Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg Am. 1969 Jun;51(4):737-55.

Hefti F, Mokhtarani M Gray, M Zhao, C and Chan C. RN624 (Anti-NGF) reduces pain and improves function in subjects with moderate to severe pain form osteoarthritis of the knee. The Journal of Pain 2006: 7:S46.

Indo Y, Tsuruta M, Hayashida Y, Karim MA, Ohta K, Kawano T et al. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nature Genetics 1996;13:485-88.

Insall JN, Dorr LD, Scott RD, Scott WN. Rationale of the Knee Society clinical rating system. ClinOrthopRelat Res. 1989 Nov;(248):13-14.

Katz N, Borenstein DG, Birbara C et al. Efficacy and safety of tanezumab in the treatment of chronic low back pain. Pain 2011; 152;2248–58.

Kivitz A, Gimbel J, Bramson C et al. Efficacy and safety of tanezumab versus naproxen in the treatment of chronic low back pain. Pain 2013;154;1009–21.

Lane NE, Schnitzer TJ, Birbara CA, Mokhtarani M, Shelton DL, Smith MD et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med 2010;363:1521-31.

Lewin GR, Rueff A, Mendell LM. Peripheral and central mechanism of NGF-induced hyperalgesia, Eur. J. Neurosci 1994; 6: 1903-12.

Lowe EM, Anand P, Terenghui RE, Chestnuts-William DV, Osborne JL. Increased nerve growth factor levels in the urinary bladder of women with idiopathic sensory urgency and interstitial cystitis. Br. J. Urol. 1997; 79:572–577.

McArthur JC, Yiannoutsos C, Simpson DM, Adornato BT, Singer EJ, Hollander H, et al. A phase II trial of nerve growth factor for sensory neuropathy associated with HIV infection. AIDS Clinical Trials Group Team 291. Neurology 2000; 54:1080-8.

Miller LJ, Fischer K, Goralnick S, Litt M, Burleson J, Arbertsen P et al. Nerve growth factor and chronic prostatitis/-chronic pelvic pain syndrome. Urology 2002;59:603–608.

Pezet S and McMahon SB. Neurotrophins: Mediators and Modulators of Pain. Ann Rev Neurosci 2006;29:507-18.

Ramer MS, Bisby MA. Adrenergic innervation of rat sensory ganglia following proximal or distal painful sciatic neuropathy: Distinct mechanisms revealed by anti-NGF treatment. Eur J Neurosci 1999;11:837-846.

Sanga, P., Katz, N., et al. (2011). "Efficacy, Safety and Tolerability of Fulranumab, an anti-NGF Antibody, in Treatment of Patients with Moderate to Severe Osteoarthritis Pain." Poster presented at the American Pain Society Annual Meeting.

Sarchielli P, Arberti A, Floridi A, Gallai V. Levels of nerve growth factor in cerebrospinal fluid of chronic daily headache patients. Neurology 2001;57:132-134.

Smeyne RJ, Klein R, Schnapp A, Long LK, Bryant S, Lewin A et al. Severe sensory and sympathetic neuropathies in mice carrying a disrupted Trk/NGF receptor gene. Nature 1994; 368:166-9.

22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 3, Randomized, Double-Blind, Multi-Dose, Placebo-Controlled Study to Evaluate the Long-Term Safety and the Efficacy of Fasinumab in Patients with Pain Due to Osteoarthritis of the Knee or Hip 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 EC. 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 protocol accurately describes the conduct of the study.

Study Title: A Phase 3 Randomized, Double-Blind, Multi-Dose, Placebo-Controlled Study to Evaluate the Long-term Safety and the Efficacy of Fasinumab in Patients with Pain Due to Osteoarthritis of the Knee or Hip

Protocol Number: R475-PN-1523

Protocol Version: R475-PN-1523 Amendment 9

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:

See appended electronic signature page

Signature Page for VV-RIM-00071798 v1.0

ESig Approval	Kristie Ota kristie.ota@regeneron.com Regulatory 22-Apr-2019 14:38:27 GMT+0000

ESig Approval	Chetachi Emeremni chetachi.emeremni@regeneron.com Biostatistics / Data Management 22-Apr-2019 15:10:45 GMT+0000

ESig Approval	Tolga Baykal tolga.baykal@regeneron.com Clinical 22-Apr-2019 20:02:11 GMT+0000

ESig Approval	Daya Gulabani daya.gulabani@regeneron.com Clinical 22-Apr-2019 20:30:55 GMT+0000

Signature Page for VV-RIM-00071798 v1.0 Approved