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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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

Compound:	Fasinumab
Study Name:	FACT OA2
Clinical Phase:	3
Protocol Number:	R475-OA-1688
Protocol Version:	R475-OA-1688 Amendment 4
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AMENDMENT HISTORY

Amendment 4

The purpose of this amendment is to update the exclusion criteria to improve patient safety. Additional changes have been made to improve clarity, ensure consistency across the fasinumab program, and to make minor corrections. The following table outlines the changes made to the protocol and the rationale:

Change and Rationale	Sections Changed
Main changes to improve patient safety:	
The exclusion criterion #22 regarding adverse cardiac events within the past 12 months prior to the screening visit has been updated to exclude patients with a *history* of adverse cardiac events, per Ethics Committee request. In addition, acute coronary syndrome has been removed from this criterion because this is covered by exclusion criterion #10.	Section 6.2.2 Exclusion Criteria, #22
In exclusion criterion #10 regarding NSAID use, the general statement regarding the use of concomitant medications for which NSAIDs are contraindicated has been removed. Specific medications that are not to be taken concomitantly with NSAIDs are listed in the prohibited medications section. In addition, patients with conditions requiring use of anti-platelet therapy has been added to this criterion.	Section 6.2.2 Exclusion Criteria, #10
A new exclusion criterion has been added to exclude patients at the highest risk of renal complications due to NSAID use, as follows: 'Patients taking concomitant ACE inhibitors/ARBs and diuretics, or presence of an estimated glomerular filtration rate (GFR) <30 mL/minute/1.73m^{2}'	Section 6.2.2 Exclusion Criteria, #40
The reasons for permanent discontinuation of study drug have been updated to ensure that patients enrolled under an earlier version of the protocol are immediately discontinued from study drug and moved to the follow up period if they meet either of the updated exclusion criteria described above, or are taking the newly added prohibited medications described above (combination therapy of diuretics with either an ACE inhibitor or ARB).	Section 7.3.2.1 Reasons for Permanent Discontinuation of Study Drug
All other changes:	
The rescreening text has been updated for clarity and to be consistent across the fasinumab program	Section 5.1.2 Rescreening
The sample size has been revised from 2700 patients to approximately 1620 patients due to the discontinuation of the 3 mg Q4W and 6 mg Q8W dose regimens.	Clinical Study Protocol Synopsis: Population Section 6.1 Number of Patients Planned
Clarified that fasinumab and fasinumab-matching placebo are referred to as 'SC study drug' and that NSAIDs (diclofenac and celecoxib) and NSAID-matching placebo are referred to as 'oral study drug'.	Throughout the document

Change and Rationale	Sections Changed
The rescue medication (acetaminophen/paracetamol) text has been updated to be consistent across the fasinumab program: • Clarified that acetaminophen/paracetamol may be taken for inadequate pain relief for OA and for other acceptable reasons (eg, headache, fever); • Added text to clarify the dosing instructions; • Added text to caution against consumption of alcoholic beverages while on acetaminophen/paracetamol	Clinical Study Protocol Synopsis: Rescue Treatment Section 7.2 Rescue Medication Section 7.7.2 Permitted Medications and Procedures
The section on Prohibited Medications and Procedures has been updated: • To include methotrexate, which should be used with caution in patients taking NSAIDs and because methotrexate clearance can be decreased with concurrent NSAIDs, leading to potential increases in methotrexate levels; • To include anticoagulants and anti-platelet therapy (eg, warfarin, heparins, factor Xa inhibitors, thrombin inhibitors, aspirin/5-aminosalicylic acid (aspirin/5-ASA) >150 mg daily, clopidogrel), which should be used with caution in patients taking NSAIDs; • To include recreational use of marijuana in addition to medical marijuana, as both have the potential to impact efficacy assessments; • To include combination therapy of diuretics with either an ACE inhibitor or angiotensin receptor blocker (ARB); • To clarify that cyclobenzaprine, carisoprodol, orphenadrine and tizanidine are muscle relaxants • To make minor corrections	Section 7.7.1 Prohibited Medications
Text has been added or updated to align with current Regeneron best practices	Section 7.4.2 Local Injection Site Reactions Section 7.5.2 Emergency Unblinding Section 12.1 Monitoring of Study Sites
Changes have been made to the Schedule of Events table and footnotes for clarity, to make minor corrections, and for consistency across the fasinumab program: • Added a separate row to the Schedule of Events table for high-sensitivity C-reactive protein • Clarified that the Early Termination/Joint Replacement (ET/JR) visit is also the pre-operative visit for patients who undergo JR. • Added event-triggered imaging to the follow-up period and Early Termination Visit during the follow-up period in the Schedule of Events Table • Removed the footnote from the erythrocyte sedimentation rate (ESR) row of the Schedule of Events table that states the ESR sample will be analyzed by the central laboratory (ESR samples will be analyzed locally using kits provided by the central lab, see row below)	Table 1 Schedule of Events Section 8.1.1 Footnotes for Schedule of Events Table, footnote #2 Section 8.1.1 Footnotes for Schedule of Events Table, footnote #4 Section 8.1.1 Footnotes for Schedule of Events Table, footnote #6 Section 8.1.1 Footnotes for Schedule of Events Table, footnote 8 Section 8.1.1 Footnotes for Schedule of Events Table, footnote #19

Change and Rationale	Sections Changed
• Clarified in footnote #4 that patients will review a "Participating in a Research Study: What You Need to Know" brochure and a "Reporting Your Pain' brochure at the screening and pre-randomization visits • Added a urine pregnancy test at week 28 • Added a footnote to state that HIV and/or hepatitis testing with be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards • Clarified that walking index joint pain NRS scores are recorded by the patient at home and not onsite at the pre-randomization visit	
The laboratory Testing text has been corrected to state that ESR testing will be performed at the site using kits provided by the central laboratory Drugs included in the urine drug test have been listed.	Section 8.2.3.11 Laboratory Testing
Corrected the text describing the Healthcare Resource Utilization Questionnaire to state that the sites (not the patients) will complete the questionnaire.	Section 8.2.2.7 Healthcare Resource Utilization Questionnaire
The efficacy analyses in the Statistical Plan have been updated to be consistent across the fasinumab program	Clinical Study Protocol Synopsis: Statistical Plan Section 10.1 Statistical Hypothesis Section 10.4.3.1 Primary Efficacy Analysis Section 10.4.3.2 Secondary Efficacy Analysis Section 10.5 Additional Statistical Data Handling Conventions
	Section 10.4.4.4 Treatment Compliance
REGN475 has been removed from the compound name on the title page and it has been clarified in the Introduction that fasinumab is also known as REGN475 (for consistency across the fasinumab program)	Title Page Section 1 Introduction
Minor edits have been made to the text throughout the document for clarity, to delete redundant text, to make minor corrections, and to ensure consistency across the fasinumab program.	Clinical Study Protocol Synopsis: Objectives, Study Design, Endpoints List of Abbreviations and Definitions of Terms Section 1 Introduction Section 2.1 Primary Objective Section 2.2 Secondary Objective(s) Section 2.3 Exploratory Objectives Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 4.3 Safety Endpoints Section 5.1 Study Description and Duration Section 5.1.1 Screening and Pre-Randomization Section 5.1.5 Follow-up Period

Change and Rationale	Sections Changed
	Section 6.2.1 Inclusion Criteria, #6 Section 6.2.1 Inclusion Criteria, #8 Section 6.2.1 Inclusion Criteria, #9 Section 6.2.2 Exclusion Criteria, #29 Section 7.1 Investigational and Reference Treatments Section 7.3.2.1 Reasons for Permanent Discontinuation of Study Drug Section 7.3.2.2 Reasons for Temporary Discontinuation of Study Drug Section 7.4.1 Acute Injection Reactions (header deleted) Section 7.5 Method of Treatment Assignment Section 7.7.1 Prohibited Medications Section 7.7.2 Permitted Medications and Procedures Table 1 Schedule of Events Section 8.1.3 Early Termination Visit Section 8.2.1.8 Instructions for Use of Diary (section added) Section 8.2.1.9 Patient Education Brochures (section added) Section 8.2.2.3 Walking Index Joint Pain Numeric Rating Score Section 8.2.2.4 Work Productivity and Activity Impairment Section 8.2.2.8 Treatment Satisfaction Questionnaire for Medication Section 8.2.3.1 Vital Signs Section 8.2.3.10 Procedures to be Performed Only in the Event of Joint Replacement Section 8.2.3.11 Laboratory Testing Section 8.2.4.1 Drug Concentration Measurements and Samples Section 9.4.3 Other Events that Require Accelerated Reporting Section 9.6.1.1 Adjudicated Arthropathy Section 9.6.1.3 Peripheral Sensory Adverse Events Section 11.2 Electronic Systems Section 12.1 Monitoring of Study Sites

Amendment 3 Global

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

Amendment 2CA (obsolete)

The purpose of this amendment was to incorporate health authority feedback. This amendment was not implemented.

Amendment 2 (obsolete)

The purpose of this amendment was to incorporate Ethics Committee feedback, to make edits for clarity and to ensure consistency across the program, and to make minor corrections. This amendment was not implemented.

Amendment 1

The purpose of this amendment was to incorporate health authority feedback, to make minor edits to the text to improve clarity, remove redundant text and to correct typos.

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3 Randomized, Double-Blind, Multi-Dose, Placebo And NSAID-Controlled Study To Evaluate The Efficacy And Safety Of Fasinumab In Patients With Pain Due To Osteoarthritis Of The Knee Or Hip
Site Location(s) **Principal Investigator**	To be determined
Objective(s)	**Primary Objective** The primary objective of the study is to evaluate the efficacy of fasinumab compared to placebo, when administered for up to 24 weeks in patients with pain due to osteoarthritis (OA) of the knee or hip. **Secondary Objective(s)** The secondary objectives of the study are: • To evaluate the efficacy of fasinumab compared to non-steroidal anti-inflammatory drugs (NSAID)s, when administered for up to 24 weeks in patients with pain due to OA of the knee or hip • To assess the safety and tolerability of fasinumab compared to placebo and compared to NSAIDs, when administered for up to 24 weeks in patients with pain due to OA of the knee or hip • To characterize the concentrations of fasinumab over time when administered for up to 24 weeks in patients with pain due to OA of the knee or hip • To evaluate the immunogenicity of fasinumab administered for up to 24 weeks in patients with pain due to OA of the knee or hip **Exploratory Objectives** • To evaluate patient-reported outcome measures in patients with pain due to OA of the knee or hip treated for up to 24 weeks with fasinumab compared to placebo and compared to NSAIDs • To evaluate the use of rescue medication in patients with pain due to OA of the knee or hip treated for up to 24 weeks with fasinumab compared to placebo and compared to NSAIDs
Study Design	This study is a randomized, double-blind, placebo- and NSAID-controlled study designed to evaluate the efficacy and safety of fasinumab in patients with OA of the knee or hip who have a history of inadequate pain relief with acetaminophen/paracetamol and a history of intolerance to or inadequate pain relief with opioids (or are unwilling to take opioids or have lack of access to opioids). The study consists of a screening period of up to 30 days, a 7 to 10 day pre-randomization/washout period (7 days with a +3 day window), a 24-week treatment period, a 20-week follow-up period, and a final phone call approximately 52 weeks after the last subcutaneous (SC) dose of study drug. **Screening and Pre-Randomization**

Prior to randomization, patients will undergo screening procedures, including X-ray of the shoulders, hips, and knees, and magnetic resonance imaging (MRI) of the index and contralateral joints must be performed and assessed by the central imaging vendor. In addition, any knee or hip joint with a K-L score of ≥3 will have MRI completed during the screening period. During the screening period, all patients will continue to take their current treatment regimen for OA pain, which must include use of an oral NSAID on a regular basis, defined as approximately 4 days per week over the last 4 weeks.

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

Randomization

Patients will be randomized on day 1 (baseline) in a 2:1:1:1 ratio to receive 1 of the following:

- Fasinumab 1 mg SC Q4W
- Diclofenac 75 mg oral, twice daily
- Celecoxib 200 mg oral once daily
- Placebo

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

Treatment

During the treatment period (day 1 through week 24), patients will be permitted to use only acetaminophen/paracetamol as rescue medication. Patients will record their use of acetaminophen/paracetamol in a diary.

The study visits during the treatment period will include 1 phone visit on day 15 (±3 day).

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

Follow-up

After the end of treatment, follow-up of patients will continue for an additional 20 weeks after the last visit. Safety and efficacy assessments will be performed similarly to those of the treatment period.

If a patient must undergo joint replacement (JR) surgery during the study, he or she will be asked to complete pre-operative imaging and to undergo post-surgery follow-up.

End of study Phone Contact

A phone contact questionnaire will be conducted at approximately 52 weeks after administration of the last dose of SC study drug 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).

Study Duration	The duration of the study is up to 72 weeks excluding 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:	The sample size has been revised from 2700 patients in the previous amendments to approximately 1620 patients in amendment 4 due to the discontinuation of fasinumab 3 mg Q4W and 6 mg Q8W dose regimens. There will be approximately 600 patients randomized to the fasinumab 1 mg SC Q4W group, 300 patients randomized to the each of the NSAID groups, and 300 patients randomized to the placebo group (a total of 1500 patients). In addition, approximately 60 patients each were enrolled in the fasinumab 3 mg SC Q4W and 6 mg SC Q8W groups under earlier versions of the protocol before dosing was discontinued in these treatment groups.
Target Population:	Men and women who are at least 18 years of age at the time of study entry with a clinical diagnosis at the screening visit of OA of the knee or hip, based on the American College of Rheumatology criteria, and with radiologic evidence of OA (K-L score ≥2) at the index joint.
Treatment(s)	
SC Study Drug Dose/Route/Schedule:	Fasinumab 1 mg SC every 4 weeks (Q4W).
Oral Study Drug Dose/Route/Schedule:	Celecoxib (200 mg oral once daily) Diclofenac (75 mg oral twice daily)
SC Study Drug Placebo Route/Schedule:	Fasinumab placebo SC Q4W
Oral Study Drug Placebo Route/Schedule:	NSAID placebo (oral, see below for schedule).
	Patients will receive study drug and reference treatments as follow to maintain the study blind: • Fasinumab 1 mg SC Q4W and NSAID-matching placebo oral, twice daily • Fasinumab-matching placebo SC Q4W and diclofenac 75 mg oral, twice daily • Fasinumab-matching placebo SC Q4W, celecoxib 200 mg oral once daily, and NSAID-matching placebo oral once daily • Fasinumab-matching placebo SC Q4W and NSAID-matching placebo oral, twice daily

Rescue Treatment:	During the 24-week treatment period, acetaminophen/paracetamol will be the only study-provided rescue medication. In the event that pain relief for OA pain is inadequate, or in the event of other pain (eg, headache) or fever, 1 to 2 tablets/capsules of acetaminophen/paracetamol may be taken no less than 4 hours apart as needed according to local standard of care. The maximum daily dose during the treatment and follow-up periods is 2500 mg (500 mg x 5 tablets/capsules) in countries where 500 mg strength tablets/capsules are available, or 2600 mg (325 mg x 8 tablets/capsules) in countries where 325 mg strength tablets/capsules are available.

Endpoint(s)

Primary:

The co-primary endpoints are:

1. Change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale scores from baseline to week 24 in patients treated with fasinumab compared to patients treated with placebo.
2. Change in the WOMAC physical function subscale scores from baseline to week 24 in patients treated with fasinumab compared to patients treated with placebo.

Secondary:

The key secondary endpoints of the study are:

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

Safety:

The safety endpoints in this study are:

1. Incidence of AA (as confirmed by independent adjudication)
2. Incidence of destructive arthropathy (DA) (as confirmed by independent adjudication)
3. Incidence of TEAEs
4. Incidence of sympathetic nervous system dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist)
5. Incidence of peripheral sensory AEs that require a neurology or other specialty consultation
6. Incidence of all-cause JRs through week 24 and through the follow-up period (week 44)

	7. Incidence of JR at telephone survey 52 weeks after completion of study drug
Procedures and Assessments	At the screening visit, patients will provide informed consent, medical history, and medication history. Determination of the K-L score of the knee or hip will be performed to establish a diagnosis of OA based on the American College of Rheumatology criteria using a K-L score cutoff of ≥2. Patients will be assessed for childbearing potential and complete a self-reported assessment of peripheral or central pain. Efficacy will be assessed by the change from baseline in the WOMAC pain and physical function subscale scores, the PGA, the Numeric Rating Scale of the average walking index joint pain, the EuroQoL 5 Dimensions 5 Level Questionnaire, the 36-item Short Form Survey, the Healthcare Resource Utilization Questionnaire, the Work Productivity and Activity Impairment-Osteoarthritis, and the Treatment Satisfaction Questionnaire for Medication. The WOMAC total and stiffness scores will also be evaluated. Safety assessments will be performed at each study visit during treatment period and upon occurrence of any joint adverse events (AEs). Potential events of AA will be monitored via clinical signs and symptoms of worsening joint pain during the study and adjudication of pre-operative imaging for patients who undergo JR during the conduct of the study. Potential events of sympathetic nervous system dysfunction will be monitored throughout the study through physical examination, AE reporting, assessment of orthostatic hypotension, and the Survey of Autonomic Symptoms. Approximately 52 weeks after administration of the last dose of SC study drug, a phone contact questionnaire will be conducted to document patient status with regard to JR surgery (if patient underwent, is scheduled for, or is on a wait list for JR surgery). Patients who had an AA will have an MRI performed of the affected joint(s).
Statistical Plan	**Statistical Hypothesis** There are 6 hypotheses for the primary and key secondary endpoints. The primary treatment comparison for the WOMAC pain and physical function subscale scores will be declared superior only if the comparisons are significant for both WOMAC pain and physical function subscale scores. A sequentially rejective multiple test procedure will be applied to control for multiplicity and to maintain study-wise Type I error rate at two-sided 0.05 level for the hypotheses (Hi, i=1,…, 6 for fasinumab 1 mg Q4W) for the primary and key secondary endpoints. **Justification of Sample Size** Assuming a 2-sided alpha level 0.05 and a 20% dropout rate up to week 24, an enrollment of 600 patients in the fasinumab 1 mg SC Q4W group and 300 patients in the placebo group will provide at least 99% power to detect an effect size of 0.46 in the WOMAC pain and physical function subscale scores (ie, absolute treatment difference of 1.1 between fasinumab and placebo with a SD of 2.4). The assumed treatment difference and SD are based on results from study R475-PN-1227. The sample size will provide 99% power to detect an effect size of 0.36 in PGA (ie, absolute treatment difference of 0.4 with a SD of 1.1, R475-PN-1227).

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

Statistical Methods

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

The primary efficacy variables will be analyzed using multiple imputation approach with mixed-effect model for repeated measure (MMRM) based on the FAS with adjustment for missing data due to lack of efficacy or adverse events assuming the WOMAC scores would on average return to baseline values. The imputed data for patients discontinued from the study treatment due to lack of efficacy or AEs will be centered at the mean baseline value. The missing data for patients who discontinued treatment due to other reasons will be imputed under missing-at-random assumption. Sensitivity analysis using tipping point approach with multiple imputation will be performed to assess the robustness of the results due to data that may be missing not-at-random.

For analysis of continuous secondary endpoints, the analysis method will be the same as that used for the primary variables. For analysis of categorical variables in secondary endpoints, eg, proportions of patients with ≥30% improvement in the WOMAC pain subscale scores at week 24, the Cochran Mantel Haenszel approach stratified by the randomization strata will be used with missing data considered as non-response.

Safety data including treatment-emergent adverse events and treatment-emergent adverse events of special interest, vital signs, physical examinations, laboratory tests, electrocardiograms, and anti-drug antibody formation will be listed and summarized by treatment group.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5-ASA	5-aminosalicylic acid
AA	Adjudicated arthropathy
ACE	Angiotensin-converting enzyme
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AUC	Area under the curve
bpm	Beats per minute
C_{max}	Maximal concentration
CRF	Case report form (electronic or paper)
CRO	Contract research organization
C_{trough}	Trough concentrations
CTCAE	Common Terminology Criteria for Adverse Events
DA	Destructive arthropathy
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQoL 5 Dimensions 5 Level Questionnaire
ESR	Erythrocyte sedimentation rate
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HbA1c	Hemoglobin A1c
HCRU	Healthcare Resource Utilization
hs-CRP	High-sensitivity C-reactive Protein
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board

IV	Intravenous
IWRS	Interactive web response system
JR	Joint replacement
K-L	Kellgren-Lawrence
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model for Repeated Measures
MRI	Magnetic Resonance Imaging
NGF	Nerve growth factor
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
PGA	Patient Global Assessment
PK	Pharmacokinetic
PPS	Per protocol set
Pre-op	Pre-operative
PT	Preferred term
QRS	Complex of Q, R, and S waves on an electrocardiogram
Q4W	Every 4 weeks
Q8W	Every 8 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation
SF-36	36-item Short Form Medical Outcomes Study Questionnaire Version 2
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TrkA	Tyrosine kinase type 1
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
US	United States
WBC	White blood cell

WOCBP	Woman of child-bearing potential
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WPAI-OA	Work Productivity and Activity Impairment-Osteoarthritis

1. INTRODUCTION

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

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

Treatment guidelines for OA suggest that opioids may be used in OA only if management with NSAIDs is ineffective, intolerable, or otherwise contraindicated (American College of Rheumatology Subcommittee on Osteoarthritis Guidelines 2000). However, the use of opioids is limited by central nervous system effects, nausea and vomiting, constipation, and potential for abuse and dependence. In addition, opioid use may be associated with both acute and chronic side effects, including drowsiness, dizziness, gastrointestinal intolerability, motor imbalance, respiratory depression, and even death. Opioid use must be closely monitored in patients who are vulnerable or are potentially vulnerable to abuse or addiction. Moreover, there is no evidence to support superiority of opioids over other available pain medications. While the efficacy of opioids in treating pain over a short duration is supported by research data (Smith 2016), long-term efficacy has not been evaluated.

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

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

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

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

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

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

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

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

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

In the phase 2/3 study of fasinumab in patients with pain due to OA of the knee or hip (R475-PN-1227), 26 AA events occurred in 24 patients. There was an increase in AA events that appeared to be related to greater fasinumab dose. Although these events were milder than the severe DA events presented at the 2012 FDA Arthritis Advisory Committee, in consideration of the lack of an observed dose response for efficacy in OA, the benefit-risk ratio was deemed unfavorable for the fasinumab 6 mg Q4W and 9 mg Q4W doses in patients with OA, in comparison to the other fasinumab doses that were studied, (ie, 1 mg Q4W and 3 mg Q4W). The dose regimens that were being evaluated in the phase 3 studies for OA pain in the knee or hip included 1 mg Q8W, 1 mg Q4W, 3 mg Q4W, and 6 mg Q8W. In April 2018, the independent Data Monitoring Committee (DMC) recommended discontinuing 6 mg Q8W and 3 mg Q4W (expected to have similar exposure to 6 mg Q8W) based on a review of unblinded data in an on-going study in the fasinumab phase 3 OA program (R475-PN-1523). Subsequently a small Regeneron team reviewed the data and agreed with this recommendation. The DMC noted imbalances in clinically relevant adverse events including time to total joint replacement, peripheral edema, arthralgia and a trend towards early fractures. The phase 3 program for OA pain in the hip or knee 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.

Fasinumab is currently being evaluated in 2 phase 3 studies in patients with pain due to OA. Study R475-PN-1523 is currently ongoing and is designed to assess the long-term safety and efficacy of multiple doses of fasinumab compared to placebo in patients with OA of the hip or knee. Study R475-OA-1611 is designed to compare the efficacy and safety of fasinumab to placebo and to naproxen, a standard-of-care NSAID for moderate-to-severe pain due to OA of the hip or knee. The phase 3 study described here, R475-OA-1688, is designed to compare the efficacy and safety

of fasinumab to placebo, and to a pooled NSAID arm (celecoxib or diclofenac, which are additional standard-of-care NSAIDs for moderate-to-severe pain due to OA of the hip or knee).

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

2. STUDY OBJECTIVES

2.1. Primary Objective

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

2.2. Secondary Objective(s)

The secondary objectives of the study are:

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

2.3. Exploratory Objectives

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

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

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

3.2. Rationale

3.2.1. Rationale for Study Design

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

The target study population was chosen because they currently have unmet medical needs with respect to incomplete pain control, in spite of the availability of NSAIDs. This study will provide efficacy and safety data for OA patients exposed for up to 24 weeks to fasinumab, a pooled NSAID comparator group (celecoxib or diclofenac), or placebo. The study will be conducted with appropriate eligibility criteria to exclude patients who may be at risk for events of joint damage and sympathetic nervous system effects.

Rescue medication (acetaminophen/paracetamol) will be made available for any patient with breakthrough pain. Specific questionnaires and physical examinations will be employed to monitor for any events of arthralgia, worsening joint pain, altered peripheral sensation, AA, and sympathetic nervous system effects.

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

The inclusion of a placebo treatment group is important to accurately determine the efficacy of fasinumab. Non-steroidal anti-inflammatory drugs are the most common medications used to treat pain due to OA. Therefore, comparison of fasinumab to the NSAIDs treatment group will aid in determining the efficacy of fasinumab compared to a frequently used and effective standard of care class of medications for OA, but that have associated clinically significant AEs. As celecoxib and diclofenac are commonly used and highly effective NSAIDs (Ong 2007), they have been selected as comparator drugs for this study. As a widely studied, standard of care therapy for OA, NSAIDs will serve as an effective calibrator to best understand the potential therapeutic benefit of fasinumab in this study population.

Inclusion of both the placebo group and the active treatment comparator group will be important to accurately estimate the risk of AEs, including the AEs of special interest of adjudicated arthropathy and sympathetic nervous system dysfunction. All patients included in the study will have regular study visits and receive diagnostic procedures (ie, X-rays, magnetic resonance imaging [MRI]) to evaluate their ongoing OA. Adverse event monitoring will be ongoing throughout the trial. A patient or investigator can choose to end participation at any time. Patients will have access to rescue medication, as appropriate. Therefore, the use of a placebo group is justified, as placebo-treated patients will not be placed at significant risk.

The patients will be stratified by the affected index joint (hip or knee), by Kellgren-Lawrence (K-L) score (2 to 3, or 4), and by geographic region to enable analysis of efficacy and safety. The

K-L stratification scheme is used here to ensure that at baseline there is an equal distribution of patients with the most severe OA at baseline across the dosing groups.

3.2.2. Rationale for Dose Selection

Previous versions of this protocol randomized patients to receive fixed-dose, subcutaneous (SC) injections of 1 mg of fasinumab Q4W, 3 mg fasinumab Q4W, 6 mg fasinumab every 8 weeks (Q8W with alternating placebo injections at the monthly visits where fasinumab will not be given, to maintain the blind), celecoxib active comparator, diclofenac active comparator, or matching placebo. Based on April 2018 recommendations from an independent Data Monitoring Committee (DMC) that reviewed unblinded data from a different ongoing phase 3 study of fasinumab (R475-PN-1523), the decision was made to discontinue further evaluation of fasinumab at 3 mg Q4W or 6 mg Q8W in the phase 3 program. This recommendation was based on an imbalance in clinically relevant adverse events including time to total joint replacement, peripheral edema, arthralgia and a trend towards fractures. Under amendment 3 global, all patients previously randomized to 3 mg Q4W or 6 mg Q8W under an earlier version of the protocol were discontinued from study drug but encouraged to otherwise continue all protocol visits and study procedures in the follow-up period and the end of study phone call.

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

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

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

In the R475-PN-1227 phase 2/3 study of fasinumab in patients with pain due to OA of the hip or knee, all SC doses (1 mg, 3 mg, 6 mg, and 9 mg Q4W) demonstrated efficacy in pain relief and physical function measures, based upon WOMAC pain and physical function scales assessed after 16 weeks of treatment. Considering the relative lack of an observed dose response for efficacy and the 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 in 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.

All randomized patients in this study will receive an orally administered NSAID or matching NSAID placebo. The dose of diclofenac will be 75 mg twice daily. The dose of celecoxib will be 200 mg once daily. These NSAID doses reflect the recommendations in the US label for treatment of pain associated with OA. In order to preserve the blind, patients randomized to celecoxib will receive celecoxib 200 mg once daily in the morning and a matching celecoxib placebo in the afternoon. Patients randomized to matching NSAID placebo will receive the placebo twice daily. All NSAIDs and matching NSAID placebo will be over-encapsulated to preserve the blind.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

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

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The co-primary endpoints are:

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

4.2.2. Secondary Endpoints

The key secondary endpoints of the study are:

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

5. Change from baseline to week 24 in PGA score in patients treated with fasinumab compared to patients treated with NSAIDs (pooled celecoxib and diclofenac arms)

4.2.3. Exploratory Endpoints

Exploratory endpoints will be defined in the Statistical Analysis Plan.

4.3. Safety Endpoints

The safety endpoints in this study are:

- Incidence of AA (as confirmed by independent adjudication)
- Incidence of DA (as confirmed by independent adjudication)
- Incidence of TEAEs
- Incidence of sympathetic nervous system dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist)
- Incidence of peripheral sensory AEs that require a neurology or other specialty consultation
- Incidence of all-cause JRs through week 24 and through the follow-up period (week 44)
- Incidence of JR at telephone survey 52 weeks after completion of study drug

4.4. Pharmacokinetic Variables

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

4.5. Anti-Drug Antibody Variables

Anti-drug antibody (ADA) variables include status (positive or negative) and titer as follows:

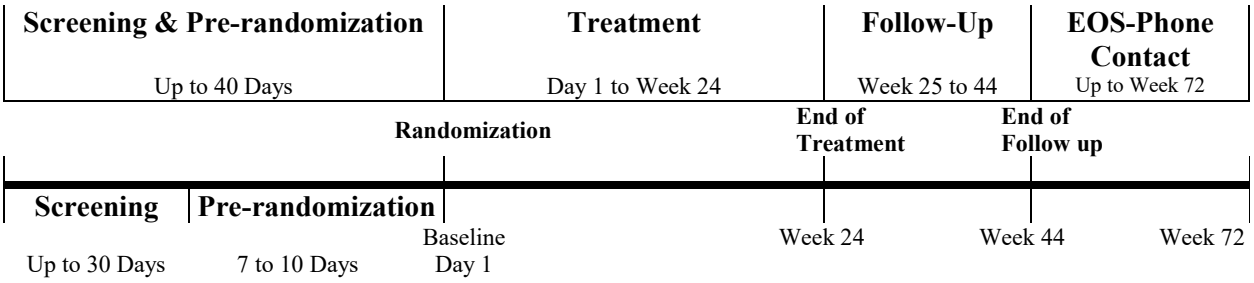
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative
- Treatment boosted ADA response, defined as any post-dose positive ADA assay response that is 9-fold or greater over baseline titer levels when baseline is positive in the ADA assay
- Titer values
- Titer category
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- Neutralizing ADA for samples that are positive in the ADA assay

5. STUDY DESIGN

5.1. Study Description and Duration

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

Figure 1: Study Flow Diagram



EOS- End of study

5.1.1. Screening and Pre-Randomization

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

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

5.1.2. Rescreening

Re-testing During Screening or Pre-randomization

An assessment that fails to meet eligibility criteria may be repeated once within the screening or pre-randomization period when approved by the sponsor or designated Medical Monitor under either of the following conditions: 1) the failure is believed by the investigator to be due to a condition that would resolve or could be treated, or 2) a laboratory value minimally exceeds the cut-off value and is not clinically relevant. Only the assessments that did not meet the eligibility criteria require repetition, if done within the screening period or pre-randomization period. Patients may not repeat any assessments if they do not meet the WOMAC criteria or have orthostatic hypotension (defined in Section 8.2.3.3) during the screening or pre-randomization visit.

Rescreening Due to Screen Failure

Rescreening can be completed for patients who fail to meet the screening visit window requirements or who are unable to complete all imaging assessments within the specified screening period. Patients who are rescreened after the pre-randomization window must be declared screen failures, be registered in the interactive web response system (IWRS) as a new patient with a new identification number, and then repeat all screening procedures, with the exception of imaging assessments. Any imaging assessments would need to be repeated only if they were taken more than 60 days from completion of the previous screening X-rays and MRI assessments. Patients cannot rescreen if they have screen failed due to not meeting the WOMAC criteria or have orthostatic hypotension (defined in Section 8.2.3.3) during the screening or pre-randomization visit.

5.1.3. Randomization

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

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

Patients will receive treatment as described in Section 7.1. The method of treatment assignment is described in Section 7.5.

5.1.4. Treatment Period

During the treatment period (day 1 through week 24), patients will be permitted to use only acetaminophen/paracetamol as rescue medication. The study visits during the treatment period will include 1 phone visit on day 15 (±3 days). Patients will record their use of acetaminophen/paracetamol in a diary. Patients should discontinue use of acetaminophen/paracetamol at least 24 hours prior to the start of study visits in order to minimize the confounding effects of the rescue medication on efficacy measurements.

Efficacy will be assessed by the change from baseline in the WOMAC pain and physical function subscale scores, the PGA, the Numeric Rating Scale (NRS) of the average walking index joint

pain, the Work Productivity and Activity Impairment-Osteoarthritis (WPAI-OA), the 36-item Short Form Survey (SF-36), the EuroQoL 5 Dimensions 5 Level Questionnaire (EQ-5D-5L), the Healthcare Resource Utilization (HCRU) questionnaire, and the Treatment Satisfaction Questionnaire for Medication (TSQM). The WOMAC total and stiffness scores will also be evaluated.

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

5.1.5. Follow-up Period

After the end of treatment, follow up of patients will continue for an additional 20 weeks after the last treatment period visit. Safety and efficacy assessments will be performed according to the schedule outlined in Table 1.

If a patient must undergo JR surgery during the study, he or she will be asked to complete pre-operative imaging and to undergo post-surgery follow-up as outlined in Table 2.

5.1.6. End of Study Phone Contact

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

5.1.7. Study Stopping Rules

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

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

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

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

5.1.8. End of Study Definition

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

5.2. Planned Interim Analysis

No interim analysis of efficacy is planned for this study. The primary efficacy analysis may be conducted when 24 week data are available for all randomized patients. No alpha adjustment is necessary, as the week 24 efficacy analysis will be the final primary analysis for efficacy. The results will not be disclosed to any site-facing personnel or to any personnel directly involved with the conduct of the study.

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

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

5.3.2. Arthropathy Adjudication Committee

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

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

The sample size for this study has been revised from 2700 patients in the previous amendments to approximately 1620 patients in amendment 4 due to the discontinuation of fasinumab 3 mg Q4W and 6 mg Q8W dose regimens. There will be approximately 600 patients randomized to the fasinumab 1 mg SC Q4W group, 300 patients randomized to the each of the NSAID groups, and 300 patients randomized to the placebo group (a total of 1500 patients). In addition, approximately, 60 patients each were enrolled in the fasinumab 3 mg SC Q4W and 6 mg SC Q8W groups prior to the implementation of the urgent safety measure to discontinue these doses.

6.2. Study Population

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

6.2.1. Inclusion Criteria

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

1. Male and female patients, at least 18 years of age, at screening

2. Provide signed informed consent
3. Body mass index ≤39 at screening visit
4. A clinical diagnosis of OA of the knee or hip based on the American College of Rheumatology criteria with radiologic evidence of OA (K-L score ≥2 for the index joint) at the screening visit, with the following definitions:
   - The index joint is defined as the joint with OA under evaluation for this study
   - A joint previously treated with JR surgery cannot be the index joint
   - A joint previously surgically modified within the past year cannot be the index joint (with the exception of cruciate ligament reconstruction surgery, patellar fracture repair surgery, or meniscal repair)
   - If a patient has a K-L score of ≥2 at more than 1 knee or hip joint, the index joint is the joint with the greatest WOMAC pain subscore at the screening visit.
   - If 2 or more knee or hip joints have a K-L score of ≥2 and the same WOMAC pain subscore, the index joint is the joint with the greater K-L score.
   - If 2 or more joints have a K-L score of ≥2, the same WOMAC pain subscores, and the same K-L scores, then the investigator may choose 1 of these joints as the index joint
5. Moderate to severe pain in the index joint defined as a WOMAC average pain subscale score of ≥4 at both the screening and randomization visits
6. Willing to discontinue current pain medications and to adhere to study requirements for rescue treatments (acetaminophen/paracetamol to be taken as needed with a maximum daily dose of 2500 mg [countries where 500 mg strength tablets/capsules are available] or 2600 mg [countries where 325 mg strength tablets/capsules are available])
7. A history of at least 12 weeks of analgesic use for pain due to OA of the knee or hip, as defined by
   a. Inadequate pain relief from acetaminophen/paracetamol AND
   b. Intolerance to or inadequate pain relief from opioid or tramadol therapy, unwillingness to take opioid or tramadol therapy for a medically acceptable reason, or lack of access to an opioid or to tramadol
8. Currently using a stable dose of NSAID, defined as using oral NSAIDs at regularly prescribed doses for approximately 4 days per week over the last 4 weeks (patients who are screen failures prior to the randomization visit but who met the NSAID use criterion at screening would still meet this criterion if they are eligible for rescreening)
9. Willing to continue a stable dose of oral NSAID during the screening period, defined as using NSAIDs for approximately 4 days per week
10. Willing to discontinue glucosamine sulfate and chondroitin sulfate treatments during the 24 weeks of treatment
11. Stable treatment with glucosamine sulfate and chondroitin sulfate treatments must be stopped during the pre-randomization period

12. Consent to allow all radiographs and medical/surgical/hospitalization records of care received elsewhere prior to and during the study period to be shared with the investigator
13. Willing to maintain current activity and exercise levels throughout the study
14. Willing and able to comply with clinic visits and study-related procedures and willing to provide follow-up information related to any JR surgery that occurs within the period of time covered by their intended participation in the study
15. Able to understand and complete study-related questionnaires

6.2.2. Exclusion Criteria

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

1. Non-compliance with the NRS recording during the pre-randomization period (4 or more consecutive missed diary entries)
2. History or presence at the screening visit of non-OA inflammatory joint disease (eg, rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudo-gout, gout, spondyloarthropathy, polymyalgia rheumatica, joint infections within the past 5 years), Paget's disease of the spine, pelvis or femur, neuropathic disorders, multiple sclerosis, fibromyalgia, tumors or infections of the spinal cord, or renal osteodystrophy
3. History or presence on imaging of arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressive OA type 1 or type 2), stress fracture, recent stress fracture, neuropathic joint arthropathy, hip dislocation (prosthetic hip dislocation is eligible), knee dislocation (patella dislocation is eligible), congenital hip dysplasia with degenerative joint disease, extensive subchondral cysts, evidence of bone fragmentation or collapse, or primary metastatic tumor with the exception of chondromas or pathologic fractures during the screening period
4. Trauma to the index joint within 3 months prior to the screening visit
5. Signs or symptoms of carpal tunnel syndrome within 6 months of screening
6. Patient is not a candidate for MRI
7. Is scheduled for a JR surgery to be performed during the study period or who would be unwilling or unable to undergo JR surgery if one eventually became necessary
8. History or presence at the screening visit of autonomic neuropathy, diabetic neuropathy, or other peripheral neuropathy, including reflex sympathetic dystrophy
9. History or diagnosis of chronic autonomic failure syndrome including pure autonomic failure, multiple system atrophy (Shy-Drager syndrome)
10. History of NSAID intolerance, or existence of a medical condition that is high risk for NSAID-associated complications (eg, high risk of gastrointestinal bleed, previous ulcer, condition requiring the use of anti-coagulants or anti-platelet therapy, or acute coronary syndrome)
11. Known allergy or sensitivity to doxycycline or related compounds, or monoclonal antibodies or sulfa drugs.

12. Poorly controlled diabetes (defined as any single value of hemoglobin A1c [HbA1c] >9.0%) at the screening visit
13. Known history of human immunodeficiency virus infection
14. Known history of ocular herpes simplex virus, herpes simplex virus pneumonia, or herpes simplex virus encephalitis
15. History of sickle cell disease, including sickle cell anemia and β-thalassemia
16. Confirmed elevated screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 times the upper limit of normal (ULN)
17. Resting heart rate of <50 beats per minute (bpm) or >100 bpm (by vital sign assessment or as captured during electrocardiogram [ECG] assessment) at the screening or randomization visits
18. History or presence of 2nd or 3rd degree heart block, 1st degree heart block with abnormal QRS complex, or bifascicular block by ECG assessment at the screening visit
19. History or presence of orthostatic hypotension, as defined in Section 8.2.3.2, at the screening, pre-randomization, or randomization visits
20. History of poorly controlled hypertension, as defined by:
    a. Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg at the screening visit
    b. Systolic blood pressure of 160 mm Hg to 179 mm Hg or diastolic blood pressure of 100 mm Hg to 109 mm Hg at the screening visit, AND a history of end-organ damage (including history of left ventricular hypertrophy, heart failure, angina, myocardial infraction, stroke, transient ischemic attack, peripheral arterial disease and moderate to advanced retinopathy [hemorrhages or exudates, papilledema])
21. Congestive heart failure with NY Heart Classification of stage III or IV (Dolgin 1994)
22. History of peripheral vascular disease, transient ischemic attack, cerebrovascular accident, myocardial infarction, unstable angina, or documented atherosclerotic cardiovascular disease
23. Significant concomitant illness including, but not limited to, psychiatric, cardiac, renal, hepatic, neurological, endocrinological, metabolic, or lymphatic disease that, in the opinion of the investigator, would adversely affect the patient's participation in the study
24. New major illness diagnosed within 2 months prior to the screening visit
25. Known history of infection with hepatitis B virus. Patients with a history of hepatitis B are eligible if there is documentation of a negative test for hepatitis B surface antigen and a positive test for antibodies to the hepatitis B virus surface antigen
26. Known history of infection with the hepatitis C virus. Patients with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test
27. History or presence of malignancy within the last 5 years prior to screening, except patients who have been treated successfully with no recurrence for >1 year of basal cell or squamous cell carcinoma of the skin or in-situ cervical cancer

28. History of hospital admission for depression or suicide attempt within 5 years or active, severe major depression at screening
29. Use of systemic, eg, IV, oral or intramuscular corticosteroids within 30 days prior to the screening visit. Intra-articular corticosteroids in the index joint within 12 weeks prior to the screening visit, or to any other joint within 30 days prior to the screening visit (topical, intra-nasal, and inhaled corticosteroids are permitted)
30. Use of a monoamine reuptake inhibitor, tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors for treatment of pain within 4 weeks prior to the screening visit
31. Has positive urine drug test results during screening (eg, amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates), unless in the opinion of the investigator, the positive test results may be due to the patient's current permitted medications.
32. History of (within 5 years prior to the screening visit) or current alcoholism, alcohol abuse, substance abuse, or abuse of prescription pain medication
33. History of cannabis use for the treatment of pain within the past 6 months prior to the screening visit
34. Ongoing participation in a clinical research study evaluating another investigational drug or having received another investigational product within 30 days or 5 half-lives of the screening visit, whichever is longer
35. Exposure to an anti-NGF antibody prior to the screening visit or known sensitivity or intolerance to anti-NGF antibodies or participation in a clinical trial evaluating anti-NGF antibodies.
36. Member of the clinical site study team and/or his/her immediate family
37. Pregnant or breastfeeding women
38. Women of childbearing potential who have a positive pregnancy test result or do not have their pregnancy test result at baseline
39. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to the 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 are not acceptable methods of contraception. Female condom and male condom should not be used together.

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

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

    GFR = 175 x (Standardized S_{Cr})$^{-1.154}$ x (age)$^{-0.203}$ (x 0.742 if female) x (1.212 if African American)

    GFR is expressed in mL/min/1.73m^2

    S_{Cr} is serum creatinine expressed in mg/dL

    Age is expressed in years

Note: HIV and/or hepatitis testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards.

6.3. Premature Withdrawal from the Study

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

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

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 8.1.3.

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

6.4. Replacement of Patients

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

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Study drug in this study includes fasinumab, NSAID (diclofenac or celecoxib), and their matching placebo. Fasinumab and its matching placebo are SC study drug. NSAID (diclofenac or celeoxib) and its matching placebo are oral study drug.

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

- Fasinumab 2 mg/mL: Each 1 mL single use pre-filled syringe delivers 0.5 mL of a 2 mg/mL solution (1 mg dose) of study drug
- Fasinumab-matching placebo: Each 1 mL single use pre-filled syringe delivers 0.5 mL of placebo solution
- Celecoxib (200 mg capsules), diclofenac (75 mg capsules) and NSAID-matching placebo capsules will be provided by the sponsor. All NSAIDs and NSAID-matching placebo will be over-encapsulated to preserve the blind.

Patients will be randomized 2:1:1:1 to receive 1 of the following treatment regimens:

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

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

NSAIDs or NSAID-matching placebo will be administered orally. A proton pump inhibitor or other gastric protective medication may be prescribed if deemed medically necessary by the investigator or sub-investigator.

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

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

7.2. Rescue Treatment

During the 24-week treatment period, acetaminophen/paracetamol will be the only study-provided rescue medication. In the event that pain relief for OA pain is inadequate, or in the event of other pain (eg, headache) or fever, 1 to 2 tablets/capsules of acetaminophen/paracetamol may be taken

no less than 4 hours apart, as needed, according to local standard of care. The maximum daily dose during the treatment and follow-up periods is 2500 mg (500 mg x 5 tablets/capsules) in countries where 500 mg strength tablets/capsules are available, or 2600 mg (325 mg x 8 tablets/capsules) in countries where 325 mg strength tablets/capsules are available (eg, North America). Where 500 mg strength tablets/capsules are available, the highest individual single dose is 1 gram. Where 325 mg tablets/capsules are available, the highest individual single dose is 650 mg.

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

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

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

7.3. Dose Modification and Study Treatment Discontinuation Rules

7.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

7.3.2. Study Drug Discontinuation

Study drug may be temporarily or permanently discontinued due to medical need, as determined by the investigator, medical monitor, or the sponsor and according to the study stopping rules (Section 5.1.7).

Patients who permanently discontinue from study drug will be encouraged to remain in the study and to complete all study assessments. Patients who agree and thus do not withdraw from the study will be asked to return to the clinic for all remaining study visits per Table 1.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete an early termination visit (Section 8.1.3).

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

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

7.3.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- A patient who is currently enrolled under an earlier version of this protocol must be immediately discontinued from study drug, undergo all end of treatment visit assessments and move directly into the 20-week safety follow-up period under this version of the protocol, if they meet any of the following conditions that were excluded after re-evaluating the safety profile of NSAIDs:
  a) They have a known medical history (at any time) of peripheral vascular disease, transient ischemic attack, cerebrovascular accident, myocardial infarction, unstable angina, or documented atherosclerotic cardiovascular disease; or
  b) They have a known GFR <30 mL/minute/1.73 m^2 or,
  c) They are currently taking combination therapy of a diuretic with either an ACE inhibitor or ARB (Note: Patients may remain in the study if they are willing and able to change their antihypertensive regimen such that they are no longer on a combination of a diuretic with either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
- A patient who was randomized under an earlier version of the protocol to 3 mg SC Q4W or 6 mg SC Q8W fasinumab
- A patient developing clinically significant peripheral sensory or motor neurologic events confirmed by a neurologist's examination and graded by the neurologist as at least moderate peripheral neuropathy limiting activities of daily living, ie, grade ≥2 according to Common Terminology Criteria for Adverse Events (CTCAE) v.4; study sites should use CTCAE v.4 criteria throughout the study for consistency
- Evidence of pregnancy
- A patient developing new or worsening signs and symptoms indicative of carpal tunnel syndrome
- Continued non-compliance with protocol-defined maximum acetaminophen/paracetamol use (with a maximum daily dose of 2500 mg [countries where 500 mg strength tablets/capsules are available] or 2600 mg [countries where 325 mg strength tablets/capsules are available]) during the treatment and follow-up periods, after appropriate counseling
- Continued non-compliance with the protocol, including usage of NSAIDs that are not permitted in the study, after appropriate counseling
- Joint replacement surgery

- Adverse events of special interest (AESIs) of:
  - Adjudicated arthropathy, as described in Section 9.6.1.1
  - Sympathetic nervous system dysfunction, as described in Section 9.6.1.2
- Hepatotoxicity. Study drug should be discontinued if the following are observed:
  1. Total bilirubin (TBL) >2x ULN or international normalized ratio >1.5, and
  2. ALT or AST >3x ULN, and
  3. No other cause for 1 and 2 is readily apparent

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

  NOTE: Study drug may be withheld in patients who do not meet criteria for permanently discontinuing study drug, until an alternative cause for drug-induced liver injury can be determined. The patient may be re-challenged if an alternative cause for elevated liver function tests is found and the liver function tests return to baseline, but only after discussion with the sponsor.
- Systemic hypersensitivity reaction deemed by the investigator to be related to study drug
- Gastrointestinal bleeding, acute coronary syndrome
- Any other medical need, as determined by the investigator
- Sponsor decision
- Patient decision

7.3.2.2. Reasons for Temporary Discontinuation of Study Drug

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

7.4. Management of Acute Reactions

7.4.1. Systemic Injection Reactions

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

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

7.4.2. Local Injection Site Reactions

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

7.5. Method of Treatment Assignment

Approximately 1500 patients will be randomized in a 2:1:1:1 ratio to receive fasinumab (1 mg Q4W), diclofenac, celecoxib, or placebo according to a central randomization scheme provided by an IWRS to the designated study pharmacist (or qualified designee). Randomization will be stratified according to the affected index joint (hip or knee), the K-L score (2 to 3, or 4) at the screening visit, and geographical region.

Prior to amendment 3 global (urgent safety measure), approximately 60 patients each were enrolled in the fasinumab 3 mg Q4W and 6 mg Q8W groups. However, dosing of these patients was discontinued, as recommended by the independent DMC in April 2018. Overall, a total of approximately 1620 patients are planned for this study.

7.5.1. Blinding

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

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

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

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

7.5.2. Emergency Unblinding

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

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

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

7.5.3. Unblinding for Regulatory Reporting Purposes

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

7.6. Treatment Logistics and Accountability

7.6.1. Packaging, Labeling, and Storage

Blinded supplies will be packaged in the following configuration and distributed to sites by Regeneron.

1. One prefilled syringe of investigational SC study drug (Fasinumab or Placebo) per carton
2. Two bottles containing 35 capsules of NSAIDs or NSAID-matching placebo per carton.

Diclofenac carton will consist of two bottles of Diclofenac 75 mg capsules. Celecoxib carton will consist of one bottle of Celecoxib 200 mg capsules and one bottle of NSAID-matching placebo capsules. NSAID-matching placebo carton will consist of two bottles of NSAID-matching placebo capsules.

A drug numbering system will be used to label blinded study drug. Lists linking drug numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

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

7.6.2. Supply and Disposition of Treatments

Subcutaneous and oral study drug will be shipped to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all unopened fasinumab and fasinumab-matching placebo will be returned to the sponsor or designee for destruction; opened fasinumab and fasinumab-matching placebo can be destroyed at the site; opened and unopened diclofenac, celecoxib and NSAID-matching placebo will be returned to the sponsor or designee for destruction.

7.6.3. Treatment Accountability

All drug accountability records must be kept current.

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

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

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

7.6.4. Treatment Compliance

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

7.7. Concomitant Medications and Procedures

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

7.7.1. Prohibited Medications

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

Opioid analgesic medications (including tramadol) are prohibited through the week 24 study visit. Patients will be directed not to take concomitant medications that contain NSAIDs (oral or topical, except up to 150 mg/day of aspirin/5-ASA, which is permitted for cardiac prophylaxis) until at least 16 weeks after the last SC study drug injection. A list of medications containing NSAIDs will be provided in the study reference manual and a reference card given to the patients.

Other excluded medications during the treatment period include:

- Any other investigational agent

- Medical or regular recreational use of marijuana
- Chondroitin sulfate
- Glucosamine
- Hyaluronic acid intra-articular injections
- Anticoagulants and antiplatelets (eg, warfarin, heparins, factor Xa inhibitors, thrombin inhibitors, aspirin/5-ASA >150 mg daily, clopidogrel)
- Muscle relaxants including cyclobenzaprine, carisoprodol, orphenadrine, tizanidine (see Section 7.7.2 for permitted muscle relaxants)
- Corticosteroids (topical, intranasal, and inhaled formulations are permitted), adrenocorticotropic hormone
- Cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus
- Azathioprine, sulfasalazine, hydroxychloroquine
- Interleukin-6 or interleukin-6 receptor antagonists
- Abatacept, ustekinumab
- Tumor necrosis factor antagonists
- IL-1 inhibitors, including diacerein
- Apremilast, and tofacitinib
- Combination therapy of diuretics with either an ACE inhibitor or ARB

7.7.2. Permitted Medications and Procedures

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

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

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

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

Joint replacement is a permitted procedure during the study.

8. SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

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

Table 1: Schedule of Events

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

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

	Screening/ Pre-randomization		Treatment Period									Follow-up Period[1]			EOS
Study Week (wk) Visit (V)/Phone	**Screen V 1**	**Pre-rand V 2**	**Baseline V 3**	**Wk 2 Phone 1**	**Wk 4 V 4**	**Wk 8 V 5**	**Wk 12 V 6**	**Wk 16 V 7**	**Wk 20 V 8**	**EOT Wk 24 V 9**	**ET[1]/ JR Pre-Op Visit**	**Wk 28 V 10**	**Wk 44 V 11**	**ET[1]/ JR Pre-Op Visit**	**Wk 72 Phone 2**
Study Day	Up to 30 Days	7 to 10 Days	1	15	29	57	85	113	141	169		197	309		505
Window (days)				±3	±7	±7	±7	±7	±7	±7		±7	±7		±7
Vital Signs[9]	X		X		X	X	X	X	X	X	X	X	X	X	
Physical Examination	X									X	X		X	X	
Orthostatic blood pressure and heart rate assessment[9,10]	X	X	X		X	X	X	X	X	X	X	X	X	X	
Joint pain questionnaire	X		X		X	X	X	X	X	X	X	X	X	X	
Survey of Autonomic Symptoms	X		X		X	X	X	X	X	X	X	X	X	X	
Neurologic examination	X Full		X Brief		X Brief	X Brief	X Brief	X Brief	X Brief	X Full	X Full	X Brief	X Full	X Full	
Adverse events	---------->														
Injection site evaluation			X		X	X	X	X	X						
Bilateral X-rays (knee, hip, shoulder)	X[11]							X		X	X		X	X	
Event-triggered imaging[12]				X	X	X	X	X	X	X	X	X	X	X	
Pre-op questionnaire (JR follow-up)[13]											X			X	
Electrocardiogram	X									X	X				
EOS phone contact[14]															X
MRI of affected joint(s) for AA patients only[15]															X

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

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

8.1.1. Footnotes for the Schedule of Events Table

1. Patients who discontinue study medication before week 24 will be encouraged to follow the visit schedule through the remainder of the study. If a patient chooses to end study participation, he or she will be asked to return to the clinic as soon as possible for an early termination visit. Imaging assessments need to be repeated if it has been >30 days since the joints were last imaged. If it has been ≤30 days since imaging assessments were completed, imaging assessments may be completed at the discretion of the investigator.
2. HIV and/or hepatitis testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards
3. Only for patients who provide written informed consent for the optional genomics sub-study. The sample should be collected at the day 1 (baseline/randomization) visit, but may be collected at any visit during the study after a patient has been randomized.
4. At the screening and pre-randomization visits, study staff will review the "Participating in a Research Study: What You Need to Know" brochure and the "Reporting Your Pain" brochure with patients to ensure they understand what a clinical study is and how to report their pain accurately. At subsequent visits, patients will be asked to review the "Reporting Your Pain" brochure themselves. At any time during the conduct of the study, patients may require retraining by study staff.
5. Subcutaneous study drug administration will be the last procedure at each dosing visit, and will be done after all laboratory, PK, ADA and research samples have been collected and all study assessments performed. Patients will be observed in the clinic for approximately 1 hour after SC study drug is administered.
6. Use of study-provided rescue medication will be recorded daily using diaries. Acetaminophen/paracetamol use will be reported from pre-randomization visit to week 24.
7. Patients will complete the WOMAC pain subscale for both hips and knees at the screening visit. Then, the WOMAC Full Survey will be completed only for the index joint at subsequent visits.
8. Walking index joint pain NRS score will be recorded by the patient each day using their diary, starting during the pre-randomization period through week 24. Walking index joint pain NRS score will be recorded by the patient at the site at the week 24 visit.
9. If the pulse is less than 45 bpm, an ECG with rhythm strip will be obtained to confirm the heart rate and rhythm.
10. Blood pressure measurements to assess orthostatic hypotension may be discontinued following regulatory approval if the safety database does not reveal an imbalance for the fasinumab treated patients.
11. If screening radiographs are inconclusive for potential joint related findings, an MRI must be performed. Confirmation from the central reader that there are no exclusionary findings on the MRI must be received before a patient can be randomized.

12. Imaging (X-ray and possibly MRI) will be performed at the investigator's discretion on any joint with worsening or exacerbation of pain beyond the fluctuations in pain typical for that patient's OA. This imaging will be submitted to the adjudication committee for review.
13. In the event that a patient must undergo joint arthroplasty during the study, the patient will complete the pre-operative JR study visit (Table 1) and the procedures outlined in the schedule of events for joint arthroplasty follow-up (Table 2). The pre-operative questionnaire would be the Knee Society for knee replacements and the Harris Hip Score questionnaire for hip replacements. The pre-operative visit should be completed before joint arthroplasty if at all possible. Pre-operative imaging will be performed and submitted to the adjudication committee.
14. The purpose of this phone contact is to ask the patient if they have had or are scheduled (or on a waiting list) to have a JR. Pre-operative images will be submitted to the central reader for adjudication, if available.
15. If the affected joint has undergone JR an X-ray may be substituted for an MRI.
16. Samples will be analyzed by the central laboratory and results evaluated by the investigator.
17. Only to be performed if postmenopausal status has to be assessed for female patients who are ≤59 years of age.
18. In the event of a positive urine pregnancy test result, the patient should have a serum pregnancy test with a negative result in order to continue study participation. If the serum pregnancy test is positive, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule.
19. Collection of samples for PK, ADA, high sensitivity C-reactive protein (hs-CRP) and research are mandatory at the time points specified above. In addition, PK, ADA, hs-CRP and research samples may be drawn at any scheduled visit or unscheduled visit if a patient experiences a treatment-related safety TEAE. Samples should be collected prior to SC study drug administration on SC study drug dosing days.
20. Research samples should be collected after the patients have been fasting overnight or for 8 hours (in the event of an afternoon visit).

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

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

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

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

8.1.3. Early Termination Visit

Patients who are permanently withdrawn from study drug early should be encouraged to continue in the study and complete all other study assessments without receiving study drug. If a patient decides to completely withdraw consent from the study, every attempt should be made to have the patient complete an early termination visit, as outlined in Table 1. Imaging assessments need to be repeated if it has been >30 days since the joints were last imaged. If it has been ≤30 days since imaging assessments were completed, imaging assessments may be completed at the discretion of the investigator.

8.1.4. Unscheduled Visits

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

8.2. Study Procedures

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

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

8.2.1.1. Informed Consent

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

8.2.1.2. Medical History

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

8.2.1.3. Medication History

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

8.2.1.4. Demographics

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

8.2.1.5. Determination of Osteoarthritis

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

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

Hip

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

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

Additional information is provided in the study reference manual.

Knee

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

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

Additional information is provided in the study reference manual.

8.2.1.6. Assessment of Childbearing Potential

Each female patient should be evaluated for childbearing potential.

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

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

8.2.1.7. Assessment of Peripheral or Central Pain

Patients will complete a self-reported survey to evaluate the peripheral versus central nature of their pain at time points indicated in Table 1.

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

8.2.1.8. Instructions for Use of Diary

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

8.2.1.9. Patient Education Brochures

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

8.2.2. Efficacy Procedures

8.2.2.1. Western Ontario and McMaster Universities Osteoarthritis Index

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

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

8.2.2.2. Patient Global Assessment of Osteoarthritis

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

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

8.2.2.3. Walking Index Joint Pain Numeric Rating Score

Walking index joint pain intensity (scored using the NRS) will be reported by the patient each day in his or her diary, starting during the pre-randomization period through week 24. Once initial eligibility criteria are confirmed during the screening period, the investigator or designee will review the NRS with the patient at the baseline visit.

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

8.2.2.4. Work Productivity and Activity Impairment

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

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

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

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

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

8.2.2.6. EuroQoL 5 Dimensions 5 Level Questionnaire

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

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

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

8.2.2.7. Healthcare Resource Utilization Questionnaire

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

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

8.2.2.8. Treatment Satisfaction Questionnaire for Medication

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

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

8.2.3. Safety Procedures

8.2.3.1. Vital Signs

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

8.2.3.2. Physical Examination

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

8.2.3.3. Assessment of Orthostatic Blood Pressure and Heart Rate

An assessment of orthostatic blood pressure will be conducted at the time points indicated in Table 1. The assessments should be conducted as per the instructions in the study manual. A patient will be determined to have orthostatic hypotension if any of the following criteria are met:

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

OR

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

OR

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

OR

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

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

8.2.3.4. Joint Pain Questionnaire

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

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

8.2.3.5. Survey of Autonomic Symptoms

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

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

8.2.3.6. Neurologic Examination

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

8.2.3.7. Imaging

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

Radiographs

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

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

MRI

During screening, MRIs of the index and contralateral joint as well as joints with a K-L score ≥3 will be sent to a central reader to confirm that there is no evidence of an exclusionary feature. 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.

8.2.3.8. Electrocardiogram

A standard 12-lead ECG will be performed at the time points indicated in Table 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 the QT and QTc intervals will be recorded. The ECG data will be read by a central reading center. Detailed procedures will be provided in a separate manual provided by the central reading center.

8.2.3.9. End of Study Phone Contact

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

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

In the event that a patient must undergo JR surgery during the treatment or follow-up periods, the patient will be discontinued from study drug and asked to return for a pre-operative visit. The pre-operative visit should be completed before JR surgery if possible and pre-operative images will be submitted to the adjudication committee for review. Following the JR surgery, the patient will complete follow-up safety evaluations at 4 weeks and 20 weeks after surgery (see Table 2).

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

All available medical history/information for patients who undergo JR surgery must be collected, including placement of prosthesis, healing of the surgical wound and the results of histopathologic examination.

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

Knee Society Score

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

Harris Hip Score

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

8.2.3.11. Laboratory Testing

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

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

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

Samples for laboratory testing will be collected at visits according to Table 1. Tests will include:

Blood Chemistry

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

Hematology

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

Urinalysis

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

Urine Electrolytes

Creatinine
Phosphorus

Other Laboratory Tests

Serum and urine samples for pregnancy testing will be collected from women of childbearing potential (as defined in Section 8.2.1.6) at time points according to Table 1. At each study visit during the treatment period, urine pregnancy testing will be done before the study drug is administered. In the event of a positive urine pregnancy test result, the patient should have a serum pregnancy test with a negative result in order to continue study 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 Table 1).

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

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

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

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

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or 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 9.4.5.

8.2.3.12. Injection Site Evaluations

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

8.2.4. Pharmacokinetic and Anti-Drug Antibody Procedures

8.2.4.1. Drug Concentration Measurements and Samples

Samples for fasinumab concentration will be collected at time points listed in Table 1. Detailed instructions for blood sample collection are included in the laboratory manual provided to study sites.

Any unused samples may be used for exploratory biomarker research.

8.2.4.2. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 1. Detailed instructions for blood sample collection are included in the laboratory manual provided to study sites.

Any unused samples may be used for exploratory biomarker research.

8.2.5. Research Samples

8.2.5.1. Biomarkers

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

8.2.5.2. Future Biomedical Research

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

8.2.6. Genomics Sub-study – Optional

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

DNA samples for the genomics sub-study will be de-identified as defined by the International Council for Harmonisation (ICH) guideline E15. Sub-study samples will be stored for up to 15 years after the final date of the database lock and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with collagen and bone turnover, OA, pain, and response to fasinumab. In addition, associations between genomic variants and prognosis or progression of OA as well as other diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug or other diseases. Analyses may include sequence

determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, and DNA copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period.

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

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

9.2. Obligations of Sponsor

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

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

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

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

9.3. Definitions

9.3.1. Adverse Event

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

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

9.3.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).

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

9.3.3. Adverse Events of Special Interest

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

Adverse events of special interest are described in Section 9.4.3.

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of the follow-up period (week 44). Refer to the study reference manual for the procedures to be followed.

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

9.4.2. Serious Adverse Events

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

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

In the event the investigator is informed of an SAE after the patient completes the follow-up period (week 44)/early termination visit, the following will apply:

- SAE with an onset within 30 days of the end of the follow-up period (week 44)/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 the follow-up period (week 44)/early termination visit - only SAEs 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.
- 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.

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

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

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

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female 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 that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest: All AESI, serious and non-serious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 9.4.2. Monitoring of AESIs is described in Section 9.6.1. Adverse events of special interest for this study are:

- Adjudicated arthropathy (as confirmed by adjudication)

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

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

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

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

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

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

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

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

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

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

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

9.4.6. Follow-up

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

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

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

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

- **Mild:** Does not interfere in a significant manner with the patient'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 patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

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

Injection Site Reactions

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

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

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

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

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

The possible answers are:

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

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

The investigator should justify the causality assessment of each SAE.

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

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

No:

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

Yes:

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

Relationship of Adverse Events to Study Conduct

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

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

The possible answers are:

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

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

The investigator should justify the causality assessment of each SAE.

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

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

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

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the course of the study

- do not reappear or worsen when dosing with study participation is resumed

Yes:

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

9.6. Safety Monitoring

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

9.6.1. Monitoring Adverse Events of Special Interest

9.6.1.1. Adjudicated Arthropathy

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

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

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

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

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

If a patient reports an increase in pain as described above, study drug administration will be withheld while imaging of the affected joint, as well as any additional imaging deemed appropriate to understand the cause of the worsening pain, is performed (Section 8.2.3.7). A decision to

perform imaging after patient reported worsening of joint pain will be documented in the respective case report form (CRF) page. Images, along with any other radiographic evaluation, will be submitted to the Adjudication Committee for review (Section 5.3.2). The investigator may consider aspiration of synovial fluid for further analysis such as cell count and crystal analysis.

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

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

Study drug dosing will be permanently discontinued for patients with findings that suggest AA; the patients will be referred for orthopedic consultation. If presence of AA is confirmed by the Adjudication Committee, the case must be reported as an AESI (Section 9.3.3, Section 9.4.3).

Any patient whose study drug is discontinued due to an AA should be encouraged to return to the clinic for all remaining study visits. Prior to the scheduled JR, the patient should complete the pre-operative study visit and, after the JR, should complete the week 4 and week 20 post-operative study visits (Section 8.2.3.10, Table 2). Pre-operative images, along with any other radiographic evaluation will be submitted to the Adjudication Committee for review (Section 5.3.2).

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

9.6.1.2. Sympathetic Nervous System Dysfunction

Sympathetic nervous system dysfunction will be monitored throughout the study through physical examination, AE reporting, assessment of orthostatic hypotension, and the Survey of Autonomic Symptoms (Section 8.2.3.5). 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 will be reported as an AESI (Section 9.4.3).

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

- If the patient is symptomatic and a clinical explanation for orthostatic hypotension is identified (such as a new medication or dehydration due to exercise or illness or excessive heat exposure), study drug will be withheld, and the patient should return to the study site for an unscheduled visit in 1 to 10 days for an unscheduled assessment of orthostatic hypotension.

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

- If the patient has asymptomatic orthostatic hypotension, study drug will be withheld, and the patient should return to the study site for an unscheduled visit in 1 to 10 days for an unscheduled assessment of orthostatic hypotension.
  - If the unscheduled assessment does not reveal orthostatic hypotension then study drug may be continued.
  - If the unscheduled assessment demonstrates orthostatic hypotension then study drug will continue to be withheld until the patient has been evaluated by a specialist (neurologist or a cardiologist) for evidence of sympathetic nervous system dysfunction.
    - If the specialist's evaluation does not reveal new sympathetic nervous system dysfunction including symptoms of bradycardia (lightheadedness), orthostatic hypotension (lightheadedness on standing), syncope, absence of sweating in conditions where sweating would be expected, or if the specialist's evaluation identifies an alternative cause such as initiation of a new medication known to cause orthostasis, then study drug may be restarted.
    - If the specialist's evaluation does reveal sympathetic nervous system dysfunction then study drug will be permanently discontinued and the case reported as an AESI (Section 9.4.3).

9.6.1.3. Peripheral Sensory Adverse Events

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

9.6.1.4. Joint Replacement Surgery

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

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

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

9.7. Investigator Alert Notification

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

10. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

There are 6 hypotheses for the primary and key secondary endpoints. The primary treatment comparison for the WOMAC pain and physical function subscale scores is declared superior only if the comparisons are significant for both WOMAC pain and physical function subscale scores. The sequentially rejective multiple test procedure (Bretz 2009) will be applied to control for multiplicity and to maintain study-wise Type I error rate at two-sided 0.05 level for the hypotheses (Hi, i=1,…, 6 for fasinumab 1 mg Q4W) for the primary and key secondary endpoints. The primary hypothesis will be tested at 0.05 level. If the primary hypothesis is rejected, the alpha level will be reallocated to other hypotheses according to the pre-specified procedure. The testing will stop when no hypothesis can be rejected at any step. Details will be provided a priori in the SAP.

- H_1: There is no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC pain or physical function subscale scores at week 24 versus there is treatment difference in WOMAC pain and physical function subscale scores at week 24
- H_2: There is no treatment difference between fasinumab 1 mg Q4W and placebo in Patient Global Assessment score at week 24 versus there is treatment difference in Patient Global Assessment score at week 24

- H_3: There is no treatment difference between fasinumab 1 mg Q4W and placebo in the proportion of patients with ≥30% improvement in the WOMAC pain subscale scores at week 24 versus there is treatment difference in proportion of patients with ≥30% improvement in WOMAC pain at week 24
- H_4: There is no treatment difference between fasinumab 1 mg Q4W and NSAIDs in the WOMAC pain subscale scores at week 24 versus there is treatment difference in WOMAC pain subscale scores at week 24
- H_5: There is no treatment difference between fasinumab 1 mg Q4W and NSAIDs in the WOMAC physical function subscale scores at week 24 versus there is treatment difference in WOMAC physical function subscale scores at week 24
- H_6: There is no treatment difference between fasinumab 1 mg Q4W and NSAIDs in Patient Global Assessment score at week 24 versus there is treatment difference in Patient Global Assessment score at week 24

10.2. Justification of Sample Size

Assuming a 2-sided alpha level 0.05 and a 20% dropout rate up to week 24, an enrollment of 600 patients in the fasinumab 1 mg Q4W group and 300 patients in the placebo group will provide at least 99% power to detect an effect size of 0.46 in the WOMAC pain and physical function subscale scores (ie, absolute treatment difference of 1.1 between fasinumab and placebo with a SD of 2.4). The assumed treatment difference and standard deviation (SD) are based on results from study R475-PN-1227. The sample size will provide 99% power to detect an effect size of 0.36 in PGA (ie, absolute treatment difference of 0.4 with a SD of 1.1, R475-PN-1227).

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

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients and is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS including patients randomized to fasinumab 1 mg Q4W, NSAIDs, and placebo. Efficacy data from patients randomized to fasinumab 3 mg Q4W or 6 mg Q8W will not be included in the analysis, but will be summarized descriptively in separate tables.

10.3.2. Safety Analysis Set

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

safety variables will be analyzed using the SAF including patients randomized to fasinumab 1 mg Q4W, NSAIDs, and placebo. Safety data from patients randomized to fasinumab 3 mg Q4W or 6 mg Q8W will not be included in the main safety analysis summaries, but will be summarized in separate tables.

10.3.3. Per-Protocol Set

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

10.3.4. Pharmacokinetic Analysis Set

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

10.3.5. Anti-Drug Antibody Analysis Set

The ADA analysis population includes all treated patients who had at least 1 non-missing ADA result following the first study dose.

10.4. Statistical Methods

10.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

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

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

10.4.3. Efficacy Analyses

10.4.3.1. Primary Efficacy Analysis

The primary efficacy variables will be analyzed using multiple imputation approach with mixed-effect model for repeated measure (MMRM) based on the FAS with adjustment for missing data due to lack of efficacy or AEs assuming the WOMAC scores would on average return to baseline values. Data collected after discontinuing treatment up to week 24 will not be used in the primary efficacy analysis, but used in a treatment policy sensitivity analysis. The imputed data for patients discontinued from the study treatment due to lack of efficacy or AEs will be centered at the mean baseline value. The missing data for patients who discontinued treatment due to other reasons will be imputed under missing-at-random assumption.

Missing data will be imputed 50 times to generate 50 complete data sets. Each imputed complete data set will be analyzed using the MMRM with terms for baseline score corresponding to the efficacy variable being analyzed, randomization strata (K-L category [2 to 3, or 4], index joint [knee, hip], and geographical region), treatment (fasinumab 1 mg Q4W, NSAIDs or placebo), visit and treatment-by-visit interaction. The MMRM will be performed using the MIXED procedure in Statistical Analysis System (SAS) with an unstructured covariance matrix to model the within-patient errors. Denominator degrees of freedom will be estimated using Kenward-Roger's approximation. The results from the 50 analyses will be combined using Rubin's formulae (PROC MIANALYZE). The least-squares mean estimates for the mean change from baseline to week 24, as well as the differences of the estimates between fasinumab 1 mg Q4W and placebo, and between fasinumab 1 mg Q4W and pooled NSAIDs group, with their corresponding standard errors, p values and associated 95% confidence intervals, will be provided.

Sensitivity analysis of treatment policy estimand for the co-primary endpoints will be performed using a similar analysis method as the primary efficacy analysis, including data collected after discontinuing treatment up to week 24. 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. Multiple imputation will be based on monotone missing data structure of the change from baseline score using regression method. Monotone missing data structure will be achieved using Markov Chain Monte Carlo method. After each imputation, a fasinumab patient's imputed data will subtract k (eg, 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 ($p>0.05$). Sensitivity analyses using PPS will also be performed for the primary and selected secondary endpoints.

10.4.3.2. Secondary Efficacy Analysis

For analysis of continuous secondary endpoints, the analysis method will be the same as that used for the primary variables. For analysis of categorical variables in secondary endpoints, eg, proportions of patients with ≥30% improvement in the WOMAC pain subscale scores at week 24, the Cochran Mantel Haenszel approach stratified by the randomization strata (K-L category [2 to 3, or 4], index joint [knee, hip], and geographical region) will be used with missing data considered as non-response.

10.4.4. Safety Analysis

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

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

The time interval to collect any AEs, including AESIs, is between the first dose of double-blinded study drug injection and the week 44 visit, as well as study drug-related SAEs occurring between the week 44 visit and the end of study.

For safety variables, 3 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 treatment period is defined as the day of the first dose of study drug through to the day of the last dose of study drug (week 20) + 4 weeks.
- The follow-up period is defined as from the end of the on-treatment period (week 24) to the week 44 visit.

10.4.4.1. Adverse Events

Definitions

Treatment-emergent AEs are defined as those that are not present at baseline or represent the exacerbation of a pre-existing 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. The focus of AE reporting in the clinical study report will be on TEAEs. Post-treatment AEs and all AEs during the study will be summarized similarly as TEAEs.

Summaries of all TEAEs by treatment group will include:

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

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

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

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

10.4.4.2. Other Safety

Vital Signs and Electrocardiograms

Vital signs (temperature, pulse, blood pressure, and respiration rate) and ECGs (heart rate, ECG intervals) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics. Potentially clinically significant values at any post-randomization time point will be summarized for each vital sign and ECG parameter.

Physical Examinations

The percentage of patients with abnormal physical examinations will be summarized.

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

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

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

10.4.4.3. Treatment Exposure

Because of the half-life of the biologic being studied, the duration of fasinumab exposure during the study will be presented by treatment group and calculated as:

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

The number and percentage of patients randomized and exposed to double-blind study drug will be presented by specific time period for each treatment group. The time periods of interest will be specified in the SAP.

10.4.4.4. Treatment Compliance

Overall treatment compliance to study drug injection is defined as the actual dose of injection compared to the prescribed dose of treatment during the treatment phase up to treatment discontinuation. It is calculated according to the following formula:

100* Total actual injection dose taken/ Planned injection dose.

The total number of actual doses of fasinumab will be summarized.

Overall treatment compliance to oral study drug is defined as the actual oral dose taken compared to the prescribed dose of treatment during the treatment phase up to treatment discontinuation. It is calculated according to the following formula:

100* Total actual oral dose taken/ Planned oral dose.

The total number of actual doses of oral study drug will be summarized.

10.4.5. Analysis of Drug Concentration Data

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

No formal statistical analysis will be performed.

10.4.6. 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.

10.5. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

General rules for handling missing data:

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

Visit windows:

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

Unscheduled assessments:

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

10.6. Statistical Considerations Surrounding the Premature Termination of a Study

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

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

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

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

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

11.2. Electronic Systems

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

- IWRS system – randomization, study drug supply
- Rave Medidata EDC system – clinical data capture
- SAS – statistical review and analysis
- Argus - pharmacovigilance and clinical safety software system – collection and reporting of SAEs and AESIs
- Electronic Clinical Outcome Assessment systems – collect patient-reported or patient clinical assessments results

12. STUDY MONITORING

12.1. Monitoring of Study Sites

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

The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in

accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements

12.2. Source Document Requirements

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

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

12.3. Case Report Form Requirements

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

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

13. AUDITS AND INSPECTIONS

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

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

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

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

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

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

14.2. Informed Consent

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

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

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

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

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

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

14.3. Patients Confidentiality and Data Protection

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

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

14.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

15. PROTOCOL AMENDMENTS

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

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

16.1. Premature Termination of the Study

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

16.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

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

17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

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

18. DATA QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol,

GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are summarized.

Data Management

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

Study Monitoring

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

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

All patient data collected during the study will be recorded on paper or 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 12.3, Section 17.1).

Study Documentation

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

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

19. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

20. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

21. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

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23. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A phase 3 randomized, double-blind, multi-dose, placebo and NSAID-controlled study to evaluate the efficacy and safety of fasinumab in patients with pain due to osteoarthritis of the knee or hip, and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study Title: A Phase 3 Randomized, Double-blind, Multi-dose, Placebo and NSAID-controlled Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Pain Due to Osteoarthritis of the Knee or Hip

Protocol Number: R475-OA-1688

Protocol Version: R475-OA-1688 Amendment 4

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

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Sponsor's Responsible Regulatory Representative

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Sponsor's Responsible Clinical Study Team Lead

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Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00048600 v1.0

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