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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A RANDOMIZED, DOUBLE-BLIND, MULTI-DOSE, PLACEBO-CONTROLLED PHASE 2/3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FASINUMAB IN PATIENTS WITH MODERATE TO SEVERE CHRONIC LOW BACK PAIN

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AMENDMENT HISTORY

Amendment 3 (26 Aug 2016)

Purpose: The purpose of this amendment includes the following:

- the addition of collection time points for urine to better monitor patient safety
- the addition of creatinine and phosphorous to routine serum and urine chemistry sampling to better monitor patient safety
- an update to the terminology "adjudicated arthropathy" to allow for consistency within the program and to allow for a more accurate description of the joint events in the trial and
- an update in the personnel who have the authorization to approve rescreening
- an update in the reporting time for AESIs

Change	Sections Changed
Urinanlysis, urine creatinine and phosphorous have been included at additional time points during the trial.	Table 1: Schedule of Events – Screening Period Through Week 16 Table 2: Schedule of Events – Follow-up Period – Week 20 through Week 36 Section 6.3.3.10: Laboratory Testing
Serum creatinine and phosphorous have been added to the laboratory collections.	Section 6.3.3.10: Laboratory Testing
Terminology updated from "destructive arthropathy" to "adjudicated arthropathy."	Synopsis: Procedures and Assessments Section 1.1: Introduction Section 3.1Study Description and Duration Section 3.3.2: Adjudication of Arthropathy Events Section 4.2.2: Exclusion Criteria Section 5.3.2: Study Drug Discontinuation Section 5.3.2.1: Reasons for Permanent Discontinuation of Study Drug Section 6.3.3.8: Imaging Section 7.2.3: Pregnancy and other Events tat Require Accelerated Reporting Section 7.4.1.1: Adjudicated Arthropathy
Personnel who can approve rescreening has been updated	Section 6.2.2: Rescreening

Change	Sections Changed
The reporting time for AESIs has been updated from 7 days to 24 hours	Section 7.2.3: Pregnancy and other Events tat Require Accelerated Reporting

Amendment 2 (20 JAN 2016)

Purpose: The purpose of this amendment is to incorporate revisions to ensure a consistent approach across the fasinumab program.

- Imaging requirements:
  - Add further detail on imaging requirements during the screening period.
  - Specify that radiographs and/or magnetic resonance imaging (MRI) will or must (rather than may or should) be performed on any joint following report of a clinically significant worsening or exacerbation of pain in that joint.
  - Specify that prior to the pre-randomization visit an MRI of the affected joint must be performed and assessed by the central reader for any screening radiographs that are inconclusive for potential joint-related findings and for any knee or hip joint that has a baseline Kellgren-Lawrence (K-L) score of ≥3, and specify that, before a patient can be randomized, confirmation must be received that there are no exclusionary findings on screening MRIs.
- Update study stopping rules to state that the Data Monitoring Committee (DMC) may recommend temporarily halting the study if the DMC has significant concerns regarding a meaningful imbalance in joint-related AEs, sympathetic nervous system dysfunction, or neurosensory disturbances.
- Add willingness to consider total joint replacement (TJR) surgery if necessary as an inclusion criterion.
- Modify exclusion criteria.
- Add clinically significant sensory and motor neurologic events grade >2 according to Common Terminology Criteria for Adverse Events (CTCAE) v.4 as a new reason for permanent discontinuation of study drug; specify that sites should use CTCAE v.4 criteria throughout the study for consistency.
- Add new signs and symptoms indicative of carpal tunnel syndrome as a new reason for permanent discontinuation of study drug.
- Modify schedule of events, study visit descriptions and study procedures
- Refine and further detail text describing safety reporting, and monitoring of adverse events of special interest (AESI).
- Refine and further detail the statistical plan
- Make minor clarifications and administrative edits.

Amendment 1 (11 JAN 2016)

Purpose: The primary purpose of this amendment is to incorporate revisions requested by the European Medicines Agency as follows:

- Clarify that the maximum dose of paracetamol/acetaminophen permitted as rescue medication for low back pain (LBP) pain is 2600 mg (325 mg x 8) per day in North America, and 2500 mg (500 mg x 5) per day in Europe
- Add confirmed elevated screening ALT or AST > 2.5 x upper limit of normal (ULN) as an exclusion criterion.
- Add continued noncompliance with protocol-defined maximum paracetamol/acetaminophen use after appropriate counseling as a reason for permanent discontinuation of study drug
- Change the notification requirement for emergency unblinding to "The investigator should promptly document and explain to the sponsor any premature unblinding"

Furthermore, administrative edits were made.

CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE	A Randomized, Double-blind, Multi-dose, Placebo-controlled Phase 2/3 Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Moderate to Severe Chronic Low Back Pain
SITE LOCATIONS	United States, Canada, Europe Multi-center
OBJECTIVES	**Primary Objective**: The primary objective of the study is to evaluate the efficacy of fasinumab compared to placebo in reducing low back pain (LBP), as measured by the change from baseline at week 16 in the average daily LBP intensity (LBPI) numerical rating scale (NRS) score. **Secondary Objectives**: Secondary objectives of the study are to evaluate the efficacy of fasinumab compared to placebo in treating LBP as measured by: • Change from baseline at week 16 in the Roland Morris Disability Questionnaire (RMDQ) total score • Change from baseline at week 16 in the Patient Global Assessment (PGA) of LBP score • Change from baseline at week 2, 4, 8, and 12 in the average daily LBPI NRS score
STUDY DESIGN	The study consists of a screening period of up to 30 days (day -37 to day -8), a 7-day pre-randomization period (day -7 to day -1), a 16-week randomized, double-blind, placebo-controlled treatment period (to day 113), and a 20-week follow-up period. Approximately 800 patients will be randomized in a 1:1:1:1 ratio to one of the following 4 treatment groups: • Fasinumab 6 mg subcutaneously (SC) every 4 weeks (Q4W) and placebo 9 mg intravenously (IV) every 8 weeks (Q8W) • Fasinumab 9 mg SC Q4W and placebo 9 mg IV Q8W • Fasinumab 9 mg IV Q8W and placebo SC Q4W • Placebo SC Q4W and placebo 9 mg IV Q8W Randomization will be stratified by baseline LBPI NRS score (<7, ≥7), duration of chronic back pain (<5 years, ≥5 years), and maximum Kellgren-Lawrence (K-L) score (≤2, >2) at any knee or hip joint at screening.
STUDY DURATION	Total duration of participation will be approximately 41 weeks, including the screening and pre-randomization periods.
POPULATION	
Sample Size:	Approximately 800 patients (200 patients per group) will be randomized into 4 treatment groups.
Target Population:	Eligible patients for this study will be men and women ≥35 years of age with chronic LBP who have a history of inadequate pain relief or intolerance to current analgesic therapy.

TREATMENTS

Study Drug Dose/Route/Schedule:	Randomized patients will receive: • 6 mg or 9 mg fasinumab SC Q4W and matching placebo 9 mg IV Q8W; • 9 mg fasinumab IV Q8W and matching placebo SC Q4W, or • placebo SC Q4W and placebo 9 mg IV Q8W. Patients randomized to SC administration will receive a loading dose equivalent to 2 times the maintenance dose on day 1.
Rescue Treatment Dose/Route/Schedule:	Paracetamol/acetaminophen is the study-provided rescue medication. In the event of inadequate LBP relief, paracetamol/acetaminophen may be taken as needed, according to local standard of care, to a maximum total dose of 2600 mg (325 mg x 8) per day in North America and 2500 mg (500 mg x 5) per day in Europe, starting at the pre-randomization visit through week 16. In order to minimize the confounding effects of rescue medication on efficacy measures, the use of paracetamol/acetaminophen is not allowed from 48 hours prior to the start of a scheduled study visit through week 16.

ENDPOINTS

Primary:	The primary endpoint is: • Change from baseline at week 16 in the average daily LBPI NRS score
Secondary:	Secondary endpoints are: • Change from baseline at week 16 in the RMDQ total score • Change from baseline at week 16 in the PGA of LBP score • Change from baseline at weeks 2, 4, 8, and 12 in the LBPI NRS score Safety endpoints are: • Percent of patients reporting treatment-emergent adverse events (TEAEs) • The incidence of anti-fasinumab antibody formation

PROCEDURES AND ASSESSMENTS	The LBPI NRS, RMDQ, PGA of LBP, Medical Outcomes Study (MOS) sleep subscale, the Short Form (36) Health Survey (SF-36), and the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaires will be administered to assess efficacy. Physical examinations, medical history, concomitant medication assessment, vital signs, electrocardiograms (ECGs), imaging, laboratory assessment, neurologic evaluations, and orthostatic hypotension assessment will be performed. The joint pain questionnaire and autonomic nervous system survey will be administered to assess safety. Adverse events (AEs), serious adverse events (SAEs), and concomitant medications will be assessed at each study visit. Radiographs and/or magnetic resonance imaging (MRI) will be performed of any joint following a report of clinically significant worsening or exacerbation of pain in that joint. Potential events of adjudicated arthropathy and sympathetic nervous system dysfunction will be monitored during the course of the study. In the event that a patient must undergo surgery for a total joint replacement (TJR) during the treatment or follow-up periods, they will be asked to return to the study site for an early termination visit before surgery and for follow-up safety evaluations at 4 weeks and 20 weeks after surgery. Samples to determine serum concentrations of functional fasinumab and anti-fasinumab antibodies will be collected at predetermined time points.
STATISTICAL PLAN	Approximately 800 patients (200 per treatment) will be randomized into 4 treatment groups. Assuming a significance level of 0.05 and [redacted], an enrollment of 200 patients per treatment group will provide at least 91% power to detect a treatment difference [redacted] between fasinumab 9 mg SC Q4W and placebo for the mean change from baseline to week 16 in the average daily LBPI NRS score [redacted]. The assumed treatment difference and common SD were estimated based on results from a phase 2b multiple dose study of tanezumab (5, 10, and 20 mg IV Q8W) versus placebo and naproxen (500 mg BID) in patients with chronic LBP. The LS mean change (standard error [SE]) from baseline to week 16 of -2.18 (0.14) and -1.25 (0.16) for tanezumab 20 mg (n = 295) and placebo (n = 230) were used to estimate the treatment difference and common SD. A combination of Hochberg method and gatekeeping method will be used for multiplicity adjustment to maintain the study-wise type I error rate at the 0.05 level. For analysis secondary endpoints that are continuous variables, the analysis method is the same as for the primary variable but without multiplicity adjustment. For analysis of categorical variables in secondary endpoints, the Cochran-Mantel-Haenszel approach stratified by the randomization strata will be used. The safety analyses will be based on reported TEAEs, adverse events of special interest (AESI), and other safety information (clinical laboratory evaluations, vital signs, and 12-lead ECG).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine Aminotransferase
ARGUS	Pharmacovigilance and clinical safety software system
AST	Aspartate Aminotransferase
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EDiary	Electronic diary
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Questionnaire
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
K-L	Kellgren-Lawrence
LBP	Low back pain
LBPI	Low back pain intensity
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measure
MOS	Medical Outcomes Study
MRI	Magnetic resonance imaging

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NGF	Nerve growth factor
NRS	Numerical rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PCSV	Potentially clinically significant value
PGA	Patient Global Assessment
PK	Pharmacokinetic
PPS	Per protocol set
PT	Preferred term
Q4W	Every 4 weeks
Q8W	Every 8 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RMDQ	Roland Morris Disability Questionnaire
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation
SF-36	Short Form (36) Health Survey
SOC	System organ class
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
TJR	Total joint replacement
TrkA	Tyrosine kinase type 1
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Many patients with acute and chronic pain do not receive adequate pain relief despite the wide variety of analgesic medications that are currently available, either because the medications are not effective in all patients, or because their use is limited by toxicity or intolerability. The limitations of currently available analgesic therapies include adverse central nervous system effects, nausea and vomiting, constipation, gastrointestinal bleeding and ulceration, cardiovascular events, renal toxicity, and potential for abuse (fasinumab Investigator's Brochure 2015). Inadequate pain relief has a profound impact on the quality of life for millions of people worldwide with an associated substantial cost to society, including healthcare cost and loss of productivity.

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

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

Fasinumab is a fully-human high-affinity monoclonal antibody directed against NGF. By selectively blocking NGF, fasinumab has the potential to be effective in modulating NGF-associated pain without some of the adverse side effects of other analgesic medications, such as opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Following an evaluation of the safety and tolerability of the antibody in a single-ascending-dose first-in-human study (study R475-PN-0817), a proof-of-concept study evaluating the effect of fasinumab on pain in 217 patients with osteoarthritis (OA) of the knee was completed (study R475–PN-0901, fasinumab Investigator's Brochure 2015). Three intravenous (IV) doses of fasinumab were evaluated (0.03, 0.1, 0.3 mg/kg), all of which were associated with statistically significant improvement in pain compared with placebo when evaluated by walking knee pain, the Western

Ontario and McMaster Osteoarthritis Index, and the Patient's Global Impression of Change questionnaire.

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 phase 2 and phase 3 studies of tanezumab in patients with pain due to OA of the knee and hip, dose-related reduction in pain and improved function were demonstrated (Lane 2010, Hefti 2006, Brown 2010). Similar findings were reported for fulranumab in patients with OA of the knee (Sanga 2011). Furthermore, in a single-dose proof-of-concept study and a phase 2 multiple-dose study of IV tanezumab in patients with non-radicular chronic low back pain (LBP), dose-related reduction in pain and improved function were demonstrated (Kivitz 2013, Katz 2011) by evaluating the Low Back Pain Intensity (LBPI) score on an 11-point numerical rating scale (NRS), the Roland Morris Disability Questionnaire (RMDQ) and the Patient Global Assessment (PGA) of Low Back Pain. In contrast, a single-dose study to evaluate the efficacy and safety of adjunctive subcutaneous (SC) fulranumab therapy in patients with LBP failed to show a treatment effect (Kelly 2011). A fasinumab single-dose proof-of-concept study in patients with sciatic pain treatment with a single-dose of 0.1 mg/kg and 0.3 mg/kg SC fasinumab failed to show an improvement in NRS pain scores. The results of the two IV tanezumab studies in patients with chronic LBP are encouraging. However, the failed small single-dose SC fulranumab study and the single-dose SC fasinumab study indicated the importance of choosing an appropriate patient population.

In clinical studies completed to date, fasinumab was generally well tolerated. Arthralgia, joint swelling, peripheral edema, hypoesthesia, and myalgia were more frequently reported in fasinumab patients compared with placebo patients. In neurological evaluations, abnormalities in vibration sense were more frequent in fasinumab patients compared with placebo patients. These adverse events (AEs) or physical examination abnormalities were mild to moderate in intensity and transient in nature (fasinumab Investigator's Brochure 2015). Data from tanezumab and fulranumab demonstrated an increased risk of arthropathy events. Adjudicated Arthropathy is an umbrella term for the following conditions: rapidly progressing OA, subchondral insufficiency fracture, or osteonecrosis (Roemer 2015). Analyses of the tanezumab data by its sponsor showed that the risk of arthropathy events increases with tanezumab dose and is further increased with the concomitant use of chronic NSAIDs (>90 days) (Lane 2010). Most cases occurred in patients with a documented history of OA. To date, 1 case of possible adjudicated arthropathy has been observed with fasinumab.

Based on the potential risk of adjudicated arthropathy events identified with tanezumab and fulranumab, the US Food and Drug Administration (FDA) placed the class of anti-NGF antibodies on clinical hold in 2010. Following review of anti-NGF antibody clinical data in March 2012, the FDA determined that clinical studies with anti-NGF therapies could resume if mitigation strategies are implemented to minimize the risk of adjudicated arthropathy. To address concerns about potential events of adjudicated arthropathy, a risk-mitigation approach is being implemented for all fasinumab studies, as outlined in Section 7.4.1.

In 2012, all sponsors were put on clinical hold after non-clinical studies of other anti-NGF monoclonal antibodies identified adverse changes in the sympathetic nervous system of mature animals of several species. After additional non-clinical data were provided to FDA, studies

with up to 16 weeks of exposure were allowed. Patients will be monitored for any signs or symptoms of potential sympathetic nervous system dysfunction.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

1.2. Rationale

1.2.1. Rationale for Study Design

This randomized, double-blind, multi-dose, placebo-controlled study is designed to evaluate the safety and efficacy of fasinumab in patients with moderate to severe chronic non-radicular LBP who have a history of intolerance or inadequate pain relief from paracetamol/acetaminophen, oral NSAIDs, and opioid therapy. This subset of patients with chronic LBP represents a patient population with an unmet medical need in whom it would be appropriate to prospectively study the hypothesis that fasinumab provides benefit and has an acceptable safety profile.

1.2.2. Rationale for Dose Selection

Dose selection for this multiple-dose study in patients with chronic non-radicular LBP is based on data from 2 completed fasinumab phase 1 studies in healthy subjects (studies R475-PN-0817 and TDU-11480), as well as data from the completed fasinumab phase 2 proof-of-concept study in patients with pain due to OA of the knee (study R475-PN-0901), and the single-dose proof-of-concept study in patients with sciatic pain (study R475-PN-0908), the dose-range evaluated in an ongoing fasinumab phase 2 study in patients with OA of the knee or hip (study R475-PN-1227), and pharmacokinetic (PK) simulations.

Single SC doses of fasinumab up to 30 mg were well tolerated in healthy male and female subjects (study TDU-11480). Single IV doses of up to 1 mg/kg were also studied in healthy male and female subjects (study R475-PN-0817). In this study, fasinumab was generally well tolerated at all but the highest IV dose (1 mg/kg). Neurosensory AEs, which were transient and not severe, led to expansion of the 1 mg/kg IV cohort and a decision to not dose-escalate beyond this level. In the 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 demonstrated efficacy with regard to pain relief and were well tolerated in Caucasian subjects with pain due to OA of the knee. The ongoing phase 2 study in patients with pain due to OA of the knee or hip (R475-PN-1227) is evaluating the efficacy and safety of 1, 3, 6, and 9 mg of fasinumab SC every 4 weeks (Q4W).

Results from completed studies evaluating tanezumab in patients with chronic LBP and in patients with pain due to OA indicate that the lowest dose studied may not be adequate to demonstrate efficacy. This fasinumab study will therefore evaluate the 2 highest SC doses being evaluated in the ongoing study in OA patients (6 mg and 9 mg SC Q4W) and also includes a 9 mg IV fasinumab dose to allow PK, efficacy, and safety comparisons. For patients randomized to SC administration, a loading dose equivalent to 2 times the maintenance dose will be administered on day 1 to achieve steady state concentrations sooner. This approach is supported by PK simulations based on completed fasinumab studies.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of fasinumab compared to placebo in reducing LBP, as measured by the change from baseline at week 16 in the average daily LBPI NRS score.

2.2. Secondary Objectives

Secondary objectives of the study are to evaluate the efficacy of fasinumab compared to placebo in treating LBP as measured by:

- Change from baseline at week 16 in the RMDQ total score
- Change from baseline at week 16 in the PGA of LBP score
- Change from baseline at week 2, 4, 8, and 12 in the average daily LBPI NRS score

2.3. Safety Objectives

Safety objectives of the study are:

- To assess the safety and tolerability of fasinumab compared with placebo in patients with LBP by evaluating:
  - The percent of patients reporting treatment-emergent adverse events (TEAEs)
  - The percent of patients experiencing clinically significant changes in vital signs, physical exams, laboratory safety tests, and electrocardiograms (ECGs)
- To assess the incidence of anti-fasinumab antibody formation

2.4. Other Objectives

Exploratory objectives of the study are:

- To evaluate the efficacy of fasinumab compared to placebo, as measured by the percentage of patients who are responders defined by 30% reduction and 50% reduction from baseline to week 16 for:
  - the average daily LBPI NRS score
  - the RMDQ total score
  - the PGA of LBP score
- To evaluate the efficacy of fasinumab compared to placebo, as measured by the change from baseline at week 16 in the Medical Outcomes Study (MOS) sleep subscale score
- To evaluate the efficacy of fasinumab compared to placebo, as measured by the change from baseline at week 16 in the Short Form (36) Health Survey (SF-36) subscale scores

- To evaluate the efficacy of fasinumab compared to placebo, as measured by the change from baseline at week 16 in the EuroQol 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L)
- To evaluate the efficacy of fasinumab compared to placebo, as measured by the percentage of patients who use rescue medication for LBP at week 16
- To characterize the PK profile of fasinumab

3. STUDY DESIGN

3.1. Study Description and Duration

The study consists of a screening period of up to 30 days (day -37 to day -8), a 7-day pre-randomization period (day -7 to day -1), a 16-week randomized, double-blind, placebo-controlled treatment period (to day 113), and a 20-week follow-up period (Figure 1). Approximately 800 patients will be randomized in a 1:1:1:1 ratio to one of the following 4 treatment groups:

- Fasinumab 6 mg SC Q4W and placebo 9 mg IV every 8 weeks (Q8W)
- Fasinumab 9 mg SC Q4W and placebo 9 mg IV Q8W
- Fasinumab 9 mg IV Q8W and placebo SC Q4W
- Placebo SC Q4W and placebo 9 mg IV Q8W

Randomization will be stratified by baseline LBPI NRS score (<7, ≥7), duration of chronic back pain (<5 years, ≥5 years), and maximum Kellgren-Lawrence (K-L) score (≤2, >2) at any knee or hip joint at screening.

- **Screening Period (up to 30 days before the pre-randomization visit):** After informed consent has been signed, patients will be screened for eligibility for enrollment based on study eligibility criteria (Section 4). A magnetic resonance imaging (MRI) of the lumbar spine will be performed during screening. A lumbar spine anterior-posterior/lateral X-ray must be obtained if the MRI of the lumbar spine shows evidence suggestive of a destructive or unstable process. X-rays of the knees, hips, and shoulders will be performed during the screening period. After the patient has otherwise met study eligibility criteria assessed during the screening period, an MRI will be performed and assessed by the central reader prior to the pre-randomization visit for any screening radiographs that are inconclusive for potential joint-related findings and for any knee or hip joints that have a K-L score of ≥3. During the screening period, patients may continue to take their current treatment regimen for LBP.
- **Pre-Randomization Period (7 days before the randomization/baseline visit [day 1]):** Patients who meet the initial eligibility criteria, as assessed during the screening period, will be instructed in the use of the electronic diary (EDiary) for recording daily use of rescue medication and LBPI score using the NRS.

Patients will be instructed to stop using all prohibited medications at the pre-randomization visit. Patients will receive paracetamol/acetaminophen to be used as study-provided rescue medication. In the event of inadequate LBP relief, paracetamol/acetaminophen may be taken as needed, according to local standard of care, to a maximum total dose of 2600 mg (325 mg x 8) per day in North America and 2500 mg (500 mg x 5) per day in Europe, starting at the pre-randomization visit through week 16.

Patients must have a mean daily LBPI NRS score ≥ 4 during the pre-randomization period, in order to be eligible for study participation. Patients may not use paracetamol/acetaminophen for 48 hours prior to the start of a scheduled study visit or during a study visit, in order to minimize the confounding effects of rescue medication on efficacy measures.

Confirmation that there are no exclusionary findings on lumbar MRIs, any hip or knee MRI of joints with a K-L score ≥ 3, or any other joint on which an MRI was performed during screening must be received before a patient can be randomized.

- **Treatment Period (day 1 through week 16):** The treatment period will begin at the randomization visit (baseline/day 1) and continue through the week 16 visit. Patients who meet study entry criteria will be randomized and will undergo baseline assessments at the day 1 visit. For patients randomized to SC administration, a loading dose equivalent to 2 times the maintenance dose will be administered on day 1.

  Patients randomized to 6 mg or 9 mg fasinumab SC Q4W and placebo IV 9 mg Q8W will receive 2 SC injections of fasinumab on day 1 (SC loading dose), 1 SC injection at weeks 4, 8, and 12, and 1 IV infusion of matching placebo on day 1 and at week 8.

  Patients randomized to 9 mg fasinumab IV Q8W and placebo SC Q4W will receive 1 IV infusion of fasinumab on day 1 and at week 8, 2 SC injections of matching placebo on day 1 (placebo for SC loading dose) and 1 SC injection of matching placebo at weeks 4, 8, and 12.

  Patients randomized to placebo SC Q4W and placebo 9 mg IV Q8W will receive 2 SC injections of matching placebo to fasinumab on day 1 (SC loading dose), 1 SC injection of matching placebo at weeks 4, 8, and 12, and 1 IV infusion of matching placebo on day 1 and at week 8.

  Study drug (fasinumab or placebo) will be administered at the study site. Patients will be observed in the clinic for approximately 2 hours after IV administration of study drug and for 1 hour after SC dosing for evidence of a hypersensitivity reaction.

  Paracetamol/acetaminophen may be taken as rescue medication in the event of inadequate LBP relief, as described previously. The use of paracetamol/acetaminophen is prohibited for 48 hours prior to the start of each scheduled study visit in order to minimize the confounding effects of rescue medication on study measures.

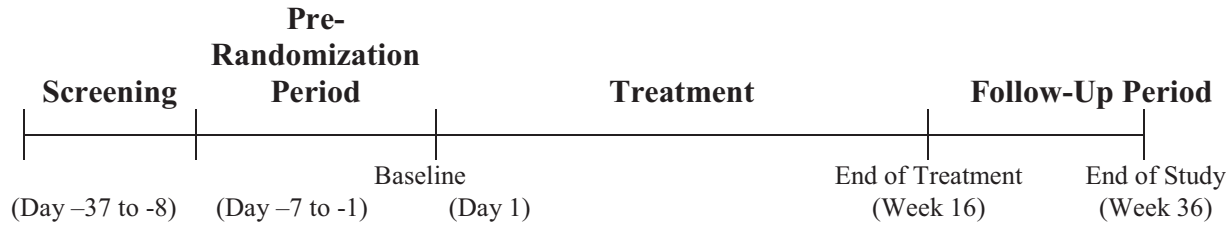
Every day, patients will report their LBPI scores using the NRS and their daily use of rescue medication for LBP in the EDiary.

Efficacy and safety assessments will be performed as outlined in Table 1. Potential events of adjudicated arthropathy will be monitored via clinical signs and symptoms of worsening joint pain during the study (eg, using the joint pain questionnaire and imaging). Potential events of sympathetic nervous system dysfunction will be monitored throughout the study via the Survey of Autonomic Symptoms.

- **Follow-up Period (week 20 through week 36 visits):** The follow-up period starts after the week 16 visit and continues through the week 36 visit.

  During the follow-up period, safety and efficacy assessments will be performed as outlined in Table 2. Potential events of adjudicated arthropathy and sympathetic nervous dysfunction will be monitored as described previously.

Figure 1: Study Flow Diagram



A comprehensive risk management approach will be implemented for 3 adverse events of special interest (AESI), adjudicated arthropathy, joint replacement, and sympathetic nervous system dysfunction; this approach is discussed in Section 7.4.1.

In order to monitor for outcomes for potential cases of adjudicated arthropathy, if a patient must undergo total joint replacement (TJR) surgery during the study, they will be asked to complete an early termination visit prior to the surgery if at all possible and to return for post-surgery follow-up as outlined in Table 3.

3.1.1. Study Stopping Rules

An independent Data Monitoring Committee (DMC) will monitor unblinded data on an ongoing basis to assess the risk/benefit profile of fasinumab. If at any time the DMC has significant concerns regarding a meaningful imbalance in joint-related AEs, sympathetic nervous system dysfunction, or neurosensory disturbances, the DMC may make a recommendation to the sponsor to temporarily halt the study (screening, randomization, dosing of study drug) 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.

3.2. Planned Interim Analysis

An administrative interim analysis is planned for this study per Section 9.5.6.

3.3. Study Committees

3.3.1. Independent Data Monitoring Committee

An independent DMC will meet periodically to review unblinded data as the study progresses, and based on the findings, will make recommendations to the sponsor about the conduct of the study.

The DMC will 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.

3.3.2. Adjudication of Arthropathy Events

All potential events of adjudicated arthropathy will be determined by an adjudication committee. Further details will be defined in the Adjudicated Arthropathy Adjudication Charter.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

The study will enroll approximately 200 patients in each of 4 treatment groups, for a total of approximately 800 randomized patients at sites in the United States, Canada, and Europe.

4.2. Study Population

Eligible patients for this study will be men and women ≥35 years of age with chronic LBP who have a history of inadequate pain relief or intolerance to current analgesic therapy.

4.2.1. Inclusion Criteria

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

1. Male or female ≥35 years of age at the screening visit
2. Provide signed informed consent
3. Body mass index ≤39
4. Clinical diagnosis of chronic moderate to severe LBP (non-radiculopathic) for ≥3 months (prior to the screening visit)
    - Quebec taskforce category 1 (pain without radiation) or category 2 (pain with proximal radiation above the knee)
    - Primary pain location between 12th thoracic vertebra and lower gluteal fold
    - At both the screening and the randomization visit, an LBPI NRS score of ≥4 over the previous 24 hours
    - During the pre-randomization period, mean daily LBPI score of ≥4

- At the screening visit, PGA of LBP of fair, poor or very poor

5. History of regular analgesic medication, such as NSAIDs, COX-2 inhibitors, opioids, paracetamol/acetaminophen, or a combination thereof
   - Taking medication >4 days per week in the month prior to screening
   - Willing to discontinue current opioid pain medications starting at pre-randomization visit through the week 16 study visit
   - Willing to discontinue current NSAID pain medications (oral or topical) starting at pre-randomization visit through 16 weeks after last dose of study drug
6. A history of inadequate pain relief or intolerance to analgesics used for chronic LBP as defined by:
   - Intolerance or inadequate pain relief from paracetamol/acetaminophen, and
   - Intolerance or inadequate pain relief from at least 1 oral NSAID, and
   - Intolerance or inadequate pain relief from at least 1 opioid, unwillingness to take opioid therapy or lack of access to opioid therapy
7. Willing to consider TJR surgery, if necessary
8. Willing and able to comply with clinic visits and study-related procedures
9. Able to understand and complete study-related questionnaires

4.2.2. Exclusion Criteria

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

1. Four or more consecutive LBPI NRS data entries missed during the pre-randomization period.
2. History of Quebec taskforce category >2 (pain with proximal radiation above the knee) lumbosacral radiculopathy within the past 2 years prior to the screening visit
3. Patient is not a candidate for MRI
4. Evidence on baseline lumbar spine MRI (or lumbar spine X-ray, if requested) of severe spinal stenosis, disc herniation with substantial neural encroachment, recent vertebral fracture, an active destructive process or marked segmental instability (as indicated by bone marrow edema or Modic type I change, respectively)
5. History of major trauma, or back surgery in the past 6 months prior to the screening visit.
6. History or presence of pyriformis syndrome
7. History or presence at the screening visit of non-OA inflammatory joint disease (eg, rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudogout, joint infections), multiple sclerosis, seronegative spondyloarthropathy, Paget's disease of the spine, pelvis, or femur, fibromyalgia, or tumors or infections of the spinal cord

8. Use of extended-release opioids or long-acting opioids such as oxycodone controlled release, oxymorphone extended release, hydromorphone, transdermal fentanyl, or methadone within 3 months prior to the screening visit
9. 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
10. Systemic (ie, oral or intramuscular) corticosteroids or intra-articular corticosteroid injections within 30 days prior to the screening visit.
11. Epidural steroid injections within 3 months prior to the screening visit
12. Botox injections for LBP within 6 months prior to the screening visit
13. History or presence on imaging of arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressing OA type 1 or type 2), stress or recent 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 pathological fractures during the screening period
14. Is scheduled for a joint replacement surgery during the study period
15. Signs and symptoms of carpal tunnel syndrome within 6 months of screening
16. History or presence at the screening visit of autonomic neuropathy, diabetic neuropathy, or other peripheral neuropathy including reflex sympathetic dystrophy
17. Evidence of autonomic neuropathy at the screening visit, as defined in the Survey of Autonomic Symptoms
18. History or diagnosis of chronic autonomic failure syndrome including pure autonomic failure and multiple system atrophy (Shy-Drager syndrome)
19. Poorly controlled diabetes (HbA1c >9.0%) at the screening visit
20. Confirmed elevated screening ALT or AST > 2.5x ULN
21. Resting heart rate of <50 beats per minute (bpm) at the screening, pre-randomization or randomization visits
22. History or presence of 2nd or 3rd degree heart block, 1st degree heart block with abnormal QRS, or bifascicular block by ECG at the screening visit
23. History or presence of orthostatic hypotension as defined in Section 6.3.3.6, at the screening, pre-randomization, or baseline visits

24. Poorly controlled hypertension
    - Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg at the screening visit
    - Systolic blood pressure of 160 mm Hg to 179 mm Hg or diastolic blood pressure of 100 mm Hg to 109 mm Hg at the screening visit, AND a history of end-organ damage (including history of left ventricular hypertrophy, heart failure, angina, myocardial infraction, stroke, transient ischemic attack (TIA), peripheral arterial disease and moderate to advanced retinopathy [hemorrhages or exudates, papilledema])
25. Congestive heart failure with NY Heart Classification of stage 3 or 4
26. Transient ischemic attack (TIA) or cerebrovascular accident within the past 12 months prior to the screening visit, or myocardial infarction or acute coronary syndromes within the past 6 months prior to the screening visit
27. 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
28. New major illness diagnosed within 2 months prior to the screening visit
29. Known history of ocular herpes simplex virus, herpes simplex virus pneumonia, or herpes simplex virus encephalitis
30. Known history of human immunodeficiency virus infection
31. 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.
32. Known history of infection with hepatitis C virus. Patients with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test.
33. 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
34. Known allergy or sensitivity to doxycycline or related compounds, or monoclonal antibodies
35. History of (within 5 years prior to the screening visit) current alcoholism, alcohol abuse, substance abuse, or abuse of prescription pain medication
36. History of cannabis use for the treatment of pain within the past 6 months prior to the screening visit
37. History of hospital admission for depression or suicide attempt within 5 years or active, severe major depression at screening
38. Current or pending worker's compensation, litigation, disability, or any other monetary settlement related to LBP

39. Ongoing participation in a clinical research study evaluating another investigational drug or having received another investigational product within 30 days or 5 half-lives, whichever is longer
40. Exposure to an anti-NGF antibody within 6 months prior to the screening visit or known sensitivity or intolerance to anti-NGF antibodies
41. Pregnant or breast-feeding women
42. Women of childbearing potential who have a positive pregnancy test result or do not have their pregnancy test result at baseline
43. Women of childbearing potential (Section 6.3.1.4) who are unwilling to use acceptable contraceptive methods during the study and for 20 weeks after the last dose of study drug. Acceptable methods of contraception include combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intra-uterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence; or condom in combination with either cap, diaphragm, or sponge with spermicide (double-barrier contraception).

4.3. Premature Withdrawal from the Study

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

The investigator and/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 withdraw prematurely from the study will be asked to complete study assessments per Section 6.2.7.

Rules for discontinuation of study treatment (temporary or permanent) are discussed in Section 5.3.2.

4.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational Treatment

Patients will be randomized to 1 of the following 4 treatment groups:

1. Fasinumab 6 mg SC Q4W and placebo 9 mg IV Q8W
2. Fasinumab 9 mg SC Q4W and placebo 9 mg IV Q8W
3. Fasinumab 9 mg IV Q8W and placebo SC Q4W
4. Placebo SC Q4W and placebo 9 mg IV Q8W

Patients randomized to treatment groups 1 or 2 (6 mg or 9 mg fasinumab) will receive SC injections of fasinumab on day 1, and at weeks 4, 8, and 12 for a total of 4 doses. These patients will also receive matching placebo IV on day 1 and at week 8. For patients randomized to SC administration, a loading dose equivalent to 2 times the maintenance dose will be administered SC on day 1.

Patients randomized to treatment groups 3 or 4 will receive matching placebo to fasinumab SC, including the loading dose on day 1.

Patients randomized to treatment group 3 will receive IV infusions of fasinumab (9 mg) on day 1 and week 8 for a total of 2 doses. Patients randomized to treatment groups 1, 2, or 4 will receive matching placebo to fasinumab IV.

Study drug (fasinumab or placebo) will be administered at the study site after all study visit procedures have been completed. All SC injections will be in the abdomen or thigh. At the day 1 and week 8 visits, patients will receive the SC injection first, followed by the IV infusion. After IV administration of study drug, patients will be observed in the clinic for approximately 2 hours for evidence of a hypersensitivity reaction, and for 1 hour after SC dosing. Instructions for study drug administration are provided in the pharmacy manual. Doses of study drug must be given within ±7 days from the scheduled dose date. If the window is missed, the dose should not be administered. The next dose should be administrated at the next scheduled dosing date.

5.2. Rescue Treatment

Study-provided paracetamol/acetaminophen is the only allowable rescue medication for LBP during the study from pre-randomization visit through end of treatment (week 16), and will be provided to all patients according to Section 6.1.

5.2.1. Paracetamol/Acetaminophen

During the 16-week treatment period, paracetamol/acetaminophen is the study-provided rescue medication. In the event of inadequate back pain relief, 1 to 2 tablets/capsules of paracetamol/acetaminophen (325 mg per tablet/capsule in North America or 500 mg per tablet/capsule in Europe) may be taken no less than 4 hours apart with a maximum allowable total dose of 2600 mg per day (325 mg x 8) in North America or 2500 mg (500 mg x 5) in Europe. In Europe, the highest individual dose is 1 gram, and in North America, the highest individual dose is 650 mg. The use of paracetamol/acetaminophen is not allowed for 48 hours

prior to the start of the scheduled study visit until after the efficacy assessments have been completed, in order to minimize the confounding effects of rescue medication on these measures.

The amount of paracetamol/acetaminophen used in the prior 24 hours will be reported by the patient each evening using the EDiary. Paracetamol/acetaminophen accountability will be conducted at each clinic visit starting at the baseline visit and continuing through the week 16 visit. Paracetamol/acetaminophen will be sourced by the sites and reimbursed by the sponsor unless country-specific regulations and customs require a different approach.

Patients should be cautioned to avoid consumption of alcoholic beverages while on paracetamol/acetaminophen. Patients should also be cautioned not to take rescue medication at intervals of less 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.

5.3. Dose Modification and Study Drug Discontinuation Rules

5.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

5.3.2. Study Drug Discontinuation

Study drug may be permanently or temporarily discontinued due to medical need, as determined by the investigator.

Patients who permanently discontinue from study drug but do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who opt to withdraw from the study will be asked to complete study assessments, per Section 6.2.7 (early termination).

Patients who discontinue from study drug early due to a potential adverse event of adjudicated arthropathy (see Section 7.4.1.1) should return to the clinic for all remaining study visits per the visit schedule.

Any patient who requires joint replacement surgery during the study will be asked to return to the site for an early termination visit (Section 6.2.7) and for the follow-up safety evaluations as described in Section 6.3.3.9.

5.3.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- A patient developing clinically significant sensory and motor neurologic events confirmed by a neurologist's examination and graded by a neurologist as a modified neuropathy grade >2 according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4 (study sites should use CTCAE v.4 criteria throughout the study for consistency)
- A patient developing new or worsening signs and symptoms indicative of carpal tunnel syndrome

- Evidence of pregnancy
- Continued noncompliance with protocol-defined maximum acetaminophen/paracetamol use after appropriate counseling
- AESI:
  - Adjudicated arthropathy, as described in Section 7.4.1.1
  - Autonomic dysfunction, as described in Section 7.4.1.2
- Hepatotoxicity: The US FDA provides general guidance for all investigational products for drug-induced liver injury. A copy of the guidance is provided in the study reference manual. This guidance provides criteria for withholding study drug if a patient develops signs and symptoms of hepatitis during a study that should be followed.
  - Study drug should be discontinued if:
    1. Total bilirubin (TBL) >2 x upper limit of normal (ULN) or international normalized ratio (INR) >1.5
    2. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x ULN
    3. No other cause for 1 and 2 is readily apparent

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

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

- Any other medical need, as determined by the investigator

5.4. Management of Infusion Reactions

Emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids, paracetamol/acetaminophen, and/or epinephrine) must be available for immediate use. Infusion reactions must be reported as AEs (Section 7.2.1) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 grading scale (Section 7.3.1).

5.4.1. Interruption of the Infusion

The infusion should be interrupted if any of the following AEs are observed:

- Cough
- Rigors/chills
- Rash, pruritus (itching)

- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically and the infusion should be terminated. If the investigator feels there is a medical need to terminate the infusion, they may do so at any time. If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

5.4.2. Termination of the Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension

5.5. Method of Treatment Assignment

Approximately 800 patients will be randomized in a 1:1:1:1 ratio to 1 of the 4 treatment groups according to a predetermined central randomization scheme generated and provided to study site personnel by the interactive voice response system (IVRS). Randomization will be stratified by baseline LBPI NRS score, duration of chronic LBP, and maximum K-L score at any knee or hip joint at screening.

5.5.1. Blinding

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

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

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

One administrative interim analysis may be conducted. No study personnel involved in the day-to-day conduct of the study will have access to unblinded data before the database is locked for this study.

5.5.2. Emergency Unblinding

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

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patient will be unblinded.
  - Unblinding of treatment assignment will be performed using the IVRS; manual unmasking (ie, via the designated study pharmacist at the study site) will not be permitted
  - The investigator should promptly document and explain to the sponsor any premature unblinding

The treatment dose level or treatment is not to be provided to site personnel, including the investigator, at any time during the conduct of the study, except in the case of a true emergency. Once unblinded by the site, the patient will no longer be allowed to receive study drug.

5.6. Treatment Logistics and Accountability

5.6.1. Packaging, Labeling, and Storage

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

Study drug (fasinumab and its placebo) will be refrigerated at the site at a temperature of [redacted]; refrigerator temperature will be logged daily. Storage instructions for study drug will be provided in the pharmacy manual.

5.6.2. Supply and Disposition of Treatments

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

5.6.3. Treatment Accountability

All drug accountability records for blinded fasinumab and its placebo, and paracetamol/acetaminophen must be kept current.

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

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

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

5.6.4. Treatment Compliance

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

5.6.5. Patient Drug Accountability

Patients will be asked to bring in their bottles of paracetamol/acetaminophen to each study visit starting at the baseline visit through the week 16 visit, and remaining medication will be counted to calculate medication use and compliance. Patients will also be instructed to report the daily use of these medications using the EDiary.

5.7. Concomitant Therapy

Any treatment administered from screening until the end of study (week 36) is considered concomitant medication. This includes medications that were started prior to the study and are ongoing during the study.

5.7.1. Permitted Therapy

Patients receiving chronic medication therapy must be on a stable dose of such medication for at least the 30 days prior to the screening visit. Monoamine reuptake inhibitors are permitted for nonpain related treatment, as are tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors. 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 (up to 100 mg/day) for cardiac prophylaxis is also permitted. Paracetamol/acetaminophen taken acutely for treatment of non-LBP is also permitted. Paracetamol/acetaminophen taken for non-LBP relief should be reported as concomitant medication. Other permitted medications are glucosamine, chondroitin sulfate, and rescue medications (discussed in Section 5.2). Topical steroids and topical non-NSAID analgesics are also permitted.

Physical therapy and chiropractic or alternative therapy (such as acupuncture) are permitted if their use was stable for the month preceding the screening visit and is expected to remain stable for the duration of the study.

5.7.2. Prohibited Therapy

Patients who meet the initial eligibility criteria at the screening visit will be asked to discontinue their current NSAID (oral or topical; except up to 100 mg/day of aspirin, which is permitted for cardiac prophylaxis) and opioid analgesic medications, starting at the pre-randomization visit.

Opioid analgesic medications (including tramadol) are prohibited through the week 16 study visit. Patients will be directed not to take concomitant medications that contain NSAIDs (oral or topical, except up to 100 mg/day of aspirin, which is permitted for cardiac prophylaxis) until at least 16 weeks after the last dose of study drug. A list of medications containing NSAIDs will be provided in the study reference manual.

Other excluded drugs are:

- Any other investigational agent
- Cyclosporine
- Azathioprine
- Medical marijuana
- Tumor necrosis factor antagonists
- Corticosteroids (topical and inhaled formulations are permitted)
- Tocilizumab
- Abatacept
- Cyclobenzaprine, carisoprodol, orphenadrine, tizanidine
- Muscle relaxants

6. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

6.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1 and Table 2. A schedule for follow-up of TJR surgery during the study is presented in Table 3.

Table 1: Schedule of Events – Screening Period Through Week 16

	Screening Period	Pre-Randomization Period	Treatment						End of Treatment Period	Treatment Period Early Termination Visit
Study Week				**1**	**2**	**4**	**8**	**12**	**16**	
Study Day (visit window)	**up to -37 to -8**	**-7 (+3) Pre-Rand Visit**	**1 Baseline**	**8 (±1)**	**15 (±3)**	**29 (±7)**	**57 (±7)**	**85 (±7)**	**113 (±7)**	**ET**
Visit Number	**1**	**2**	**3**	**Ph call 1**	**4**	**5**	**6**	**7**	**8**	**ET**
Screening/Baseline:										
Informed Consent	X									
Inclusion/Exclusion	X	X	X							
Genomics sub-study informed consent[1]	X									
Medical History	X									
Medication History	X									
Demographics	X									
Height	X									
Bilateral radiograph of knees, hips and shoulders[2]	X									
Lumbar spine MRI[3]	X									
MRI of any knee or hip with baseline K-L ≥3 [2]	X								X	X[4]
NRS/EDiary training[5,7]		X								
Assessment of peripheral or central pain	X									
painDETECT Questionnaire	X									
Randomization			X							
Treatment:										
SC Study Drug Injection[6]			LOADING DOSE			X	X	X		
IV Study Drug Infusion[6]			X				X			
Dispense paracetamol/acetaminophen		X	X			X	X	X		
Paracetamol/acetaminophen accountability			X		X	X	X	X	X	X

	Screening Period	Pre-Randomization Period	Treatment						End of Treatment Period	Treatment Period Early Termination Visit
Study Week				1	2	4	8	12	16	
Study Day (visit window)	up to -37 to -8	-7 (+3) Pre-Rand Visit	1 Baseline	8 (±1)	15 (±3)	29 (±7)	57 (±7)	85 (±7)	113 (±7)	ET
Visit Number	1	2	3	Ph call 1	4	5	6	7	8	ET
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Efficacy:										
Reporting Your Pain - patient education brochure[7]	X	X	X		X	X	X	X	X	
LBPI NRS [8]	X	X	X		X	X	X	X	X	X
Roland Morris Disability Questionnaire			X		X	X	X	X	X	X
Patient Global Assessment LBP	X		X		X	X	X	X	X	X
MOS Sleep Scale Survey			X		X	X	X	X	X	X
SF-36			X		X	X	X	X	X	X
EQ-5D-5L			X		X	X	X	X	X	X
Safety:										
Weight	X								X	X
Vital Signs[9]	X	X	X		X	X	X	X	X	X
Physical Examination[10]	X								X	X
Electrocardiogram	X								X	X
Joint Pain Questionnaire	X		X		X	X	X	X	X	X
Event-triggered imaging[11]					X	X	X	X	X	X
Orthostatic blood pressure	X	X	X		X	X	X	X	X	X
Survey of autonomic symptoms	X		X			X	X	X	X	X
Neurologic examination	FULL		BRIEF		BRIEF	BRIEF	BRIEF	BRIEF	FULL	FULL
SC injection site evaluation			X			X	X	X		
Adverse Events	X	X	X	X	X	X	X	X	X	X
Pre-op questionnaire (TJR) [12]										X
Laboratory Testing: [6]										
Hematology	X		X			X	X	X	X	X

	Screening Period	Pre-Randomization Period	Treatment						End of Treatment Period	Treatment Period Early Termination Visit
Study Week				**1**	**2**	**4**	**8**	**12**	**16**	
Study Day (visit window)	**up to -37 to -8**	**-7 (+3) Pre-Rand Visit**	**1 Baseline**	**8 (±1)**	**15 (±3)**	**29 (±7)**	**57 (±7)**	**85 (±7)**	**113 (±7)**	**ET**
Visit Number	**1**	**2**	**3**	**Ph call 1**	**4**	**5**	**6**	**7**	**8**	**ET**
Blood Chemistry	X		X			X	X	X	X	X
HbA1c	X									
FSH and estradiol [13]	X									
Pregnancy test (WOCBP) [14]	SERUM		URINE		URINE	URINE	URINE	URINE	SERUM	SERUM
Urinalysis/Urine Creatinine and Phosphorous	X		X			X	X	X	X	X
PK/Drug Concentration and ADA Samples: [6]										
PK/Drug conc. Sample			X		X	X	X	X	X	X
ADA sample			X						X	X
Genomics sub-study sample[1]			X							
Research serum/plasma sample			X		X	X	X	X	X	X

1. Only for patients who provide written informed consent for the optional genomics sub-study. The sample should be collected at the baseline visit, but may be collected at any subsequent visit during the study.
2. If screening radiographs are inconclusive for potential joint-related findings, an MRI of the affected joint must be performed and assessed by the central reader. After the patient has otherwise met study eligibility criteria assessed during the screening period, an MRI of any knee or hip joint that has a baseline K-L score of ≥3 must be performed prior to the pre-randomization visit. Confirmation that the image has been accepted and confirmed query-free by the central reader must be received by the site before the pre-randomization visit. Confirmation from the central reader that there are no exclusionary findings on MRI must be received from the central reader before a patient can be randomized.
3. A lumbar spine AP/Lateral should be obtained if the MRI of the lumbar spine shows evidence suggestive of a destructive or unstable process.
4. Early Termination: Imaging assessments (X-rays of the knees, hips, and shoulders, and MRI) need to be repeated only if it has been >30 days since the joint was last imaged. If it has been ≤30 days since imaging assessments were completed, imaging assessments may be completed at the discretion of the investigator.
5. Patients will be trained on using the EDiary after initial patient eligibility has been confirmed during the screening period. Patients will use the EDiary to report their daily NRS LBP score and daily use of paracetamol/acetaminophen through the week 16 visit.
6. Study drug administration will be the last procedure at each dosing visit, and will be done after all laboratory samples have been collected and all study assessments and procedures are performed including blood draws for drug concentration and ADA. At the day 1 and week 8 visits, patients will receive the SC injection first, followed by the IV infusion. After IV administration of study drug, patients will be observed in the clinic for approximately 2 hours for evidence of a hypersensitivity reaction, and for 1 hour after SC dosing.

7. At the screening and pre-randomization visits, study staff will review the "Reporting Your Pain" brochure with the patient to ensure the patient understands how to report pain accurately. At subsequent clinic visits patients will be asked to review the "Reporting Your Pain" brochure themselves. At the screening visit, study staff will also review with the patient the "Participating in a Research Study: What You Need to Know" brochure.
8. Low back pain intensity NRS score will be recorded by the site at the screening visit and at the pre-randomization visit, and by the patient each day (at approximately 6:00 PM) using the EDiary, starting during the pre-randomization period through week 16.
9. If the pulse is less than 45 bpm at any visit after the randomization visit, an ECG with rhythm strip will be obtained and sent to the central reader to confirm the heart rate and rhythm.
10. The physical examination should include an exam of the knee, hip, and shoulder joints.
11. Imaging (X-ray and/or MRI) will be considered for worsening joint pain, despite treatment with analgesics, which is inconsistent with the normal progression of OA and lasts for at least 2 weeks (or less, at the discretion of the investigator).
12. In the event that a patient must undergo TJR surgery during the study, the patient will complete the early termination visit and the procedures outlined in the schedule of events for TJR follow-up (Table 3). The early termination visit should be completed before TJR surgery if at all possible. TJR questionnaires are Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements.
13. To be performed only if postmenopausal status has to be assessed for female patients ≤59 years of age.
14. In the event of a positive urine pregnancy test result, the patient must have a serum pregnancy test with a negative result in order to continue study participation. If the serum pregnancy test is positive, the patient must be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 5.3.2).

Table 2: Schedule of Events – Follow-up Period – Week 20 through Week 36

	Follow-up Period				End of Study	Follow-up Period Early Termination
Study Week	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	
Study Day (visit window)	**141(±7)**	**169(±7)**	**197(±7)**	**225(±7)**	**253(±7)**	
Visit Number	**9**	**Ph call 2**	**Ph call 3**	**Ph call 4**	**10**	ET
Treatment:						
Concomitant Meds	X	X	X	X	X	X
Efficacy:						
Reporting Your Pain - patient education brochure[1]	X					
LBPI NRS	X				X	X
Roland Morris Disability Questionnaire	X				X	X
Patient Global Assessment LBP	X				X	X
MOS Sleep Scale Survey	X				X	X
SF-36	X				X	X
EQ-5D-5L	X				X	X
Safety:						
Vital Signs[2]	X				X	X
Physical Examination					X	X
Electrocardiogram					X	X
Joint Pain Questionnaire	X				X	X
Event-triggered imaging[3]	X				X	X
Orthostatic blood pressure	X				X	X
Survey of autonomic symptoms	X				X	X
Neurologic examination	BRIEF				FULL	FULL
Adverse Events	X	X	X	X	X	X
MRI of any knee or hip with baseline K-L ≥3 [4]					X	X[3]
Pre-op questionnaire (TJR) [5]						X
Laboratory Testing:						
Hematology					X	X
Blood Chemistry					X	X
Pregnancy test (WOCBP)	URINE				SERUM	SERUM
Urinanlysis/Urine Creatinine and Phosphorous					X	X

	Follow-up Period				End of Study	Follow-up Period Early Termination
Study Week	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	
Study Day (visit window)	**141(±7)**	**169(±7)**	**197(±7)**	**225(±7)**	**253(±7)**	
Visit Number	**9**	**Ph call 2**	**Ph call 3**	**Ph call 4**	**10**	ET
PK/Drug Concentration and ADA Samples:						
PK/Drug conc. sample	X				X	X
ADA sample					X	X
Research serum/plasma sample					X	X

1. The patient will be asked to review the "Reporting Your Pain" brochure themself.
2. If the pulse is less than 45 bpm at any visit after the randomization visit, an ECG with rhythm strip will be obtained and sent to the central reader to confirm the heart rate and rhythm.
3. Imaging (X-ray and/or MRI) will be considered for worsening joint pain, despite treatment with analgesics, which is inconsistent with the normal progression of OA and lasts at least 2 weeks (or less, at the discretion of the investigator)
4. Imaging assessments (X-rays of the knees, hips, and shoulders, and MRI) need to be repeated only if it has been >30 days since the joint was last imaged. If it has been ≤30 days since imaging assessments were completed, imaging assessments may be completed at the discretion of the investigator.
5. In the event that a patient must undergo TJR surgery during the study, the patient will complete the early termination visit and the procedures outlined in the schedule of events for TJR follow-up (Table 3). The early termination visit should be completed before TJR surgery if at all possible. TJR questionnaires are Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements.

Table 3: Schedule of Events - Follow-up for Patients Who Undergo Total Joint Replacement Surgery

	Follow-up Period[1]	
	Post-Operative	**Long-Term**
	Follow-up Visit 1 4 weeks after the date of the joint replacement surgery	**Follow-up Visit 2** 20 weeks after the date of the joint replacement surgery
Follow-up Study Day (Visit Window)	**F/U Day 29 (±7)**	**F/U Day 140 (±7)**
Treatment:		
Concomitant medications	**X**	**X**
Safety:		
Vital signs	**X**	**X**
Physical examination with joint exam	**X**[1]	**X**
Medical history related to the total joint replacement	**X**	**X**
Joint pain questionnaire	**X**	**X**
Post-operative assessment questionnaire[2]	**X**	**X**
Event-triggered imaging[3]	**X**	**X**
MRI of any knee or hip with a baseline K-L ≥3		**X**

1. Relevant information related to the surgery should be collected, including placement of the prosthesis and healing of the surgical wound.
2. Formal post-operative assessment of joint replacements will be done by completing the Knee Society Score questionnaire for knee replacements or the Harris Hip Score questionnaire for hip replacements. Full details of these assessments are provided in the study reference manual.
3. Imaging (X-ray and/or MRI) will be considered for worsening joint pain, despite treatment with analgesics, which is inconsistent with the normal progression of OA and lasts at least 2 weeks (or less, at the discretion of the investigator).

6.2. Study Visit Descriptions

6.2.1. Screening Period (Up to Day -37 to Day -8)

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

All pain assessments at the screening visits and subsequent visits should be completed prior to the physical exam. The patient reported outcomes assessments should be completed prior to all other assessments.

An MRI of the lumbar spine will be performed during screening. A lumbar spine AP/lateral X-ray should be obtained if the MRI of the lumbar spine shows evidence suggestive of a destructive or unstable process. X-rays of the knees, hips or shoulders will be performed during the screening period. After the patient has otherwise met study eligibility criteria assessed during the screening period and prior to the pre-randomization visit, an MRI will be performed and assessed by the central reader for any screening radiographs that are inconclusive for any potential joint-related findings and for any knee or hip joint with a K-L score ≥ 3. Confirmation from the central reader that the image has been accepted and is query-free must be received before the pre-randomization visit is conducted. Confirmation from the central reader that there are no exclusionary findings on MRI must be received before a patient can be randomized.

6.2.2. Rescreening

Patients who do not meet eligibility criteria may rescreen once only after approval by the Sponsor or designee.

- If rescreening is performed during the screening window (day –37 to day –8) assessments that did not meet the eligibility criteria must be repeated and completed prior to the pre-randomization visit. If repeat assessments are completed after the end of the screening window but prior to the pre-randomization visit, then all screening procedures must be repeated with the exception of imaging. Imaging assessments (X-rays and MRIs) need to be repeated only if they were done >60 days from the date of the original screening X-rays and MRI.
- If rescreening is performed during the pre-randomization period, all screening procedures must be repeated with the exception of imaging. Imaging assessments (X-rays of the knees, hips, shoulders, and lumbar spine, if applicable, and MRIs) need to be repeated only if they were done more than 60 days from the date of the screening X-rays and MRI.

- If rescreening is performed after the screening window and pre-randomization period end, patients must re-consent and all screening procedures must be repeated with the exception of imaging. Imaging assessments (X-rays of the knees, hips, shoulders, and lumbar spine, if applicable, and MRIs) need to be repeated only if they were done more than 60 days from the date of the screening X-rays and MRI.

6.2.3. Pre-Randomization Visit (Day -7 [+3])

Patients who complete screening and meet the initial eligibility criteria will return to the site to undergo Ediary training for recording their daily LBP score and use of paracetamol/acetaminophen through the week 16 visit, and for completion of the remaining assessments per the schedule of events. Patients will be instructed to stop using all prohibited medications. During the pre-randomization period, patients may take study-provided rescue medication in the event of inadequate LBP relief, per Section 5.2. Rescue medication must be discontinued 48 hours prior to the baseline/randomization visit.

6.2.4. Baseline/Randomization Visit (Day 1)

If a patient has met all screening eligibility criteria, study sites will complete the procedures as detailed in the schedule of events for the baseline visit. The patient reported outcomes assessments at this and subsequent visits should be completed prior to all other assessments. All laboratory samples at this and subsequent visits must be collected and all study procedures must be performed before study drug is administered. At dosing study visits, urine pregnancy testing will be done and read before the study drug is administered. In the event of a positive urine pregnancy test result, the patient should have a serum pregnancy test with a negative result in order to continue study participation. If the serum pregnancy test is positive, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 6.2.7).

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

6.2.5. Weeks 1 through 16

Complete visits and assessments are outlined in the schedule of events (Table 1). The patient reported outcomes should be completed prior to all other assessments. All study procedures should be completed before administration of study drug. The last dose of study drug is administered at week 12. Patients who discontinue study drug should return for the remaining study visits, if possible. If patients are not able to continue study participation, they should return for an early termination visit, at which the treatment-period early termination visit assessments will be performed per the schedule of events.

At dosing study visits, urine pregnancy testing will be done and read before the study drug is administered. Study drug will be withheld in the event of a positive urine pregnancy test result. In the event of a positive urine pregnancy test result, a serum pregnancy test must be performed. If the serum pregnancy test is negative, the patient may continue study participation. If the serum pregnancy test is positive, the patient must be permanently discontinued from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (Section 6.2.7).

6.2.6. Weeks 20 through 36

Complete visits and assessments are outlined in the schedule of events (Table 2). The patient reported outcomes should be completed prior to all other assessments. If patients are not able to continue study participation, they should return for an early termination visit, at which the follow-up period early termination visit assessments will be performed, per the schedule of events.

6.2.7. Early Termination Visit (as Applicable)

Patients who discontinue study drug should be encouraged to continue participation in the study. Patients who are willing to continue do not need to complete an early termination visit and will be asked to participate in all remaining scheduled site visits and telephone contacts through week 36. Assessments should be completed according to the schedule of events (Table 1 and Table 2). If patients decline to return to the study site for an early termination visit they should be contacted by telephone to collect any safety information.

If patients decline to return to the study site for their scheduled week 16 visit, they should be contacted by telephone to collect any safety information.

6.2.8. Visits in the Event of Total Joint Replacement Surgery

In the event that a patient must undergo TJR surgery during the study, the patient will complete the early termination visit (week 16 or week 36 assessments as outlined in Section 6.2.7) and the procedures outlined in the schedule of events for TJR follow-up (Table 3). The early termination visit should be completed before TJR surgery if at all possible. All patient-reported pain outcomes should be completed before the physical examination.

6.2.9. Unscheduled Visits

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

6.3. Study Procedures

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

6.3.1.1. Informed Consent

All patients must sign and date an Institutional Review Board (IRB)-approved or Ethics Committee (EC)-approved informed consent form (ICF) before any study procedures are performed, per Section 13.2.

6.3.1.2. Medical History

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

6.3.1.3. Medication History

The investigator or designee will query patients on the medication(s) they have taken for their LBP (medication history), including information on their ability to tolerate the medication, and will record the information on an eCRF for this purpose.

6.3.1.4. Assessment of Childbearing Potential

Each female patient should be evaluated for childbearing potential.

Women will be considered to be of childbearing potential unless:

- They are postmenopausal, or
- They have had a tubal ligation, a bilateral oophorectomy, bilateral salpingectomy, or hysterectomy

In women ≥59 years of age, postmenopausal 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 follicle-stimulating hormone (FSH) levels >40 IU/L and serum estradiol levels <5 ng/dL (see Section 6.3.3.10).

6.3.1.5. EDiary Training

When initial patient eligibility has been determined during the screening period, patients will return to the site for a pre-randomization visit. At this visit, patients will be instructed on the use of the NRS for scoring their LBP pain, and they will be trained on the EDiary to report their LBP NRS score and their daily paracetamol/acetaminophen use for LB pain.

6.3.1.6. Reporting Your Pain (Patient Education)

The patient education brochure "Reporting Your Pain" will be used to have an interactive discussion with patients at both the screening and pre-randomization visits to ensure patients understand how to report their pain accurately. At subsequent clinic visits, patients will be asked to review the "Reporting Your Pain" brochure themselves. The "Participating in a Research Study: What You Need to Know" brochure will also be reviewed with the patient at the screening visit to ensure appropriate patient expectations in participating in a clinical trial (see Section 6.1).

6.3.1.7. Assessment of Peripheral vs. Central Pain

Patients will complete the Assessment of Peripheral vs. Central Pain, a self-reported survey, to evaluate the peripheral versus central nature of their pain at the time points indicated in Section 6.1.

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

6.3.1.8. Assessment of Neuropathic vs. Nociceptive Pain

Patients will complete the painDETECT questionnaire to evaluate the neuropathic versus nociceptive nature of their pain at the time points indicated in Section 6.1. The questionnaire is self-administered and consists of 7 questions that address the quality of neuropathic pain

symptoms. The first 5 questions ask about the gradation of pain on a 6-point Likert scale (0 = never; 1 = hardly noticed; 2 = slightly; 3 = moderately; 4 = strongly; 5 = very strongly). Question 6 asks about the pain course pattern (scored from -1 to 2), and question 7 asks about radiating pain, answered 'yes' or 'no' (scored as 0 or 2, respectively).

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

6.3.2. Efficacy Procedures

6.3.2.1. Daily Low Back Pain Intensity Numerical Rating Score

At the screening visit and the pre-randomization visit, the investigator or designee will record the LBPI NRS score indicating pain over the past 24 hours based on the patient's report. Once initial eligibility is confirmed, from the pre-randomization visit to the week 16 study visit, LBPI NRS scores will be reported by the patient into the EDiary (Section 6.3.1.5) every day at approximately 6 PM. A copy of the assessment is provided in the study reference manual.

6.3.2.2. Roland Morris Disability Questionnaire

The RMDQ is a self-administered, widely used health status measure for LBP (Roland 1983). It measures pain and function, using 24 items describing limitations to everyday life that can be caused by LBP. The score of the RMDQ is the total number of items checked – ie, from a minimum of 0 to a maximum of 24. Patients will complete the questionnaire at the time points indicated in Section 6.1.

6.3.2.3. Patient Global Assessment of Low Back Pain

The PGA of LBP is a patient-rated assessment of their current disease state on a 5-point Likert scale (1 = very well; 2 = well; 3 = fair; 4 = poor; and 5 = very poor). Patients will complete the assessment scale at the time points indicated in Section 6.1.

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

6.3.2.4. Short Form (36) Health Survey

The SF-36 is a self-administered survey of general health. It measures 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these 8 health domains, and 2 summary measures of physical and mental health: the physical component summary and the mental component summary. Patients will complete the survey at the time points indicated in Section 6.1.

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

6.3.2.5. Medical Outcomes Study Sleep Survey

The MOS Sleep Survey is a self-administered 12-question survey of sleep habits (Hays 1992). Patients will complete the questionnaire at time points indicated in Section 6.1.

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

6.3.2.6. EQ-5D-5L

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, anxiety/depression. Each dimension has 5 ordinal levels of severity: "no problem" (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 range 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 Section 6.1.

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

6.3.3. Safety Procedures

6.3.3.1. Physical Examination

Patients will have a thorough and complete physical examination including an examination of the knees, hips, and shoulders at the time points indicated in Section 6.1. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Measurements of patient height and weight should be recorded at the time points indicated in Section 6.1.

6.3.3.2. Vital Signs

Vital signs including temperature, pulse, and respiration will be collected at time points indicated in Section 6.1. Pulse will be measured over a 1-minute period. At visits at which study drug is administered, vital signs should be measured before administration of study drug. If the pulse is less than 45 bpm at any visit after the randomization visit, an ECG with rhythm strip will be obtained to confirm the heart rate and rhythm.

6.3.3.3. Electrocardiogram

A standard 12-lead ECG will be performed at the time points indicated in Section 6.1 with the patient in the supine position for approximately 5 minutes and prior to blood samples being drawn. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT, QTc intervals will be recorded. The ECG data will be read by a central reading center. Detailed procedures will be provided in a separate manual provided by the central reading center.

6.3.3.4. Joint Pain Questionnaire

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

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

6.3.3.5. Survey of Autonomic Symptoms

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

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

6.3.3.6. Assessment of Orthostatic Blood Pressure

An assessment of orthostatic blood pressure will be conducted at the time points indicated in Section 6.1. The assessments should be conducted as per the instructions in the study manual. A patient will be determined to have orthostatic hypotension if any of the following criteria are met:

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

  OR

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

  OR

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

  OR

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

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

6.3.3.7. Neurological Evaluation

A full or a brief neurological examination will be performed at the time points indicated in Section 6.1. Neurological findings at baseline that are not exclusionary should be recorded in 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, coordination/balance, and assessment of signs and symptoms of carpal tunnel syndrome. It 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 judgment of the neurologist.

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

6.3.3.8. Imaging

Radiographs of the large joints (knees, hips, and shoulders) will be taken using a standard approach at the time points indicated in Section 6.1. At screening, an MRI of the affected joint must be performed if radiographic images are inconclusive for potential joint-related findings. Magnetic resonance imaging will also be performed on any hip or knee joint with a K-L score of ≥3 at screening. Confirmation that there are no exclusionary findings on MRIs must be received before the patient can be randomized. In addition, radiographs and/or an MRI will be performed of any joint following a report of clinically significant worsening or exacerbation of pain in that joint. Detailed procedures will be provided in a separate manual provided by the central imaging center. Radiograph or MRI will be sent to a central reader, where the images will be digitized.

Radiographs

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

Radiographs of the knees, hips, and shoulders will be sent to a central reader, and evaluated to confirm no evidence of adjudicated arthropathy.

MRI

An MRI of the lumbar spine will be taken using standard Acquisition Sequences at the time point indicated in Section 6.1 to assess for evidence of the following: disc degeneration or herniation, disc signal and height loss, Modic endplate changes, bone marrow edema, central subarticular or foraminal stenosis, spondylolisthesis, spondylolysis, and facet joint arthropathy. If the MRI suggests a adjudicated or unstable spinal process, flexion/extension radiographs may be requested.

An MRI of any hip or knee joint with a baseline K-L score ≥3 will be acquired at the time points indicated in Section 6.1. Prior to subject randomization, MRIs will be sent to a central reader and evaluated to confirm no evidence of adjudicated arthropathy or other exclusionary features. Confirmation from the central reader that the image has been accepted and is query-free must be received by the site before the pre-randomization visit. Confirmation from the central reader that there are no exclusionary findings on MRI must be received before a patient can be randomized. Additionally, 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.

Detailed acquisition and analysis parameters will be provided in a separate imaging charter provided by the central imaging center.

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

In the event that a patient must undergo TJR surgery during the study, the patient will be discontinued from study drug and will complete the early termination visit (week 16 or week 36 assessments as outlined in Section 6.2.7) and the procedures outlined in the schedule of events for TJR surgery follow-up (Table 3). The early termination visit should be completed before TJR surgery if at all possible. All pain patient-reported outcomes should be completed before the physical examination.

In the event the early termination visit is not performed pre-operatively, standard of care pre-operative images of the joint with TJR must be obtained and submitted to the central imaging vendor. Imaging of all other joints per early termination visit procedures will be done post-operatively at the first TJR follow-up study visit if not done before surgery.

All available medical history/information for patients who undergo TJR surgery must be collected, including histopathologic examination.

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

Knee Society Score

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

Harris Hip Score

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

6.3.3.10. Laboratory Testing

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

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

All samples will be collected before study drug administration. Missed tests should be reported in the source documents and in the eCRF, as appropriate. Central laboratory kits will be provided for sample collection and shipment. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites. Samples for laboratory testing will be collected at time points according to Section 6.1.

Blood Chemistry

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

Hematology

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

Urinalysis

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

Urine Chemistries

Creatinine Phosphorous

Other Laboratory Tests

Serum and urine samples for pregnancy testing will be collected from women of childbearing potential (as defined in Section 6.3.1.4) at time points according to Section 6.1. At dosing study visits, urine pregnancy testing will be done before the study drug is administered. In the event of a positive urine pregnancy test result, the patient should have a serum pregnancy test with a negative result in order to continue study participation. If the serum pregnancy test is positive, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 5.3.2).

To assess postmenopausal status for women ≤59 years of age, serum samples to test for FSH levels and estradiol levels will be collected for analysis at the central laboratory according to Section 6.1 and Section 6.3.1.4.

Samples will be collected for HbA1c testing at time points according to Section 6.1.

Blood samples for research (Section 6.3.5) 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 7.2.5.

6.3.3.11. Injection Site Evaluation

An injection site evaluation will be conducted following the SC injection of study drug at each dosing visit according to Section 6.1.

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

Samples for drug concentration will be collected at time points listed in Section 6.1.

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

6.3.4.2. Anti-drug Antibody Measurements and Samples

Samples for ADA assessment will be collected before administration of study drug at time points listed in Section 6.1. Detailed instructions for blood sample collection are included in the laboratory manual provided to study sites. Samples testing positive for anti-fasinumab binding antibodies will also be tested for neutralizing antibodies.

6.3.5. Research Samples

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

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

Research serum and plasma samples will be collected and stored, and may be used to measure biomarkers related to collagen and bone turnover, OA, pain, and NGF, and may include C-telopeptide of type I collagen (CTX-I; a marker for breakdown of type I collagen found in bone), C-telopeptide of type II collagen (CTX-II), high-sensitivity C-reactive protein, matrix metalloproteinase-generated fragment of C-reactive protein, and tartrate-resistant acid phosphatase 5b (TRAP-5b; an osteoclast activity marker). Samples may be used to study other markers of collagen and bone turnover, OA, pain, and NGF. If necessary, the samples may also be used to identify markers associated with toxicity. All samples will be single coded to maintain patient confidentiality. The samples may be stored for up to 15 years.

6.3.5.2. Optional Genomics Sub-study

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

DNA samples for the genomics sub-study will be de-identified as defined by the International Conference on Harmonisation (ICH) guideline E15. Sub study samples may be stored and used for up to 15 years after the final date of the clinical study report.

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

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

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

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

7.1.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

7.1.3. Adverse Events of Special Interest

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

in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted.

Adverse events of special interest are described in Section 7.2.3.

7.2. Recording and Reporting Adverse Events

7.2.1. Adverse Events

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

Information on follow-up for AEs is provided in Section 7.2.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 7.2.5.

7.2.2. 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.

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

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study/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 study/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

7.2.3. Pregnancy and Other Events that Require Accelerated Reporting

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

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

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), by telephone within 24 hours of identification, any pregnancy occurring in a female patient during the study or within 20 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE.

Adverse Events of Special Interest: Adverse events of special interest must be reported within 24 hours of identification using the reporting function of the eCRF for AESIs. Any AESIs that meet reporting requirements for an SAE will also be reported through the SAE reporting process per Section 7.2. Monitoring of AESIs is described in Section 7.4. Events considered to be AESI are:

- Adjudicated arthropathy
- Sympathetic nervous system dysfunction

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

7.2.4. Reporting Adverse Events Leading to Withdrawal from the Study

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

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

7.2.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

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

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

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

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

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 7.3.1.

7.2.6. Follow-up

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

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

7.3. Evaluation of Severity and Causality

7.3.1. Evaluation of Severity

The severity of infusion reactions will be graded using the current version of the NCI-CTCAE grading system (under "General Disorders and Administration Site Conditions") (Appendix 2). All other AEs will be graded according to the following scale:

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

7.3.2. Evaluation of Causality

Relationship of AEs to Study Drug:

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

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

The possible answers are:

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

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

For a list of factors to consider in assessing the relationship of AEs to study drug, see Appendix 1.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

Relationship of AEs to Injection Procedure:

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

Is there a reasonable possibility that the adverse event may have been caused by the injection procedure?

The possible answers are:

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

Related: There is a reasonable possibility that the event may have been caused by the injection procedure

For a list of factors to consider in assessing the relationship of AEs to the injection procedure, see Appendix 1.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

7.4. Safety Monitoring

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

7.4.1. Monitoring Adverse Events of Special Interest

7.4.1.1. Adjudicated Arthropathy

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

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

If a patient reports an increase in joint pain as described above, then study drug administration will be withheld. Imaging of the affected joint will be performed, as well as any additional imaging deemed appropriate to understand the cause of the worsening pain (Section 6.3.3.8). The decision to perform imaging after patient reports of worsening joint pain will be documented in the respective CRF page. Images, along with any other radiographic evaluation, will be submitted to the adjudication committee for review (Section 3.3.2).

If routine imaging suggests adjudicated arthropathy, then study drug administration will be withheld. Any additional imaging deemed appropriate will be obtained. Images, along with any other radiographic evaluation, will be submitted to the adjudication committee for review (Section 3.3.2).

If the adjudication does not confirm adjudicated arthropathy, study drug may be restarted.

Patients with findings that suggest adjudicated arthropathy will have their dosing terminated and will be referred for orthopedic consultation. If joint replacement is warranted, the site should

make all attempts to complete the pre-operative visit prior to surgery, and at the week 4 and week 20 post-operative study visits (Section 6.2.8 and Section 6.3.3.9). Pre-operative images, along with any other radiographic evaluation, will be submitted to the adjudication committee for review (Section 3.3.2).

If a patient chooses to have a TJR that is not prompted by worsening joint pain, the patient may continue receiving study drug while awaiting TJR surgery. If a patient choose to discontinue study drug while awaiting TJR, they should be encouraged to return to the clinic for remaining study visits. Prior to the scheduled TJR surgery, the patient should discontinue study drug and complete the pre-operative study visit, and subsequently, the week 4 and week 20 post-operative study visits (Section 6.2.8 and Section 6.3.3.9). Pre-operative images, along with other radiographic evaluation, will be submitted to the adjudication committee for review (Section 3.3.2).

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

7.4.1.2. Sympathetic Nervous System Dysfunction

Sympathetic nervous system dysfunction will be monitored throughout the study through physical examination, AE monitoring, assessment of orthostatic hypotension, and the Survey of Autonomic Symptoms (Section 6.3.3.5). New onset or worsening of signs and symptoms of autonomic dysfunction will be evaluated by the investigator.

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 should 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 a patient is determined to have orthostatic hypotension, study drug should be withheld and the AE should be entered in the eCRF.

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 should 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 orthostatic hypotension has resolved, study drug may be restarted. If the orthostatic hypotension has not resolved, then study drug should be withheld, and the patient should 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, or absence of sweating in conditions where sweating would be expected, then study drug can be given at the next visit. If the specialist's evaluation does reveal sympathetic nervous system dysfunction, then study drug will be permanently discontinued.

If the patient has asymptomatic orthostatic hypotension, study drug should 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 should 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, or absence of sweating in conditions where sweating would be expected, then study drug can be restarted. If the specialist's evaluation does reveal sympathetic nervous system dysfunction, then study drug will be permanently discontinued.

7.5. Investigator Alert Notification

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

8. STUDY VARIABLES

8.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), disease characteristics including baseline LBPI NRS score, duration of chronic back pain, maximum K-L score at any knee or hip joint at screening, use of paracetamol/acetaminophen as rescue medication during the pre-randomization period, medical history, and medication history for each patient.

8.2. Primary and Secondary Endpoints

The primary endpoint in the study is the change from baseline at week 16 in the average daily LBPI NRS score.

Secondary endpoints are:

- Change from baseline at week 16 in the RMDQ total score
- Change from baseline at week 16 in the PGA of LBP score
- Change from baseline at weeks 2, 4, 8, and 12 in the LBPI NRS score

Safety endpoints are:

- Percent of patients reporting TEAEs
- The incidence of anti-fasinumab antibody formation

8.3. Exploratory Endpoints

Exploratory endpoints are:

- The change from baseline at week 16 in the percentage of patients who are responders defined by 30% reduction and 50% reduction for:
  - average daily LBPI NRS score
  - RMDQ total score
  - PGA of LBP score
  - Change from baseline at week 16 in the MOS sleep subscale score
  - Change from baseline at week 16 in the SF-36 subscale scores
  - Change from baseline at week 16 in the EQ-5D-5L
  - Change from baseline at week 16 in the percentage of patients who use rescue medication for LBP

8.4. Pharmacokinetic Variables

The PK variables may include, but are not limited to, serum concentration of fasinumab at scheduled time points listed in Section 6.1.

8.5. Anti-drug Antibody Variables

Samples for ADA evaluation will be collected at baseline and subsequent study visits. A listing of ADA results will be provided.

9. 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 8.

9.1. Statistical Hypothesis

The primary endpoint in the study is the change from baseline at week 16 in the average daily LBPI NRS score. The following hypotheses will be tested:

H1i: fasinumab group #i versus placebo, where i=1, 2, 3.

Group #1 = fasinumab 6 mg SC Q4W and placebo IV Q8W

Group #2 = fasinumab 9 mg SC Q4W and placebo IV Q8W

Group #3 = fasinumab 9 mg IV Q8W and placebo SC Q4W

Placebo = placebo SC Q4W and placebo IV Q8W

A combination of Hochberg method and gatekeeping method will be used for multiplicity adjustment of the 3 hypotheses above. Hochberg method will be applied for hypotheses H_{11} (fasinumab 6mg SC Q4W versus placebo) and H_{12} (fasinumab 9 mg SC Q4W versus placebo) at a 2-sided alpha level of 0.05. The larger of the 2 p-values from the analysis for H_{11} and H_{12} will be compared with 0.05. If the larger p-value is less than or equal to 0.05, both H_{11} and H_{12} will be rejected and fasinumab 6 mg SC and 9 mg SC will be declared statistically significantly better than placebo. If the larger p-value is greater than 0.05, the smaller p-value of the 2 p-values from the analysis for H_{11} and H_{12} will be compared with 0.025. If the smaller p-value is less than or equal to 0.025, the corresponding hypothesis will be rejected and the treatment group declared statistically significantly better than placebo.

If both H_{11} and H_{12} are positive, then H_{13} (fasinumab 9 mg IV Q8W) will be tested at a 2-sided alpha level of 0.05.

9.2. Determination of Sample Size

Approximately 800 patients (200 patients per treatment) will be randomized into 4 treatment groups. Assuming a significance level of 0.05 [redacted], an enrollment of 200 patients per treatment group will provide at least 91% power to detect a treatment difference [redacted] between fasinumab 9 mg SC Q4W and placebo for the mean change from baseline to week 16 in the average daily LBPI NRS score [redacted]. The assumed treatment difference and common SD were estimated based on results from a phase 2b multiple dose study of tanezumab (5, 10, and 20 mg IV Q8W) versus placebo and naproxen (500 mg BID) in patients with chronic LBP (Kivitz 2013). The Least Squares (LS) mean change (SE) from baseline to week 16 of -2.18 (0.14) and -1.25 (0.16) for tanezumab 20 mg (n = 295) and placebo (n = 230) were used to estimate the treatment difference and common SD.

9.3. Analysis Sets

9.3.1. Efficacy Analysis Set

The full analysis set (FAS) includes all randomized patients and it is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

9.3.2. 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.

9.3.3. Per-Protocol Set

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

9.3.4. Other Analysis Sets

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

The ADA population includes all treated patients who received any study drug and who had at least 1 non-baseline ADA result.

9.4. Patient Disposition

The following will be provided:

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

9.5. Statistical Methods

9.5.1. Demography and Baseline Characteristics

Baseline demographic, disease characteristics, and exposure to study drug will be summarized descriptively by treatment group using descriptive statistics. Continuous variables will be summarized with mean, median, SD, minimum, and maximum. Categorical variables will be summarized with frequency and percentage. Details of the statistical methods will be provided in the SAP.

9.5.2. Efficacy Analyses

9.5.2.1. Primary Efficacy Analysis

The primary efficacy variable, change from baseline in LBPI score, will be analyzed using a mixed-effect model repeated measure (MMRM) approach. The model will include the randomization strata, baseline LBPI score, treatment, visit, and treatment-by-visit interaction. The least-squares means estimates for the mean change from baseline to week 16, as well as the differences of the estimates between fasinumab doses and placebo, with their corresponding standard errors, p-values and associated 95% confidence intervals will be provided from the MMRM model. Data from all patients, including data collected after discontinuing treatment up to week 16, will be used in the primary efficacy analyses according to the intent-to-treat principle using the MMRM approach with no imputation for missing data. Sensitivity analysis using pattern mixture model with multiple imputation will be performed to assess the robustness of the

results due to treatment discontinuation. Additional sensitivity analyses will be performed the same way for the primary and selected secondary endpoints using the PPS. Details on the sensitivity analysis will be provided in the SAP.

9.5.2.2. Secondary Efficacy Analysis

Tests will be performed at the 2-sided, 5% significance level without multiplicity adjustment. For analysis of continuous variables in secondary endpoints, the analysis method is the same as for the primary variables. For analysis of categorical variables in secondary endpoints, the Cochran-Mantel-Haenszel approach stratified by the randomization strata will be used.

9.5.3. Safety Analysis

9.5.3.1. Adverse Events

Definitions

For safety variables, the following observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from first dose of study drug to 4 weeks after the last dose of SC study drug or 8 weeks after the last dose of IV study drug, whichever is later.
- The follow-up period is defined as from the end of the on-treatment period (week 16) to the end of study visit (week 36).

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

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 7.3.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

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

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

9.5.3.2. Other Safety

Vital Signs

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

Laboratory Tests

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

Number and percentage of patients with a potentially clinically significant value (PCSV) 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.

9.5.3.3. Treatment Exposure

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

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

The observation period will be presented by treatment dose cohort and calculated as:

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

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

The time periods of interest will be specified in the SAP. In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, mean, SD, median, minimum and maximum.

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

9.5.3.4. Treatment Compliance

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

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

Treatment compliance will be presented by specific ranges for each treatment group. The ranges of interest will be specified in the SAP.

9.5.4. Analysis of Pharmacokinetic Data

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

9.5.5. Descriptive Analysis of Anti-Drug Antibody Data

Summaries of anti-fasinumab antibody data will be provided. Safety and efficacy will be evaluated relative to the results from the ADA assay.

9.5.6. Interim Analysis

An administrative analysis may be conducted by a team of independent statisticians and programmers. The administrative analysis may include an assessment of drug concentrations. The results of this interim analysis will be used to make appropriate business decisions. There is no intention to stop the study early or to modify the conduct of the study based upon this information. The results will only be reviewed by Regeneron Senior Management and other personnel not directly involved with the conduct of the study.

Detailed interim analysis timing and analyses will be prespecified in the SAP.

9.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- Baseline will be defined as the average daily LBPI score for the 5 days before randomization. If any of the 5 baseline scores are missing, the baseline value will be calculated over the remaining observations. Similarly, the week 16 value will be defined as the average daily LBPI score for the 7 days before and including day 113 (week 16). If any of the 7 week 16 scores are missing, the week 16 value will be calculated over the remaining observations. A patient missing all 5 baseline scores will not be eligible for study entry.

General rules for handling missing data:

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

Visit windows:

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

Unscheduled assessments:

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

9.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

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

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

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

10.2. Electronic Systems

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

- IVRS – randomization and collection of drug usage
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- A pharmacovigilance and clinical safety software system (ARGUS) – collection and reporting of SAEs and AESIs
- EDiary - recording daily use of rescue medication and LBPI score using the NRS

11. STUDY MONITORING

11.1. 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. In accordance with ICH guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

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

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

11.3. Case Report Form Requirements

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

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

12. AUDITS AND INSPECTIONS

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

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

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

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

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

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

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

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

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

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

13.3. Patient Confidentiality and Data Protection

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

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF without an IRB/EC-approved amendment.

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

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study 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.

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

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

16.2. Retention of Records

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

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

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

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Double-blind, Multi-dose, Placebo-controlled Phase 2/3 Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Moderate to Severe Chronic Low Back Pain, dated 26 August, 2016, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Conference on 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 IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

Appendix 1: Factors to Consider in Assessing the Relationship of AEs to Study Drug or Injection Procedure

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

No:

- due to external causes such as environmental factors or other treatment/s being administered
- due to the patient's/subject's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug or injection procedure
- do not reappear or worsen when dosing with study drug or injection procedure is resumed
- are not a known response to the study or injection procedure, etc. based upon pre-clinical data or prior clinical data

Yes:

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

NOTE: This list is not exhaustive.

Appendix 2: The National Cancer Institute Common Terminology Criteria for Adverse Events

For infusion reactions:

General disorders and administration site conditions					
	Grade				
Adverse Event	1	2	3	4	5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					