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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Moderate-to-Severe Chronic Low Back Pain and Osteoarthritis of the Hip or Knee

Compound:	REGN475/Fasinumab
Study Name:	FACT CLBP 1
Clinical Phase:	3
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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Moderate-to-Severe Chronic Low Back Pain and Osteoarthritis of the Hip or Knee
Site Location(s) **Principal Investigator**	To be determined
Objectives	**Primary Objective** The primary objective of the study is to evaluate the efficacy of fasinumab in relieving chronic low back pain (CLBP) as compared to placebo in patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and osteoarthritis (OA) of the knee or hip when treated for up to 16 weeks. **Secondary Objectives** The secondary objectives of the study are: • To evaluate the safety and tolerability of fasinumab compared to placebo when patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip are treated for up to 16 weeks • To characterize the concentrations of fasinumab in serum over time when patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip are treated for up to 16 weeks • To evaluate the immunogenicity of fasinumab when treated for up to 16 weeks in patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip **Exploratory Objectives** The exploratory objectives are: • To evaluate the patient-reported outcomes when patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip are treated for up to 16 weeks with fasinumab compared to placebo • To evaluate the use of rescue medication in patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip when treated for up to 16 weeks with fasinumab compared to placebo
Study Design	This is a phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of fasinumab in patients with moderate-to-severe non-radicular CLBP who have radiographically confirmed OA of the knee or hip, and who have a history of inadequate relief of their CLBP or intolerance to current analgesic therapy and inadequate relief of their CLBP from non-pharmacologic therapy. The study consists of a screening period of up to 30 days, a 7 (+3 day)-day pre-randomization period during which all pain medication except study-provided rescue medication will be discontinued, a 16-week treatment

period, a 20-week follow-up period, and a final phone contact approximately 52 weeks after the last dose of study drug is administered. Additionally at this time, patients with confirmed adjudicated arthropathy (AA) during the study with have imaging of the AA joint(s).

Screening and Pre-randomization

Prior to randomization, patients will undergo screening procedures, including X-ray of the shoulders, hips, and knees, and magnetic resonance imaging (MRI) of the lumbar spine. An MRI will also be performed on any knee joint with a Kellgren-Lawrence (K-L) score of ≥3 and any hip joint with a K-L score of ≥2. 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. Randomization visits cannot occur until there is confirmation from the central reader that there are no exclusionary findings on the joint and lumbar spine images (X-rays and MRI, as applicable). During the screening period patients may continue to take their current pain medications.

Patients will then complete a pre-randomization period, during which all pain medication, except for the study-provided rescue medication (acetaminophen/paracetamol), will be discontinued. The pre-randomization visit will be 7 (+3) days before randomization. Patients will be instructed to stop using all prohibited medications at the pre-randomization visit. Patients will receive paracetamol/acetaminophen to be used as a study-provided rescue medication. In the event of inadequate CLBP relief, paracetamol/acetaminophen may be taken according to the regional standard-of-care, with a maximum daily dose of 2500 mg (countries where 500 mg strength tablets/capsules are available) or 2600 mg (countries where 325 mg strength tablets/capsules are available). Paracetamol/acetaminophen must not be taken within 24 hours prior to the randomization visit. Patients will be instructed in the use of the electronic diary (eDiary) for recording daily use of rescue medication and for recording Low Back Pain Intensity (LBPI) Numerical Rating Scale (NRS) score.

Randomization visits cannot occur until there is confirmation from the central imaging vendor that there are no exclusionary findings on the joint and lumbar spine images (X-rays and MRI, as applicable)**.**

Randomization

Eligible patients will be randomized on day 1 (baseline) to 1 of 2 treatment arms in a 1:1 ratio as follows:

- Fasinumab 3 mg subcutaneous (SC) every 4 weeks (Q4W)
- Fasinumab-matching placebo SC Q4W

Treatment

During the treatment period (day 1 through week 16), patients will be permitted to use only acetaminophen/paracetamol as rescue medication. The treatment period will include both study visits and a phone contact on day 8 (±3 days). Patients will record their use of acetaminophen/paracetamol in their eDiary. Patients should discontinue use of acetaminophen/paracetamol for at least 24 hours prior to the start of study visits in order to minimize the confounding effects of the rescue medication on efficacy measurements.

Efficacy assessments for evaluation of CLBP will include the daily average LBPI NRS, Roland Morris Disability Questionnaire (RMDQ), PGA of LBP, Brief Pain Inventory-short form (BPI-sf), the Medical Outcomes Study Sleep

	Scale Revised (MOS Sleep-R), 36-item Short Form Survey (SF-36), the EuroQoL 5 Dimensions 5 Level Questionnaire (EQ-5D-5L), Work Productivity and Activity Impairment-Low Back Pain (WPAI-LBP), Healthcare Resource Utilization (HCRU), and the Treatment Satisfaction Questionnaire for Medication (TSQM). Efficacy assessments will be performed at the study visits. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale scores will be performed at baseline for safety reporting and application of study stopping criteria and at the week 16 study visit, as well as at any early termination visit during the treatment period, in support of pain relief for OA in patients who have CLBP and OA. Safety assessments will be performed at each study visit during treatment period and upon occurrence of any joint (AEs). Potential events of AA will be monitored via clinical signs and symptoms of worsening joint pain during the study (eg, using the joint pain questionnaire and imaging) and adjudication of pre-operative imaging for patients who undergo joint replacement (JR) surgery during the conduct of the study. Potential events of sympathetic nervous system (SNS) dysfunction will be monitored throughout the study through physical examination, AE reporting, assessment of orthostatic hypotension, and the Survey of Autonomic Symptoms. **Follow-up** After the end of treatment, follow-up of patients will continue for an additional 20 weeks after the last treatment period visit. Both safety and efficacy assessments will be performed during this period. Potential events of AA and SNS dysfunction will be monitored, as previously described for the treatment period. If a patient must undergo JR surgery during the study, he or she will be asked to complete pre-operative imaging and to undergo post-surgery follow-up. **End of Study Phone Contact and Additional Imaging** Phone contact will be made approximately 52 weeks after administration of the last dose of fasinumab or placebo to document patient status with regard to JR surgery (if patient underwent, is scheduled for, or is on a wait list for JR surgery). Additionally, patients who had an AA confirmed during the study will have an MRI performed of the affected joint(s). If the AA joint(s) have undergone JR, an X-ray may be substituted for an MRI.
Study Duration	The duration of the study is up to 64 weeks excluding the screening and pre-randomization periods. Patients who discontinue study drug will be requested to return for all scheduled visits and to complete all planned assessments, including phone contacts.
Population	
Sample Size:	The study will enroll approximately 1020 patients at about 140 global sites. Each arm (fasinumab and placebo) will enroll approximately 510 patients.
Target Population:	Men and women who are at least 18 years of age at the time of study entry with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip and who have a history of inadequate pain relief or intolerance to current analgesic therapy and inadequate pain relief from non-pharmacologic therapy.

Treatments

Study Drug	Fasinumab
Dose/Route/Schedule:	3 mg SC Q4W
Placebo	Fasinumab-matching placebo
Route/Schedule:	3 mg SC Q4W
Rescue Treatment:	Starting at pre-randomization to the end of the 16-week treatment period, acetaminophen/paracetamol is the only study-provided rescue medication. In the event of inadequate pain relief for CLBP, acetaminophen/paracetamol may be taken as needed according to the local standard of care. The maximum daily dose during the treatment and follow-up periods is currently 2500 mg (countries where 500 mg strength tablets/capsules are available) or 2600 mg (countries where 325 mg strength tablets/capsules are available). Use of acetaminophen/paracetamol as study-provided rescue medication will be reported daily using diaries. Acetaminophen/paracetamol must not be taken within 24 hours prior to visits during the treatment period.

Endpoints

Primary: The primary endpoint is change in the daily average LBPI NRS score from baseline to week 16 in patients treated with fasinumab compared to patients treated with placebo.

Secondary: The secondary endpoints of the study are:

- Change from baseline to week 16 in RMDQ total score in patients treated with fasinumab compared to patients treated with placebo
- Change from baseline to week 16 in PGA of LBP score in patients treated with fasinumab compared to patients treated with placebo
- Proportion of patients who are responders as defined by ≥30% reduction from baseline to week 16 in daily average LBPI NRS score in patients treated with fasinumab compared to patients treated with placebo
- Change from baseline to week 16 in the BPI-sf pain interference score in patients treated with fasinumab compared to patients treated with placebo

Safety: The safety endpoints in this study are:

- Incidence of AA (as confirmed by an independent adjudication committee)
- Incidence of destructive arthropathy (DA) (as confirmed by an independent adjudication committee)
- Incidence of treatment-emergent adverse event (TEAEs)
- Incidence of SNS dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist)
- Incidence of peripheral sensory AEs that require a neurology consultation
- Incidence of all-cause JR surgeries through week 16 and through the end of follow-up period (week 36)
- Incidence of JRs at telephone survey approximately 52 weeks after last dose of study drug

Procedures and Assessments	At the screening visit, patients will provide informed consent, medical history, and medication history. Determination of a patient's diagnosis of CLBP and OA of the knee or hip will be assessed according to the inclusion and exclusion criteria, along with other requirements for study participation. Patients will be assessed for childbearing potential, if appropriate. Efficacy assessments for evaluation of CLBP will include the daily average LBPI NRS, RMDQ, PGA of LBP, BPI-sf, the MOS SLEEP-R, SF-36, the EQ-5D-5L, WPAI-LBP, HCRU, and the TSQM. The WOMAC pain subscale scores will be performed at baseline for safety reporting and application of study stopping criteria, and at the week 16 study visit and in the event of an early termination visit during this time, in support of pain relief for OA in patients with CLBP and OA. Safety assessments will be performed at each study visit during treatment period and upon occurrence of any joint AEs. Potential events of AA will be monitored via clinical signs and symptoms of worsening joint pain during the study (eg, using the joint pain questionnaire and imaging) and adjudication of pre-operative imaging for patients who undergo JR surgery during the conduct of the study. Potential events of SNS dysfunction will be monitored throughout the study through physical examination, AE reporting, assessment of orthostatic hypotension, and the Survey of Autonomic Symptoms.
Statistical Plan	**Statistical Hypothesis** The primary endpoint in the study is the change from baseline to week 16 in the average daily LBPI NRS score. The following hypothesis will be tested: H01: There is no treatment difference between fasinumab 3mg Q4W and placebo in the change from baseline to week 16 in the average daily LBPI NRS score. The secondary null hypotheses of interest are: H02: There is no treatment difference between fasinumab 3mg Q4W and placebo in the change from baseline to week 16 in the RMDQ total score H03: There is no treatment difference between fasinumab 3mg Q4W and placebo in the change from baseline to week 16 in the PGA LBP score H04: There is no treatment difference between fasinumab 3mg Q4W and placebo in the change from baseline to week 16 in the BPI-sf. Fixed sequence hierarchical testing will be applied to maintain the study wise Type-I error rate at the 2 sided 0.05 level for the primary and key secondary endpoints. Secondary endpoints will only be tested if the primary endpoint is statistically significant in favor of fasinumab. Details will be provided a priori in the statistical analysis plan. **Justification of Sample Size** Approximately 1020 patients will be randomized in a 1:1 ratio to either fasinumab (3mg Q4W) or placebo. Assuming a 2-sided alpha level of 0.05 and a 20% dropout rate at week 16, an enrolment of 510 patients per arm will provide 90% power to detect an effect size of 0.23 in the daily average LBPI NRS score (ie, an absolute treatment difference of 0.5 between fasinumab 3mg Q4W and placebo with an associated standard deviation [SD] of 2.2). This sample size also provides at least 99% power to detect an effect size of 0.42 (absolute treatment difference of 2.2 with an associated

SD of 5.2) in the RMDQ total score and 0.44 (absolute treatment difference of 0.4 with an associated SD of 0.9) in the PGA at week 16. The sample size assumptions are based on results of the R475-PN-1524 study data on file at Regeneron Pharmaceuticals, Inc.

Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, Q1, Q3, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Demographic and baseline characteristics, including medical history and exposure to study drug will be summarized descriptively by treatment group, and by all patients combined.

The primary efficacy variables will be analyzed using multiple imputation approach with mixed-effect model for repeated measure (MMRM) based on the full analysis set (FAS) with adjustment for missing data due to lack of efficacy or adverse events assuming the LBPI NRS scores would on average return to baseline values. The imputed data for patients discontinued from the study due to a lack of efficacy or adverse events will be centered at the mean baseline value.

Sensitivity analysis using pattern mixture model and tipping point approach with multiple imputation to impute missing data 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 per-protocol set (PPS).

For analysis of continuous secondary endpoints, the analysis method will be the same as that used for the primary variables. For analysis of categorical variables in secondary endpoints, eg, proportions of patients with ≥30% reduction from baseline to week 16 in the daily average LBPI NRS score; the Cochran Mantel Haenszel approach stratified by the randomization strata will be used with missing data considered as non-response.

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AA	Adjudicated arthropathy
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BDI-II	Beck Depression Inventory - II
BPI-sf	Brief Pain Inventory-short form
bpm	Beats per minute
CLBP	Chronic low back pain
C_{max}	Maximal concentration
CRF	Case report form (electronic or paper)
CRO	Contract research organization
C_{trough}	Trough concentrations
CTCAE	Common Terminology Criteria for Adverse Events
DA	Destructive arthropathy
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
eDiary	Electronic diary
EQ-5D-5L	EuroQoL 5 Dimensions 5 Level Questionnaire
ESR	Erythrocyte sedimentation rate
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCRU	Healthcare Resource Utilization
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board

IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
JR	Joint replacement
K-L	Kellgren-Lawrence
LBP	Low back pain
LBPI	Low back pain intensity
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeat measure
MOS Sleep-R	Medical Outcomes Study Sleep Scale Revised
MRI	Magnetic resonance imaging
NGF	Nerve growth factor
NRS	Numerical Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
PCSV	Potentially clinically significant value
PGA	Patient Global Assessment
PHQ-8	Patient Health Questionnaire 8-Item Version
PK	Pharmacokinetic
PPS	Per-protocol set
PT	Preferred term
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QRS	Complex of Q, R, and S waves on an electrocardiogram
RBC	Red blood cell
RMDQ	Roland Morris Disability Questionnaire
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation
SF-36	36-item Short Form Survey
SNS	Sympathetic nervous system
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction

TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TrkA	Tyrosine kinase type 1
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Woman/women of childbearing potential
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WPAI-LBP	Work Productivity and Activity Impairment-Low Back Pain

1. INTRODUCTION

Low back pain (LBP) remains a major international health problem with lifetime prevalence ranging widely from 49 to 70% (van Tulder, 2002) up to 80 to 85% (WHO Scientific Group, 2003). The majority of patients with LBP (90%) experience non-specific LBP with the most important symptoms being pain and disability (van Tulder, 2002) (Deyo, 2001). Pain in patients with non-specific LBP may arise from multiple pathologies including facet osteoarthritis, central and foramen stenosis, disc herniation, and muscle spasm. Most patients are believed to recover rapidly from LBP with approximately 90% no longer consulting a physician within 3 months (Croft, 1998). This does not necessarily imply resolution of symptoms and subsequent episodes of LBP are common. Estimates for recurrence range from 24% to 80% at 1 year due to the variation in definitions for recurrence and remission (Hoy, 2014). A literature review found that between 42% and 75% of patients still experienced pain after 12 months, and that the risk of LBP was about twice as high for those with a history of LBP (Hestbaek, 2003).

Chronic low back pain (CLBP) is characterized as LBP that persists for ≥3 months. Recent guidelines from the American College of Physicians recommend that patients with CLBP are first treated with non-pharmacologic interventions. If ineffective, non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line treatments and tramadol (opiod) or duloxetine (serotonin-norepinephrine reuptake inhibitor) as second-line treatments (Qaseem, 2017). Evidence for non-pharmacologic management is low to moderate quality, at best, and dependent on the intervention. The risks associated with long-term use of NSAIDs have been well characterized and include gastrointestinal bleeding and increased risk of cardiovascular events (Lanas, 2010) (Trelle, 2011). Opioid use is limited by central nervous system effects, nausea and vomiting, constipation, and the potential for abuse and dependence. Opioid use may be associated with drowsiness, dizziness, motor imbalance, respiratory depression, and even death, and must be closely monitored in patients who are vulnerable to abuse or addiction. Moreover, there is no evidence to support the superiority of opioids over other available pain medications. While treatment with opioids over a short duration is supported by research data, long-term efficacy has not been evaluated. Thus, there remains an unmet medical need for alternative treatment options that have a more effective analgesic effect, particularly as there are a significant number of patients who are intolerant to or do not have adequate pain relief from current treatment options. Inadequate pain relief has a profound impact on quality of life for millions of people worldwide with an associated substantial cost to society, including healthcare costs (Salmon, 2016) and loss of productivity (Dibonaventura, 2011).

Neurotrophins are a family of peptide growth factors that play a role in the development, differentiation, survival, and death of neuronal and non-neuronal cells (Chao, 2006). Nerve growth factor (NGF) was the first neurotrophin to be identified, and its role in the development and survival of both peripheral and central neurons in the developing 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 controlling pain. Administration of NGF provokes pain in both rodents (Lewin, 1994) and humans (McArthur, 2000), while NGF antagonists 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 a loss of deep pain perception (Indo, 1996) (Einsardottir, 2004). In addition, NGF is elevated in the synovial fluid of patients with rheumatoid arthritis and other types of arthritis (Aloe, 1992) (Halliday, 1998). Nerve growth factor is also up-regulated in injured and inflamed tissues in conditions such as cystitis, prostatitis, and chronic headache (Lowe, 1997) (Miller, 2002) (Sarchielli, 2001). Thus, it was postulated that NGF blockage would provide pain relief via a novel mechanism, avoiding the limitations of many currently used analgesic medications, such as NSAIDs and opioids.

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

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

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

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

To date, of the completed studies in the fasinumab program, 26 AA events have occurred in 24 patients. There was an increase in AA events that appeared to be related to a greater fasinumab dose. Although these events were milder than the DA events presented at the 2012 FDA Arthritis Advisory Committee, because efficacy in OA was not greater with the 6 mg or 9 mg Q4W regimens compared with the 3 mg Q4W regimen, the benefit-risk ratio was deemed unfavorable for the fasinumab 6 mg Q4W and 9 mg Q4W dose regimens in patients with OA in comparison to the other, lower fasinumab dose regimens studied. Accordingly, those higher dose regimens are no longer being studied in the OA program. The current study evaluates a lower fasinumab dose that potentially has a more favorable benefit-risk profile in this patient population that also has OA of the knee or hip.

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

Since the FDA removed the clinical hold, Regeneron Pharmaceuticals, Inc. (Regeneron) has conducted or initiated several clinical trials of fasinumab. In completed clinical studies to date, fasinumab was associated with a low rate of discontinuation due to AEs. Patients treated with fasinumab generally had more frequent events than did placebo-treated patients of arthralgia, joint swelling, peripheral edema, altered peripheral sensation (eg, paresthesia, dysesthesia), and myalgia. As noted above, there is a dose-related trend for AAs; more severe DAs have infrequently been observed.

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

The phase 3 study described here is designed to evaluate the efficacy and safety of fasinumab compared to placebo for moderate-to-severe non-radicular CLBP in patients who also have

radiographically confirmed OA of the knee or hip, and who have a history of inadequate pain relief or intolerance to current analgesic therapy and inadequate pain relief from non-pharmacologic therapy.

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

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of fasinumab in relieving CLBP as compared to placebo in patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip when treated for up to 16 weeks.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of fasinumab compared to placebo when patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip are treated for up to 16 weeks
- To characterize the concentrations of fasinumab in serum over time when patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip are treated for up to 16 weeks
- To evaluate the immunogenicity of fasinumab when treated for up to 16 weeks in patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip

2.3. Exploratory Objectives

The exploratory objectives are:

- To evaluate the patient-reported outcomes when patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip are treated for up to 16 weeks with fasinumab compared to placebo
- To evaluate the use of rescue medication in patients with a clinical diagnosis of moderate-to-severe non-radicular CLBP and OA of the knee or hip when treated for up to 16 weeks with fasinumab compared to placebo

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Fasinumab is expected to provide effective pain relief based on improvement in the Low Back Pain Intensity (LBPI) Numerical Rating Scale (NRS) score and improved functionality based on Roland Morris Disability Questionnaire (RMDQ).

3.2. Rationale

3.2.1. Rationale for Study Design

The present study is a phase 3, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of fasinumab in patients with moderate-to-severe non-radicular CLBP, who also have radiographically confirmed OA of the knee or hip, and who have a history of inadequate relief of their CLBP or intolerance to current analgesic therapy and inadequate relief of their CLBP from non-pharmacologic therapy. This study will evaluate the efficacy and safety of fasinumab compared to placebo using the LBPI NRS score as the primary endpoint.

The target population will consist of patients who have inadequate CLBP relief with acetaminophen/paracetamol, or who are unable to tolerate or have inadequate CLBP relief with NSAIDs and opioids (or unwilling to take opioids). The patients will also have inadequate CLBP relief from non-pharmacologic management. This population was chosen because these patients have unmet medical needs with respect to inadequate pain relief despite the availability of the aforementioned therapeutic options. Thus, this population is appropriate for prospectively studying the hypothesis that fasinumab provides effective relief for CLBP with an acceptable safety profile at the dose being administered.

The study will be conducted with appropriate eligibility criteria to exclude patients who may be at increased risk for events of joint damage and SNS dysfunction. Specific questionnaires, physical examinations, and imaging will be employed to monitor for any events of arthralgia, worsening joint pain, AA, altered peripheral sensation, and SNS effects. Inclusion of the placebo treatment group is important to determine accurately the efficacy of fasinumab at the dose being evaluated and to estimate the risk of AEs, including the AEs of special interest (AESI) of AA and SNS dysfunction. Rescue medication (paracetamol/acetaminophen) will be made available to any patient with breakthrough pain. Therefore, the use of a placebo group is justified, as placebo-treated patients will not be placed in significant discomfort. A patient or investigator can choose to end participation at any time.At randomization, patients will be stratified by baseline LBPI NRS score (<7, ≥7), duration of CLBP (<5 years, ≥5 years), maximum Kellgren-Lawrence (K-L) score (2-3; 4) for any knee or hip joint at screening, and by geographical region.

3.2.2. Rationale for Dose Selection

As the target population for this study has concomitant OA of the knee or hip, randomized patients will receive a fixed-dose, subcutaneous (SC) injection of fasinumab 3 mg Q4W or fasinumab-matching placebo Q4W. This is the proposed maximum dose of fasinumab at this dosing frequency for patients who have OA of the knee or hip.

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

Single SC doses of fasinumab of up to 30 mg were well tolerated in healthy male and female subjects in the TDU-11480 study. All single IV doses of fasinumab in the R475-PN-0817 study

in healthy male and female subjects were generally well tolerated at all but the highest IV dose (1 mg/kg). The occurrence of neurosensory AEs, which were transient and non-severe, led to the decision to refrain from escalating above the 1 mg/kg IV dose and instead, to expand enrollment of the 1 mg/kg IV cohort.

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

In the R475-PN-1227 phase 2 study of fasinumab in patients with pain due to OA of the hip or knee, all SC doses (1 mg, 3 mg, 6 mg, and 9 mg Q4W) demonstrated greater efficacy relative to placebo in pain relief and physical function measures, based upon WOMAC pain and physical function scales assessed after 16 weeks of treatment. Considering the relative lack of an observed dose-response for efficacy and the increased risk of AA with both the 9 mg and 6 mg Q4W doses, the latter doses are no longer being evaluated in studies of fasinumab for the treatment of pain due to OA. Neuromuscular AEs, such as arthralgia and paresthesia, were reported more frequently in fasinumab-treated patients than in placebo-treated patients, though these events were typically mild or moderate in intensity.

An ongoing phase 2/3 study in patients with non-radicular CLBP (R475-PN-1524) is evaluating the efficacy and safety of fasinumab (6 mg Q4W SC, 9 mg Q4W SC and 9 mg Q8W IV) compared to placebo. The study enrolled patients with CLBP, some of whom had advanced OA, and an event of AA in 1 such patient led the FDA to place the study on partial clinical hold until the protocol could be amended to either exclude patients with OA of the knees, hips, or shoulders or reduce the doses. As 563 of 800 planned patients had been randomized at the time of the partial clinical hold, Regeneron performed an unplanned interim analysis of the data. This interim analysis showed evidence of efficacy with improvement in LBPI NRS pain scores in all fasinumab groups compared to placebo at the 8- and 12-week time points. The interim safety results were generally consistent with what has been previously reported for fasinumab studies.

The maximum fasinumab doses being evaluated in the OA program are 3 mg Q4W and 6 mg Q8W. The PK of fasinumab is described as linear, with concentrations in serum and exposure, as measured by similar area under the concentration-time curve (AUC), increasing in a dose-proportional manner. Therefore, the 6 mg Q8W dose is expected to achieve similar AUC to that of the 3 mg Q4W dose studied in the R475-PN-1227 trial. Maximal concentration (C_{max}) and trough concentrations (C_{trough}) of the 6 mg Q8W dose are expected to be within the range observed in the phase 2 study, R475-PN-1227. However, in a patient population with CLBP, a more frequent administration of fasinumab, ie, 3 mg Q4W, may be more beneficial in providing effective CLBP relief in patients with concomitant OA of the knee or hip.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

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

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The primary endpoint is change in the daily average LBPI NRS score from baseline to week 16 in patients treated with fasinumab compared to patients treated with placebo.

4.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- Change from baseline to week 16 in RMDQ total score in patients treated with fasinumab compared to patients treated with placebo
- Change from baseline to week 16 in Patient Global Assessment (PGA) of LBP score in patients treated with fasinumab compared to patients treated with placebo
- Proportion of patients who are responders as defined by ≥30% reduction from baseline to week 16 in daily average LBPI NRS score in patients treated with fasinumab compared to patients treated with placebo
- Change from baseline to week 16 in the Brief Pain Inventory Short Form (BPI-sf) pain interference score in patients treated with fasinumab compared to patients treated with placebo

4.2.3. Exploratory Endpoints

Exploratory endpoints will be defined in the Statistical Analysis Plan (SAP).

4.3. Safety Endpoints

The safety endpoints in this study are:

- Incidence of AA (as confirmed by an independent adjudication committee)
- Incidence of DA (as confirmed by an independent adjudication committee)
- Incidence of treatment-emergent adverse event (TEAEs)
- Incidence of SNS dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist)
- Incidence of peripheral sensory AEs that require a neurology consultation
- Incidence of all-cause joint replacement (JR) surgeries through week 16 and through the end of follow-up period (week 36)

- Incidence of JRs at telephone survey approximately 52 weeks after last dose of study drug

4.4. Pharmacokinetic Variables

The PK variable is fasinumab concentration measured in samples collected at time points specified in Table 1.

4.5. Anti-Drug Antibody Variables

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

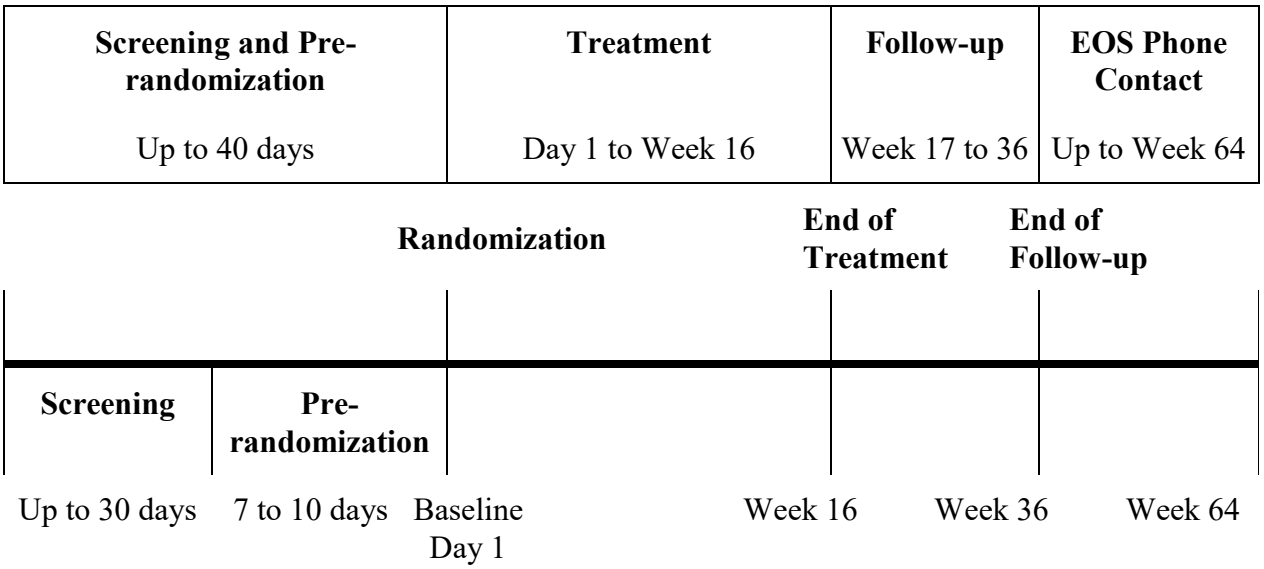
- Treatment emergent - defined as any post-dose ADA positive response when baseline results are negative
- Treatment boosted - defined as any post-dose ADA response that is at least 9-fold over baseline titer levels when baseline results are positive
- Titer values
- Titer category
  - Low (titer <1,000)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

5. STUDY DESIGN

5.1. Study Description and Duration

This is a phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of fasinumab in patients with moderate-to-severe non-radicular CLBP who have radiographically confirmed OA of the knee or hip, and who have a history of inadequate relief of their CLBP or intolerance to current analgesic therapy and inadequate relief of their CLBP from non-pharmacologic therapy. The study consists of a screening period of up to 30 days, a 7 (+3 day)-day pre-randomization period during which all pain medication except study-provided rescue medication will be discontinued, a 16-week treatment period (with the last Q4W dose of study drug administered at week 12), a 20-week follow-up period, and a final phone contact approximately 52 weeks after the last dose of study drug is administered (Figure 1).

Figure 1: Study Flow Diagram



EOS- End of study

5.1.1. Screening and Pre-randomization

Prior to randomization, patients will undergo screening procedures, including X-ray of the shoulders, hips, and knees, and magnetic resonance imaging (MRI) of the lumbar spine. An MRI will also be performed on any knee joint with a K-L score of ≥3 and any hip joint with a K-L score of ≥2. 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. During the screening period, patients may continue to take their current pain medications.

Patients will then complete a pre-randomization period, during which all pain medication, except for the study-provided rescue medication (acetaminophen/paracetamol), will be discontinued. The pre-randomization visit will be 7 (+3) days before randomization. Patients will be instructed to stop using all prohibited medications at the pre-randomization visit. Patients will receive paracetamol/acetaminophen to be used as a study-provided rescue medication. In the event of inadequate CLBP relief, paracetamol/acetaminophen may be taken according to the regional standard-of-care, with a maximum daily dose of 2500 mg (countries where 500 mg strength tablets/capsules are available) or 2600 mg (countries where 325 mg strength tablets/capsules are available). Paracetamol/acetaminophen must not be taken within 24 hours prior to the randomization visit. Patients will be instructed in the use of the electronic diary (eDiary) for recording daily use of rescue medication and for recording LBPI NRS score.

Randomization visits cannot occur until there is confirmation from the central imaging vendor that there are no exclusionary findings on the joint and lumbar spine images (X-rays and MRI, as applicable).

5.1.2. Rescreening

Patients who do not meet eligibility criteria may rescreen once if it is believed that the reason for failure was due to a condition that would resolve or could be treated, or a lab value that

minimally exceeded the cut-off value, and only after approval of the Sponsor or designated Medical Monitor. Patients cannot rescreen if they do not meet the LBPI NRS or PGA criteria, if they have orthostatic hypotension at the screening, pre-randomization, or randomization visit or have exclusionary findings on screening imaging.

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

5.1.3. Randomization

Eligible patients will be randomized on day 1 (baseline) to 1 of 2 treatment arms in a 1:1 ratio as follows:

- Fasinumab 3 mg SC Q4W
- Fasinumab-matching placebo SC Q4W

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

5.1.4. Treatment Period

During the treatment period (day 1 through week 16), patients will be permitted to use only acetaminophen/paracetamol as rescue medication. The treatment period will include both study visits and a phone contact on day 8 (±3 days). Patients will record their use of acetaminophen/paracetamol in their eDiary. Patients should discontinue use of acetaminophen/paracetamol for at least 24 hours prior to the start of study visits in order to minimize the confounding effects of the rescue medication on efficacy measurements.

Efficacy assessments for evaluation of CLBP will include the daily average LBPI NRS, RMDQ, PGA of LBP, BPI-sf, the Medical Outcomes Study Sleep Scale Revised (MOS Sleep-R), 36-item Short Form Survey (SF-36), the EuroQoL 5 Dimensions 5 Level Questionnaire (EQ-5D-5L), Work Productivity and Activity Impairment-Low Back Pain (WPAI-LBP), Healthcare Resource Utilization (HCRU), and the Treatment Satisfaction Questionnaire for Medication (TSQM). Efficacy assessments will be performed at the study visits outlined in Table 1. The WOMAC pain subscale scores will be performed at baseline for safety reporting and application of study stopping criteria and as outlined in Table 1 in support of pain relief for OA in patients CLBP and with OA.

Safety assessments will be performed at each study visit during treatment period, as outlined in Table 1 and upon occurrence of any joint AEs. Potential events of AA will be monitored via clinical signs and symptoms of worsening joint pain during the study (eg, using the joint pain questionnaire and imaging) and adjudication of pre-operative imaging for patients who undergo JR surgery during the conduct of the study. Potential events of SNS dysfunction will be monitored throughout the study through physical examination, AE reporting, assessment of orthostatic hypotension, and the Survey of Autonomic Symptoms.

5.1.5. Follow-up Period

After the end of treatment, follow-up of patients will continue for an additional 20 weeks after the last treatment period visit. Safety and efficacy assessments will be performed according to the schedule outlined in Table 1. Potential events of AA and SNS dysfunction will be monitored, as previously described for the treatment period.

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

5.1.6. End of Study Phone Contact and Additional Imaging

Phone contact will be made approximately 52 weeks after administration of the last dose of fasinumab or placebo to document patient status with regard to JR surgery (if patient underwent, is scheduled for, or is on a wait list for JR surgery). Additionally, patients who had an AA confirmed during the study will have an MRI performed of the AA joint(s). If the AA joint(s) have undergone JR, an X-ray may be substituted for an MRI.

5.1.7. Study Stopping Rules

An independent Data Monitoring Committee (DMC) will monitor unblinded data on an ongoing basis to assess the risk/benefit profile of fasinumab. The DMC will review the totality of evidence including patient safety data and apply the formal program-wide statistical stopping criteria as detailed in the DMC charter. Based on these reviews, in the context of the totality of evidence, if the DMC has significant concerns at any time regarding a meaningful imbalance between treatment groups in joint-related AEs, SNS dysfunction, or neurosensory disturbances, the DMC may make a recommendation to temporarily halt, alter, or terminate:

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

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

Study stopping criteria for clinical studies involving fasinumab are detailed in the DMC charter.

5.1.8. End of Study Definition

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

5.2. Planned Interim Analysis

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

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

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

5.3.2. Arthropathy Adjudication Committee

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

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

The study will enroll approximately 1020 patients at about 140 global sites. Each arm (fasinumab and placebo) will enroll approximately 510 patients.

6.2. Study Population

Eligible patients for this study include male and female patients who are at least 18 years of age at the time of study entry with non-radicular CLBP and concomitant OA of the knee or hip, who have a history of inadequate relief of their CLBP or intolerance to current analgesic therapies and inadequate relief of their CLBP from non-pharmacologic therapy.

6.2.1. Inclusion Criteria

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

1. Male and female patients ≥18 years of age at screening visit
2. Body mass index ≤39 at screening visit
3. Clinical diagnosis of non-radicular moderate-to-severe CLBP for ≥3 months (prior to screening visit) as defined by the following:
    a. Quebec taskforce category 1 (pain without radiation) or 2 (pain with proximal radiation above the knee), and
    b. Primary pain between 12th thoracic vertebra and lower gluteal folds, and
    c. At both screening and randomization visit, a LBPI NRS score ≥4 over previous 24 hours, and
    d. Mean daily LBPI score ≥4 during pre-randomization period, and
    e. PGA of LBP of fair, poor, or very poor at screening visit

4. Clinical diagnosis of OA in at least 1 hip or knee joint based on the American College of Rheumatology Criteria with radiographic evidence of OA (K-L ≥2) at screening as described in Section 8.2.1.8
5. History of inadequate relief of CLBP from non-pharmacologic therapy (eg, exercise, physical therapy, acupuncture, or multidisciplinary rehabilitation)
6. History of inadequate pain relief or intolerance to analgesics used for CLBP defined by:
    a. Inadequate pain relief from paracetamol/acetaminophen, and
    b. Intolerance or inadequate pain relief from at least 1 oral NSAID, and
    c. Intolerance or inadequate pain relief from at least 1 opioid or tramadol, unwillingness to take opioid therapy for a medically acceptable reason, or lack of access to opioid therapy
7. History of regular use of analgesic medications for LBP pain (defined as an average of 4 days per week over the 4 weeks prior to the screening visit), including NSAIDs, selective cyclooxygenase 2 inhibitors, opioids, paracetamol/acetaminophen, or combinations thereof
8. Willing to discontinue current pain medications and to adhere to study requirements for rescue treatments (paracetamol/acetaminophen to be taken as needed with a maximum daily dose of 2500 mg (countries where 500 mg strength tablets/capsules are available) or 2600 mg (countries where 325 mg strength tablets/capsules are available)
9. Willing to maintain current activity and exercise levels throughout the study
10. Willing to undergo joint replacement (JR) surgery, if necessary
11. Willing and able to comply with clinic visits and study-related procedures and willing to provide follow-up information related to any JR surgery that occurs within the period of time covered by their intended participation in the study
12. Consent to allow all radiographs and medical/surgical/hospitalization records of care received elsewhere prior to and during the study period to be shared with the investigator
13. Provide signed informed consent
14. Able to understand and complete study-related questionnaires

6.2.2. Exclusion Criteria

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

1. Non-compliance with the LBPI NRS data entries during the pre-randomization period, as defined by more than 2 missing entries
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 X-ray, if requested) of severe spinal stenosis, disc herniation with substantial nerve compression, recent vertebral fracture, an

active destructive process or marked segmental instability (eg, severe scoliosis, bone marrow edema, or Modic type 1 change)

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. Current or pending worker's compensation, litigation, disability, or any other monetary settlement related to LBP
8. History or presence on imaging of arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressive OA type 1 or type 2), recent fracture, recent stress fracture, neuropathic joint arthropathy, hip dislocation (prosthetic hip dislocation is eligible), knee dislocation (patella dislocation is eligible), congenital hip dysplasia with degenerative joint disease, extensive subchondral cysts, evidence of bone fragmentation or collapse, or primary metastatic tumor with the exception of chondromas, or pathological fractures during the screening period
9. History or presence at the screening visit of non-OA inflammatory joint disease (eg, rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudo-gout, gout, spondyloarthropathy, joint infections within the past 5 years, Paget's disease of the spine, pelvis, or femur, neuropathic disorders, multiple sclerosis, fibromyalgia, tumors or infections of the spinal cord, or renal osteodystrophy)
10. History of hospital admission for depression or suicide attempt within 2 years or active, severe major depression at screening
11. Beck Depression Inventory - II (BDI-II) score ≥29 at screening
12. Use of a monoamine reuptake inhibitor, tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors for treatment of CLBP within 4 weeks prior to the screening visit
13. Use of extended-release or controlled-release opioids (eg, oxycontin), transdermal fentanyl or methadone within 3 months prior to the screening visit
14. Use of opioids with a morphine equivalent dose of ≥30 mg per day for more than 4 days per week
15. Use of systemic (ie, oral or intramuscular) corticosteroids or intra-articular corticosteroids in any joint within 30 days prior to the screening visit (topical, intranasal, and inhaled corticosteroids are permitted)
16. Epidural steroid injections within 3 months prior to the screening visit
17. Botox injections for LBP within 6 months prior to the screening visit
18. History of cannabis use for the treatment of LBP within the past 6 months prior to the screening visit
19. History of (within 5 years prior to the screening visit) or current alcoholism, alcohol abuse, substance abuse, or abuse of prescription pain medication
20. Is scheduled for JR surgery during the study period
21. Signs and symptoms of carpal tunnel syndrome within 6 months of screening

22. History or presence at the screening visit of autonomic neuropathy, diabetic neuropathy, or other peripheral neuropathy, including reflex sympathetic dystrophy
23. Evidence of autonomic neuropathy
24. History or diagnosis of chronic autonomic failure syndrome, including pure autonomic failure and multiple system atrophy (Shy-Drager syndrome)
25. Poorly controlled diabetes (defined as any single value of hemoglobin A1c [HbA1c] >9.0%) at the screening visit
26. Confirmed elevated screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5x upper limit of normal (ULN)
27. Resting heart rate of <50 beats per minute (bpm) or >100 bpm (by vital sign assessment or as captured during electrocardiogram [ECG] assessment) at the screening or randomization visits
28. History or presence of second or third degree heart block, first degree heart block with abnormal complex of Q, R, and S waves on an electrocardiogram (QRS), or bifascicular block by ECG at the screening visit
29. History or presence of orthostatic hypotension, as defined in Section 8.2.3.8, at the screening, pre-randomization, or baseline visits
30. History of poorly controlled hypertension, as defined by:
    a. Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg at the screening visit
    b. Systolic blood pressure of 160 mm Hg to 179 mm Hg or diastolic blood pressure of 100 mm Hg to 109 mm Hg at the screening visit, AND a history of end-organ damage (including history of left ventricular hypertrophy, heart failure, angina, myocardial infraction, stroke, transient ischemic attack, peripheral arterial disease and moderate to advanced retinopathy [hemorrhages or exudates, papilledema])
31. Congestive heart failure with New York Heart Classification of stage III or IV (Dolgin, 1994)
32. Transient ischemic attack 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
33. Known history of human immunodeficiency virus (HIV) infection
34. Known history of ocular herpes simplex virus, herpes simplex virus pneumonia, or herpes simplex virus encephalitis
35. 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
36. Known history of infection with the hepatitis C virus. Patients with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test

37. 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
38. New major illness diagnosed within 2 months prior to the screening visit
39. 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
40. Known allergy or sensitivity to doxycycline or related compounds, excipients, or monoclonal antibodies
41. 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
42. Exposure to an anti-NGF antibody prior to the screening visit or known sensitivity or intolerance to anti-NGF antibodies
43. Member of the clinical site study team and/or his/her immediate family
44. Pregnant or breastfeeding women
45. Women of childbearing potential (WOCBP)* who have a positive pregnancy test result or do not have their pregnancy test result at baseline
46. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 20 weeks after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;
    b. intrauterine device; intrauterine hormone-releasing system;
    c. bilateral tubal ligation;
    d. vasectomized partner;
    e. and or sexual abstinence†, ‡.

    *Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

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

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

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

6.3. Premature Withdrawal from the Study

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

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

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

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

6.4. Replacement of Patients

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

7. STUDY TREATMENTS

7.1. Investigational Treatment

Fasinumab drug product is supplied for this study in 1 mL single-use pre-filled syringes that deliver 0.5 mL of 6 mg/mL solution to provide a single 3 mg dose of study drug.

All patients will receive SC injections of fasinumab or fasinumab-matching placebo. Patients will be randomized to 2 treatment arms in a 1:1 ratio to receive either fasinumab 3 mg SC Q4W or fasinumab-matching placebo SC Q4W. All SC injections will be in the abdomen, thigh, or upper arm. Instructions for dose preparation and study drug administration are provided in the pharmacy manual.

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

7.2. Rescue Treatment

Starting at pre-randomization to the end of the 16-week treatment period, acetaminophen/paracetamol is the only study-provided rescue medication. In the event of inadequate pain relief for CLBP, acetaminophen/paracetamol may be taken as needed according to the local standard of care. The maximum allowed daily dose during the treatment and follow-up periods is 2500 mg (countries where 500 mg strength tablets/capsules are available) or 2600 mg (countries where 325 mg strength tablets/capsules are available). Use of acetaminophen/paracetamol as study-provided rescue medication will be reported daily using

diaries. Acetaminophen/paracetamol must not be taken within 24 hours prior to visits during the treatment period.

Acetaminophen/paracetamol will be sourced by the study sites and reimbursed by the sponsor unless country-specific regulations and customs require a different approach.

7.3. Dose Modification and Study Treatment Discontinuation Rules

7.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

7.3.2. Study Drug Discontinuation

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

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

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

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

In the event that a patient must undergo JR surgery during the treatment or follow-up periods, he/she will be discontinued from study drug and asked to return to the study site for a pre-operative visit and for follow-up safety evaluations (as described in Section 8.2.3.11). Pre-operative imaging (X-rays and/or MRI) will be obtained and submitted to the independent adjudication committee for review to exclude or confirm the presence of an AA event. Instructions for the submission process are provided in the study manual.

7.3.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Evidence of pregnancy
- A patient developing clinically significant peripheral sensory or motor neurologic events confirmed by a neurologist's examination and graded by the neurologist as moderately severe peripheral neuropathy limiting activities of daily living, grade ≥2 according to Common Terminology Criteria for Adverse Events (CTCAE) v.4; study sites should use CTCAE v.4 criteria throughout the study for consistency
- A patient developing new or worsening signs and symptoms indicative of carpal tunnel syndrome
- Continued noncompliance with protocol-defined maximum acetaminophen/ paracetamol use (with a maximum daily dose of 2500 mg [countries where 500 mg strength tablets/capsules are available] or 2600 mg [countries where 325 mg strength

tablets/capsules are available]) during the treatment and follow-up periods, after appropriate counseling

- Continued noncompliance with the protocol, including usage of NSAIDs or other medications that are not permitted in the study
- Joint replacement surgery
- Adverse event of special interest
  - Adjudicated arthropathy, as described in Section 9.6.1.1
  - Sympathetic nervous system dysfunction, as described in Section 9.6.1.2
- Hepatotoxicity: Study drug should be discontinued if any of the following is observed:

  1. Total bilirubin (TBL) >2x ULN or international normalized ratio >1.5, and
  2. ALT or AST >3x ULN, and
  3. No other cause for 1 and 2 is readily apparent

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

  NOTE: Study drug may be withheld in patients who do not meet criteria for permanently discontinuing study drug, until an alternative cause for drug-induced liver injury can be determined. The patient may be re-challenged if an alternative cause for elevated liver function tests is found and the liver function tests return to baseline, but only after discussion with the sponsor.
- Serious or severe allergic reactions considered related to study drug Any other medical need, as determined by the investigator
- Sponsor decision
- Patient withdraws consent

7.3.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug may be temporarily discontinued due to medical need, as determined by the investigator. Study drug will be temporarily withheld while awaiting imaging adjudication for worsening joint pain or when routine imaging suggests AA and prompts the need for additional imaging (Section 9.6.1.1), or for patients who are determined to have orthostatic hypotension or determined to have new or worsening symptoms suggestive of SNS dysfunction while awaiting evaluation by a specialist (Section 9.6.1.2).

7.4. Management of Acute Reactions

7.4.1. Acute Injection Reactions

7.4.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use.

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

All systemic injection reactions must be reported as AEs (as defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

7.5. Method of Treatment Assignment

Approximately 1020 patients will be randomized in a 1:1 ratio to receive either fasinumab 3 mg or placebo Q4W according to a central randomization scheme provided by an interactive web response system (IWRS). Randomization will be stratified by geographical region, baseline LBPI NRS score (<7, ≥7), duration of CLBP (<5 years, ≥5 years), and maximum K-L score (2-3; 4) of any knee or hip joint at the screening visit.

7.5.1. Blinding

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

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

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

Selected individuals not involved in the conduct of the study may have access to unblinded data as needed for safety review or other data review. No study personnel involved in the day-to-day conduct of the study will have access to any unblinded data before the database is locked for this study.

7.5.2. Emergency Unblinding

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

If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment.
- Only the affected patients will be unblinded.

- The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient.
- The investigator will notify Regeneron and/or designee before unblinding the patient, whenever possible.

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

7.5.3. Unblinding for Regulatory Reporting Purposes

Treatment assignments for certain patients may be unblinded to Pharmacovigilance and Risk Management personnel for the purpose of regulatory reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs).

7.6. Treatment Logistics and Accountability

7.6.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label 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 will be stored at the site [redacted] Storage instructions will be provided in the pharmacy manual.

7.6.2. Supply and Disposition of Treatments

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

7.6.3. Treatment Accountability

All drug accountability records must be kept current.

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

- dispensed to each patient,
- returned from each patient (if applicable),
- 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.

7.6.4. Treatment Compliance

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

7.7. Concomitant Medications and Procedures

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

7.7.1. Prohibited Medications

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

Opioid analgesic medications (including tramadol) and muscle relaxants 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 150 mg/day of aspirin, which is permitted for cardiac prophylaxis) until at least 16 weeks after the last study drug injection. A list of medications containing NSAIDs will be provided in the study reference manual.

Other excluded medications during the treatment and follow-up period include:

- Any other investigational agent
- Medical marijuana
- Cyclobenzaprine, carisoprodol, orphenadrine, tizanidine
- Corticosteroids (topical, intranasal, and inhaled formulations are permitted), adrenocorticotropic hormone
- Cyclosporine, mycophenolate mofetil, tacrolimus
- Azathioprine, sulfasalazine, hydroxychloroquine
- IL-6 or IL-6 receptor antagonists
- Abatacept, ustekinumab
- Tumor necrosis factor antagonists
- IL-1 inhibitors, including diacerein
- Apremilast, and tofacitinib
- Tocilizumab

7.7.2. Permitted Medications and Procedures

Monoamine reuptake inhibitors are permitted for non-pain-related treatment (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors). Patients receiving these chronic medications 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 150 mg/day) for cardiac prophylaxis is permitted. Acetaminophen/paracetamol taken acutely for treatment of pain other than CLBP is permitted, however, the total daily dosage limits cannot be exceeded regardless of the reason for acetaminophen/paracetamol use. Acetaminophen/paracetamol taken for pain other than CLBP relief will be reported in the eDiary as "other" during the treatment period. Acetaminophen/paracetamol use during the follow-up period will be reported as concomitant medication. Topical steroids are permitted.

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

In the event that a patient must undergo JR surgery during the study, the patient will complete the early termination visit and the procedures outlined in the schedule of events for JR follow-up (Table 2). The early termination visit should be completed before JR surgery if possible and pre-operative images will be submitted to the adjudication committee for review.

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

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

Table 1: Schedule of Events

	Screening/ Pre-rand		Treatment Period								Follow-up Period						
Study Week	**Screen**	**Pre-rand**	**Base-line**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**EOT Wk 16**	**ET[1]/ JR Pre-op**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**ET[2]/ JR Pre-op**	**EOS Wk 64**
Study Visit/Phone	**Visit 1**	**Visit 2**	**Visit 3**	**Phone 1**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**		**Visit 9**	**Phone 2**	**Phone 3**	**Phone 4**	**Visit 10**		**Phone 5[19]**
Study Day (visit window)	**Up to 30 days**	**7 to 10 days**	**1**	**8 (±1)**	**15 (±3)**	**29 (±7)**	**57 (±7)**	**85 (±7)**	**113 (±7)**		**141 (±7)**	**169 (±7)**	**197 (±7)**	**225 (±7)**	**253 (±7)**		**449 (±7)**
Screening/Baseline:																	
Inclusion/Exclusion	X	X	X														
Main study informed consent	X																
[redacted]	X																
Medical history	X																
Medication history	X																
Demographics[4]	X																
Lumbar spine MRI[5]	X																
LBPI NRS/eDiary training[6]		X	X														
BDI-II	X																
Randomization			X														
Patient-Completed Assessments/Efficacy:																	
Patient education brochures[7]	X	X	X		X	X	X	X									
LBPI NRS[8, 9]	X	X	X		X	X	X	X	X	X	X						
RMDQ			X		X	X	X	X	X	X							
PGA LBP	X		X		X	X	X	X	X	X							
PHQ-8			X				X		X	X							
WOMAC pain subscale score, both knees and both hips			X						X	X							
Peripheral or central pain assessment			X														
PainDETECT Questionnaire			X														
BPI-sf			X		X	X	X	X	X	X							

	Screening/ Pre-rand		Treatment Period								Follow-up Period						
Study Week	**Screen**	**Pre-rand**	**Base-line**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**EOT Wk 16**	**ET[1]/ JR Pre-op**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**ET[2]/ JR Pre-op**	**EOS Wk 64**
Study Visit/Phone	**Visit 1**	**Visit 2**	**Visit 3**	**Phone 1**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**		**Visit 9**	**Phone 2**	**Phone 3**	**Phone 4**	**Visit 10**		**Phone 5[19]**
Study Day (visit window)	**Up to 30 days**	**7 to 10 days**	**1**	**8 (±1)**	**15 (±3)**	**29 (±7)**	**57 (±7)**	**85 (±7)**	**113 (±7)**		**141 (±7)**	**169 (±7)**	**197 (±7)**	**225 (±7)**	**253 (±7)**		**449 (±7)**
MOS Sleep-R			X			X	X	X	X	X							
SF-36			X			X	X	X	X	X							
EQ-5D-5L			X			X	X	X	X	X							
WPAI-LBP			X			X	X	X	X	X							
HCRU	X						X		X	X							
TSQM	X						X		X	X							
Treatment:																	
SC study drug injection[10]			X			X	X	X									
Study drug accountability			X			X	X	X									
Dispense to home paracetamol/ acetaminophen		X	X		X	X	X	X									
Paracetamol/ acetaminophen accountability			X		X	X	X	X	X	X							
eDiary compliance[9]			X		X	X	X	X									
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety:																	
Weight	X								X	X					X	X	
Vital signs	X	X	X		X	X	X	X	X	X	X				X	X	
Orthostatic blood pressure and heart rate assessment[11, 12]	X	X	X		X	X	X	X	X	X	X				X	X	
Electrocardiogram	X								X	X							
Physical examination	X								X	X					X	X	
Neurologic examination	X Full		X Brief		X Brief	X Brief	X Brief	X Brief	X Full	X Full	X Brief				X Full	X Full	

	Screening/ Pre-rand		Treatment Period								Follow-up Period						
Study Week	**Screen**	**Pre-rand**	**Base-line**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**EOT Wk 16**	**ET[1]/ JR Pre-op**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**ET[2]/ JR Pre-op**	**EOS Wk 64**
Study Visit/Phone	**Visit 1**	**Visit 2**	**Visit 3**	**Phone 1**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**		**Visit 9**	**Phone 2**	**Phone 3**	**Phone 4**	**Visit 10**		**Phone 5[19]**
Study Day (visit window)	**Up to 30 days**	**7 to 10 days**	**1**	**8 (±1)**	**15 (±3)**	**29 (±7)**	**57 (±7)**	**85 (±7)**	**113 (±7)**		**141 (±7)**	**169 (±7)**	**197 (±7)**	**225 (±7)**	**253 (±7)**		**449 (±7)**
Survey of autonomic symptoms	X		X		X	X	X	X	X	X	X				X	X	
Joint pain questionnaire	X		X		X	X	X	X	X	X	X				X	X	
Event-triggered imaging[13]				X	X	X	X	X	X	X	X				X	X	
Adverse events	---------->																
SC injection site evaluation			X			X	X	X									
Bilateral X-rays (knee, hip, shoulder)	X[14]								X[16]	X[16]					X[16]	X[16]	
MRI (any knee with K-L ≥3 and any hip with K-L ≥2 at screening)[15]	X																
Pre-op questionnaire (JR)[17, 18]										X						X	
EOS phone contact[19]																	X
MRI affected joint(s) - AA patients only[20]																	X
Laboratory Testing:																	
Hematology[21]	X					X	X	X	X	X					X	X	
Blood chemistry[21]	X					X	X	X	X	X					X	X	
ESR	X																
HbA1c[21]	X																
Urinalysis and urine electrolytes[21]	X								X	X					X	X	
FSH and estradiol[21,22]	X																
Pregnancy test (for WOCBP)[23]	X[21] Serum		X Urine		X Urine	X Urine	X Urine	X Urine	X Urine	X Urine					X Urine	X Urine	

	Screening/ Pre-rand		Treatment Period								Follow-up Period						
Study Week	**Screen**	**Pre-rand**	**Base-line**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**EOT Wk 16**	**ET[1]/ JR Pre-op**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**ET[2]/ JR Pre-op**	**EOS Wk 64**
Study Visit/Phone	**Visit 1**	**Visit 2**	**Visit 3**	**Phone 1**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**		**Visit 9**	**Phone 2**	**Phone 3**	**Phone 4**	**Visit 10**		**Phone 5[19]**
Study Day (visit window)	**Up to 30 days**	**7 to 10 days**	**1**	**8 (±1)**	**15 (±3)**	**29 (±7)**	**57 (±7)**	**85 (±7)**	**113 (±7)**		**141 (±7)**	**169 (±7)**	**197 (±7)**	**225 (±7)**	**253 (±7)**		**449 (±7)**
PK, Antibody, and Research Samples:																	
PK sample[24]			X		X	X	X		X	X					X	X	
ADA samples[24]			X						X	X					X	X	
[redacted]			X														
Biomarker serum and biomarker plasma[24,25]			X			X		X	X	X					X	X	

AA: Adjudicated arthropathy
ADA: Anti-drug antibody
BPI-sf: Brief Pain Inventory-Short Form
BDI-II: Beck Depression Inventory - II
EOS: End of study
EOT: End of treatment
ET: Early termination
EQ-5D-5L: EuroQoL 5 Dimensions 5 Level Questionnaire
ESR: Erythrocyte sedimentation rate
FSH: Follicle stimulating hormone
HbA1c: Glycated hemoglobin
HCRU: Healthcare Resource Utilization
JR: Joint replacement
LBP: Low Back Pain
LBPI: Low Back Pain Intensity
MOS Sleep-R: Medical Outcomes Study Sleep Scale Revised
MRI: Magnetic resonance imaging
NRS: Numerical Rating Scale
PGA: Patient Global Assessment
PHQ-8: Patient Health Questionnaire 8-Item Version
PK: Pharmacokinetic
Pre-op: Pre-operative
Pre-rand: Pre-randomization
RMDQ: Roland Morris Disability Questionnaire
SC: Subcutaneous
SF-36: 36-item Short Form Survey
TSQM: Treatment Satisfaction Questionnaire for Medication
Wk: Week
WOCBP: Women of childbearing potential
WOMAC: Western Ontario and McMaster Osteoarthritis Index
WPAI-LBP: Work Productivity and Activity Impairment-Low Back Pain

8.1.1. Footnotes for the Schedule of Events Table

1. Patients who discontinue study drug before week 16 will be encouraged to follow the visit schedule through the remainder of the study. If a patient chooses to end study participation at or before week 16, he/she will be asked to return to the clinic as soon as possible for an early termination (ET) visit.
2. Patients who discontinue study participation after week 16 will be asked to return to the clinic as soon as possible for an early termination (ET) visit following early termination assessments.

[redacted]

4. Patients' demographic characteristics will be recorded, including age, height, weight, gender, race, and ethnicity.
5. At the request of the central reader, a lumbar spine anterior-posterior/lateral should be obtained if the MRI of the lumbar spine shows evidence suggestive of a destructive or unstable process. Confirmation from the central reader that there are no exclusionary findings on MRI and X-ray (if requested) must be received before a patient can be randomized.
6. Patients will be trained to use 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 (entered to week 20) and daily use of paracetamol/acetaminophen (entered to week 16). Retraining should occur as needed throughout the conduct of the study.
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 and baseline visit, study staff will review with the patient the "Participating in a Research Study: What You Need to Know" brochure. At any time during the conduct of the study, patients may require retraining by study staff.
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 and to week 20.
9. A review of compliance with daily entry of LBPI NRS and rescue medication use will occur at specified study visits, as well as re-education of patients, if applicable. Patients will record their daily LBPI NRS score in the eDiary up to week 20 and their rescue medication usage up to week 16.
10. 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.

11. Assessments for orthostatic hypotension may be discontinued following regulatory approval if the safety database does not reveal an imbalance for the fasinumab-treated patients.
12. If the pulse is less than 45 bpm at any visit, an ECG with rhythm strip will be obtained and sent to the central reader to confirm the heart rate and rhythm.
13. Imaging (X-ray and/or MRI) will be performed on any joint following a report of clinically significant worsening or exacerbation of pain in that joint. This imaging will be submitted to the adjudication committee for review.
14. If screening radiographs are inconclusive for potential joint-related findings, an MRI of the affected joint must be performed. Confirmation from the central reader that there are no exclusionary findings on X-ray and MRI must be received before a patient can be randomized. Imaging may be performed during pre-randomization, if needed.
15. After the patient has otherwise met study eligibility criteria assessed during the screening period, an MRI of any knee with screening K-L ≥3 or hip with screening K-L ≥2 must be performed. Confirmation from the central reader that there are no exclusionary findings on MRI must be received before a patient can be randomized.
16. Imaging assessments (X-rays and MRI) need to be repeated only if it has been >30 days since the joints were last imaged for the modality. If it has been ≤30 days since imaging assessments were completed, imaging assessments may be completed at the discretion of the investigator.
17. In the event that a patient must undergo JR surgery during the study, the patient will complete the pre-operative visit (early termination assessments, as applicable) and the procedures outlined in the schedule of events for JR follow-up (Table 2). The pre-operative visit should be completed before JR surgery if possible. Pre-operative images will be submitted to the adjudication committee for review.
18. Joint replacement questionnaires are Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements.
19. The purpose of this phone contact is to ask the patient if he/she has had or is scheduled (or on a waiting list) to have JR surgery. Pre-operative images will be submitted to the central reader for adjudication, if available.
20. If the AA joint(s) has undergone JR, an X-ray may be substituted for an MRI.
21. Samples will be analyzed by the central laboratory and results will be evaluated by the investigator.
22. The follicle-stimulating hormone (FSH) and estradiol laboratory tests are to be performed only if postmenopausal status has to be assessed for female patients who are ≤59 years of age.
23. 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.

24. PK, ADA, and biomarker samples may also be drawn at any non-specified scheduled visit or any unscheduled visit if a patient experiences a treatment-related safety TEAE. Samples should be collected prior to study drug administration on study drug dosing days.
25. Biomarker samples should be collected after the patients have been fasting overnight or for 8 hours (in the event of an afternoon visit).

Table 2: Follow-up Period for Patients Who Undergo Joint Replacement Surgery

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

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

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

8.1.3. Early Termination Visit

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

8.1.4. Unscheduled Visits

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

8.2. Study Procedures

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed to determine study eligibility or characterize the baseline population:

8.2.1.1. Main Study Informed Consent

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

[redacted]

8.2.1.3. 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. This history will include a patient's history of surgical procedures.

8.2.1.4. 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 electronic clinical report form ([e]CRF) for this purpose.

8.2.1.5. Demographics

Patients' demographic characteristics will be recorded, including age, height, weight, gender, race, and ethnicity. Patient weight will also be recorded at designated visits during the treatment period and the follow-up period, as well as at early termination or pre-operative visits in the event of a JR surgery (Table 1).

8.2.1.6. Beck Depression Inventory – II Assessment

The BDI-II assessment will be performed at screening as part of the determination of eligibility for participation in the study. Patients with a score of ≥29, indicative of severe depression, at the screening visit will be excluded. The BDI-II is a 21-item patient-completed questionnaire with each item scored on a scale of 0 to 3 (Beck, 1996). Total scores range from 0 to 63 with higher scores indicating worse depression. Cut-offs for severity of depression have been identified as follows: 0-13: minimal depression; 14-19: mild depression; 20-28: moderate depression; and 29-63 as severe depression.

8.2.1.7. Assessment of Childbearing Potential

Each female patient will be evaluated for childbearing potential.

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

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

8.2.1.8. Determination of Osteoarthritis

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

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

Hip

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

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

Additional information is provided in the study reference manual.

Knee

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

- Knee pain

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

Additional information is provided in the study reference manual.

8.2.1.9. Assessment of Peripheral or Central Pain

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

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

8.2.1.10. eDiary Training

At the pre-randomization visit, patients will be instructed on the use of the NRS for scoring their LBP. Patients will be trained on the use of the eDiary to report their LBPI NRS score and their daily paracetamol/acetaminophen use for CLBP and other non-CLBP related reasons. Retraining should occur as needed throughout the conduct of the study.

8.2.1.11. Patient Education Brochures

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 (Table 1). 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.

8.2.2. Patient-Completed Assessments and Efficacy Procedures

8.2.2.1. Western Ontario and McMaster Osteoarthritis Index

The WOMAC index is used to assess patients with OA of the hip or knee using 24 parameters reported using a Likert scale. This index can be used to monitor the course of a disease or to determine effectiveness of study drugs. For this CLBP study, patients will complete the WOMAC Pain Subscale only using the 5 parameters of pain, at the time points indicated in Table 1. The WOMAC Pain Subscale scores will be performed at baseline for safety reporting in the event an AA is detected and for the application of study stopping criteria and as outlined in Table 1 in support of assessing pain relief for OA in patients who have CLBP and OA. If possible, the assessment should be administered and entered by the same person throughout the study.

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

8.2.2.2. Low Back Pain Intensity Numerical Rating Scale 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 patients' reports as indicated in Table 1. Once initial eligibility is confirmed, from the pre-randomization visit to the week 20 study visit, LBPI NRS scores will be reported by the patient into the eDiary (Section 8.2.1.10) every day at approximately 6 PM.

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

8.2.2.3. Roland Morris Disability Questionnaire Total Score

The RMDQ is a self-administered, validated, 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 LPB. 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 Table 1.

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

8.2.2.4. Patient Global Assessment of Low Back Pain Score

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

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

8.2.2.5. PainDETECT Questionnaire

Patients will complete the PainDETECT questionnaire to evaluate the neuropathic versus nociceptive nature of their pain at the time points indicated in Table 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.

8.2.2.6. Brief Pain Inventory Short Form

The BPI-sf is a self-administered questionnaire (for patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. With a recall period of 24 hours, the questionnaire contains the front and back body diagrams, the 4 pain severity items and 7 pain interference items rated on 0–10 scales, and the question about percentage of pain relief by analgesics. The BPI assesses pain at its "worst," "least," "average," and "now" (current pain). The BPI pain interference is typically scored as the mean of the 7 interference items. Patients will complete the questionnaire at the time points indicated in Table 1.

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

8.2.2.7. Medical Outcomes Study Sleep Scale Revised

The MOS Sleep-R is a brief, self-administered assessment designed to measure key aspects of sleep (Maurish, 2012). With a 4-week recall period, the MOS Sleep-R has 12-items with 5 response options, and yields scores on 6 sub-scales, each consisting of 1 to 4 items: sleep disturbance, sleep quantity, sleep adequacy, somnolence, shortness of breath or headache, and snoring; and 2 global indices reflecting a respondent's overall sleep quality across multiple domains of sleep outcomes: Sleep Problem Index I and Sleep Problem Index II. Lower scale scores indicate worse sleep problems. Patients will complete the questionnaire at time points indicated in Table 1.

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

8.2.2.8. Short Form-36 Health Survey

The SF-36 Health Survey version 2 standard is a health status measure with a 4-week recall period (Ware, 1992) (Ware, 1993). The SF-36 measures 8 concepts: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health. Two summary measures of physical and mental health are constructed from the 8 scales. Patients will complete the questionnaire at time points indicated in Table 1. Higher scores on the scales and summary measures indicate better health status.

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

8.2.2.9. Patient Health Questionnaire 8-Item Version

The Patient Health Questionnaire 8-Item Version (PHQ-8) is a standardized patient-reported measure of depression symptoms (Kroenke, 2001). It has 8 questions containing mood, anxiety, alcohol, eating, and somatoform modules. With a recall period of 2 weeks, depression severity is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. The PHQ-8 total score for the 8 items ranges from 0 to 24, with scores of 5, 10, 15, and 20 representing cut-off points for mild, moderate, moderately severe and severe depression, respectively. Patients will complete the questionnaire at time points indicated in Table 1.

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

8.2.2.10. EuroQoL 5 Dimensions 5 Level Questionnaire

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

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

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

8.2.2.11. Work Productivity and Activity Impairment - Low Back Pain

The WPAI-LBP is a validated measure of impairments in work and daily activities (Reilly, 1993) (Zhang, 2010). This assessment will be administered according to time points in Table 1.

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

8.2.2.12. Healthcare Resource Utilization Questionnaire

The HRCU questionnaire is a tool designed to capture, over a preceding 8-week period, healthcare utilization events that are not collected as part of the safety assessments in the current study. Examples of these types of events include a patient's use of walking aid, emergency room visits, and physician office visits. Patients will complete the questionnaire at time points indicated in Table 1. Overall healthcare resource use will be computed based on responses to the HCRU questionnaire, as well as any hospital visits that are captured in the safety database.

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

8.2.2.13. Treatment Satisfaction Questionnaire for Medication

The TSQM is a standardized instrument to assess patients' satisfaction with medication (Atkinson, 2004). The questionnaire provides scores on 4 domains – side effects, effectiveness, convenience, and global satisfaction. The TSMQ will be administered according to time points in Table 1.

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

8.2.3. Safety Procedures

8.2.3.1. Weight

Patient weight will be recorded at screening and at designated visits during the treatment period and the follow-up period, as well as at an early termination or pre-operative visit in the event of a JR surgery (Table 1).

8.2.3.2. Vital Signs

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

8.2.3.3. Physical Examination

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

8.2.3.4. Joint Pain Questionnaire

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

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

8.2.3.5. Survey of Autonomic Symptoms

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

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

8.2.3.6. Neurologic Examination

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

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

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

8.2.3.7. Imaging

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

Radiographs

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

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

MRI

An MRI of the lumbar spine will be taken using standard acquisition sequences at the time point indicated in Table 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 an adjudicated or unstable spinal process, flexion/extension radiographs may be requested. Confirmation from the central reader that there are no exclusionary findings on MRI, and X-ray if applicable, must be received before a patient can be randomized.

An MRI of any knee with K-L ≥3 and any hip with K-L ≥2 will be obtained at the time point indicated in Table 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 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.

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

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

8.2.3.8. Assessment of Orthostatic Blood Pressure and Heart Rate

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

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

OR

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

OR

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

OR

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

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

8.2.3.9. Electrocardiogram

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

8.2.3.10. End of Study Phone Contact and Additional Imaging

An end of study phone contact will be conducted approximately 52 weeks following the last dose of study drug. Patients will be asked whether they underwent JR surgery following the last in-clinic visit of the follow-up period or whether they are scheduled (or on a waiting list) for JR surgery. In addition, any serious adverse events (SAEs) reported by the patient during the post follow-up period (from week 36 to the end of study phone contact) and considered related to study drug by the investigator should also be collected. Patients who had JR surgery will also be asked to submit pre-operative imaging (X-ray and MRI, if available) for adjudication. Additionally, patients who had a confirmed AA prior to week 36 will have an MRI performed of the affected joint(s). If the affected joint has undergone JR, an X-ray may be substituted for an MRI.

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

In the event that a patient must undergo JR surgery during the treatment or follow-up periods, he/she will be discontinued from study drug and asked to return for a pre-operative visit (Table 1), and for follow-up safety evaluations at 4 weeks and 20 weeks after surgery (Table 2).

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

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

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

Knee Society Score

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

Harris Hip Score

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

8.2.3.12. Laboratory Testing

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

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

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

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

Blood Chemistry

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

Hematology

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

Urinalysis

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

Urine Electrolytes

Creatinine
Phosphorus

Other Laboratory Tests

Serum and urine samples for pregnancy testing will be collected from WOCBP (as defined in Section 8.2.1.7) at time points according to Table 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 (Table 1).

To assess postmenopausal status for women ≤59 years of age, serum samples to test for FSH levels and estradiol levels will be collected for analysis at the central laboratory according to Section 8.2.1.7.

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

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

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.4.5.

8.2.3.13. Injection Site Evaluations

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

8.2.4. Pharmacokinetic and Anti-Drug Antibody Procedures

8.2.4.1. Drug Concentration Measurements and Samples

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

Any unused samples may be used for exploratory biomarker research.

8.2.4.2. Anti-Drug Antibody Measurements and Samples

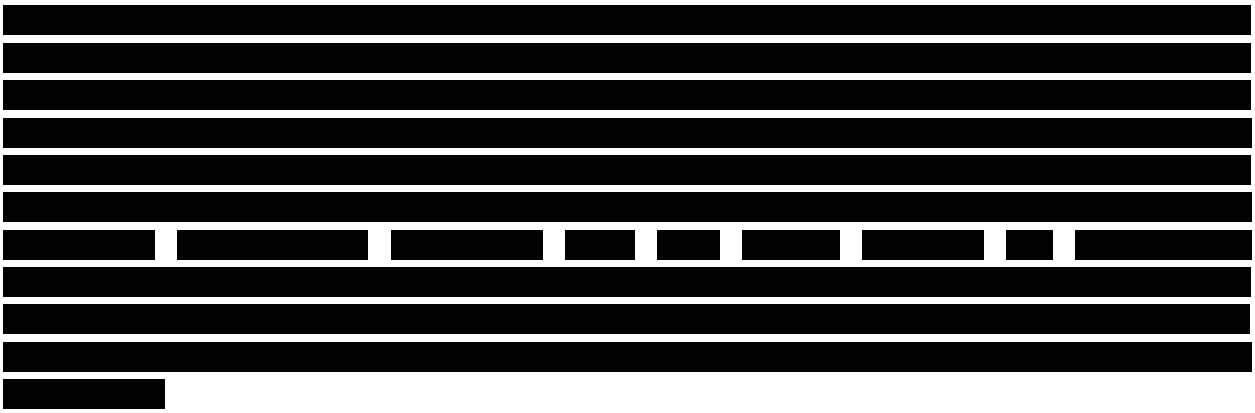
Samples for ADA assessment will be collected at time points listed in Table 1. Detailed instructions for blood sample collection are included in the laboratory manual provided to study sites.

Any unused samples may be used for exploratory biomarker research.

8.2.5. Research Samples

8.2.5.1. Biomarker Serum and Biomarker Plasma Samples

Serum and plasma samples will be collected at time points according to Table 1. These samples should be collected after the patients have been fasting overnight or for 8 hours (in the event of an afternoon visit) and prior to the administration of study drug. [redacted]



9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the IRB or EC all unanticipated problems involving risks to patients, according to local regulations. 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 or EC, regardless of assessed causality, according to local regulations.

9.2. Obligations of Sponsor

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

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

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

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

9.3. Definitions

9.3.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug that 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 that is temporally associated with the use of a study drug, whether or not considered related to the study drug.

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

9.3.2. Serious Adverse Event

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

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

9.3.3. Adverse Events of Special Interest

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

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of the follow-up period (week 36). Refer to the study reference manual for the procedures to be followed.

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

9.4.2. Serious Adverse Events

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

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

In the event the investigator is informed of an SAE after the patient completes the follow-up period (week 36)/early termination visit, the following will apply:

- SAE with an onset within 30 days of the end of the follow-up period (week 36)/early termination visit - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of the follow-up period (week 36)/early termination visit - only SAEs deemed by the investigator to be drug-related will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.
- SAE reported by the patient at the end of study phone contact and deemed by the investigator to be drug-related will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

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

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

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

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

- Adjudicated arthropathy (as confirmed by adjudication)

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

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

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's Medical/Study Director within 30 days.

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

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

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

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

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

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

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

9.4.6. Follow-up

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

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

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

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

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

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

Injection Site Reactions

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

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

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

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

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

The possible answers are:

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

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

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below:

Relationship of Adverse Events to Injection Procedure or Study Procedure:

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

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

The possible answers are:

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

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

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

A list of factors to consider when assessing the relationship of AEs to injection procedure or study procedure is provided below.

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

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

No:

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

- follow a reasonable temporal sequence following the time of administration of the dose of study drug or injection procedure, study procedure, or background treatment, etc.
- resolve or improve after discontinuation of study drug or injection procedure, study procedure, or background treatment, etc.
- reappear or worsen when dosing with study drug or injection procedure, study procedure, or background treatment, etc. is resumed
- are known or suspected to be a response to the study drug or injection procedure, study procedure, or background treatment, etc. based upon preclinical data or prior clinical data

NOTE: This list is not exhaustive.

9.6. Safety Monitoring

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

9.6.1. Monitoring Adverse Events of Special Interest

9.6.1.1. Adjudicated Arthropathy

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

- Rapidly progressive OA type 1 and 2
- Subchondral insufficiency fractures
- Osteonecrosis
- Destructive arthropathy

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

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

If a patient reports an increase in pain as described above, study drug administration will be withheld while imaging of the affected joint, as well as any additional imaging deemed appropriate to understand the cause of the worsening pain, is performed (Section 8.2.3.7). A decision to perform imaging after patient reported worsening of joint pain will be documented in the respective CRF page. Images, along with any other radiographic evaluation, will be submitted to the adjudication committee for review (Section 5.3.2). The investigator may consider aspiration of synovial fluid for further analysis such as cell count and crystal analysis.

If routine imaging suggests the presence of 1 of the types of AA, study drug administration will be withheld. Any additional imaging deemed appropriate will be obtained. The images, along with results of any other radiographic evaluation, will be submitted to the Adjudication Committee for review (Section 5.3.2).

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

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

Any patient whose study drug is discontinued due to an AA should be encouraged to return to the clinic for all remaining study visits. If JR surgery is warranted, prior to the scheduled JR, the patient should complete the pre-operative study visit and, after the JR, should complete the week 4 and week 20 post-operative study visits (Section 8.2.3.5, Table 1). Pre-operative images, along with any other radiographic evaluation will be submitted to the Adjudication Committee for review (Section 5.3.2).

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

9.6.1.2. Sympathetic Nervous System Dysfunction

Sympathetic nervous system dysfunction will be monitored throughout the study through physical examination, AE reporting, assessment of orthostatic hypotension, and the Survey of Autonomic Symptoms (Section 8.2.2.5). New onset or worsening of signs and symptoms of autonomic dysfunction will be evaluated by the investigator. Sympathetic nervous system dysfunction will only be diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist.

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

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

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

9.6.1.3. Peripheral Sensory Adverse Events

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

9.6.1.4. Joint Replacement Surgery

Any elective JR surgery planned before completion of the ICF would be part of the exclusion criteria and would not be considered an AE.

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

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

An end of study phone contact will be conducted approximately 52 weeks following the last dose of study drug to evaluate the number of patients who have undergone or are scheduled for JR surgery as described in Section 8.2.3.10.

9.7. Investigator Alert Notification

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

10. STATISTICAL PLAN

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

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

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

H_{01}: There is no treatment difference between fasinumab 3mg Q4W and placebo in the change from baseline to week 16 in the average daily LBPI NRS score.

The secondary null hypotheses of interest are:

H_{02}: There is no treatment difference between fasinumab 3mg Q4W and placebo in the change from baseline to week 16 in the RMDQ total score

H_{03}: There is no treatment difference between fasinumab 3mg Q4W and placebo in the change from baseline to week 16 in the PGA LBP score

H_{04}: There is no treatment difference between fasinumab 3mg Q4W and placebo in the change from baseline to week 16 in the BPI-sf.

Fixed sequence hierarchical testing will be applied to maintain the study wise Type-I error rate at the 2 sided 0.05 level for the primary and key secondary endpoints. Secondary endpoints will

only be tested if the primary endpoint is statistically significant in favor of fasinumab. Details will be provided a priori in the SAP.

10.2. Justification of Sample Size

Approximately 1020 patients will be randomized in a 1:1 ratio to either fasinumab (3mg Q4W) or placebo. Assuming a 2-sided alpha level of 0.05 and a 20% dropout rate at week 16, an enrolment of 510 patients per arm will provide 90% power to detect an effect size of 0.23 in the daily average LBPI NRS score (ie, an absolute treatment difference of 0.5 between fasinumab 3mg Q4W and placebo with an associated standard deviation [SD] of 2.2). This sample size also provides at least 99% power to detect an effect size of 0.42 (absolute treatment difference of 2.2 with an associated SD of 5.2) in the RMDQ total score and 0.44 (absolute treatment difference of 0.4 with an associated SD of 0.9) in the PGA at week 16. The sample size assumptions are based on results of the R475-PN-1524 study data on file at Regeneron.

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

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

10.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug. Patients randomized to placebo who receive fasinumab at least once will be classified to the fasinumab treatment arm. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

10.3.3. 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 any major protocol deviations through week 16 leading to exclusion from the per-protocol set. The PPS will be used to perform sensitivity analysis for the primary and selected secondary endpoints.

10.3.4. Pharmacokinetic Analysis Set

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

10.3.5. Anti-Drug Anti-Body Analysis set

The ADA population includes all patients who had received any study drug or placebo (safety population) and had at least 1 non-missing ADA result following the first dose of study drug.

10.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, Q1, Q3, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

10.4.1. Patient Disposition

The following will be provided:

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

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics, including medical history and exposure to study drug will be summarized descriptively by treatment group, and by all patients combined.

10.4.3. Efficacy Analyses

10.4.3.1. Primary Efficacy Analysis

The primary efficacy variables will be analyzed using multiple imputation approach with mixed-effect model for repeated measure (MMRM) based on the FAS with adjustment for missing data due to lack of efficacy or adverse events assuming the LBPI NRS scores would on average return to baseline values. The imputed data for patients discontinued from the study due to a lack of efficacy or adverse events will be centered at the mean baseline value.

Missing data will be imputed 50 times to generate 50 complete data sets. Each imputed complete data set will be analyzed using the MMRM with terms for baseline score corresponding to the efficacy variable being analyzed, randomization strata, treatment, visit, and treatment-by-visit interaction. The fitting of MMRM will be performed using the MIXED procedure in Statistical Analysis System (SAS) with an unstructured covariance matrix to model the within-patient errors.

Denominator degrees of freedom will be estimated using Kenward-Roger's approximation. The results from the 50 analyses will be combined using Rubin's formula (PROC MIANALYZE). The least-squares mean estimates for the mean change from baseline to week 16, as well as the differences of the estimates between fasinumab and placebo, with corresponding standard errors, p values and associated 95% confidence intervals, will be provided. Data from all patients, including data collected after discontinuing treatment up to week 16, will be used in the efficacy analyses according to the intent to-treat principle. Sensitivity analysis using pattern mixture model and tipping point approach with multiple imputation to impute missing data 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.

10.4.3.2. Secondary Efficacy Analysis

For analysis of continuous secondary endpoints, the analysis method will be the same as that used for the primary variables. For analysis of categorical variables in secondary endpoints, eg, proportions of patients with ≥30% reduction from baseline to week 16 in the daily average LBPI NRS score; the Cochran Mantel Haenszel approach stratified by the randomization strata will be used with missing data considered as non-response.

10.4.4. Safety Analysis

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

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

The time interval to detect any AEs, including AESIs, is between the first dose of double blinded study drug injection and the week 36 visit.

10.4.4.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from first dose of study drug to the day of the last dose of study drug (week 12) + 4 weeks.
- The follow up period is defined as the time from the end of the on-treatment period (week 16) to the week 36 visit.

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

Analysis

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

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1), presented by SOC and PT

- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a pre-specified grouping)

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

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

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

10.4.4.2. Other Safety

Vital Signs

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 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.

10.4.4.3. Treatment Exposure

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

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

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

10.4.4.4. Treatment Compliance

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

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

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

10.4.5. Analysis of Drug Concentration Data

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

No formal statistical analysis will be performed.

10.4.6. Analysis of Anti-Drug Antibody Data

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

Plots of drug concentrations will be examined and the influence of ADAs on individual PK profiles evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

10.5. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed.

General rules for handling missing data:

- Rules for handling missing data for efficacy assessments will be provided in the SAP
- 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 for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

Visit windows:

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

Unscheduled assessments:

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

10.6. Statistical Considerations Surrounding the Premature Termination of a Study

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

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

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

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

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

11.2. Electronic Systems

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

- IVRS/IWRS system – randomization, study drug supply
- Rave Medidata EDC system – clinical data capture
- Statistical Analysis System – statistical review and analysis
- Argus – pharmacovigilance and clinical safety software system for the collection and reporting of SAEs and AESIs
- Electronic Clinical Outcome Assessment (eCOA) systems – collect subject reported outcome or subject clinical assessment results

12. STUDY MONITORING

12.1. Monitoring of Study Sites

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

The investigator must allow study-related monitoring, IRB or EC review, audits, and inspections from relevant health regulatory authorities.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents,

that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2. Source Document Requirements

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

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

12.3. Case Report Form Requirements

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

The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs.

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

13. AUDITS AND INSPECTIONS

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

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

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB, or EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in

any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

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

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

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

14.2. Informed Consent

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

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

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

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

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

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

14.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by 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.

14.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

15. PROTOCOL AMENDMENTS

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

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

16.1. Premature Termination of the Study

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

16.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

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

17.2. Retention of Records

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

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

18. DATA QUALITY ASSURANCE

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

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

Data Management

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

Study Monitoring

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

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

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

Study Documentation

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

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

19. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

20. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

21. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

22. REFERENCES

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23. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Moderate-to-Severe Chronic Low Back Pain and Osteoarthritis of the Hip or Knee, and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

Signature of Sponsor's Responsible Officers

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

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

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Moderate-to-Severe Chronic Low Back Pain and Osteoarthritis of the Hip or Knee

Protocol Number: R475-PN-1612

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00014095 v1.0

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