REGENERON
Biostatistics and Data Management

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STATISTICAL ANALYSIS PLAN
VERSION: FINAL

A Randomized, Double-Blind, Multi-Dose, Placebo-Controlled Phase 2/3 Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Moderate to Severe Chronic Low Back Pain

Compound:	REGN475 (Fasinumab)
Protocol Number:	R475-PN-1524
Clinical Phase:	Phase 2/3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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Study Medical Director:	[redacted]
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
C_{last}	Concentration corresponding to t_{last}
C_{max}	Maximum observed drug concentration
C_{trough}	Concentration measured at the end of a dosing interval at steady state (taken directly before next administration)
CMH	Cochran-Mantel-Haenszel
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	EuroQol Group Questionnaire
FAS	Full analysis set
FDA	Food and Drug Administration
HbA1c	Hemoglobin A1c
ICF	Informed consent form
ICH	International Conference on Harmonization
IV	Intravenous
IVRS	Interactive Voice Response System
K-L	Kellgren-Lawrence
LBP	Lower Back Pain
LBPI NRS	Lower Back Pain Intensity Numerical Rating Scale
LS	Least-Squares
MCII	Minimum Clinical Important Improvement
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measures
MNAR	Missing not-at-random
MOS-Sleep	Medical Outcomes Study-Sleep scale
MRI	Magnetic resonance imaging

NGF	Nerve growth factor
NRS	Numeric Rating Scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
PCSV	Potentially clinically significant value
PGA	Patient Global Assessment
PK	Pharmacokinetic
PPS	Per protocol set
PT	Preferred term
Q1	First Quartile
Q3	Third Quartile
Q4W	Every 4 (weeks)
Q8W	Every 8 (weeks)
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RMDQ	Roland Morris Disability Questionnaire
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form (36) Health Survey
SOC	System organ class
TEAE	Treatment-emergent adverse event
TJR	Total joint replacement
t_{last}	Time of the last measurable (positive) drug concentration
TrkA	Tyrosine kinase type 1
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. OVERVIEW

This Statistical Analysis Plan (SAP) is intended to be a detailed description (expanding on the statistical analyses described in the protocol) of the definitions and statistical techniques to be used for the analyses of data collected in the R475-PN-1524 study. This SAP will be finalized prior to database lock to ensure the credibility of the study results by pre-specifying the statistical methods for the data analyses before unblinding of treatment assignments.

This plan may be revised during the study to accommodate protocol amendments and adapt to unexpected issues in study execution that may affect planned analyses.

Background/Rationale

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

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

Single SC doses of fasinumab up to 30 mg were well tolerated in healthy male and female subjects (study TDU-11480). Single IV doses of up to 1 mg/kg were also studied in healthy male and female subjects (study R475-PN-0817). In this study, fasinumab was generally well tolerated at all but the highest IV dose (1 mg/kg). Neurosensory AEs, which were transient and not severe, led to expansion of the 1 mg/kg IV cohort and a decision to not dose-escalate beyond this level. In the phase 2 proof-of-concept study of fasinumab in patients with pain due to OA of the knee, multiple IV doses of up to 0.3 mg/kg demonstrated efficacy with regard to pain relief and were well tolerated in Caucasian subjects with pain due to OA of the knee. The phase 2 study in patients with pain due to OA of the knee or hip (R475-PN-1227) evaluated the efficacy and safety of 1, 3, 6, and 9 mg of fasinumab SC every 4 weeks (Q4W).

Results from completed studies evaluating tanezumab in patients with chronic LBP and in patients with pain due to OA indicate that the lowest dose studied may not be adequate to demonstrate efficacy in subjects with non-radicular chronic low back pain. This fasinumab study will therefore evaluate the 2 highest SC doses that were evaluated in the recently completed study (R475-PN-1227) in OA patients (6 mg and 9 mg SC Q4W) and also includes a 9 mg IV fasinumab dose to allow PK, efficacy, and safety comparisons. For patients randomized to SC administration, a loading dose equivalent to 2 times the maintenance dose will be administered on day 1 to achieve steady state concentrations sooner. This approach is supported by PK

simulations based on completed fasinumab studies.

The U.S. Food and Drug Administration (FDA) placed the study on partial clinical hold before enrollment was completed and dosing was prematurely terminated before all randomized patients had completed treatment. The study was enrolling patients with chronic low back pain, some of whom had advanced osteoarthritis, to doses that exceeded those being pursued in the concurrent or planned osteoarthritis studies which limits dosing to 6 mg SC Q8W. Since an event of adjudicated arthropathy was observed in the CLBP study in a patient with advanced OA using a dose higher than that being evaluated in the ongoing OA study, the FDA requested that the study be placed on hold until the protocol could be amended to either remove patients with OA or reduce the doses. A decision was made not to amend the protocol to enable dosing to be resumed. At the time of the clinical hold, 563 patients had been randomized into the study. Patients will be encouraged to remain in the study and be followed for all study visits until completion of the week 36 visit to continue to monitor safety and to allow complete data collection.

The planned analyses take this change into account.

1.1. Study Objectives

1.1.1. Primary Objective

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

1.1.2. Secondary Objectives

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

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

1.1.3. Safety Objectives

Safety objectives of the study are:

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

- To assess the incidence of anti-fasinumab antibody formation

1.1.4. Other Objectives

Exploratory objectives of the study are:

- To evaluate the efficacy of fasinumab compared to placebo, as measured by the percentage of patients who are responders defined by 30% reduction and 50% reduction from baseline to week 16 for:
  - Average daily LBPI NRS score
  - RMDQ total score
  - PGA of LBP score
- To evaluate the efficacy of fasinumab compared to placebo, as measured by the change from baseline to week 16 in the Medical Outcomes Study (MOS) sleep subscale score
- To evaluate the efficacy of fasinumab compared to placebo, as measured by the change from baseline to week 16 in the Short Form (36) Health Survey (SF-36) subscale scores
- To evaluate the efficacy of fasinumab compared to placebo, as measured by the change from baseline to week 16 in the EuroQol 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L)
- To evaluate the efficacy of fasinumab compared to placebo, as measured by the percentage of patients who use rescue medication for LBP at week 16
- To characterize the PK profile of fasinumab

1.1.5. Modifications from the Statistical Section in the Final Protocol

This SAP is based on Protocol R475-PN-1524 Amendment 3.

1.1.6. Revision History for SAP Amendments

None.

2. INVESTIGATION PLAN

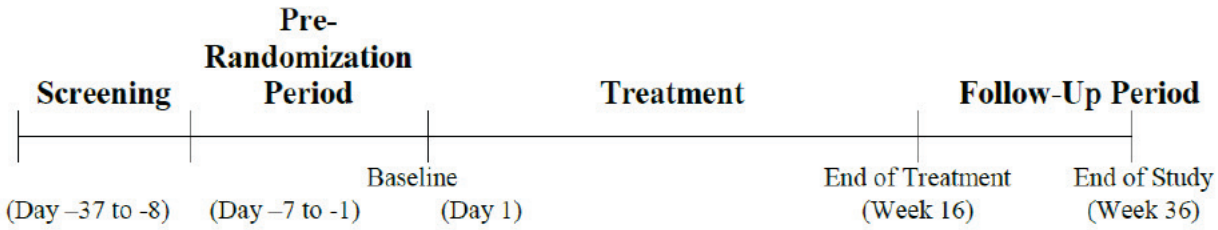
2.1. Study Design and Randomization

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

- Fasinumab 6 mg SC Q4W and placebo 9 mg IV Q8W
- Fasinumab 9 mg SC Q4W and placebo 9 mg IV Q8W
- Fasinumab 9 mg IV Q8W and placebo SC Q4W
- Placebo SC Q4W and placebo 9 mg IV Q8W

Randomization will be stratified by baseline LBPI NRS score (<7, ≥7), duration of chronic back pain (<5 years, ≥5 years), and maximum Kellgren-Lawrence (K-L) score (≤2, >2) at any knee or hip joint at screening. For patients randomized to SC administration, a loading dose equivalent to 2 times the maintenance dose will be administered on day 1.

Figure 1 Study Flow Diagram



2.2. Sample Size and Power Considerations

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

2.3. Study Plan

Study assessments and procedures are presented by study period and visit in Appendix 10.1 Table 1 and Table 2. A schedule for follow-up on TJR surgery during the study is presented in Appendix 10.1 Table 3.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following population of analysis will be used for all statistical analysis:

3.1. The Modified Intent to Treat Set (mITT)

The modified intent to treat set (mITT) includes all randomized patients per IVRS who received at least one dose of study drug based on the treatment allocated (as randomized) including data up to 5 weeks after the last dose of study drug.

3.2. The Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients per IVRS and it is based on the treatment allocated (as randomized). The FAS will be used to perform sensitivity analysis for the primary and selected secondary endpoints.

3.3. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated).
Patients randomized to the 'Placebo SC Q4W and Placebo 9mg IV Q8W" treatment arm who receive at least one dose of active treatment will be classified in the active treatment group in the SAF. Patients randomized to any of the treatment groups receiving active fasinumab doses who wrongly receive another dose of fasinumab will be classified to the arm of the lowest dose of fasinumab received. For example a patient randomized to the 'Fasinumab 9mg SC Q4W and placebo 9mg IV Q8W' who wrongly receives treatment with fasinumab 6mg SC at least once will be classified under the 'Fasinumab 6mg SC Q4W and placebo 9mg IV Q8W' treatment arm. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

3.4. The PK Analysis Set

The PK analysis set includes all randomized patients who received any study drug and have at least 1 qualified (non-missing) blood sample following the first administration of study drug; it is based on the treatment received (as treated).

3.5. The Anti-Drug Antibody Analysis Set

The anti-drug (fasinumab) antibody (ADA) analysis will include all randomized and treated patients who have at least 1 post-dose ADA result after the first dose of study treatment.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

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

The following demographic and baseline characteristic variables will be summarized by treatment group based on data collected in the eCRF:

- Age at screening (years)
- Age category based on tertiles.
- Age category (<65, >=65 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino: Yes or No)
- Baseline Weight(kg)
- Baseline Height(cm)
- Baseline Body mass index (BMI) calculated from weight and height
- Baseline LBPI NRS score
- Baseline LBPI NRS score strata (< 7, ≥ 7)
- Duration of chronic back pain (years)
- Duration of chronic back pain strata (< 5 years, ≥ 5 years)
- Maximum Kellgren-Lawrence score at any knee or hip joint at screening
- Maximum Kellgren-Lawrence score at any knee or hip joint at screening (≤2, >2)
- Use of rescue medication during pre-treatment period (Paracetamol/Acetaminophen: Yes or No)

Additional baseline characteristics will be summarized if needed.

4.2. Medical History

Patient medical history will be dictionary coded by Preferred Term (PT) and associated Primary System Organ Class (SOC) according to the MedDRA version 18.0.

4.3. Pre-Treatment / Concomitant Medication

Medications and procedures will be recorded from the day of informed consent until the EOS visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the WHO Drug Dictionary (WHODD) March 2015 version. Prior medications are defined as medications starting prior to the first

administration of study drug. Prior procedures are defined as procedures performed prior to the first administration of study drug.

Concomitant medications are defined as medications starting prior to ***or*** during the on-treatment period (as defined in section 4.5) and ending during or after the on-treatment period.

Post treatment medications are medications starting after the on-treatment period.

Prohibited medications include medications containing NSAIDS (oral or topical; except up to 100mg/day of aspirin for cardiac prophylaxis) and opioid analgesic medications (including tramadol). Opioid analgesic medications (including tramadol) are prohibited through the week 16 study visit. Patients will be directed not to take concomitant medications that contain NSAIDS (oral or topical, except up to 100mg/day of aspirin, which is permitted for cardiac prophylaxis) until at least 16 weeks after the last dose of study drug. Other excluded drugs include:

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

Prohibited concomitant medications will be summarized separately by ATC class, preferred term and treatment group.

Patients will be counted once in all ATC categories linked to the medication.

4.4. Efficacy Variable

4.4.1. Primary Efficacy Variable

The primary endpoint in the study is the change from baseline to week 16 in the average daily Low Back Pain Intensity (LBPI) score on an 11-point (0-10) Numerical Rating Scale (NRS).

Baseline average daily LBPI NRS score is defined as the average of the non-missing daily LBPI NRS scores for 5 days prior to randomization (from Day -4 to Day 1). Average daily LBPI NRS scores is defined as the average of the non-missing daily LBPI NRS scores for the 7days before and including nominal visit. The daily NRS score for the week 16 nominal visit day is missing for all patients due to operational difficulties which resulted in the daily entry not being captured on the clinical visit day since diaries are available starting at 6pm and clinical visits typically happen during the day with diaries being returned at the end of the visit. Therefore the average at week 16 will be based on 6 days.

4.4.2. Secondary Efficacy Variable(s)

The secondary endpoints in the study are:

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

The total score of the Roland Morris Disability Questionnaire (RMDQ) is the total number of items checked by the patient (range of 0 to 24, with lower scores indicative of better function). The Patient global assessment (PGA) of LBP is a patient assessed 5 point Likert scale of LBP (1=very well; 2=well; 3=fair; 4=poor; and 5=very poor).

4.4.3. Exploratory Variable(s)

Exploratory endpoints in the study are:

- The percentage of patients who are responders defined by 30% reduction and 50% reduction from baseline to week 16 in:
  - Average daily LBPI NRS score
  - RMDQ total score
  - PGA of LBP score
- Cumulative distribution of percent change from Baseline in average LBPI score to Week 16
- Cumulative distribution of percent change from Baseline in RMDQ total score to Week 16
- Change from baseline to weeks 2, 4, 8, 12 and 16 in the MOS-Sleep subscale score
- Change from baseline to weeks 2, 4, 8, 12 and 16 in the SF-36 subscale scores
- Change from baseline to weeks 2, 4, 8, 12 and 16 in the EQ-5D-5L visual analogue scale (VAS) and utility index scores
- Usage of rescue medication (percentage of patients who use rescue medication for LBP, number of days of usage, and weekly average amount taken during weeks 2, 4, 8 12, and 16)

4.5. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, ECG and physical exam.

Unless otherwise noted, the baseline value is defined as the last available value before the first dose of study treatment.

4.5.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (the latest current available version).

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A Serious Adverse Event is an adverse event (AE) that is classified as serious according to the criteria specified in the protocol.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

4.5.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) for the fasinumab program include adjudicated arthropathy and sympathetic nervous system dysfunction, as specified in the protocol.

AESI are selected using e-CRF specific tick box on the AE page.

4.5.3. Laboratory Safety Variables

Clinical laboratory tests will consist of blood analyses (including hematology and clinical chemistry) and urinalysis. Clinical laboratory values will be converted and analyzed in international units, including associated normal ranges provided by the central laboratory. International units will be used in all listings and tables.

Clinical laboratory values in conventional (US) units will also be available in the database, with associated normal ranges (analyses can be provided upon request). Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in the result summaries. Potentially clinically significant values (PCSV) ranges will be applied to the laboratory test values as applicable. The following PCSV categories will be used for the laboratory PCSV analysis tables:

- Red Blood Cells and Platelets
- White Blood Cells
- Metabolic Function
- Electrolytes
- Renal Function
- Liver Function
- Lipid Panel
- Urinalysis

4.5.4. Vital Signs

Vital sign parameters will include temperature, pulse (measured over a 1-minute period), and respiratory rate. As well as supine BP, 1 min and 3 min standing BP, supine heart rate, 1 min and 3 min heart rate which are used in the assessment of orthostatic hypotension. Both actual values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in the result summaries. Potentially clinically significant values (PCSV) ranges will be applied to the vital sign parameter values as applicable (see Appendix 10.2 for PCSV definitions).

4.5.5. 12-Lead Electrocardiography (ECG)

12-Lead ECG parameters include P-R interval, QT interval, QTc interval including QTcF and QTcB, QRS interval, Ventricular rate and Heart rate.

QTcF and QTcB are defined as follows:

$QTcF\ (ms) = QT/RR^{1/3}$ and $QTcB\ (ms) = QT/RR^{1/2}$,

where QT is the uncorrected QT interval measured in ms, and RR is 60/HR with HR being the heart rate in beats per minutes. Electrocardiogram assessments will be described as normal or abnormal. Potentially clinically significant values (PCSV) ranges will be applied to the ECG parameter values as applicable (see Appendix 10.2 for PCSV definitions).

4.5.6. Orthostatic Hypotension

A patient will be determined to have orthostatic hypotension if any of the following criteria are met:

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

  OR

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

  OR

- An increase in either 1 min or 3 min 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

4.5.7. Physical Examination Variables

Physical exam assessments will be described as normal or abnormal.

4.5.8. Neurological Examination Variables

Neurological evaluations of specific domains as listed in the protocol will be described as normal or abnormal.

4.5.9. Other Safety Variables

Survey of Autonomic Symptoms questionnaire: number of patients reporting health symptoms during the past 6 months for each symptom/health problem assessed as well the severity of symptoms reported at each scheduled visits.

Joint Pain Questionnaire: number of patients with pain in joints lasting more than 2 weeks at each scheduled visits.

Pregnancy on study will be assessed.

4.6. Anti-Drug Antibody (ADA) Variables

Serum samples collected at baseline, week 16 (end of treatment) and week 36 (end of study) or ET (early termination) will be analyzed for anti-drug antibody (ADA) analysis. ADA variables include status (positive or negative) and titer as follows:

- Total number of patients whose response in the ADA assay is negative at all times
- Total number of patients whose response in the ADA assay is positive at any time point analyzed
- Pre-existing immunoreactivity - defined either as a positive ADA assay response at baseline with all post-dose ADA assay results negative, **OR** a positive assay response at baseline with all post-dose ADA assay responses less than 9-fold over baseline titer levels
- Treatment-emergent - defined as any post-treatment positive ADA assay response when the baseline is ADA negative or missing
- Treatment-boosted – defined as any post-dose positive ADA assay response that is at least 9-fold over the baseline titer level when baseline is positive in the ADA assay.
- Titer
  - Titer values
  - Titer category
    - Low (titer <1,000)
    - Moderate (1,000≤ titer ≤10,000)

- High (titer >10,000)

Neutralizing activities of ADA will be assessed for samples that are positive in the ADA assay.

4.7. Pharmacokinetic Variables

The PK variable is the serum concentration of fasinumab at scheduled time points.

5. STATISTICAL METHODS

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

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

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be descriptively summarized by treatment group and overall for the study based on the FAS. Parameters to be summarized include those described in Section 4.1 .

Continuous data will be summarized using the number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

5.2. Medical History

Relevant medical histories at study entry will be descriptively summarized by treatment group and overall for the study based on the FAS.

All reported patient's medical history and surgical history will be presented by primary SOC, PT and treatment group. Primary SOCs will be sorted by decreasing frequency in the combined fasinumab group. Within each primary SOC, PTs will be sorted by decreasing frequency in the combined fasinumab group.

5.3. Prior/Concomitant Medications

All prior medications, dictionary coded by WHO, will be descriptively summarized by ATC class, preferred term and treatment group and overall for the study based on the safety analysis set. Summaries will present patient counts (and percentages) for all prior medications in decreasing frequency of the overall incidence of ATC followed by therapeutic class. In case of equal frequencies across anatomic or therapeutic categories, alphabetical sorting order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, but may be counted several times for the same medication.

All concomitant medications, dictionary coded by WHO, will be descriptively summarized by ATC class, preferred term and treatment group, for patients in the SAF. Summaries will present patient counts (and percentages) for the concomitant medication groups described in Section 4.3 for all concomitant medications, in decreasing frequency of the fasinumab group incidence of ATC followed by therapeutic class. In case of equal frequencies across anatomic or therapeutic categories, alphabetical sorting order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, hence may be counted several times for the same medication.

The following will be summarized:

- Prior Medications
- Concomitant medications
- Post-treatment medications
- On-study (Concomitant + Post-Treatment) Medications

5.4. Prohibited Medications

Prohibited medications, dictionary coded by WHO, will be descriptively summarized by ATC class, preferred term and treatment group for patients in the SAF similar to the summary of concomitant medications.

5.5. Patient Disposition

The disposition of patients in the study will summarized by treatment group and overall for all patients. The following summaries will be provided:

Summary of total screened patients, numbers of subjects in FAS, and SAF by treatment and total. Summaries of discontinuations from treatment and discontinuations from the study including reasons for discontinuation will also be presented by treatment and overall.

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Treatment Compliance

Compliance with protocol-defined investigational product will be calculated based on the safety set as follows:

Treatment compliance will be calculated as:

$$\frac{\begin{array}{c}\#\ of\ actual\ injections/infusions\ \ of\ study\ drug\ recieved \\ during\ exposure\ period\end{array}}{\begin{array}{c}\#\ of\ planned\ injections/infusions\ of\ study\ durg\ during\ exposure\ period \\ on\ or\ before\ the\ time\ patient\ discontinued\ from\ the\ treatment\ phase\ of\ the\ study\end{array}}\ x\ 100\%$$

The loading dose at baseline will not be counted as a separate injection/infusion. The treatment compliance will be presented by the descriptive statistics and the number (%) of patients who have 1, 2, 3 and 4 SC injections or 1 and 2 IV infusions, respectively.

5.6.2. Exposure to Investigational product

The treatment exposure to fasinumab and placebo SC doses during the study will be presented by treatment and calculated as:

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

The treatment exposure to fasinumab and placebo IV doses during the study will be presented by treatment and calculated as:

- (Date of last study drug administration – date of first study drug administration) + 56

The duration of exposure during the study will be summarized for each treatment group using the number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum.

The number (%) of patients with exposure periods will be presented by specific time periods. The time periods of interest is specified as: ≥ 1 day, ≥ 8 days, ≥ 15 days, ≥ 29 days, ≥ 57 days, ≥ 85 days, and ≥ 113 days.

The duration of observation period during the study is calculated as:

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

The number (%) of patients with observation periods will be presented by specific time periods. The time periods of interest is specified as: ≥ 1 day, ≥ 8 days, ≥ 15 days, ≥ 29 days, ≥ 57 days, ≥ 85 days, and ≥ 113 days.

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

5.7. Analyses of Efficacy Variables

5.7.1. Analysis of Primary Efficacy Variable(s)

The primary endpoint in the study is the change from baseline to week 16 in the average daily LBPI NRS score. The following hypotheses will be tested (with no control for multiplicity):

- H_1: No difference in the change from baseline to week 16 in the average LBPI NRS score for fasinumab 6mg SC Q4W and Placebo.
- H_2: No difference in the change from baseline to week 16 in the average LBPI NRS score for fasinumab 9mg SC Q4W and Placebo.
- H_3: No difference in the change from baseline to week 16 in the average LBPI NRS score for fasinumab 9mg IV Q8W and Placebo.

Statistical Model

The primary efficacy variable, change from baseline in LBPI score, will be analyzed using a mixed-effect model repeated measures (MMRM) approach based on the mITT. The model will include the randomization strata, baseline LBPI score, treatment, study week, and treatment-by-week interaction. Denominator degrees of freedom will be estimated using Kenward-Roger's approximation. Data from all patients, including data collected after discontinuing treatment up to the earlier of withdrawal of consent, week 16 or 5 weeks after the last dose of study drug, will be used in the primary efficacy analyses according to the intent-to-treat principle using the MMRM approach with no imputation for missing data.

The fitting of MMRM will be performed using MIXED procedure in SAS with an unstructured covariance matrix to model the within-patient errors. If the model does not converge using unstructured covariance matrix, a simpler covariance structure with fewer parameters will be

used according to the following order: heterogeneous autoregressive (1)ARH(1), Compound symmetry (CSH), Toeplitz (TOEP).

The Least-Squares means estimates for the mean change from baseline to week 16, as well as the differences of the estimates between fasinumab doses and placebo, with their corresponding standard errors, p-values and associated 95% confidence intervals will be provided from the MMRM model. The graph of LS-mean +/- SE by visit will be provided. In addition, the absolute value at week 16 and change from baseline to week 16 in LBPI NRS score will be summarized and graphed by visit.

Sample SAS codes that can be used to implement the MMRM analysis are shown below:

```
proc mixed data=LBPI_NRS;
  class subid trt week stratum1 stratum2 stratum3;
  model chg = baseline trt stratum1 stratum2 stratum3 week trt*week
/ddfm = kr;
  repeated week / type=un subject=subid;
  lsmeans trt*week/ slice=week pdiff cl;
run;
```

Where stratum1, stratum2, and stratum3 are baseline LBPI NRS score (<7, ≥7), duration of chronic back pain (<5 years, ≥5 years), and maximum K-L category (≤2, >2).

Sensitivity analysis:

Sensitivity analyses will be performed the same way for the primary and secondary variables (RMDQ total score and PGA) using the FAS.

Subgroup analysis:

Descriptive analyses will be performed on the primary endpoint and the secondary endpoints (RMDQ total score and PGA) to summarize the treatment effects across subpopulations defined by baseline randomization strata (baseline LBPI NRS score, duration of chronic back pain , and maximum K-L score category), demographics (age group, sex, race) and baseline characteristics (weight and BMI categories). Subgroup analysis by osteoarthritis (OA) subgroup will be performed. OA subgroup is defined as:

1. Medical History of OA
2. Kellgren Lawrence Grade ≥ >=2 radiographic evidence of hip or Grade ≥ >=3 radiographic evidence of knee
3. Either (1) or (2)

Subgroup analysis based on other medical conditions may also be performed.

5.7.2. Analysis of Secondary Efficacy Variables

All secondary efficacy variables will be analyzed based on the mITT using the same MMRM as described in Section 5.7.1 to compare fasinumab doses with placebo without multiplicity adjustment. These models will include fixed effect terms for randomization strata, corresponding baseline value, treatment, visit, and treatment-by-visit interaction. LS mean with standard errors, LS mean difference with standard error, and its 95 % confidence interval will be provided. The graph of LS-mean +/- SE by visit will be provided. In addition, for each secondary variable, absolute value and change from baseline value will be summarized and graphed by visit.

5.7.3. Analysis of Exploratory Variables

Responder analyses

The percentage of patients who are responders based on the variables listed in Section 4.5.3 are defined by 30% reduction and 50% reduction from baseline to week 16 will be summarized by the treatment group. These response-based categorical exploratory variables will be analyzed for FAS using the Cochran-Mantel-Haenszel (CMH) test, stratified by the randomization strata.

Cumulative distribution of percent change from baseline in average daily LBPI score and RMDQ total score will be presented by treatment group. The cumulative distribution plot displays a continuous plot of the percent change from baseline on the X-axis and the percent of patients experiencing that change on the Y-axis. Different responder definitions can be identified along the cumulative distribution curve.

Continuous endpoints

All continuous exploratory variables will be analyzed for FAS using the same MMRM as described in Section 5.7.1 to compare fasinumab doses with placebo without multiplicity adjustment. These models will include fixed effect terms for randomization strata, corresponding baseline value, treatment, visit, and treatment-by-visit interaction. LS mean with standard errors, LS mean difference with standard error, and its 95 % confidence interval will be provided. The graph of LS-mean +/- SE by visit will be provided. In addition, each variable, absolute value and change from baseline value will be summarized and graphed by visit.

Rescue Medication

The percentage of patients who use rescue medication between baseline and week 16 will be summarized by the treatment group. The categorical exploratory variable will be analyzed for FAS using the Cochran-Mantel-Haenszel (CMH) test, stratified by the randomization strata.

Number of days patients used rescue medication during the treatment period (Day1 to Week 2, Week 2 to Week 4, Week 4 to Week 8, Week 8 to Week 12, Week 12 to Week 16) will be summarized descriptively by treatment group. Weekly average amount of rescue medication use will be summarized descriptively by treatment group.

5.8. Analysis of Safety Data

The analysis of safety and tolerability will be performed on the SAF, as defined in Section 3.3. The safety analysis will be based on the reported AEs and other safety information (clinical

laboratory evaluations, vital signs, physical exam and 12-lead ECG). Thresholds for Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Appendix 10.2.

The summary of safety results will be presented for each treatment group.

Period of observation: The observation period will be divided into three segments: pre-treatment, on-treatment, and follow-up period.

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from first dose of study drug to 4 weeks after the last dose of SC study drug or 8 weeks after the last dose of IV study drug, whichever is later.
- The Post/Treatment follow-up period is defined as from the end of the on-treatment period+1 day to the end of study visit (week 36).

Unless otherwise noted, summaries of safety variables will use data from the on-treatment period. Listings of safety variables will include data from all periods and values occurring during the pre-treatment and follow-up period will be flagged in the listings.

Day 1 is the first day of investigational product, Day –1 is the day before, and there is no Day 0.

The time interval to detect any on-treatment event or abnormality is the on-treatment period. Data collected outside this interval will be excluded from the estimation of descriptive statistics and identification of abnormalities for laboratory evaluations, ECGs and vital signs. All post-baseline data during the interval will be using in the PCSV analysis including scheduled and unscheduled assessments.

5.8.1. Adverse Events

The verbatim text, the PT, and the primary SOC will be listed in patient listings. Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs.

Pre-treatment AEs are defined as AEs that developed or worsened during the pre-treatment period.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period.

Post-treatment AEs are defined as AEs that developed or worsened more than 28 days after the last SC dose of investigational product or 56 days after the last IV dose of investigational product.

The focus of adverse event reporting in the clinical study report will be on TEAEs. Post-treatment AEs and AEs during the combined study periods will also be summarized.

For details on handling missing data and partial dates, see Section 6.

Summaries of all TEAEs in each treatment group will include:

- Overview of TEAEs, summarizing number of events, summarizing number and percentage of patients with any
  - Total number of TEAEs
  - Total number of Serious TEAEs
  - Patients with any TEAEs
  - Patients with Serious TEAEs
  - Patients with TEAE leading to permanent treatment discontinuation
  - Patients with TEAE leading to withdrawal from study
  - Patients with TEAE leading to death
  - Patients with any AESI's
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- Treatment-related TEAEs by SOC, PT, and severity
- TEAEs Resulting in Permanent Study Drug Discontinuation by SOC and PT
- AESI by SOC and PT
- Post-Treatment TEAEs by SOC and PT
- Post-Treatment TEAEs by SOC, PT, and severity
- All On-Treatment and Post-Treatment AEs by SOC and PT
- All On-Treatment and Post-Treatment AEs by SOC, PT, and severity
- Serious TEAEs by SOC and PT
- Non-serious TEAEs by SOC and PT
- Post-treatment Serious AEs by SOC and PT
- All Serious AEs by SOC and PT
- Listing of Patients with Serious TEAEs
- Listing of Patients with AESIs
- Listing of deaths
- Listing of AEs leading to death

Counts will be provided by treatment group for each PT within each SOC. Percentages will be calculated using the number of patients from the SAF in each treatment group.

Primary SOCs will be sorted by decreasing frequency of investigational product, with the total overall classes coming first and labeled "Any class". Within each primary SOC, PTs will be sorted by decreasing frequency of investigational product. For tables presenting severity of events, the worst severity will be chosen for patients with multiple instances of the same event.

A second type of table with counts of each primary SOC in decreasing order of frequency will be provided. A third type of table with counts of each PT in decreasing order of frequency will also be provided.

Common TEAEs (preferred terms ≥5% in any treatment group) will be summarized in the report.

5.8.2. Analysis of Adverse Events of Special Interest

Treatment emergent adverse events of special interest for adjudicated arthropathy and sympathetic nervous system dysfunction will be presented by SOC and PT. The summaries will be sorted by decreasing incidence of PT within each SOC in the combined fasinumab group.

5.8.3. Total Joint Replacements (TJRs)

Total and partial joint replacements of any joints will be summarized by treatment group. Number of replacements in joints that were positively adjudicated will be summarized by treatment group. TJRs will also be summarized by KL score of the affected joint.

5.8.4. Clinical Laboratory Measurements

A treatment-emergent Potential Clinically Significant abnormal value (PCSV) is a laboratory value that was normal or abnormal but not meeting PCSV criteria at Screening and Baseline but became abnormal and met PCSV criteria after treatment with study drug. PCSV summary will be constructed for on-treatment period, post-treatment period and overall during the study.

Baseline clinical laboratory analytes and change from Baseline in clinical laboratory analytes to each scheduled assessment time will be summarized with descriptive statistics. Summary statistics will include using the number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum. Scatter plot of change scores from baseline of LBPI vs. Alkaline phosphatase will be plotted by treatment group and visit. Mean change from baseline in Alkaline phosphatase values along with standard error bars will be plotted over time by treatment group.

5.8.5. Analysis of Vital Signs

Vital signs (pulse, sitting blood pressures, orthostatic blood pressure/heart rate, and temperature) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics. The graphs of mean (or median) value of some vital sign parameter vs. visit will also be plotted.

PCSV summary including orthostatic hypotension will be constructed for on-treatment period, post-treatment period and overall during the study.

5.8.6. Analysis of 12-Lead ECG

ECG parameters (P-R interval, QT interval, QTc interval, QRS interval, Ventricular rate and Heart rate) will be summarized by baseline and change from baseline to each scheduled and collected assessment time. PCSV summary of ECG parameters will be provided for on-treatment period, post-treatment period and overall during the study.

ECG status (i.e. normal, abnormal) will be reported. Newly occurring ECG findings will be summarized.

5.8.7. Physical Exams

The percentage of patients with new-onset abnormal physical examinations will be summarized using frequency and percentage by body system by visit..

5.8.8. Analysis Other Safety Variables

Summaries and listings will be provided for the Survey of Autonomic Symptoms and Joint Pain Questionnaire. Arthropathy adjudications based on the imaging data will also be summarized.

5.9. Analysis of Pharmacokinetic and Antibody Data

5.9.1. Analysis of Pharmacokinetic Data

Summaries of concentrations of functional fasinumab will be presented by nominal time point and dose. 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 day and visit (linear and log scales).

5.9.2. Analysis of Anti-drug Antibody Data

The ADA variables described in Section 4.6 will be summarized using descriptive statistics by dose/cohort group in the ADA analysis set. Prevalence of pre-existing immunogenicity, 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 treatment-emergent or treatment-boosted ADA assay response on individual PK profiles will be evaluated.

Listings of ADA positivity and titers presented by patient, time point, and dose cohort/group will also be provided.

Impact of ADA on Safety and Efficacy

Correlation analysis of safety versus treatment-emergent ADA positivity status may be performed on the SAF. Assessment will focus on the following safety events:

- Hypersensitivity (SMQ : Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis[Narrow])

Number (%) of patients with the above mentioned safety events may be summarized by ADA status (positive or negative), during the TEAE period.
In addition, correlation analysis of key efficacy endpoints versus treatment-emergent ADA status in patients who discontinued due to lack of efficacy may be summarized.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

6.2. Data Handling Convention for repeat measurements

Orthostatic Hypotension data

This applies specifically to the data handling of repeat measurements in the assessment of orthostatic hypotension. Per protocol, if the initial vital assessments for orthostatic hypotension is consistent with the definition of orthostatic hypotension, the supine, standing blood pressure or pulse should be repeated up to 2 more times. The guidelines for the repeat assessments are shown below:

Initial Assessment	Repeat Assessment 1	Repeat Assessment 2	Does Patient meet OH criteria	Value to be used in the analysis
Does not meet OH definition	N/A	N/A	No	Initial Assessment
Meets OH definition - repeat	Does not meet definition - repeat	Does not meet definition	No	Repeat Assessment 2
Meets OH definition - repeat	Does not meet definition - repeat	Meets OH definition	Yes, AE of OH reported.	Repeat Assessment 2
Meets OH definition - repeat	Meets OH definition	N/A	Yes, AE of OH reported.	Repeat Assessment 1

Baseline for the assessment of orthostatic hypotension vital assessments uses the last available assessment prior to the start of study drug. Measurements post baseline will not be averaged. Rather frequency counts for patients meeting criteria for orthostatic hypotension will reflect the scenario as shown in the table.

Patient reported outcomes data

Should there be duplicate data entries for PRO ediary data, the first entry for the day will be used.

6.3. Data Handling Convention for Missing Data

Missing/Incomplete AE/Concomitant medication dates

Imputation of AE and Concomitant Missing and Partial start dates:
Every effort will be made to collect the start dates of all AEs and concomitant medications. However, in the case the start date of an AE or concomitant medication is incomplete or missing,

it will be assumed to have occurred on or after the first dose of study medication, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the first dose of study medication date, then the start date of the first dose will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.

Imputation of Partial AE and concomitant Medication Partial end dates:
When only year is present, missing AE/concomitant medication end day and month will be imputed to the earlier of (study end date, 31DECYYYY).
When both month and year present, missing AE/concomitant medication end day will imputed to the last day of the month.
There will be no attempt to impute completely missing AE or concomitant medication end dates. Events with an end date missing will be assumed to be ongoing at the time of data cut off.

Missing/Incomplete Medical history dates

Medical history start dates are used to determine the duration of chronic back pain at baseline per eCRF data. Completing missing medical history dates will not imputed. Missing month will be imputed to January and missing day will be imputed to the first day of the month.

Adverse event

If the intensity of a TEAE is missing, it will be classified as "severe" in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

Other safety data

For laboratory results below the quantification (LOQ), half of the LOQ will be imputed for calculating the descriptive summary.

No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

Date of first / last injection

Date of first injection is the first non-missing start date of dosing recorded in the CRF "Investigational Product" module.

If a patient's date of the last dose is totally missing or unknown, his/her last visit date in the treatment period will be substituted.

Missing item data for questionnaires

LBPI NRS

Baseline average daily LBPI NRS score is defined as the average of the non-missing daily LBPI NRS scores for 5 days prior to randomization (from Day -4 to Day 1). For each week, the average daily LBPI score is defined as the average of the non-missing daily LBPI NRS scores for the 7days before and including the visit day .

RMDQ

RMDQ total score will be set to missing if any item is missing.

SF-36

The Half-Scale rule will be used to impute missing item responses in the SF-36 subscale scores i.e. a score will be computed if the respondent answers at least 50% of items in that scale. The missing items in the scale will be imputed by the mean of available items rounded to the nearest whole number.

The bodily pain subscale consists of Q7 and Q8 of the instrument. Since Q7 is based on 6pt Likert score and Q8 is based on a 5pt Likert scale and because mean imputation will be meaningless, the bodily pain subscale score will not be imputed if any of the questions making up the scale is missing.

EQ-5D-5L

Index will be set to missing if any of the 5 dimensions is missing.

MOS-Sleep
MOS-Sleep subscale scores will be computed if at least 50% of items are available. The missing items will be imputed by the mean of available items.

6.4. Data handling for the SF-36 instrument.

Due to scoring differences amongst the instrument's 36 items, 10 of the items will need to be reverse coded to ensure consistency in reporting such that higher scores are indicative of better health. The SF-36 items needing reverse coding are: Q1, Q6, Q7, Q8, Q9a, Q9d, Q9e, Q9h, Q11b, Q11d.

6.5. Visit Windows

By-visit analysis (including efficacy, laboratory data, vital signs, ECG, ADA) will be summarized by the nominal visit number and no visit window will be defined. Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator. For assessments without a nominal visit number such as EOT and EOS assessments, a visit number will be assigned based on the actual visit date using the study day and visit window as in Appendix 10.2 Table 1 Schedule of Events.

The following visit windows will be used to map the unscheduled visits, early end of treatment visits, early study termination visits and daily electronic dairy entries, based on the study day:

Visit No.	Visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	Day -37 to day -8	≤8
2	Pre-randomization	Day -7 to -4	-7 to -3
3	Baseline	1	1
4	Week 2	15	[12,18]

5	Week 4	29	[22, 36]
6	Week 8	57	[50, 64]
7	Week 12	85	[78, 92]
8	Week 16 (End of Treatment)	113	[106, 120]
9	Week 20	141	[134, 148]
10	Week 36 (End of Study)	253	[246,260]

*Study days are calculated from the first administration of study drug (Day 1)

If multiple measurements occur within the same analysis window, the following rules will be used to determine the analysis value:

- When multiple valid measurements occur within the same analysis window, the closest to the target study day will be used in the analysis.
- When multiple valid measurements occur within equal distance from the target study day, the value after the target study day will be used in the analysis.

Both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values from laboratory, vital sign or ECG as well as the baseline values.

6.6. Unscheduled Assessments

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on available assessments of scheduled and unscheduled visits. For by visit summaries, only scheduled assessments are included.

6.7. Pooling of Centers for Statistical Analyses

There is no pooling of centers planned for the statistical analysis.

7. INTERIM ANALYSIS

An administrative interim analysis may be conducted by a team of independent statisticians and programmers. The results of this interim analysis will be used to make appropriate business decisions.

Since the time that dosing was stopped in this study, two unblinded interim analysis of efficacy have been conducted. The first unblinded interim analysis was conducted immediately after being placed on clinical hold and the second was conducted at the time when the last patient who received study drug before the trial was placed on clinical hold would have completed the 16week time point.

No new or unexpected safety signals were observed.

The conduct of these administrative interim analyses was performed by independent personnel not involved with the conduct of the study. Regeneron personnel directly involved in the conduct of the study including study medical monitor and biostatistician remain blinded at the subject level.

8. SOFTWARE

All analyses will be done using SAS Version 9.3 or later version if available. .

9. REFERENCES

ICH. (1996, July 30). ICH Harmonized tripartite guideline: Structure and content of clinical study reports (E3). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

ICH. (1997, July 17). ICH Harmonized tripartite guideline: General considerations for clinical trials (E8). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

10. APPENDIX

10.1. Schedule of Time and Events

Table 1 Schedule of Events – Screening and Treatment Periods

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

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

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

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

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

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

Table 2 Schedule of Events – Follow-up Period

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

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

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

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

Table 3 Schedule of Events – Follow-up for Patients who undergo Total Joint Replacement Surgery

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

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

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

10.2. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	Treatment Emergent PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN*	Enzyme activity must be expressed in ULN, not in IU/L.
	>5 and ≤ 10 ULN and baseline ≤ 5 ULN	FDA DILI Guidance July 2009.
	>10 and ≤ 20 ULN and baseline ≤ 10 ULN	Each category is calculated independently.
	>20 ULN and baseline ≤ 20 ULN	* At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided

Parameter	Treatment Emergent PCSV	Comments
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. FDA DILI Guidance July 2009. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. FDA DILI Guidance July 2009.

Parameter	Treatment Emergent PCSV	Comments
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. FDA DILI Guidance July 2009. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
ALT/AST and Total Bilirubin	(ALT >3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN) (ALT >3 ULN and TBILI>1.5 ULN) and baseline (ALT <=3 ULN or TBILI <=1.5 ULN)	FDA DILI Guidance July 2009.

Parameter	Treatment Emergent PCSV	Comments
ALT/AST and Total Bilirubin and ALP	(ALT >3 ULN and TBILI>2 ULN and ALP < 2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN or ALP >=2 ULN) (AST>3 ULN and TBILI>2 ULN and ALP < 2 ULN) and baseline (AST <=3 ULN or TBILI <=2 ULN or ALP >=2 ULN)	FDA DILI Guidance July 2009.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria

Parameter	Treatment Emergent PCSV	Comments
Uric Acid		Harrison- Principles of internal Medicine 17th Ed., 2008.
Hyperuricemia	>408 µmol/L and <=408 µmol/L at baseline	Two independent criteria
Hypouricemia	<120 µmol/L and >= 120 µmol/L at baseline	
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride		Two independent criteria
Hypochloremia	<80 mmol/L and baseline ≥ 80 mmol/L	
Hyperchloremia	>115 mmol/L and baseline ≤ 115 mmol/L	
Sodium		Two independent criteria
Hyponatremia	≤129 mmol/L and baseline > 129 mmol/L	
Hypernatremia	≥160 mmol/L and baseline <160 mmol/L	
Potassium		FDA Feb 2005.
Hypokalemia	<3 mmol/L and baseline ≥ 3 mmol/L	Two independent criteria
Hyperkalemia	≥5.5 mmol/L and baseline <5.5 mmol/L	

Parameter	Treatment Emergent PCSV	Comments
Glucose		
Hypoglycaemia	(≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	ADA Jan 2008.
Albumin	≤25 g/L and >25 g/L at baseline	
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black);	Increase in WBC: not relevant.
	<2.0 Giga/L and >=2.0 Giga/L at baseline (Black)	
	≥16.0 Giga/L and < 16 Giga/L at baseline	To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	

Parameter	Treatment Emergent PCSV	Comments
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).

Parameter	Treatment Emergent PCSV	Comments
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 v/v and > 0.32 v/v at baseline forFemale ≥0.55 v/v and < 0.55 v/v at baseline for Male ; ≥0.5 v/v and < 0.5 v/v at baseline for Female	Two Criteria are independent
RBC	Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs		

Parameter	Treatment Emergent PCSV	Comments
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension	Su SBP < 160 mmHg - SBP St – Su ≤ - 20 mmHg DBP St – Su ≤ - 10 mmHg Su SBP ≥ 160 mmHg – SBP St – Su ≤ - 30 mmHg DBP St – Su ≤ - 15 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

Parameter	Treatment Emergent PCSV	Comments
ECG		Ref.: CPMP 1997 guideline. ICH E14 2005
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms & < 120 ms at baseline	
QTc	Absolute values (ms) >450 ms and baseline <=450 ms >480 ms and baseline <=480 ms >500 ms and <= 500 ms at baseline Increase from baseline Increase from baseline 30-60 ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula. ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.