NCT03285646

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol 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**
Compound:	**REGN475**
Protocol Number:	**R475-PN-1612**
Sponsor:	**Regeneron Pharmaceuticals, Inc.**
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Clinical Trial Manager (CTM):	[redacted]
Medical Director (MD):	[redacted]
Version/Date:	**1.0 / 29Nov2018**

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AA	Adjudicated arthropathy
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
ARGUS	Pharmacovigilance and clinical safety software system
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
BPI-sf	Brief Pain Inventory-short form
C_{max}	Maximum observed drug concentration
CLBP	Chronic low back pain
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
C_{trough}	Concentration measured at the end of a dosing interval at steady state (taken directly before next administration)
DA	Destructive arthropathy
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQoL 5 Dimensions 5 Level Questionnaire
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HCRU	Healthcare Resource Utilization
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation

IRB	Institutional Review Board
IVRS	Interactive voice response system
JR	Joint replacement
K-L	Kellgren-Lawrence
LBP	Low back pain
LBPI	Low back pain intensity
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measure
MOS Sleep-R	Medical Outcomes Study Sleep Scale Revised
MRI	Magnetic resonance imaging
NGF	Nerve growth factor
NRS	Numeric Rating Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PCSV	Potentially clinically significant value
PGA	Patient Global Assessment
PK	Pharmacokinetic
PPS	Per protocol set
PT	Preferred term
Q4W	Every 4 weeks
Q8W	Every 8 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RMDQ	Roland Morris Disability Questionnaire
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SF-36	36-item Short Form Survey

SNS	Sympathetic nervous system
SOC	System organ class
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
TrkA	Tyrosine kinase type 1
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WPAI-LBP	Work Productivity and Activity Impairment-Low Back Pain

1. OVERVIEW

The purpose of the Statistical Analysis Plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the definitions and statistical methods to be used in the analysis of data for study R475-PN-1612.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. These revisions will be based on blinded review of the study and data, and a final plan will be issued prior to database lock and before unblinding of the study.

1.1. Background/Rationale

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 Chronic Low-Back Pain (CLBP).

The target population for the study are patients who have inadequate CLBP relief with acetaminophen/paracetamol, and who are unable tolerate or have inadequate CLBP relief with NSAIDs and opioids (or unwilling to take opioids) and who have inadequate CLBP relief from non-pharmacologic management. The target population for this study will also have concomitant radiographically confirmed OA of the knee or hip.

An unplanned interim analysis in the R475-PN-1524 study in patients with non-radicular CLBP showed evidence of efficacy with improvement in LBPI NRS pain scores in all fasinumab groups (6mg SC Q4W, 9 mg SC Q4W and 9 mg IV Q8W) compared to placebo at the 8 and 12-week timepoints.

At the time the protocol for this study was written, the maximum fasinumab dosages being evaluated in the OA program were 3mg SC Q4W and 6mg SC 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 6mg Q8W dose was expected to achieve similar AUC to that of the 3mg Q4W dose.

Therefore, in this target population of patients with CLBP with concomitant OA of the knee or hip, the 3mg SC Q4W dose or matching placebo was chosen as the dose regimen under study since 3mg was considered the maximum dose expected to be tolerable in CLBP patients who also had OA.

On May 3, 2018, following the independent and multidisciplinary fasinumab Data Monitoring Committee (DMC) review, the DMC recommended based on the risk benefit assessment of the entirety of the available data that higher dose regimens (3mg Q4W and 6mg Q8W) of fasinumab be discontinued across the OA program. As a result of this decision, dosing in this R475-PN-1612 evaluating the 3mg SC Q4W dose in patients with moderate-to-severe non-radicular CLBP who have radiographically confirmed OA of the knee or hip was discontinued for all patients who were still on study drug and the study was closed to enrollment.

At the time of the study drug discontinuation, 63 patients had been randomized into the study. Patients will be encouraged to remain in the study and be followed for the off-treatment period study visits until completion of the study to continue to monitor safety for patients that were randomized.

1.2. Study Objectives

1.2.1. Primary Objectives

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.

1.2.2. 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

1.2.3. 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

1.2.4. Modifications from the Statistical Section in the Final Protocol

The following lab safety endpoint is not listed in the statistical section of the protocol but is included in the analysis plan:

- High-sensitivity C-reactive protein (hs-CRP)

1.2.5. 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, 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.

Approximately 1020 patients were to be randomized in a 1:1 ratio to one of the following treatment groups:

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

Randomization is stratified by geographical region (Europe, North America, Other), 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.

Due to the recommendation of the DMC, dosing has been discontinued in this study. At the time of study drug discontinuation for all patients, sixty-three patients had been randomized.

This statistical analysis plan reflects this change in dosing as a result of the IDMC recommendation.

2.2. Sample Size and Power Considerations

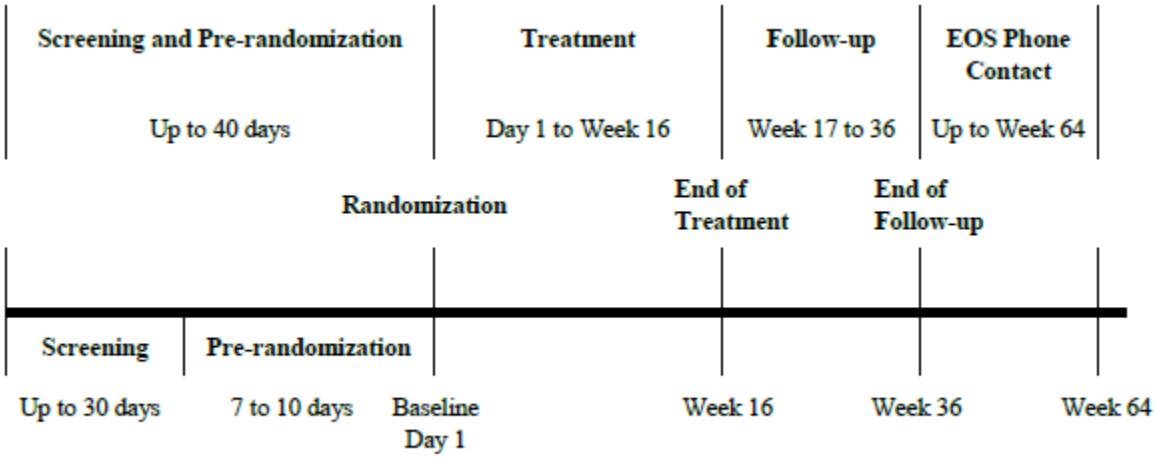
Approximately 1020 patients were to be randomized in a 1:1 ratio to either fasinumab (3mg Q4W) or placebo. Assuming a 2-sided alpha level of 0.05 and a 20% dropout rate at week 16, an enrolment of 510 patients per arm will provide 90% power to detect an effect size of 0.23 in the daily average LBPI NRS score (i.e., 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.

2.3. Study Plan

Study Visits

The study consists of a screening period of up to 30 days (Screening Period), followed by a 7 to 10 day pre-randomization period (Pre-Randomization Period), a 16-week randomized, double-blind, placebo-controlled treatment period (Treatment Period), a 20-week follow-up period, and an end of study phone contact at 52 weeks following the last dose of study drug to determine whether a joint replacement (JR) has been conducted or is scheduled (or the patient is on a waiting list). See Figure 1 for the Study Flow Diagram.

Figure 1: Study Flow Diagram



EOS- End of study

The Schedule of Events table is presented in Appendix 11.1.

Prior to randomization, patients will undergo screening procedures. 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 study-provided rescue medication (acetaminophen/paracetamol) will be discontinued. Paracetamol/acetaminophen must not be taken within 24 hours prior to the randomization visit.

Following randomization (day 1), patients will enter into the treatment phase of the study during which study drug will be administered at scheduled visits and patients are permitted to use only acetaminophen/paracetamol as rescue medication. Use of acetaminophen/paracetamol is prohibited within 24 hours prior to the start of the study visits to minimize the confounding effects of the rescue medication on efficacy measurements. During the treatment period, efficacy and safety assessments will be performed at each study visit as outline in the schedule of events.

At the end of the 16-week treatment period, follow-up of patients will continue for an additional 20-weeks after the last treatment visit. Safety and efficacy assessments will be performed as outlined in the schedule of events.

Phone contact will be made approximately 52 weeks after administration of the last dose of study drug to document patient status with regards to JR surgery (if a patient underwent, is schedule for, or is on a waitlist for JR surgery).

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

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following populations will be used for all statistical analyses.

3.1. Full Analysis Set (FAS)

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.

3.2. The Safety Analysis Set (SAF)

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.

3.3. The Pharmacokinetic (PK) 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.

3.4. The Anti-Drug Antibody (ADA) 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.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (e.g. age, sex, race, ethnicity, weight, height, etc.), disease characteristics including Maximum Kellgren-Lawrence score for any knee or hip joint at screening, baseline LBPI NRS Score, Duration of CLBP, geographical region, medical history, and medication history for each patient.

The following demographic and baseline characteristic variables will be summarized by treatment group:

- Age at screening (years)
- 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 or Latino, Not Hispanic or Latino, Not Reported)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) calculated from weight and height
- Geographical region (Europe, North America, Other)
- Baseline LBPI NRS score
- Baseline LBPI NRS score strata (<7, ≥7)
- Maximum K-L score for any knee or hip joint at screening per IVRS/IWRS (2-3, 4)
- Maximum K-L score for any knee or hip joint at screening
- Duration of CLBP at baseline strata (<5 years, ≥5 years)
- Duration of CLBP (years)
- History of analgesic intolerance and inadequate pain relief

Additional baseline characteristics will be summarized as needed.

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®).

4.3. Prior, Concomitant, and Prohibited Medications and Procedures

Medications and Procedures will be recorded from the day of informed consent until the End of Follow-up Clinic Visit. Medications will be coded to the Anatomical Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Medication and Procedure Classifications

Prior medications and procedures are defined as medications or procedures starting prior to the first dose of study drug.

Concomitant medications or procedures are defined as medications or procedures starting prior to or during the on-treatment period (as defined in Section 5.9) **AND** ending during or after the on-treatment period.

Post treatment medications or procedures are medications or procedures starting after the on-treatment period (as defined in Section 5.9).

Prohibited Medication

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 the prohibited medications containing NSAIDs is provided in Appendix 11.3.

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

4.4. Efficacy Variables

4.4.1. Primary Efficacy Variable(s)

The primary efficacy endpoint assessed for the study is:

- Change from baseline to week 16 in the average daily LBPI NRS Score

4.4.2. Secondary Efficacy Variable(s)

The secondary efficacy endpoints assessed for the study are:

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

4.4.3. Exploratory Efficacy Variable(s)

The exploratory efficacy endpoints to be assessed in the efficacy are:

- Change from baseline to week 16 in MOS Sleep-R Subscale Scores
- Change from baseline to week 16 in the 36-item Short Form Survey (SF-36) Subscale Scores
- Change from baseline to week 16 in the EuroQoL 5 Dimensions 5 Level Questionnaire (EQ-5D-5L) Scores
- Percentage of patients who used rescue medication
- Change from baseline to week 16 in Work Productivity and Activity Impairment-Low Back Pain (WPAI-LBP) questionnaire
  - percent of work time missed due to CLBP
  - percent of impairment while working due to CLBP
  - percent of overall work impairment due to CLBP
  - percent activity impairment due to CLBP
- Change from baseline to week 16 in the WOMAC pain subscale score

4.5. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, ECG, Survey of Autonomic Symptoms Questionnaire, neurological exams and physical exams. Unless otherwise noted, the baseline value is defined as the last available value before the first dose of study drug.

Adverse events (AE) and Serious Adverse Events (SAE) will be collected from the time of informed consent signature and then at each visit until the End of Follow-up Clinic Visit. All AEs are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class SOC" according to the MedDRA® (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 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.

4.5.1. Safety Variables

The safety endpoints in the study are:

- Incidence of Adjudicated Arthropathy (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 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

The raw incidence rate is defined as the number of events divided by the duration of the observation period and presented as number of events per 100 patient-years.

Additional safety endpoints that may be evaluated include:

- Survey of Autonomic Symptom scores from baseline to week 16 and from baseline to week 36

4.5.2. 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.

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

Events considered to be AESIs for the study are:

- Adjudicated arthropathy (as confirmed by adjudication)
- Sympathetic nervous system dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist)
- Peripheral sensory AEs that require a neurology or other specialty consultation
- JR surgery (AESI defined in Protocol Section 9.6.1.4 as elective JR surgery not due to new or worsening disease)

4.5.3. Laboratory Safety Variables

The clinical laboratory tests include blood chemistry, hematology, urinalysis, urine chemistries, hs-CRP, and others. Samples for laboratory testing will be collected at the time points specified in the Schedule of Events (Appendix 11.1). Clinical laboratory values will be in standard international (SI) units, including associated normal ranges provided by the central laboratory, and grouped by function in summary tables. Clinical laboratory values in conventional (US) units will also be available in the database, with associated normal ranges.

Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in central lab result summaries. Potentially clinically significant values (PCSV) ranges will be applied to central lab test values as applicable (see Appendix 11.2 for PCSV definitions).

4.5.4. Biomarker variables

Biomarker analysis will be performed in a separate biomarker SAP.

4.5.5. Vital Signs

Vital Sign parameters include:

- Body temperature (°C)
- Supine/standing/orthostatic systolic and diastolic blood pressures (mmHg) and pulse (bpm)
- Respiratory rate (bpm)

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 11.2 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 or 3-minute standing systolic blood pressure of ≥20 mmHg or a decrease in the standing diastolic blood pressure of ≥10 mmHg from the supine systolic or diastolic blood pressure

OR

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

OR

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

OR

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

Confirmed orthostatic hypotension is defined as initial assessment meeting the above orthostatic hypotension criteria confirmed by subsequent repeated assessments per protocol or if initial assessment met the above orthostatic hypotension criteria yet repeated assessments were not performed.

4.5.7. 12-Lead Electrocardiography

Standard12-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 corrections are defined as follows:

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 minute.

Potentially clinically significant values (PCSV) ranges will be applied to the ECG parameter values as applicable (see Appendix 11.2 for PCSV definitions).

4.5.8. Physical and Neurological Examination Variables

Physical examination assessments will be described as normal or abnormal for each body system examined. Neurological evaluations of specific domains as listed in the protocol will be described as normal or abnormal.

4.5.9. Other Safety Variables

- Joint Pain Questionnaire:
  - Number of subjects with significantly worse joint pain in any joint at each scheduled visit
  - Number of subjects with significantly worse joint pain by joint at each scheduled visit
- Joint space width for specified joints at each scheduled visit.
- Joint replacement:
  - number and percentage of patients with joint replacement (all JRs)

4.6. Pharmacokinetic Variables

The Pharmacokinetic (PK) variable will be fasinumab concentrations in serum at specified sampling time points.

4.7. Anti-Drug Antibody Variables

Samples for Anti-Drug Antibody (ADA) evaluation will be collected at baseline and at subsequent study visits.

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

- Total subjects negative in the ADA assay at all time points analyzed
- Pre-existing immunoreactivity - a positive ADA response at baseline with all post-dose ADA results negative, or a positive ADA response at baseline with all post-dose ADA responses less than 9-fold over baseline titer levels.
- Treatment emergent - defined as any post-dose positive ADA response when baseline results are negative
  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
  - Indeterminate - A positive result in the ADA assay at the last collection time point analyzed only, regardless of any missing samples
  - Transient - Not persistent or indeterminate regardless of any missing samples
- Treatment boosted - defined as any post-dose positive ADA response that is at least 9-fold over the baseline level when baseline is positive in the ADA assay
- Titer Values
- Titer category: low (titer <1,000); moderate (1,000≤ titer ≤10,000); high (titer >10,000)
- Neutralizing ADA activity for samples positive in the ADA assay

5. STATISTICAL METHODS

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

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 based on the FAS. Parameters to be summarized include those described in Section 4.1.

5.2. Medical History

Medical history will be descriptively summarized by treatment group and overall for the FAS. Summaries will show patient counts (percentages) by primary SOC and PT. The tables will be sorted by decreasing frequency of primary SOC in the fasinumab group. Within each primary SOC, PTs will be sorted by decreasing frequency in the fasinumab group.

5.3. Prior and Concomitant Medications

Prior Medications

All prior medications, dictionary coded by WHO, will be descriptively summarized by treatment group based on the FAS. Summaries will present patient counts (and percentages) for all prior medications, by decreasing frequency of the fasinumab group incidence of ATC followed by ATC level 2, ATC level 4 and preferred term. In case of equal frequency across anatomic or therapeutic categories, alphabetical 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.

Concomitant Medications

All concomitant medications, dictionary coded by WHO, will be descriptively summarized by treatment group based on the SAF. Summaries will present patient counts (and percentages) for the concomitant medication groups described in Section 4.3 for all concomitant medications, by decreasing frequency of the fasinumab group incidence of ATC followed by ATC level 2, ATC level 4 and preferred term. In case of equal frequency across anatomic or therapeutic categories, alphabetical 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

When medication start/end date is missing, the rules for determining whether a medication is prior, concomitant, or post-treatment, are specified in Section 6.3.

5.4. Prohibited Medications

Number and percentage of patients with prohibited medications will be descriptively summarized by treatment group based on the SAF. The tables will be sorted by decreasing frequency of ATC Level 2, ATC Level 4, and preferred term in the fasinumab group.

The number of patients with NSAID use during the treatment period will be summarized by treatment group based on the SAF.

Total NSAIDs-use days during the treatment period and within 16 weeks after last study drug administration (before AA for patients with AA) will be summarized by treatment group for patients in the SAF.

5.5. Patient Disposition

The disposition of patients in the study will be summarized by treatment group and overall for FAS.

5.5.1. Screening Disposition

Percentages will be calculated using the number of screened patients as the denominator.

- Screened patients (defined as having signed the ICF).
- Patients randomized (defined in the protocol as having received a randomization number per IVRS).
- Patients did not meet inclusion/exclusion criteria but randomized (if applicable).
- Patients treated but not randomized (if applicable).
- Screen Fail patients. Reason for screen failure will be provided.

Additionally, the following listings will be provided (if applicable):

- Listing of Patients Treated but not Randomized.
- Listing of Screening Failures and reasons for all screen failed patients.

5.5.2. Treatment and Study Disposition

Unless otherwise noted, percentages will be calculated using the number of patients in FAS as the denominator. This will be summarized by treatment group and overall for the study. Summaries will provide the frequency (and percentage as applicable) of patients that met the criteria for the following variables:

- Patients randomized (defined as having received a randomization number). This row will reflect grouping based on randomization assignment.

- Patients randomized but not treated. This row will reflect grouping based on randomization assignment.
- Patients randomized and treated.
- Patients who completed study treatment, patients who discontinued treatment and reason for treatment discontinuation.
- Patients who completed the study, patients who withdrew from the study and reason for study withdrawal.

Additionally, the following listings will be provided (if applicable):

- Listing of Patients Randomized but not Treated.
- Listing of Patients Randomized but not Treated with the Randomized treatment.
- Listing of Patient Disposition for all Randomized Patients.

5.5.3. Analysis Set

Summary of the number (and percentage) of patients in each analysis set will be presented by treatment group and overall.

5.6. Extent of Study Treatment Exposure and Compliance

The analysis population is based on the SAF.

5.6.1. Measurement of Treatment Compliance

Compliance with protocol-defined investigational product will be calculated by treatment group as follows:

$$\frac{Number\ of\ actual\ injections\ of\ study\ drug\ received\ during\ the\ treatment\ expsoure\ period}{Number\ of\ planned\ injections\ of\ study\ drug\ during\ the\ treatment\ exposure\ period\ on\ or\ beforethe\ time\ that\ the\ patient\ discontinued\ from\ the\ treatment\ phase\ of\ the\ study} \ x\ 100$$

Treatment compliance will be presented by the descriptive statistics and the number (%) of patients who have 1, 2, 3, and 4 SC injections will be displayed.

5.6.2. Exposure to Investigational Product

The duration of treatment exposure to fasinumab and placebo SC doses will be calculated as:

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

The duration of exposure 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 duration periods will be presented by specific time periods. The time periods of interest are specified as: ≥ 1 day, ≥ 29 days, ≥ 57 days, ≥ 85 days, and ≥ 113 days.

5.6.3. Length of Study Observation

The length of the observation period (days) will be calculated as:

- (Date of last study visit [up to End of Follow-up Clinic Visit] – date of first study drug dose) +1.

The observation duration 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 observation periods will be presented by specific time periods. The time periods of interest are specified as: ≥ 1 day, ≥ 29 days, ≥ 57 days, ≥ 85 days, ≥ 113 days, ≥ 141 days, ≥ 169 days, ≥ 197 days, ≥ 225 days, ≥ 253 days, and ≥ 449 days

5.7. Protocol Deviations

All major and minor protocol deviations are collected and reviewed on an ongoing basis throughout the study as described in the Protocol Deviation Definitions Document (PDDD).

Protocol deviations will be summarized for patients incurring any major deviation by count and percentage, and patients incurring each type of major deviation by count and percentage for FAS.

A patient listing of all major and minor protocol deviations will be provided.

5.8. Analysis of Efficacy Data

As a result of the DMC recommendation resulting in treatment discontinuation for all patients, no hypothesis testing will be conducted. The analysis of efficacy data will be descriptive based on the FAS by treatment group.

5.8.1. Analysis of Primary Efficacy Variable(s)

5.8.1.1. Primary Efficacy Analysis

The primary efficacy endpoint in the study is:

- Change from baseline to week 16 in the average daily LBPI NRS Score

Primary efficacy data will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics based on the FAS by treatment group.

No sensitivity analyses will be performed for the primary efficacy variable.

5.8.2. Analysis of Additional Efficacy Variable(s)

Analyses of continuous efficacy endpoints will use the same analysis method as the primary efficacy variable.

For analysis of categorical efficacy endpoints, e.g., proportions of patients with ≥30% reduction from baseline to week 16 in the daily average LBPI NRS score, the Cochran Mantel Hanszel approach stratified by the randomization strata will be used with missing data considered as non-response.

Rescue Medication

The percentage of patients who use rescue medication between baseline and week 16 will be summarized by the treatment group using the FAS.

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 by treatment group.

5.9. Analysis of Safety Data

The analysis of safety and tolerability will be performed on the SAF, as defined in Section 3.2.

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs, 12-lead ECG, Physical Examination, etc.).

Treatment-Emergent Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Appendix 11.2.

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

- The pre-treatment period is defined as the time between when the patients give informed consent and the start of study drug.
- The on-treatment period is defined as the time from first dose of study drug up to 28 days after the last dose of study drug.
- The post-treatment period is defined as the time starting 29 days after last dose of study drug (after the on-treatment period) to up to 24 weeks post the last dose of study drug (up to week 36).

Day 1 is the first day of study drug, Day –1 is the day before Day 1, and there is no Day 0.

The time interval to detect any on-treatment event or abnormality is between the first dose of double-blind study drug injection and the end of treatment plus 28 days. Data collected outside this interval will be excluded from the on-treatment estimation of descriptive statistics and identification of abnormalities for laboratory evaluations, ECGs and vital signs. All post-baseline data during the interval will be used in the PCSV analysis including scheduled and unscheduled assessments.

5.9.1. Safety Endpoints

Raw incidence rates will be summarized by treatment group based on the SAF.

5.9.2. Adverse Events

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

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

- *Treatment-Emergent Adverse Events (TEAE)* are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.
- *Post-Treatment Adverse Events* are defined as AEs that developed or worsened more than 28 days after the last dose of study drug.

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

Summaries of TEAEs by treatment group will include:

- Overview of TEAEs, summarizing number of events, summarizing number and percentage of patients within the specified category
  - Total number of TEAEs
  - Total number of Serious TEAEs
  - Patients with any TEAEs
  - Patients with any Serious TEAEs
  - Patients with any TEAEs leading to death
  - Patients with any TEAEs leading to withdrawal from study
  - Patients with any TEAEs leading to permanent study treatment discontinuation
- All TEAEs by SOC and PT
- All TEAEs by SOC, PT, severity
- Study drug related TEAEs by SOC and PT
- TEAEs resulting in Permanent Study Drug Discontinuation by SOC and PT
- AESI by SOC and PT
- Serious TEAEs by SOC and PT

Listing to include:

- Listing of AEs leading to death
- Listing of TEAEs leading to permanent study treatment discontinuation
- Listing of TEAEs leading to withdrawal from study
- Listing of Patients with Serious TEAEs
- Listing of Patients with AESIs
- Listing of all Joint Replacements

Counts will be provided according to treatment group for each PT within each primary SOC. Percentages will be calculated based on the SAF in each treatment group.

Primary SOCs will be sorted by decreasing frequency in the fasinumab group. Within each primary SOC, PTs will be sorted by decreasing frequency in the fasinumab group. For tables presenting severity of events, the worst severity will be chosen for patients with multiple instances of the same event.

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

5.9.3. Adverse Events of Special Interest

AESIs will be listed and summarized by treatment group based on the SAF.

Radiograph data related to AA including change from baseline in joint space width will be summarized by SAF over time.

Knee Society Score questionnaire or Harris Hip Score questionnaire results will be listed if applicable.

5.9.4. Clinical Laboratory Measurements

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics based on the SAF by treatment group.

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

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

A Treatment-Emergent Potential Clinically Significant abnormal value (PCSV) is a laboratory value that was normal at Screening and Baseline but became abnormal and met PCSV criteria after treatment with study drug. Definition of PCSV is listed in Appendix 11.2. Treatment Emergent Potentially clinically significant values (PCSVs) will be summarized based on the SAF by treatment group. Additional exploratory analyses using alternative cut-points may be conducted.

For hs-CRP, plots of means and medians of the observed values and change from baseline over time will presented by treatment group.

5.9.5. Analysis of Vital Signs

Vital signs (temperature, pulse, blood pressure, orthostatic blood pressure/heart rate, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics by treatment group and combined fasinumab for the SAF.

PCSV summary including orthostatic hypotension will be summarized.

5.9.6. Analysis of 12-Lead ECG

ECG parameters (Ventricular Rate, PR Interval, QRS Interval, QT Interval, RR Interval, QTcF QTcB interval) will be summarized by baseline and change from baseline to each scheduled

assessment time. PCSV summary of ECG parameters will be provided for on-treatment period, follow-up period, and overall for the SAF.

ECG status (i.e. normal, abnormal) will be reported. Shift tables will be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal) by treatment.

5.9.7. Physical Exams

The number and percentage of patients with new-onset abnormal physical examinations will be summarized by body system by visit based on the SAF.

5.9.8. Joint Pain Questionnaire

The number and percentage of patients with significantly worse joint pain will be summarized by visit and joint based on the SAF.

5.9.9. Arthropathy Adjudications

The number and percentage of patients with images requiring arthropathy adjudication as well as the number and percentage of those patients with confirmed adjudicated arthropathy will be summarized based on the SAF. Subtypes of AAs and outcomes of AAs will also be summarized. Patient listings of cases confirmed by adjudication will be provided.

5.9.10. Neurological Exam

The number and percentage of patients with new-onset abnormal neurological examinations will be summarized by Neurological evaluations by visit based on the SAF.

5.9.11. Analysis of Pharmacokinetics and Drug Concentration Data

Summaries of concentrations of functional fasinumab will be presented by nominal time point and dose. Plots of mean or median concentration of functional fasinumab will be presented by nominal day and dose.

5.9.12. Analysis of Anti-Drug Antibody Data

The ADA variables described in Section 4.7 will be summarized using descriptive statistics by dose/cohort group in the ADA analysis set. Prevalence of treatment-emergent and treatment-boosted ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts. For treatment emergent ADA, occurrence (N) and percent of patients (%) with persistent, transient and indeterminate ADA will be reported. The influence of treatment-emergent or treatment-boosted ADA assay response on individual PK profiles may be evaluated.

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

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 treatment-emergent ADA positivity status, 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.

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

6.1. Definition of Baseline for Variables

Unless otherwise specified, the baseline assessment for all efficacy measurements/ patient reported outcomes will be the latest available valid measurement prior to or on the day of randomization. Baseline for safety assessments such as labs, ECGs, vital signs etc. will be the latest assessment prior to the start of treatment.

6.2. Data Handling Conventions for Patient reported Outcomes data

LBPI NRS

Baseline Average daily LBPI NRS score is defined as the average of the non-missing daily LBPI NRS scores for 7 days prior to randomization (from Day -6 to Day 1). Average daily LBPI NRS scores is calculated using the non-missing entries of the days as defined in the visit window mapping for electronic diaries in Section 6.4.

RMDQ

The total score of the RMDQ is the total number of items checked by the patient (range of 0 to 24, with lower scores indicative of better function). The score can therefore vary from 0 to a maximum value of 24.

PGA LBP

The PGA LBP is a patient assessed 5-point Likert scale of LBP (1=very well; 2=well; 3=fair; 4=poor; and 5=very poor).

BPI-sf

The BPI-sf pain interference domain is a measure of how much pain has interfered with seven daily activities (items 9A-9G) including general activity, walking, normal work, mood, enjoyment of life, relations with others and sleep. The BPI-sf pain interference score is measured as the mean of the seven interference items.

WPAI-LBP

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes as follows:

Questions:

1 = Currently employed?

2= hours missed due to LBP

3= hours missed due to other reasons

4= hours actually worked

5= degree LBP affected productivity while working

6= degree LBP affected regular activities

Scoring for the WPAI is as follows:

Percent work time missed due to LBP = $Q2 / Q2 + Q4$

Percent impairment while working due to problem = $Q5 / 10$

Percent overall work impairment due to problem = $Q2 / (Q2 + Q4) + \left[\left(1 - \frac{Q2}{Q2+Q4}\right) x \left(\frac{Q5}{10}\right)\right]$

Percent activity impairment due to problem = $Q6 / 10$

Multiply scores by 100 to express as a percentage

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 responded answers at least 50% of items in that scale. The missing items in the scale will be imputed by the mean of the 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 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.

Western Ontario and McMaster osteoarthritis index (WOMAC)

WOMAC scores will be computed when one pain item, one stiffness item, or at most 3 physical function items are missing. The missing items will be imputed by the mean of available items within the same subscale. The scores will be set to missing if more items are missing.

HealthCare Resource Use (HCRU) Questionnaire

HCRU include the following categories

1. Use of walking aid over the past 8 weeks
2. Healthcare office visits over the past 8 weeks
    a. Any use

b. # of use
c. Any use related to OA
d. Any use related to CLBP
e. # of use related to OA
f. # of use related to CLBP

3. Emergency department (ED) visit over the past two months
   a. Any ED visits
   b. # of ED visits
   c. Any ED visit related to OA
   d. Any ED visit related to CLBP
   e. # of ED visits related to OA
   f. # of ED visits related to CLBP
4. Hospitalization visit
   a. Any hospitalization
   b. # of hospitalization
   c. Length of hospitalization
   d. # of hospitalization related to OA
   e. # of hospitalization related to CLBP

Treatment Satisfaction Questionnaire for Medication (TSQM)

TSQM Scale scores computed by adding the items loading on each factor. The lowest possible score is subtracted from this composite score and divided by the greatest possible score minus the lowest possible score. This provided a transformed score between 0 and 1 that should be multiplied by 100. (see below) *[Note that only one item may be missing from each scale before the subscale should be considered invalid for that respondent]*

- **EFFECTIVENESS**

([(Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100

If one item is missing

([(Sum(Item 1? + Item 2? + Item 3?)) – 2] divided by 12) * 100

- **SIDE-EFFECTS**

If Question 4 is answered 'No' then score = 100

Else…

([Sum(Item 5 to Item 8) – 4] divided by 16) * 100

If one item is missing

([(Sum(Item5? to Item8?)) – 3] divided by 12) * 100

- **CONVENIENCE**

([Sum(Item 9 to Item 11) – 3] divided by 18) * 100

If one item is missing

([(Sum(Item9? to Item11?)) – 2] divided by 12) * 100

- **GLOBAL SATISFACTION**

([Sum(Item 12 to Item 14) – 3] divided by 14) * 100

If either Item 12 or 13 is missing

([(Sum(Item12? to Item14?)) – 2] divided by 10) * 100

If Item 14 is missing

([(Sum(Item12 and Item13)) – 2] divided by 8) * 100

Beck Depression Inventory – II (BDI-II)

The BDI-II total score is a sum of each of the 21 items rated on a 4-point scale ranging from 0 to 3 based on the severity of each item. The maximum total score is 63. Total Score of 0-13 is considered minimal range; 14-19 is mild; 20-28 is moderate, and 29-63 is severe depression.

Assessment of Peripheral vs. Central Pain

The instrument assesses widespread pain as well as symptom severity. Widespread pain is a sum of the areas in which pain is indicated with a score ranging from 1- 19. Symptom severity is a measured on a scale of 1-12 by assigning points to responses according to the following rule:

No problem – 0 points; Slight or Mild Problem – 1 point; Moderate problem- 2; Severe problem -3;

And assigning a point of 1 to responses of 'Yes' for questions with a 'Yes'/'No' answer.

6.3. General Data Handling Conventions

Date of first/ last dose of study treatment

The date of first injection is the first non-missing start date of dosing recorded in the eCRF.

The date of the last injection is equal to the last date of administration reported on injection administration case report form page or missing if the last administration date is unknown.

Handling of Adverse Event and Injection Site Reaction Severity and relatedness

If the severity of a TEAE is missing, it will be classified as "severe" in the frequency tables by severity of TEAEs.

If the assessment of relationship of a TEAE to the study drug or study conduct is missing, it will be classified as "related" to the investigation product.

Handling of Missing/Incomplete AE/Concomitant Medication dates

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 (e.g., month and year) clearly indicates that the event started prior to treatment. Thus, if the AE does not clearly indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as "treatment-emergent". This is for classification purposes in the frequency tables and will not be used in the listings.

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 are present, missing AE/concomitant medication end date will be imputed to the last day of the month.

There will be no attempt to impute completely missing AE/concomitant medication end dates. Events with an end date missing will be assumed to be ongoing at the time of data cut off.

Handling of Adverse Events classification with missing or partial date/time of first study drug administration

When the date and time of first study drug dose is missing, the date of randomization will be used as the start date for classification of AEs.

When the time of the first study treatment dose is missing, all AEs that occurred on the date of the first study drug dose will be considered as TEAEs.

Missing/Incomplete Medical history dates

Medical history start dates are used to determine the duration of OA 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.

Laboratory Safety Variables below LLOQ or above ULOQ

For central laboratory data below the lower limit of quantification (LLOQ), half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses.

Missing laboratory, ECG, vital sign, physical exam, neurological exam

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

Handling of Potentially Clinically Significant Abnormalities (PCSA)

If a patient has a missing baseline value they will be grouped in the category "normal/missing at baseline".

For PCSAs with 2 conditions, one based on a change from baseline value and the other on a threshold value or a normal range, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; e.g., for eosinophils the PCSA is >0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

6.4. Visit Windows

By-visit analysis (including efficacy, laboratory data, vital signs, ECG, ADA) will be summarized by the nominal visit number. 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 Unscheduled, 'EOT Week 16', and 'EOS Week 64' assessments, a visit number will be assigned based on the actual visit date using the study day analysis window based on the targeted visit study day in Appendix 11.1 Table 2 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:

Table 1: Visit Windows

Visit No.	Visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	Day -30 to Day -11	≥ -30 and ≤ -11
2	Pre-randomization Phone Call	Day -10 to -7	-10 to -1
3	Baseline#	1	1
4	Week 1	8	[2, 11]
5	Week 2	15	[12,20]
6	Week 4	29	[21,43]
7	Week 8	57	[44,71]
8	Week 12	85	[72,99]
9	Week 16	113	[100,127]
10	Week 20	141	[128,155]
11	Week 24	169	[156,183]
12	Week 28	197	[184,211]
13	Week 32	225	[212,239]
14	Week 36	253	[240,267]
15	Week 64	449	[436,456+]

*Study days are calculated from the first dose of study drug (Day 1).
Baseline for the LBPI electronic diary entry will be mapped from day -7 to day 1.

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

- When multiple valid measurements occur within the same visit window, the one 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.

6.5. 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, unscheduled visit will be mapped to a visit using the visit windows described in Section 6.4 and then included in the by-visit summaries.

7. TIMING OF STATISTICAL ANALYSES

The analyses will be performed based on two different database locks:

- **Week 36 Analysis:** takes place when the last patient completes the last safety follow-up visit and includes all patient data collected up through the week 36 visit. The efficacy and safety analyses will be conducted at this time.
- **Week 64 analysis:** takes place when the patient data collected up to the time the last patient completes assessments at week 64 phone call. The only additional analysis to be conducted at this time is the analysis of incidence of JRs at the telephone survey approximately 52 weeks after the last dose of study drug and updating of outputs with any data change from the Week 36 Analysis.

8. INTERIM ANALYSES

No interim efficacy analysis is planned.

9. SOFTWARE

All clinical data analyses will be done using SAS Version 9.4 and above.

10. REFERENCES

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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.

11. APPENDIX

11.1. Schedule of Events and Visits

Study assessments and procedures are presented by study period and visit in Table 2.

Table 2: 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							
MOS Sleep-R			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)**
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																

	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)**
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	
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

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 3). 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 3: 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

Footnotes for Table of 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.

11.2. Reference for Criteria for Treatment-Emergent Potentially Clinically Significant Values (PCSV)

The PCSV criteria below should be used as a reference; the actual criteria for each study should be determined and agreed to by the study team prior to database lock as part of SAP and should be based on the study population, indication, and potential effects of study treatment.

Table 4: Criteria for Treatment-Emergent Potentially Clinically Significant Values (PCSV)

Parameter	Treatment Emergent PCSV	Comments
Clinical Chemistry		
ALT*	>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
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
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin <=35% Total Bilirubin or Total Bilirubin <=1.5 ULN) at baseline	Conjugated bilirubin dosed on a case-by-case basis.
ALT/AST and Total Bilirubin	(ALT >3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN) (AST >3 ULN and TBILI>2 ULN) and baseline (AST <=3 ULN or TBILI <=2 ULN) (ALT >3 ULN and TBILI>1.5 ULN) and baseline (ALT <=3 ULN or TBILI <=1.5 ULN) (AST >3 ULN and TBILI>1.5 ULN) and baseline (AST <=3 ULN or TBILI <=1.5 ULN)	FDA DILI Guidance July 2009.
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.

Parameter	Treatment Emergent PCSV	Comments
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
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison - Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride Hypochloremia Hyperchloremia	 <80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hypernatremia	 ≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalaemia Hyperkalaemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.

Parameter	Treatment Emergent PCSV	Comments
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.
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.
HbA1c	>8% and <= 8% at baseline	
Albumin	≤25 g/L and >25 g/L at baseline	
hs-CRP	2 ULN or > 10 mg/L (if ULN not provided)	FDA Sept. 2005
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black) ≥16.0 Giga/L and < 16 Giga/L at baseline	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
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.

Parameter	Treatment Emergent PCSV	Comments
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).
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		
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.

Parameter	Treatment Emergent PCSV	Comments
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.
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	

Parameter	Treatment Emergent PCSV	Comments
QTc	Absolute values (ms) >450 ms and baseline <=450 ms >480 ms and baseline <=480 ms >500 ms and <= 500 ms at baseline	To be applied to any kind of QT correction formula.
	Increase from baseline Increase from baseline 30-60 ms Increase from baseline >60 ms	ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients' listings.

11.3. Prohibited Non-Steroidal Anti-Inflammatory Drug (NSAID) Medication List

Table 5 List of Prohibited Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Generic Name	Brand Name(s)
Aceclofenac	Hifenac, Cincofen, Nacsiv, Acenac
Amtolmetinum guacilum	Amtoril, Artricol, Artromed
Aspirin/acetyl salicylic acid*	Anacin, Ascriptin, Aspirin, Bufferin, Ecotrin, Excedrin,
Celecoxib	Celebrex
Choline and magnesium salicylates	CMT, Tricosal, Trilisate
Diclofenac potassium	Cataflam
Diclofenac sodium	Voltaren, Voltaren XR
Diclofenac sodium with misoprostol	Arthrotec
Diflunisal	Dolobid
Droxicam	
Etodolac	Lodine, Lodine XL
Etoricoxib	Acoxxel, Algix, Arcoxia, Exinef, Exxiv, Tauxib, Turox
Fenoprofen calcium	Nalfon
Flurbiprofen	Ansaid
Ibuprofen	Advil, Motrin, Motrin IB, Nuprin
Dexibuprofen	Atriscal, Cefalex VL, Detaran, Dolomagon, Fenextra, Seractil, Taflax, Xialox
Indomethacin	Indocin, Indocin SR
Ketoprofen	Actron, Orudis, Orudis KT, Oruvail
Ketorolac	Toradol
Magnesium salicylate	Arthritab, Bayer Select, Doan's Pills, Magan, Mobidin, Mobogesic
Meclofenamate sodium	Meclomen
Mefenamic acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Naprelan
Naproxen sodium	Aleve, Anaprox

Nimesulide	Actalide, Ainedix, Ainex, Algimesil, Algolider, Antalor, Aeuma, Aulin, Cimelide, Deflogen, Dimesul, Domes, Fansulide, Isodol, Ledoren, Medinex, Mesulid, Mifepex, Minesulin, Neosulida, Nerelid, Nidolon, Nimalox, Nimelide, Nimesil, Nimesilam
Oxaprozin	Daypro
Parecoxib	Dynastat, Rayzon, Valdyne
Piketoprofen	Calmatel, Picalm, Zemalex
Piroxicam	Feldene, Fexicam
Salsalate	Amigesic, Anaflex 750, Disalcid, Marthritic, Mono-Gesic, Salflex, Salsitab
Sodium salicylate	various generics
Sulindac	Clinoril
Tolmetin sodium	Tolectin

***Note: Up to 150 mg/day asprin/acetyl salicylic acid is permitted for cardiac prophylaxis.**

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ESig Approval	[redacted] 07-Dec-2018 19:58:41 GMT+0000
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