NCT03949673

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title:	Study to Evaluate Arthroplasty Specimens in the Phase 3 Fasinumab Program for Osteoarthritis of the Knee and Hip
Compound:	Fasinumab
Protocol Number:	R475-OA-1816
Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	Original Statistical Analysis Plan / 23NOV2020

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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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AA	Adjudicated arthropathy
DA	Destructive Arthropathy
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IWRS	Interactive Web Response Systems
K-L	Kellgren-Lawrence
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
Q4W	Every 4 weeks
Q8W	Every 8 weeks
RPOA-1	Rapidly Progressive Osteoarthritis Type 1
RPOA-2	Rapidly Progressive Osteoarthritis Type 2
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SIF	Subchondral Insufficiency Fractures
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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 strategy and statistical methods to be used in the analysis of data for R475-OA-1816 study.

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 data lock and before code breaking.

1.1. Background/Rationale

This is a non-randomized, exploratory study within the fasinumab phase 3 program. The parent studies for this study will be the ongoing fasinumab phase 3 studies, R475-PN-1523 (1-year treatment period), R475-OA-1688 (6-month treatment period), and R475-OA-1611 (2-year treatment period). These parent studies enroll patients with a clinical diagnosis of Osteoarthritis (OA) of the knee or hip based on the American College of Rheumatology criteria with radiologic evidence of OA (Kellgren-Lawrence [K-L] score ≥2) at the index joint at the screening visit. R475-OA-1688 has had a placebo arm, a fasinumab arm (1 mg every 4 weeks [Q4W]) and an non-steroidal anti-inflammatory drug (NSAID) arm (celecoxib 200 mg daily or diclofenac 75 mg twice per day). R475-OA-1611 has had a placebo arm, 2 fasinumab arms (1 mg Q4W, 1 mg every 8 weeks [Q8W]) and an NSAID arm (naproxen 500 mg twice per day). R475-PN-1523 has had a placebo arm and multiple fasinumab dosing arms (1 mg Q8W, 1 mg Q4W, 3 mg Q4W, 6 mg Q8W, 6 mg Q4W, and 9 mg Q4W).

Eligible patients for this study will be those participating in 1 of the parent studies and who subsequently plan to undergo a knee or hip joint arthroplasty during the parent study. Patients will consent to this study after notifying the site that they are planning a knee or hip joint arthroplasty. Patients who were discontinued from 3 mg Q4W or 6 mg Q8W fasinumab, [redacted] and entered the 20-week follow-up period of a parent study are eligible for this study if they undergo joint replacement before the end of the follow-up period.

1.2. Study Objectives

1.2.1. Objective

The objective of this exploratory study is to evaluate the cellular and connective tissue composition of joints from patients with OA who have been treated with fasinumab, compared with those treated with placebo or NSAIDs.

1.2.2. Modifications from the Statistical Section in the Final Protocol

NA.

1.2.3. Revision History for SAP Amendments

NA.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a non-randomized, exploratory study designed to evaluate changes in joint tissue of patients with OA of the knee or hip who are treated with fasinumab, compared with those who are treated with placebo or NSAIDs.

Patients will follow the screening and pre-randomization requirements for their parent study. If a patient decides to undergo a knee or hip joint arthroplasty during the parent study, he/she can consent to this study after notifying the site of his/her intended surgery.

If a patient is eligible for and consents to this study, the site will coordinate with the patient's surgeon and/or pathologist to provide information regarding the processing, storage, and shipping of tissue samples obtained from the arthroplasty.

This study will enroll approximately 50 patients. This study will be conducted at a subset of sites operationalizing the parent studies.

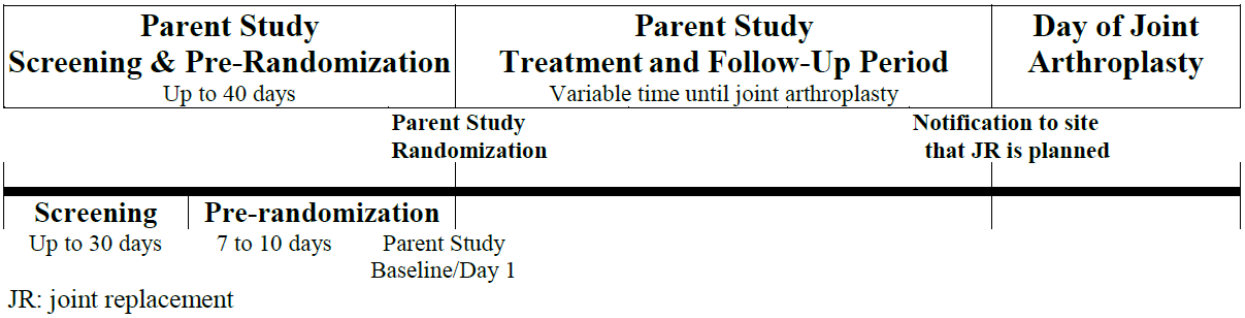
2.2. Sample Size and Power Considerations

Approximately 50 patients will be enrolled from the parent studies, R475-PN-1523, R475-OA-1611, and R475-OA-1688. The sample size is not based on power calculations; however it is considered adequate to meet the study objectives.

2.3. Study Plan

An overview of the study timeline is shown in Figure 1.

Figure 1: Study Flow Diagram



The Study event table is presented in Section 9.1.

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 (ICH, 1998), the following population of analysis will be used for all statistical analysis:

3.1. The Arthroplasty Analysis Set

The arthroplasty analysis set includes all patients who are enrolled in this study, have histological evaluation data and is based on the treatment received in their parent study (as treated).

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and disease characteristics variables will be summarized:

- Age at screening (year)
- Age group (< 65, 65-74, >=75 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, No, Not Reported, and Unknown)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) calculated from weight and height
- Geographic Region (North America, Europe, and Asia Pacific/South Africa)
- Index Joint (Knee or Hip) per Interactive Web Response Systems (IWRS)
- Kellgren-Lawrence score (2, 3, 4) of the replaced joint
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score of the replaced joint at screening
- Duration of OA at baseline
- History of analgesic intolerance and inadequate pain relief
- Adjudicated Arthropathy (AA) status of the replaced joint
- AA subtype (Rapidly Progressive Osteoarthritis Type 1 [RPOA-1], RPOA Type 2 [RPOA-2], Subchondral Insufficiency Fractures [SIF], Destructive Arthropathy [DA])

Additional baseline characteristics as number of injection, days between last injection and joint replacement will be listed.

4.2. Endpoint

The endpoint for this exploratory study is descriptive histological evaluation of the synovium, cartilage, and bone.

The following evaluation variables will be summarized:

- Gross/Microscopic Description
- Scoring pre-specified features of the synovium, cartilage and bone

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, minimum, 1st & 3rd quartiles, and maximum.

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

5.1. Subject Disposition

The disposition of patients in the study will be summarized by treatment received in their parent studies. The following summaries will be provided:

- The total number of patients in the arthroplasty analysis set
- A listing of patients in the arthroplasty analysis set

5.2. Protocol Deviations

All protocol deviations have been collected and reviewed on an ongoing basis throughout the study as described in the Protocol Deviation Plan.

Protocol deviations will be summarized for patients incurring any deviation by count and percentage, and patients incurring each type of deviation by count and percentage for arthroplasty analysis set.

A patient listing of all protocol deviations will be provided.

5.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics described in Section 4.1 will be descriptively summarized by treatment received in their parent studies.

5.4. Histological Analysis

Data from the histological analysis will be summarized descriptively by the treatment received (Placebo, NSAID, and fasinumab) in their parent studies. A listing of the variables described in Section 4.2 will be provided.

Subtype tables for the histological analysis by AA status will be provided to analyze the patients with AA on replaced joint separately from those without AA.

6. INTERIM ANALYSIS

No interim analyses is planned.

7. SOFTWARE

All analyses will be done using Statistical Analysis System (SAS) Version 9.4 and above.

8. REFERENCES

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.

9. APPENDIX

9.1. Schedule of Time and Events

Table 1: Schedule of Events

	Visit 1 Visit 2	**Visit 1 Visit 2**
	Screening Day 11	**Screening Day 11**
Study Day	N/A[2]	1
Study Procedure		
Inclusion Criteria	X[3]	
Informed Consent	X	
Harvesting of tissue from arthroplasty		X

1. Day of arthroplasty.
2. The day of screening follows when a site learns about a plan for arthroplasty, but prior to the actual procedure.
3. Patients will be eligible if they are participating in a parent study and plan to have an arthroplasty during.

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