Clinical Study Protocol

STUDY TO EVALUATE ARTHROPLASTY SPECIMENS IN THE PHASE 3 FASINUMAB PROGRAM FOR OSTEOARTHRITIS OF THE KNEE AND HIP

Compound:	Fasinumab
Clinical Phase:	2
Protocol Number:	R475-OA-1816
Protocol Version:	R475-OA-1816 Original
Date of Issue:	*See appended electronic signature page*
Medical /Study Director:	[redacted] Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

[redacted]

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	Study to Evaluate Arthroplasty Specimens in the Phase 3 Fasinumab Program for Osteoarthritis of the Knee and Hip
Site Location(s)	The site locations for this study are a subset of those at which the parent studies, R475-PN-1523, R475-OA-1611, and R475-OA-1688, are operational.
Principal Investigator	To be determined.
Objective	The objective of this exploratory study is to evaluate the cellular and connective tissue composition of joints from patients with osteoarthritis (OA) who have been treated with fasinumab, compared with those treated with placebo or non-steroidal anti-inflammatory drugs (NSAIDs).
Study Design	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.
Study Duration	Not applicable for the individual patient.
End of Study Definition	The end of study is defined as the last arthroplasty surgery for the last patient enrolled in this study.
Population	
Sample Size:	This study will enroll approximately 50 patients.
Target Population:	Eligible patients for this study will be participating in 1 of the parent studies and will undergo knee or hip arthroplasty during the parent study. Patients enrolled in the parent studies are men and women who are at least 18 years of age at the time of parent study entry with a clinical diagnosis at the screening visit of OA of the knee or hip, based on the American College of Rheumatology criteria, and with radiologic evidence of OA [K-L score ≥2] at the index joint.
Endpoint	The endpoint for this exploratory study is descriptive histological evaluation of the synovium, cartilage, and bone.
Procedures and Assessments	Collection of arthroplasty samples: Tissue samples will be collected at the time of the arthroplasty surgery. A centrally located pathologist will

	evaluate any slides prepared locally and will oversee processing of tissue shipped in formalin. Hematoxylin and eosin, a basic staining for tissue morphology, will be performed on all samples. Additional stains to be considered include Safranin O/Toluidine blue (stain proteoglycans), Goldner's trichrome (stains collagen fibers), and Alizarin Red S (stains calcium crystals). Immunohistochemistry will be considered but will be limited by the formalin fixation. [redacted] Safety Procedures: Safety procedures described in the parent study protocols will be followed.
Statistical Plan	Statistical hypothesis: No formal hypothesis testing will be performed in this exploratory study. Justification of samples size: It is estimated that 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. Consequently, the sample size may exceed 50 patients to meet the study objectives. Histological analysis: Data from the histological analysis will be summarized descriptively by the treatment received in their parent studies.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
CRF	Case report form (electronic or paper)
[redacted]	[redacted]
[redacted]	[redacted]
DMC	Data Monitoring Committee
EC	Ethics Committee
EDC	Electronic data capture
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
JR	Joint Replacement
K-L	Kellgren-Lawrence
MRI	Magnetic Resonance Imaging
NGF	Nerve growth factor
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
Q4W	Every 4 weeks
Q8W	Every 8 weeks
Regeneron	Regeneron Pharmaceuticals, Inc.
RPOA-1	Rapidly progressive osteoarthritis type 1 (thinning of cartilage)
RPOA-2	Rapidly progressive OA type 2 (partial or complete collapse of articular bone)
SAP	Statistical analysis plan
SIF	Subchondral insufficiency fractures

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1. INTRODUCTION

Fasinumab, also known as REGN475, is a fully-human, high-affinity monoclonal antibody directed against nerve growth factor (NGF), which is a molecule with an important role in pain perception. By selectively blocking NGF, fasinumab has the potential to modulate NGF-associated pain without many of the adverse side effects associated with other analgesic medications, such as opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Indeed, in studies to date, fasinumab has demonstrated clinically significant improvement in pain and physical function in patients with pain due to osteoarthritis (OA) of the knee or hip and in patients with chronic low back pain, compared with placebo.

Completed studies to date also show that patients treated with fasinumab more frequently experience arthralgia, joint swelling, and peripheral edema, compared with patients treated with placebo. In the phase 2/3 study of fasinumab in patients with OA of the hip or knee, R475-PN-1227, thinning of cartilage (rapidly progressive OA type 1; RPOA-1), partial or complete collapse of articular bone (rapidly progressive OA type 2; RPOA-2) and subchondral insufficiency fractures (SIF) occurred at a higher frequency in patients treated with fasinumab. A dose relationship between fasinumab and arthropathy was demonstrated, with 75% of the arthropathies occurring in the 2 highest dose groups (6 mg and 9 mg every 4 weeks [Q4W]), including both RPOA-2 events reported. Approximately, 60% of the arthropathies reported were the RPOA-1 subtype. [redacted]

Given the mechanism of action of fasinumab, it is possible that analgesia may predispose the patient to increased loading of joints with existing structural damage, thereby exacerbating destructive changes. However, other mechanisms that might influence the joint's underlying structural integrity could also potentially contribute to this process, for example: (1) perturbation of bone healing/turnover, (2) perturbation of cartilage turnover, (3) ischemia and (4) inflammation.

Osteoarthritis itself is a destructive process that tends to evolve over many years, although some patients exhibit the typical degenerative changes over a short period (Bartlett, 2011). All the tissues of the joint may show evidence of degeneration, most notably cartilage, subchondral bone and synovium (Loeser, 2012). Cartilage may show fissuring or erosion, clustering of chondrocytes, accumulation of calcium crystals, and loss of proteoglycan. Subchondral bone may show thickening, cyst formation, necrosis and ingrowth of neurovascular structures. Synovium may show one or more phenotypes including villous hyperplasia, fibrosis or inflammatory infiltrates. A predominance of, or a change from these typical patterns in patients treated with fasinumab may provide insight into the mechanism of joint events.

The purpose of this exploratory study is to evaluate arthroplasty specimens taken from patients who undergo joint replacement (JR) while participating in the fasinumab phase 3 program for pain due to OA of the knee and hip. The tissue removed during joint arthroplasty includes subchondral bone, cartilage, and synovium. Given that joint related AEs are identified risks in the fasinumab program, it is hypothesized that evaluation of tissue from arthroplasty specimens may provide insight into the mechanisms of these events. Patients in this study (R475-OA-1816) will be participants in 1 of 3 ongoing phase 3 studies (R475-PN-1523, R475-OA-1611, and R475-OA-1688) of fasinumab for pain due to OA of the knee and hip. Hereafter, the term 'parent studies' will be used to refer to the R475-PN-1523, R475-OA-1611, and R475-OA-1688 studies.

Additional background information on fasinumab and the fasinumab development program, including an assessment of the benefit-risk profile, can be found in the Investigator's Brochure.

2. STUDY OBJECTIVE

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.

3. RATIONALE

3.1. Rationale for Study Design

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 (1-year treatment period). These parent studies enroll patients with a clinical diagnosis of 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. Studies R475-OA-1688 and R475-OA-1611 each have had a placebo arm, 3 fasinumab arms (1 mg Q4W, 3 mg Q4W, 6 mg Q8W) and an NSAID arm (naproxen 500 mg twice per day in R475-OA-1611; celecoxib 200 mg daily or diclofenac 75 mg twice per day in R475-OA-1688). 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 and entered the 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.

In the phase 2/3 study of patients with pain due to OA of the knee or hip (R475-PN-1227), approximately 5% of patients in each treatment group had joint arthroplasty performed during the 36-week study. Comparing changes in joint histology in patients who have been exposed to fasinumab versus those treated with placebo may reveal changes specific to anti-NGF therapy, which could aid in the understanding of the mechanism underlying the arthropathies. It is anticipated that a sufficient number of patients will be enrolled from the parent studies to meet the study objectives.

During a joint replacement, the surgeon must remove subchondral bone, cartilage, and synovium. Because OA is asymmetric within the joint, in addition to removing the degenerated section of joint, the surgeon must often remove a relatively spared region of the joint to create a flat seat for the prosthesis. In this study, tissue removed during arthroplasty will be collected and evaluated in a designated central reference pathology laboratory to determine if fasinumab treatment affects the typical pathologic changes observed in OA.

3.2. Rationale for Dose Selection

There is no additional specific dosing requirement of study drug to patients for this exploratory study. Dosing of study drug to patients will be performed as indicated in the parent study protocol.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will be those listed in the parent study protocols.

4.2. Endpoint

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

5. Study Design

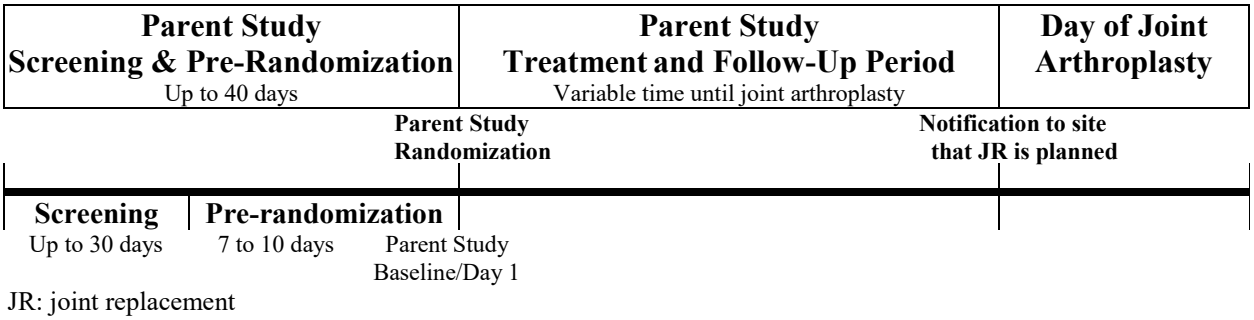
5.1. Study Description and Duration

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.

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

Figure 1: Study Flow Diagram



JR: joint replacement

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.

5.1.1. End of Study Definition

The end of study is defined as the last arthroplasty surgery for the last patient enrolled in this study.

5.2. Planned Interim Analysis

No interim analysis is planned.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

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

6.2. Study Population

Eligible patients for this study will be participating in 1 of the parent studies and will undergo knee or hip arthroplasty during the parent study. Patients enrolled in the parent studies are men and women who are at least 18 years of age at the time of parent study entry with a clinical diagnosis at the screening visit of OA of the knee or hip, based on the American College of Rheumatology criteria, and with radiologic evidence of OA [K-L score ≥2] at the index joint).

6.2.1. Inclusion Criteria

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

1. Previously randomized to R475-PN-1523, R475-OA-1611, or R475-OA-1688 and received at least 1 dose of study drug
2. Notified the site that they are planning a knee or hip arthroplasty during the parent study between randomization and 24 weeks after the last dose of SC study drug
3. Patient's surgeon/pathologist is willing to coordinate with the site regarding preparation, storage, and shipping of joint tissue samples collected during arthroplasty surgery
4. Willing and able to comply with clinic visits and study-related procedures
5. Provide informed consent signed by study patient or legally acceptable representative

6.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

6.3. Premature Withdrawal from the Study

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

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

7. STUDY SCHEDULE OF EVENTS AND PROCEDURES

7.1. Schedule of Events

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

Table 1: Schedule of Events

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

7.1.1. Footnotes for the Schedule of Events Table

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 the time between randomization and 24 weeks after the last dose of SC study drug

7.2. Study Procedures

7.2.1. Procedures Performed Only at the Screening Visit

Inclusion criteria assessments will be performed at the screening visit. Patients will be consented for this study after notifying the site of an intended arthroplasty during the parent study.

7.2.2. Collection of Arthroplasty Tissue Samples

Tissue samples will be collected at the time of the joint arthroplasty surgery. Detailed procedures for collection, freezing, shipping and storage of tissue samples will be provided in a separate document.

7.2.3. Histological Evaluation of Tissue Samples

A centrally located pathologist will evaluate any slides prepared locally and will oversee processing of tissue shipped in formalin. Hematoxylin and eosin, a basic staining for tissue morphology, will be performed on all samples. Additional stains to be considered include Safranin O/Toluidine blue (stain proteoglycans), Goldner's trichrome (stains collagen fibers), and Alizarin Red S (stains calcium crystals). Immunohistochemistry will be considered but will be limited by the formalin fixation.

[redacted]

[redacted]

7.2.6. Safety Procedures

Safety procedures described in the parent study protocols will be followed.

8. SAFETY DEFINITIONS, REPORTING, AND MONITORING

8.1. Obligations of Investigator

The investigator obligations are described in the parent study protocols.

8.2. Obligations of Sponsor

The sponsor obligations are described in the parent study protocols.

8.3. Definitions

Safety definitions, including definitions for AEs, serious adverse events, and adverse events of special interest, are defined in the parent study protocols.

8.4. Recording and Reporting Adverse Events

Safety reporting and monitoring for this study will be performed through the safety reporting and monitoring of the parent studies. For instructions, please reference the appropriate section of the parent study protocols. This includes the evaluation of severity and causality for all AEs.

9. STATISTICAL PLAN

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

Analysis variables are listed in Section 4.

9.1. Statistical Hypothesis

No formal hypothesis testing will be performed in this exploratory study.

9.2. Justification of Sample Size

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. Consequently, the sample size may exceed 50 patients to meet the study objectives.

9.3. 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).

9.4. Statistical Methods

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

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

9.4.1. Patient Disposition

The following will be provided:

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

9.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by the treatment received in their parent studies, and by all patients combined.

9.4.3. Histological Analysis

Data from the histological analysis will be summarized descriptively by the treatment received in their parent studies.

9.5. Statistical Considerations Surrounding the Premature Termination of a Study

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

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

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

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

The CRF (case report form [electronic or paper]) data for this exploratory study will be collected with an electronic data capture (EDC) tool, Rave Medidata.

10.2. Electronic Systems

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

- Rave Medidata EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis

11. STUDY MONITORING

11.1. Monitoring of Study Sites

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

The investigator must allow study-related monitoring.

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

11.2. Source Document Requirements

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

The investigator must keep all source documents on file with the CRF. Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.3. Case Report Form Requirements

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

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

12. AUDITS AND INSPECTIONS

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

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection

- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

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

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

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

13.3. Patients Confidentiality and Data Protection

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

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

14. PROTOCOL AMENDMENTS

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

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

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

16.2. Retention of Records

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

regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

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

17. DATA QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are summarized.

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 10.1).

Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 11.1, Section 11.2, and Section 12)

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 11.1).

All subject/patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient final CRF (Section 11.3 and Section 16.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 11.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 16.2).

18. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

19. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

20. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

21. REFERENCES

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Siebuhr AS, Petersen KK, Arendt-Nielsen L, Egsgaard LL, Eskehave T, Christiansen C, et al. Identification and characterisation of osteoarthritis patients with inflammation derived tissue turnover. Osteoarthritis Cartilage. 2014 Jan;22(1):44-50

22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: "Study to Evaluate Arthroplasty Specimens in the Phase 3 Fasinumab Program for Osteoarthritis of the Knee and Hip" and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study Title: Study to Evaluate Arthroplasty Specimens in the Phase 3 Fasinumab Program for Osteoarthritis of the Knee and Hip

Protocol Number: R475-OA-1816

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

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