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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

PHASE 3 RANDOMIZED, PLACEBO-CONTROLLED STUDY TO ASSESS SAFETY, TOLERABILITY AND EFFICACY OF GARETOSMAB IN PATIENTS WITH FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

Compound:	Garetosmab (REGN2477)
Study Name:	OPTIMA
Clinical Phase:	3
Protocol Number:	R2477-FOP-2175
Protocol Version:	R2477-FOP-2175 Amendment 5
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Medical/Study Director:	[redacted]

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AMENDMENT HISTORY

Amendment 5

The purpose of this amendment is to define additional key secondary endpoints, to update the statistical aspects of the study including the prespecified hierarchical testing strategy for the primary and key secondary endpoints, type-I error control, and analyses, and add the EU CT number.

The following table outlines the changes made to the study protocol and the affected sections:

Description of Change	Brief Rationale	Section # and Name
Several secondary endpoints were designated as key secondary endpoints and the prespecified hierarchical inferential approach for these endpoints was defined.	Aligned endpoints listed in the objectives to the statistical testing hierarchy.	Clinical Study Protocol Synopsis: Objectives, Endpoints Section 2.1 Primary Objective Section 2.2 Secondary Objectives Section 4.1.2.1 Key Secondary Endpoints Section 4.1.2.2 Secondary Efficacy Endpoints Section 4.1.2.3 Other Secondary Endpoints Section 11.4.3.2 Secondary Efficacy Analysis Section 11.1 Statistical Hypothesis
Renamed and updated the definitions of the efficacy and safety analysis sets and safety analysis periods	Aligned population definitions with ICH E9 guidance.	Section 7.4 Replacement of Patients Section 11.3 Analysis Sets Section 11.4.5 Safety Analysis
[redacted]	[redacted]	Clinical Study Protocol Synopsis: Statistical Plan Section 11.4.4 Control of Multiplicity

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
[redacted]	[redacted]	Clinical Study Protocol Synopsis: Statistical Plan Section 11.4.3 Efficacy Analyses
[redacted]	[redacted].	Section 4.2 Estimands for Primary and Key Secondary Objectives
Added the EU CT number	Per EU CTR requirements	Title Page
Specified the collection of menstrual history and confirmation of contraception use (male and female) throughout the ETP	To continue collecting the information until the last patient completes week 84	Table 3 Schedule of Events: ETP Table 4 Schedule of Events: Continued ETP
Update the analysis of immunogenicity section	Edited description to describe the current process	Section 11.4.7 Analysis of Immunogenicity Data
Minor edits	For consistency, clarity, and to correct typographical errors and section numbering.	Throughout the document
The term "adjudicated as positive" has been removed throughout the document when referring to new HO lesions	Term has been removed to clarify the endpoint language	Throughout the document

Amendment 4

The purpose of this amendment is to extend the duration of double-blind, placebo-controlled treatment to beyond 12 months. Extended treatment allows for patients to choose to continue with the assigned treatment group to generate safety and efficacy data beyond 12 months until the last global patient reaches week 84.

The following table outlines the changes made to the study protocol and the affected sections:

Description of Change	Brief Rationale	Section # and Name
Added blinded treatment extension or unblinded Observation Period to the study	To offer extended treatment to patients willing to continue assigned treatment groups beyond week 56 of the double-blind treatment period (DBTP).	Clinical Study Protocol Synopsis: Objectives

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
	-Patients can elect to remain blinded at week 56 and continue to receive assigned treatment in the Extended Treatment Period (ETP). The ETP provides for a minimum of 6 additional months of assigned treatment (for a minimum total treatment duration of 18 months of study treatment). Treatment in the ETP will be continued until the last global patient reaches week 84. OR -Patients can elect not to enter the ETP at week 56. After a patient has decided not to enter the ETP, the patient will be unblinded to assigned treatment group, will no longer receive study treatment, and will enter an Observation Period. During the Observation Period, long-term patient status (ie, survival and any pertinent safety events [ie, severe bleeding]) will be assessed by a phone call every 2 months. All patients that enter the Observation Period (regardless of assigned treatment in the DBTP) will be followed for long term status. The Observation Period will continue until the last global patient reaches week 84. Added rationale that the ETP will allow better understanding of the safety profile of garetosmab for a minimum of 18 months. Added new other secondary objectives for added ETP. Follow-Up Safety Visit was redefined to 30 weeks after the last dose of study drug administration for everyone who receives treatment, except for patients who are unblinded at the end of the DBTP that were treated with placebo (placebo patients unblinded at week 56 do not participate in the Follow-Up Safety Visit). The schedule of events are now presented in 4 tables.	Clinical Study Protocol Synopsis: Study Duration Clinical Study Protocol Synopsis: End of Study Definition Clinical Study Protocol Synopsis: Endpoints Section 2.2.2 Secondary Objectives Section 3.2.1 Rationale for Study Design Section 3.3.1 Risk-Benefit Assessment for Garetosmab Section 4.1.2.3Other Secondary Endpoints Section 4.1.3 Exploratory Endpoints Section 6.1Study Description and Duration Figure 1Study Flow Diagram (updated) Figure 2 Study Flow Diagram from First Patient In Until End of Study (new) Figure 3 Patient Decision Tree (new) Section 6.1.2 Double-Blind Treatment Period Section 6.1.2.1 Extended Treatment Period Section 6.1.2.2 Observation Period Section 6.1.3 Follow-up Safety Visit Section 6.1.5End of Study Definition

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
		Section 8.5 Blinding Section 8.8.1Prohibited Medications and Procedures Section 9.1 Schedule of Events Table 2 Schedule of Events: Screening and DBTP (including Early Termination) Section 9.1.1 Footnotes for Schedule of Events for Table 2, footnotes #3 Table 3 Schedule of Events: ETP (new) Section 9.1.2 Footnotes for Schedule of Events for Table 3 (new section) Table 4Schedule of Events: Continued ETP (new) Section 9.1.3 Footnotes for Schedule of Events for Table 4 (new section) Table 5 Schedule of Events: Observation Period (new) Section 9.1.4Footnotes for Schedule of Events for Table 5 (new section) Section 9.1.5 Early Termination Visit
Clarified follow-up of AEs if bleeding event occurs	Emphasized the importance of unscheduled visits used for follow up of AEs such as bleeding events.	Section 9.1.6Unscheduled Visits
Clarified follow-up of daily flare-up diary assessment	Specified the daily diary to be used during the DBTP	Section 9.2.3.2 Daily FOP Flare-Up Diary
Updated radiation exposure with extended treatment	Added CT scan at 18 months (end of ETP) and updated total exposure data. Also included information on repeating a CT scan at week 56 if needed due to poor imaging	Section 3.3.7 Radiation Exposure

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
	quality, as the week 56 CT scan data is the primary endpoint, thus imaging quality is critical.	Section 6.1.2 Double-Blind Treatment Period Section 9.1.1 Footnotes for Schedule of Events for Table 2, footnotes #12 Section 9.2.3.1 Low-Dose Whole Body CT to Assess New HO Formation
A patient experience interview was added to the schedule of events to occur at week 52 of the DBTP (or early termination visit prior to week 52)	The patient experience interviews will be conducted to understand patients' experienced symptoms changes and overall experience with study participation. Results of the interviews will also be used to contextualize findings on clinical outcomes assessments and meaningful change.	Table 2 Schedule of Events: Screening and DBTP (including Early Termination) Section 9.1.1 Footnotes for Schedule of Events for Table 2, footnote #15 Section 9.2.3.10 Patient Experience Interview
Patients may receive post-trial access of garetosmab	Continuation of garetosmab may be permitted after end of study based on specific criteria outlined in section 8.2.2.3. Patients in the ETP who continue onto a post-trial access program can omit the 30-week Follow-Up Safety Visit to allow for continuation of treatment without interruption.	Section 8.2.2.3 Continuation of Garetosmab after End of Study (new section)
Updated statistical analysis plan based on extended treatment to a minimum of 18 months	Updated the statistical analysis plan to align with the change in study design.	Section 11.3.3 Extended Treatment Period Safety Analysis Set (new section) Section 11.3.4 Pooled Safety Analysis Set (new section) Section 11.4.1 Patient Disposition Section 11.4.2 Demography and Baseline Characteristics Section 11.4.3.3 Other Secondary Efficacy (new section) Section 11.4.5 Safety Analysis

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
		Section 11.4.5.1 Adverse Events Section 11.4.5.2 Other Safety Section 11.4.5.3 Treatment Exposure Section 11.4.5.4 Treatment Compliance Section 11.5.2 Second Step Analysis (new section) Section 11.5.3 Final Analysis
Added range for vital sign assessments	Added a window ±30 min to footnote that describes vital sign assessments in Schedule of Events for DBTP, ETP, and continued ETP.	Section 9.1.1 Footnotes for Schedule of Events for Table 2, footnote #17 Section 9.1.2 Footnotes for Schedule of Events for Table 3, footnote #7 (new section) Section 9.1.3 Footnotes for Schedule of Events for Table 4, footnote #5 (new section))
Clarified urinalysis collection	Reworded urinalysis footnote for clarity in Schedule of Events for DBTP, ETP, and continued ETP.	Section 9.1.1 Footnotes for Schedule of Events, footnote #22 Section 9.1.2 Footnotes for Schedule of Events for Table 3, footnote #11 (new section) Section 9.1.3 Footnotes for Schedule of Events for Table 4, footnote #9 (new section)
Clarified collections for future biomedical research and pharmacogenomic sub-studies	Reworded biomedical research and pharmacogenomics sub-studies footnote for clarity in Schedule of Events for DBTP, ETP, and continued ETP.	Section 9.1.1 Footnotes for Schedule of Events, footnote #27
Correlated visit time points to study weeks	Added visit number where study week is mentioned to better define time point.	Throughout the document
Changed title of treatment period from treatment period to DBTP	The treatment period is now divided into DBTP and ETP; DBTP and ETP are used as appropriate to define the groups.	Throughout the document

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
Study investigator updated	The study principal investigator was added.	Clinical Study Protocol Synopsis: Principal Investigator
Study director updated	Change in responsibilities for the study	Title page
Minor edits	For consistency, clarity, and to correct typographical errors and section numbering.	Throughout the document

Amendment 3

The purpose of this amendment is to remove the optional exploratory assessments of lung volumes by helium gas dilution and body plethysmography. Some minor changes were made for clarification and to align with the feedback received from health authorities (HAs).

Additionally, changes were made in the protocol text to comply with the new European Union Clinical Trial Regulation (EU CTR) requirements. These EU CTR imposed changes have no impact on the safety or physical or mental integrity of the clinical trial participants, or the scientific value of this global clinical trial.

The following table outlines the changes made to the study protocol and the affected sections:

Description of Change	Brief Rationale	Section # and Name
Updated for compliance with the new EU Clinical Trial Regulation (CTR).	The EU-CTR 536/2014 requires the presentation of protocol information in accordance with specific guidelines.	Table 1 Study Interventions Administered (new table) Section 12.2.1 Monitoring of Study Sites Section 12.4.2 Retention of Records Section 12.4.3 Recruitment Strategy (new section) Section 12.4.4 Data Protection (new section) Section 13.5 Clinical Study Data Transparency
Text added to ensure consistency of flare-up and CAJIS evaluations.	To ensure consistency of efficacy assessments, text was added to advise that the same physician/clinician should perform the clinical assessments of flare-ups and CAJIS evaluation, at all visits for the	Synopsis: Endpoints Section 5.3 Clinical Endpoint Measures

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
	mentioned assessments for a given patient, whenever possible.	
Text on assessment of PK and Immunogenicity was added to the protocol synopsis.	To maintain consistency with the protocol main body.	Synopsis: Procedures and Assessments
For sites in China, no blood samples will be collected from patients for the ACVR1 gene sequencing. At screening, ACVR1 mutation in these patients will be confirmed only by prior documentation of any known ACVR1 FOP causing mutation. Protocol text was revised to clarify the same.	The analysis of whole blood sample for ACVR1 gene sequencing is not feasible in China for this study. Hence, no blood samples will be collected from patients for the ACVR1 gene sequencing in China. Additionally, at screening, ACVR1 mutation in these patients will be confirmed only by prior documentation of any known ACVR1 FOP causing mutation.	Synopsis: Procedures and Assessments Section 6.1.1 Screening Period Section 9.1.1 Footnotes for Schedule of Events, footnote #7 Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit
[redacted]	[redacted]	Section 2.3 Exploratory Objectives
Protocol text on helium gas dilution test and body plethysmography assessment was deleted.	Helium gas dilution test and body plethysmography assessment will not be carried out to decrease the patient burden, as many sites and patients will be unable to perform these assessments.	Section 4.1.3 Exploratory Endpoints Section 5.3 Clinical Endpoint Measures Table 2 Schedule of Events Section 9.1.1 Footnotes for Schedule of Events, footnote #12 Section 9.2.3.11 Pulmonary Function
Modified the following exploratory endpoints: [redacted]	[redacted]	Section 4.1.3 Exploratory Endpoints

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
Revised the reference for providing the additional details in the study reference manual, instead of study manual.	This change was done for consistency.	Section 9.1.1 Footnotes for Schedule of Events, footnote #20 Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 9.2.3.2 Daily FOP Flare Up Diary Section 9.2.3.4 EQ-5D-3L Section 9.2.3.6 Cumulative Analog Joint Involvement Scale Score Section 9.2.3.7 Patient Global Impression of Severity Section 9.2.3.8 Patient's Global Impression of Change Section 9.2.3.9 Clinician's Global Impression of Change Section 9.2.3.11 Pulmonary Function Section 9.2.4.3 Vital Signs Section 9.2.4.6 Menstrual History and Confirmation of Contraception Use Section 9.2.4.7 Ear, Nose, and Throat Consultation
For sites in China, no blood samples will be collected from patients for the optional genomic DNA sub-study.	The analysis of whole blood sample for optional genomic DNA sub-study is not feasible in China for this study.	Section 1.1 Section 9.1.1 Footnotes for Schedule of Events, footnote #23
Removed the reference for providing the additional details in the study manual for some assessments.	Assessments for measurement of body weight, physical examination, and electrocardiogram are standard assessments at site and no further guidance is required to be provided in the study reference manual.	Section 9.2.4.2 Body Weight Section 9.2.4.4 Physical Examination Section 9.2.4.5 Electrocardiogram
Added text to specify that central lab in China or United States may be used for analysis of exploratory biomarker samples.	Text was added to clarify that a central lab in China may be utilized in addition to the lab in the United States for analysis of exploratory biomarker samples.	Section 9.2.7 Exploratory Biomarker Procedures

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
Low dose of aspirin is considered as ≤100 mg or ≤150 mg/day, based on local country practice. Protocol text is revised to present the same.	This revision was made as per the feedback received from HA.	Section 7.2.2 Exclusion Criteria, criterion #10 Section 8.8.2 Permitted Medications and Procedures
In Schedule of Events table, correction was made to present week 1 as corresponding to day 8 instead of day 7.	This revision is for correcting the typographical error that was missed in the previous protocol version.	Table 2 Schedule of Events
Concomitant medications and procedures will be recorded at week 1 (day 8) visit. Addition of "X" in Schedule of Events table is made to reflect the same.	This edit was missed in the previous protocol version and is added now.	Table 2 Schedule of Events
Clarified financing and insurance information.	This change was made in response to feedback received from HA to clarify that financial and insurance information will be provided as per the local/national laws and regulations/requirements.	Section 17 Financing and Insurance
Minor edits.	For consistency, clarity, and to correct typographical errors and section numbering.	Throughout the protocol

Amendment 2

The purpose of this amendment is to provide the updates requested by health authorities. Other minor changes were made for general clarification. The following table outlines the changes made to the protocol and the affected sections:

Description of Change	Brief Rationale	Section # and Name
Clarified the mechanism of action of garetosmab	These updates were requested by a regulatory agency.	Section 1 Introduction
Added a section to present the Estimands for Primary and Key Secondary Objectives		Section 4.2 Estimands for Primary and Key Secondary Objectives (new) Section 4.2.1 Estimands for Primary Efficacy Objective (new) Section 4.2.2 Estimands for Key Secondary Objectives (new)

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
Clarified that all randomized patients who received study drug will be included in the intent-to-treat (ITT) analysis set to minimize the amount of missing data. Added the randomization stratification based on previous participation in the R2477-FOP-1623 (LUMINA-1) study		Section 7.4 Replacement of Patients Section 8.2.2 Study Drug Discontinuation Section 8.4 Method of Treatment Assignment Section 9.1.5 Early Termination Visit
Revised the reasons for permanent discontinuation of study drug due to epistaxis		Section 8.2.2.1 Reasons for Permanent Discontinuation of Study Drug
Added details for the major signs and symptoms to be considered by the investigator when assessing for an FOP flare-up.		Section 5.3 Clinical Endpoint Measures Section 9.2.3.1 Low-Dose Whole Body CT to Assess new HO Formation Section 9.2.3.3 Clinician Flare-Up Assessment (Investigator Assessed)
Minor changes to description of the hierarchy testing sequence were made to clarify the hierarchy of endpoint testing sequence Minor changes to the description of the timing of the first step analysis to clarify that the first time the study treatment will be unblinded for the first step analysis is at the end of the double-blind Treatment Period.		Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity
Revised the exclusion criterion for women of childbearing potential (WOCBP) to add tubal occlusion as a highly effective contraception method and clarify when pregnancy testing, and contraception are required	The exclusion criterion was updated to further clarify the exclusion criteria based on the clinical trials facilitation group (CTFG) guidance.	Section 7.2.2 Ex~~In~~clusion Criteria, #25
Clarified the timing for sample collection for platelet flow cytometry and added instruction for when post-administration blood sample for drug concentration can be omitted	The description was revised to improve readability	Section 9.1.1 Footnotes for Table 1 Schedule of Events, footnotes #19 and #22

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
Minor editorial corrections and clarifications	Minor editorial corrections and clarifications	Throughout the document

Amendment 1

The purpose of this amendment is to provide the correct description of the placebo presentation.

Description of Change	Brief Rationale	Section # and Name
Added the correct description of the placebo presentation	Provided the correct placebo description	Synopsis: Dose/Route/Schedule – Placebo Route Schedule Section 8 Investigational and Reference Treatments

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

^{18}F NaF	Fluorine-18-labelled sodium fluoride
ACVR1	Type I activin A receptor
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
BMP	Bone morphogenic protein
BP	Blood pressure
BSAP	Bone specific alkaline phosphatase
CAJIS	Cumulative Analog Joint Involvement Scale
CGIC	Clinician's Global Impression of Change
COVID-19	Coronavirus Disease 2019
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CT	Computed tomography
DBTP	Double-blind treatment period
EC	Ethics Committee
ECG	Electrocardiogram
ED	Effective dose
EDC	Electronic data capture
EQ-5D-3L	EuroQol 5 dimensions questionnaire with a 3-level scale
ENT	Ear, nose, and throat
EU CTR	European Union Clinical Trial Regulation
FAS	Full analysis set
FBR	Future biomedical research
FEV1	Forced expiratory volume in 1 second
FOP	Fibrodysplasia ossificans progressiva
FOP I-ADL	FOP Independent Activities of Daily Living
FSH	Follicle-stimulating hormone
FDA	US Food and Drug Administration
FVC	Forced vital capacity
GCP	Good Clinical Practice
GPS	Global Patient Safety
HbA1c	Hemoglobin A1c
HGRAC	Human Genetic Resource Administration of China
hs-CRP	High sensitivity C-reactive protein
HO	Heterotopic ossification
HR	Heart rate
HRQoL	Health-related quality of life

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

ICF	Informed consent form
IB	Investigator's brochure
ICH	International Council for Harmonisation
ICRP	International Commission on Radiological Protection
INR	International normalization ratio
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LH	Luteinizing hormone
mSv	Millisievert
NAb	Neutralizing anti-drug antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
P1NP	N-terminal propeptide
PCSV	Potentially clinically significant value
PET	Positron emission tomography
PGIC	Patient's Global Impression of Change
PGIS	Patient's Global Impression of Severity
PK	Pharmacokinetic
Q4W	Every 4 weeks
RBC	Red blood Cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RBQM	Risk-Based Quality Management
RR	Rate ratio
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SF-36	Short-Form 36
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
tAP	Alkaline phosphatase
TEAE	Treatment-emergent adverse event
WBC	White blood cell
WOCBP	Women of childbearing potential

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

TABLE OF CONTENTS

AMENDMENT HISTORY 2
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 14
CLINICAL STUDY PROTOCOL SYNOPSIS 23
1. INTRODUCTION 29
2. STUDY OBJECTIVES 32
2.1. Primary Objective 32
2.2. Secondary Objectives 32
2.2.1. Key Secondary Objectives 32
2.2.2. Secondary Objectives 32
2.3. Exploratory Objectives 33
3. HYPOTHESIS AND RATIONALE 34
3.1. Hypotheses 34
3.2. Rationale 34
3.2.1. Rationale for Study Design 34
3.2.2. Rationale for Dose Selection 35
3.3. Risk-Benefit 35
3.3.1. Risk-Benefit Assessment for Garetosmab 35
3.3.2. Risk of Epistaxis and Monitoring 36
3.3.3. Risk of Skin and Soft Tissue Infections and Monitoring 37
3.3.4. Potential Risk for Reproductive Organ Adverse Events in Male Patients and Monitoring 37
3.3.5. Potential Risk for Embryofetal Toxicity and Pregnancy Monitoring and Prevention 38
3.3.6. Potential Iatrogenic Injuries 39
3.3.7. Radiation Exposure 39
3.3.8. Study Conduct in Response to COVID-19 39
4. ENDPOINTS 41
4.1. Primary and Secondary Endpoints 41
4.1.1. Primary Endpoints 41
4.1.1.1. Primary Efficacy Endpoint 41
4.1.1.2. Primary Safety Endpoint 41
4.1.2. Secondary Endpoints 41

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

4.1.2.1. Key Secondary Endpoints....41
4.1.2.2. Secondary Efficacy Endpoints....41
4.1.2.3. Other Secondary Endpoints....42
4.1.3. Exploratory Endpoints....42
4.2. Estimands for Primary and Key Secondary Objectives....43
4.2.1. Estimand for Primary Efficacy Objective:....43
4.2.2. Estimands for Key Secondary Objectives:....43
5. STUDY VARIABLES....46
5.1. Demographic and Baseline Characteristics....46
5.2. Efficacy Variables....46
5.2.1. Quantitative Whole-Body CT....46
5.3. Clinical Endpoint Measures....46
5.4. Biochemical Markers of Bone Formation....48
5.5. Safety Variables....48
5.6. Pharmacokinetic and Total Target Variables....48
5.7. Immunogenicity Variables....48
5.8. Research Biomarker Variables....49
6. STUDY DESIGN....50
6.1. Study Description and Duration....50
6.1.1. Screening Period....53
6.1.2. Double-Blind Treatment Period....54
6.1.2.1. Extended Treatment Period....55
6.1.2.2. Observation Period....55
6.1.3. Follow-up Safety Visit....55
6.1.4. Study Stopping Rules....55
6.1.4.1. Study Stopping Criteria....55
6.1.5. End of Study Definition....56
6.2. Planned Interim Analysis....56
6.3. Study Committees....56
6.3.1. Independent Data Monitoring Committee....56
6.3.2. Adjudication of New Heterotopic Ossification Lesions....56
7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS....57
7.1. Number of Patients Planned....57

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

7.2. Study Population 57
7.2.1. Inclusion Criteria 57
7.2.2. Exclusion Criteria 57
7.3. Premature Withdrawal from the Study 60
7.4. Replacement of Patients 60
8. STUDY TREATMENTS 61
8.1. Investigational and Reference Treatments 61
8.2. Dose Modification and Study Treatment Discontinuation Rules 61
8.2.1. Dose Modification 61
8.2.2. Study Drug Discontinuation 61
8.2.2.1. Reasons for Permanent Discontinuation of Study Drug 61
8.2.2.2. Reasons for Temporary Discontinuation of Study Drug 62
8.2.2.3. Continuation of Garetosmab after End of Study 62
8.3. Management of Acute Reactions 62
8.3.1. Acute Intravenous Infusion Reactions 62
8.3.1.1. Interruption of the Intravenous Infusion 62
8.3.1.2. Termination of the Intravenous Infusion 63
8.4. Method of Treatment Assignment 64
8.5. Blinding 64
8.6. Emergency Unblinding 64
8.7. Treatment Logistics and Accountability 65
8.7.1. Packaging, Labeling, and Storage 65
8.7.2. Supply and Disposition of Treatments 65
8.7.3. Treatment Accountability 65
8.7.4. Treatment Compliance 65
8.8. Concomitant Medications and Procedures 65
8.8.1. Prohibited Medications and Procedures 66
8.8.2. Permitted Medications and Procedures 66
9. STUDY SCHEDULE OF EVENTS AND PROCEDURES 68
9.1. Schedule of Events 68
9.1.1. Footnotes for Schedule of Events for Table 2 72
9.1.2. Footnotes for Schedule of Events for Table 3 77
9.1.3. Footnotes for Schedule of Events for Table 4 81

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

9.1.4. Footnotes for Schedule of Events for Table 5 82
9.1.5. Early Termination Visit 83
9.1.6. Unscheduled Visits 83
9.2. Study Procedures 83
9.2.1. Procedures Performed Only at the Screening/Baseline Visit 83
9.2.2. Procedures Related to Study Drug Administration 84
9.2.3. Efficacy Procedures 84
9.2.3.1. Low-Dose Whole Body CT to Assess New HO Formation 84
9.2.3.2. Daily FOP Flare-Up Diary 84
9.2.3.3. Clinician Flare-Up Assessment (Investigator Assessed) 85
9.2.3.4. EQ-5D-3L 85
9.2.3.5. The Short Form – 36 Survey (SF-36) 85
9.2.3.6. Cumulative Analog Joint Involvement Scale Score (CAJIS) 85
9.2.3.7. Patient Global Impression of Severity (PGIS) 86
9.2.3.8. Patient's Global Impression of Change (PGIC) 86
9.2.3.9. Clinician's Global Impression of Change (CGIC) 86
9.2.3.10. Patient Experience Interview 86
9.2.3.11. Pulmonary Function 86
9.2.4. Safety Procedures 86
9.2.4.1. Monitoring of Adverse Events and Concomitant Medications 86
9.2.4.2. Body Weight 87
9.2.4.3. Vital Signs 87
9.2.4.4. Physical Examination 87
9.2.4.5. Electrocardiogram 87
9.2.4.6. Menstrual History and Confirmation of Contraception Use 87
9.2.4.7. Ear, Nose, and Throat Consultation 88
9.2.4.8. Platelet Flow Cytometry 88
9.2.4.9. Laboratory Testing 88
9.2.5. Drug Concentration and Activin A (Target) Measurements 90
9.2.6. Immunogenicity Measurements and Samples 90
9.2.7. Exploratory Biomarker Procedures 90
9.2.8. Future Biomedical Research (Optional) 90
9.2.9. Pharmacogenomic Analysis (Optional) 91

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

10. SAFETY EVALUATION AND REPORTING 92
10.1. Recording and Reporting Adverse Events 92
10.1.1. General Guidelines 92
10.1.2. Reporting Procedure 93
10.1.3. Events that Require Expedited Reporting to Sponsor 93
10.2. Definitions 94
10.2.1. Adverse Event 94
10.2.2. Serious Adverse Event 94
10.2.3. Adverse Events of Special Interest 94
10.2.4. Infusion Reactions 95
10.2.5. Severity 95
10.2.6. Causality 95
10.3. Safety Monitoring 96
10.4. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators 97
11. STATISTICAL PLAN 98
11.1. Statistical Hypothesis 98
11.2. Justification of Sample Size 98
11.3. Analysis Sets 98
11.3.1. Full Analysis Set 98
11.3.2. Safety Analysis Set 98
11.3.3. Pharmacokinetic Analysis Sets 98
11.3.4. Immunogenicity Analysis Sets 98
11.4. Statistical Methods 99
11.4.1. Patient Disposition 99
11.4.2. Demography and Baseline Characteristics 99
11.4.3. Efficacy Analyses 99
11.4.3.1. Primary Efficacy Analysis 99
11.4.3.2. Secondary Efficacy Analysis 100
11.4.3.3. Other Secondary Efficacy 101
11.4.3.4. Dose Response Analysis 101
11.4.4. Control of Multiplicity 101
11.4.5. Safety Analysis 102

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

11.4.5.1. Adverse Events 102
11.4.5.2. Other Safety 103
11.4.5.3. Treatment Exposure 103
11.4.5.4. Treatment Compliance 104
11.4.6. Pharmacokinetics 104
11.4.6.1. Analysis of Drug Concentration Data 104
11.4.7. Analysis of Immunogenicity Data 105
11.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data 105
11.5. Timing of Statistical Analyses 105
11.5.1. First Step Analysis: 106
11.5.2. Second Step Analysis 106
11.5.3. Final Analysis 106
11.6. Statistical Considerations Surrounding the Premature Termination of a Study 106
12. QUALITY CONTROL AND QUALITY ASSURANCE 107
12.1. Data Management and Electronic Systems 107
12.1.1. Data Management 107
12.1.2. Electronic Systems 107
12.2. Study Monitoring 107
12.2.1. Monitoring of Study Sites 107
12.2.2. Source Document Requirements 108
12.2.3. Case Report Form Requirements 108
12.3. Audits and Inspections 108
12.4. Study Documentation 109
12.4.1. Certification of Accuracy of Data 109
12.4.2. Retention of Records 109
12.4.3. Recruitment Strategy 109
12.4.4. Data Protection 109
13. ETHICAL AND REGULATORY CONSIDERATIONS 111
13.1. Good Clinical Practice Statement 111
13.2. Informed Consent 111
13.3. Patient Confidentiality and Data Protection 111
13.4. Institutional Review Board/Ethics Committee 112
13.5. Clinical Study Data Transparency 112

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

14. PROTOCOL AMENDMENTS 113
15. PREMATURE TERMINATION OF THE STUDY OR CLOSEOUT OF A SITE 114
15.1. Premature Termination of the Study 114
15.2. Close-out of a Site 114
16. CONFIDENTIALITY 114
17. FINANCING AND INSURANCE 114
18. PUBLICATION POLICY 114
19. REFERENCES 115
20. INVESTIGATOR'S AGREEMENT 117
SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS 118

LIST OF TABLES

Table 1: Study Interventions Administered 61
Table 2: Schedule of Events: Screening and DBTP (including Early Termination) 69
Table 3: Schedule of Events: ETP 76
Table 4: Schedule of Events: Continued ETP 79
Table 5: Schedule of Events: Observation Period 82

LIST OF FIGURES

Figure 1: Study Flow Diagram 51
Figure 2: Study Flow Diagram from First Patient In Until End of Study[1] 51
Figure 3: Patient Decision Tree 52

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	Phase 3 Randomized, Placebo-Controlled Study to Assess Safety, Tolerability, and Efficacy of Garetosmab in Patients with Fibrodysplasia Ossificans Progressiva
Site Locations	The study will be conducted at multiple sites globally.
Principal Investigator	Professor Richard Keen, BSc, PhD, FRCP
Objectives	**Primary Objectives:** The primary efficacy objective of the study is to assess the effect of garetosmab ([redacted] mg/kg, [redacted]mg/kg) versus placebo on the formation of new heterotopic ossification (HO) lesions from baseline to week 56, as determined by low-dose computed tomography (CT). The primary safety objective of the study is to assess the safety and tolerability of garetosmab ([redacted] mg/kg,[redacted] mg/kg) versus placebo from baseline to week 56. **Secondary Objectives:** The key secondary objectives of the study are: • To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on the number per patient of clinician-assessed flare-up episodes to week 56 • To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on the proportion of patients with new HO lesions as determined by CT at week 56 • To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on volume of new HO lesions as determined by CT at week 56 • To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on the occurrence of patient-reported flare-up episodes through week 56 All other secondary objectives will compare the [redacted] mg/kg dose group to the placebo group and the [redacted] mg/kg dose group to the placebo group at week 28 and week 56 unless otherwise specified: • To assess the effect of garetosmab versus placebo on the number of new HO lesions per patient from baseline to week 28 as determined by CT • To assess the effect of garetosmab versus placebo on the number per patient of clinician-assessed flare-up episodes to week 28 • To assess the effect of garetosmab versus placebo on the proportion of patients with new HO lesions as determined by CT at week 28 • To assess the effect of garetosmab versus placebo on volume of new HO lesions as determined by CT at week 28 • To assess the effect of garetosmab versus placebo on the occurrence of patient-reported flare-up episodes through week 28 • To assess the effect of garetosmab versus placebo on the occurrence of clinician-assessed flare-up episodes • To assess the effect of garetosmab versus placebo on the number per patient of patient-reported flare-up episodes

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

	• To characterize the concentrations of total activin A • To evaluate concentrations of garetosmab • To assess the immunogenicity of garetosmab • To assess the effect of garetosmab versus placebo in pulmonary function assessed by pulmonary function tests • To assess clinical outcomes (ie, joint function [Cumulative Analog Joint Involvement Scale (CAJIS)]) at baseline and over time after the first dose of garetosmab versus placebo • To assess the effect of garetosmab versus placebo on patient's disease severity assessed by the Patient Global Impression of Severity (PGIS) • To assess the effect of garetosmab versus placebo on patient's change in disease assessed by the Patient's Global Impression of Change (PGIC) • To assess the effect of garetosmab versus placebo on clinician's change in disease assessed by the Clinician's Global Impression of Change (CGIC) • To assess the safety and efficacy of garetosmab beyond 12 months.
Study Design	R2477-FOP-2175 is a phase 3, randomized, multi-center, multinational, parallel-group, placebo-controlled study to assess the efficacy of garetosmab on the reduction of heterotopic bone formation, and its safety, tolerability, and pharmacokinetics (PK) in fibrodysplasia ossificans progressiva (FOP) patients with active disease caused by any FOP-causing variant of type I activin A receptor (ACVR1). Approximately 66 patients will be enrolled 1:1:1 into the 3 parallel arms of the study. The study consists of several periods and a Follow-up Safety Visit. **Screening Period:** 4 weeks in duration (from study day -28 to day -1 [visit 1]). All patients will undergo an informed consent process and screening procedures. Screening procedures may be conducted over multiple days. **Double-Blind Treatment Period (DBTP):** 56 weeks in duration (from study day 1 [visit 2] to week 56 [visit 17]). All patients will be randomized to double-blind treatment with garetosmab [redacted] mg/kg, garetosmab [redacted] mg/kg, or placebo. **Extended Treatment Period (ETP)**: 28+ weeks in duration (study week 56+ [visit 17+]) for those who choose to continue double-blind treatment. Patients who complete the DBTP and elect to extend double-blind treatment continue until the last global patient completes week 84. **Observation Period:** 28+ weeks in duration (study week 56+ [visit 17+]) for those who choose to discontinue from double-blind treatment. Patients who complete the DBTP and elect to go unblinded and stop treatment will be followed to assess survival and any pertinent safety events (ie, severe bleeding). Patients will not receive treatment and may participate in other studies. **Follow-Up Safety Visit:** 30 weeks from the last dose administered (study week 84+ [visit 24+]) for all patients who receive treatment, except for patients who are unblinded that were treated with placebo (placebo-treated patients unblinded at week 56 [visit 17] do not participate in the Follow-Up Safety Visit). Consists of a safety follow-up visit 30 weeks after the last study drug administration. Efficacy assessments will include whole body CT for HO lesions, assessment of flare-ups, CAJIS, pulmonary function tests, change in disease severity, and quality of life (EuroQol 5 dimensions questionnaire with a 3-level scale [EQ-5D-3L] and Short-Form 36 [SF-36]). Safety assessment will include adverse events (AEs), vital signs, physical examination, Electrocardiograms (ECGs), serum and urine laboratory testing,

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

	ear nose, and throat (ENT) consultation, coagulation parameters, platelet flow cytometry, and menstrual cycle history. Patients who participated in the phase 2, R2477-FOP-1623 study (LUMINA-1) can enroll if they meet the inclusion criteria and do not meet the exclusion criteria.
Study Duration	The duration of the DBTP for a patient is 56 weeks, excluding the Screening Period. The ETP will begin after week 56 (visit 17) and continue until the last global patient completes week 84 (visit 24) and the Follow-Up Safety Visit (if applicable), and results of the primary analyses of safety and efficacy are available to the sponsor. All patients who receive treatment, except for patients who are unblinded that were treated with placebo, will be followed until 30 weeks after administration of last dose (placebo patients unblinded at week 56 [visit 17] do not participate in the Follow-Up Safety Visit). If at the time patients reach week 84 (visit 24), and visit data from the last patient randomized into the study through week 84 (visit 24) have not been collected and validated, and results of the primary analyses of safety and efficacy are not yet assessed by the sponsor, patients will continue to receive garetosmab every 4 weeks beyond week 84 (visit ≥25).
End of Study Definition	The end of study is defined as the date the last global patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).
Population	
Sample Size:	Approximately 66 patients will be enrolled globally.
Target Population:	The study population consists of patients with FOP.
Treatments	
Investigational Drug	Garetosmab is supplied as a liquid drug product and will be administered intravenous (IV) in this study.
Dose/Route/Schedule:	Patients will receive either garetosmab IV ([redacted] mg/kg) every 4 weeks (Q4W), garetosmab IV ([redacted] mg/kg) Q4W, or matching placebo Q4W.
Placebo Route/Schedule:	Placebo to match garetosmab is supplied as a liquid solution without the monoclonal antibody (or the protein).
Endpoints	
Primary:	**Primary Efficacy Endpoint:** The primary efficacy endpoint is the number of new HO lesions at week 56. **Primary Safety Endpoint:** The primary safety endpoint is the incidence and severity of treatment emergent adverse events of special interest (AESIs) from baseline to week 56.
Secondary:	**Key Secondary Endpoints:**

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- Number of clinician-assessed flare-ups through week 56
- Occurrence of new HO lesions at week 56 (Yes/No)
- Total volume of new HO lesions at week 56
- Occurrence of patient-reported flare-ups through week 56 (Yes/No)

Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Number of new HO lesions at week 28
- Number of clinician-assessed flare-ups through week 28
- Occurrence of new HO lesions at week 28 (Yes/No)
- Total volume of new HO lesions at week 28
- Occurrence of patient-reported flare-ups through week 28 (Yes/No)
- Occurrence of clinician-assessed flare-ups through weeks 28 and 56 (Yes/No)
- Number of patient-reported flare-ups through weeks 28 and 56
- Change from baseline in joint function assessment by physician to week 28 and week 56 by the CAJIS
- Change from baseline in pulmonary function as assessed by spirometry at week 28 and week 56
- Change from baseline in disease severity to week 28 and week 56 by the PGIS
- Change since the start of the study in disease severity to week 28 and week 56 by the PGIC
- Change since the start of the study in disease severity to week 28 and week 56 by the CGIC

For patients continuing extended treatment, additional other secondary efficacy endpoints are:

- Number of new HO lesions at week 84
- Occurrence of new HO lesions at week 84 (Yes/No)
- Total volume of new HO lesions at week 84
- Number of clinician-assessed flare-ups through week 84
- Occurrence of clinician-assessed flare-ups through week 84 (Yes/No)

Note: To ensure consistency of assessments, it is advised that the same clinician performs the clinician-assessed FOP flare-ups and CAJIS evaluations, at all visits for the mentioned assessments for a given patient, whenever possible.

Procedures and Assessments

Efficacy Assessments

Efficacy procedures and assessments include low-dose whole body CT, the FOP flares assessment via patient diary, the clinician's assessment of flares via the clinician-reported flares, the Europol 5 dimensions questionnaire with a 3-level scale (EQ-5D-3L), the physician assessment of cumulative analog joint involvement scale (CAJIS), Patient Global Impression of Severity (PGIS), Patient's Global Impression of Change (PGIC), Clinician's Global Impression of Change (CGIC), the Short-Form 36 (SF-36) and assessment of pulmonary function.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Safety Assessments

Safety procedures and assessments include TEAEs, vital signs assessment, physical examination, ENT consultation, coagulation parameters, a menstrual cycle history, electrocardiogram, platelet flow cytometry, and laboratory testing.

PK and Immunogenicity Assessments

PK analysis will include measurement of concentration of functional garetosmab and total Activin A. Immunogenicity analysis will include measurement of anti-drug antibody (ADA) and neutralizing anti-drug antibody (NAb) (when NAb assay becomes available).

ACVR1 Gene Sequencing

All patients will have a whole blood sample collected, preferably at the screening visit, for future ACVR1 gene sequencing. For patients without prior documentation of ACVR1 at screening, the results from this test will be used for documentation. DNA samples will be stored until processing.

Note: For sites in China, no blood samples will be collected from patients for the ACVR1 gene sequencing. At screening, ACVR1 mutation in these patients will be confirmed only by prior documentation of any known ACVR1 FOP causing mutation.

Biomarker Procedures

Blood will be collected for the analysis and discovery of biomarkers, including but not limited to those related to bone and cartilage formation (eg, bone specific alkaline phosphatase [BSAP], N-terminal propeptide [P1NP], Collagen-10), and inflammation (eg, High sensitivity C-reactive protein [hs-CRP]) as well as mechanism based biomarkers related to the activin A and activin receptor pathway including but not limited to activin and bone morphogenic protein (BMP) ligands or markers that may elucidate the mechanism of action of garetosmab.

Blood for a separate optional genomics sub-study will also be collected in patients who consent to analysis. This analysis will be an exploratory pharmacogenomics analysis that may include genome-wide analysis that is additional to the mandatory ACVR1 gene sequencing noted above.

Statistical Plan

[redacted]

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

[redacted]

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

1. INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare, severely disabling, congenital genetic disease characterized by progressive multi-focal heterotopic ossification (HO) of skeletal muscle, ligaments, tendons, and fascia. Heterotopic ossification is the abnormal growth of bone in non-skeletal tissues. FOP is estimated to occur in approximately 1 in 0.63 to 1.86 million individuals based on reports of diagnosed cases (Liljesthröm, 2020). There are approximately 800 confirmed cases of FOP globally. No ethnic, racial, gender, or geographic predisposition has been reported. Palovarotene, a retinoic acid receptor gamma (RARγ) selective agonist, is approved only in Canada for the reduction of HO in adults and children >8 years for females and >10 years for males with FOP.

At birth, FOP is manifest by valgus deformities of the great toes as well other deformities of other bone and joint structures (Pignolo, 2019). The disease is characterized postnatally by progressive ossification of soft tissues, which can lead to joint immobility, skeletal deformity, severe disability, and early mortality. Symptoms begin in early childhood and include painful inflammatory soft tissue swellings (called flare-ups) most commonly on the head, neck, or back (Cohen, 1993) (Pignolo, 2016). Disease flare-up episodes are not predictable in their occurrence, are variable in severity and duration, and may or may not result in new HO (Kaplan, 2016) (Pignolo, 2016). Importantly, HO and disability may develop insidiously without acute flare-up symptoms as reported in 47% of patients in an FOP natural history study (Pignolo, 2016). Furthermore, a study with fluorine-18-labelled sodium fluoride (^{18}F-NaF) positron emission tomography (PET)/computed tomography (CT) imaging has also demonstrated HO progression without signs of a flare-up in 4 out of 5 patients with FOP over a 0.5- to 2-year period, indicating that the condition can be chronic, and patients can have progressive HO in the absence of clinical symptoms (Botman, 2019). Most patients with FOP are confined to a wheelchair by the third decade of life, requiring lifelong assistance to perform activities of daily living (Cohen, 1993) (Pignolo, 2016), and early mortality is common, with median lifespan terminating in the fifth decade (Kaplan, 2009). Such early mortality is principally due to cardiorespiratory failure from thoracic insufficiency syndrome, pneumonia, and complications of falls (Kaplan, 2010).

Fibrodysplasia ossificans progressiva is caused by dominant missense mutations in the intracellular domain of activin receptor type 1A (ACVR1, also known as ALK2), a bone morphogenetic protein (BMP) type I receptor which is expressed in many tissues of the body, including skeletal muscle and cartilage (Huning, 2014). Although FOP is caused by a variety of such mutations, the great majority of FOP patients carry the point mutation, c.617G>A; p.R206H, which alters arginine (R) 206 to a histidine (H) (Huning, 2014). A significant breakthrough in the understanding of FOP occurred in 2015 when it was demonstrated that FOP-causing mutations of ACVR1 render this receptor responsive to activin A and initiate signaling through the SMAD 1/5/8 pathway, akin to that obtained from osteogenic BMPs (Hatsell, 2015) (Hino, 2015). In contrast, when activin A engages wildtype ACVR1 receptors, it forms a non-signaling complex, and as a result activin A antagonizes BMP pathway signaling mediated by wild-type ACVR1(Aykul, 2020) (Hatsell, 2015). The ACVR1[R206H] variant was subsequently expressed in a conditional-inducible mouse model of FOP. These mice developed progressive HO at anatomic locations similar to those seen in patients with FOP, as detected by ^{18}F-NaF PET/CT which labeled active HO and volumetric CT (Hatsell, 2015) (Upadhyay, 2017). Inhibition of activin A with the neutralizing anti-activin A antibody garetosmab blocked the development of new HO lesions and

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

also resulted in stasis or partial resorption of existing (but nascent) HO lesions. These results suggested a fundamental role for activin A in the initiation and progression of HO, and that an anti-activin A antibody might provide beneficial clinical impact on HO in patients with FOP (Upadhyay, 2017). Recently, experiments in the ACVR1[R206H] FOP mice have been extended to another FOP-causing ACVR1 variant, R258G. This ACVR1[R258G] mouse model developed HO much like the ACVR1[R206H] mouse model, and HO was again inhibited by garetosmab. Hence, inhibition of activin A is a promising therapeutic approach for halting HO in FOP, whether it arises as a result of the most common FOP-causing variant of ACVR1, ACVR1[R206H], or any of the other FOP-causing variants of ACVR1 reported to date.

Garetosmab is a fully human monoclonal antibody (mAb) that selectively binds activin A, AB, and AC, blocking their ability to interact with their corresponding type I receptors and hence block signaling. Garetosmab has been studied in 2 completed trials in healthy adult subjects. R2477-HV-1525 was a first-in-human (FIH), double-blind, placebo-controlled, single-ascending dose study in women of non-childbearing potential (30 healthy subjects were exposed). R2477-1033-HV-1621 was a randomized, double-blind, placebo-controlled, ascending-dose study to assess the safety, tolerability, and pharmacodynamic (PD) effects of garetosmab alone and in combination with trevogrumab (an anti-myostatin mAb) in healthy postmenopausal women and healthy adult men (56 healthy subjects were exposed to garetosmab alone or in combination with trevogrumab). The results of the studies in healthy subjects showed that overall, garetosmab was well tolerated with no significant safety findings observed.

The clinical benefit of garetosmab for the treatment of FOP was demonstrated in the phase 2, double-blind, placebo-controlled, 28-week treatment study (LUMINA-1), followed by 2 open-label periods. While garetosmab did not have a significant effect on the planned primary endpoint, total lesion activity (measuring a reduction in the size and activity of pre-existing HO lesions), there was a striking reduction in the number of new HO lesions as assessed by both ^{18}F-NaF PET and CT in adult patients with FOP. These substantive and clinically meaningful reductions were largely demonstrated by significant decreases in the incidence and volume of new lesions after 28 weeks of treatment. Moreover, garetosmab reduced the incidence of patient- and investigator-reported flare-up events. Results from the open-label period showed sustained efficacy with long-term treatment through week 76. From a safety perspective, the majority of treatment-emergent adverse events (TEAEs) were mild to moderate in severity. Infusion reactions were balanced between treatment groups with no serious or severe events. Notable imbalances in TEAEs included epistaxis, acne, madarosis (thinning of the eyelashes or eyebrows), and a composite of skin infections including abscesses, carbuncle, folliculitis, and furuncle.

There were 5 deaths in LUMINA-1 which were all observed during the open-label period: 3 of the deaths were consistent with causes common to patients with FOP (complications from falls and intestinal obstruction). The fourth death occurred as a result of a hemorrhagic stroke to the deep structures of the brain leading to acute respiratory failure in a patient with difficult-to-control arterial hypertension. The fifth death was ultimately determined to be due to sudden cardiac arrest. There was no association between epistaxis and patient deaths. Only 3 of the 5 patients who died experienced epistaxis at an earlier time in the study, and these epistaxis events were limited in frequency, and mild to moderate in severity. Apart from the hemorrhagic stroke, mortality appears rather consistent with common causes of death in patients with FOP, and with the life expectancy in patients with FOP of similar age and disease severity as measured by the clinical staging of FOP developed by Pignolo et al (Pignolo, 2018). According to this classification of FOP clinical stages,

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

scores for 2 of the patients who died correlated with an end-of-life clinical stage. Among the other 3 deaths, 1 patient had a profound clinical stage, 1 patient had a moderate clinical stage, and 1 patient had a severe clinical stage. Additional details are provided in the Investigator's Brochure (IB).

However, while a consistent linkage and causal explanation between death and garetosmab treatment could not be established, in the absence of statistically significant benefit that was conclusively demonstrated with type-I error control, and without a control in the open-label period of the LUMINIA-1 study during which these deaths occurred to formally establish an absence of association between mortality and treatment, this study is being conducted to confirm the benefit:risk of garetosmab. Specifically, this phase 3 R2477-FOP-2175 study incorporates the learnings and understandings of the biology of FOP gained from the global LUMINA-1 study to design a study that confirms the efficacy of garetosmab on the reduction of new HO lesions and further evaluates safety using a longer placebo-controlled period.

Additional background information on the study drug and development program can be found in the IB.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary efficacy objective of the study is to assess the effect of garetosmab ([redacted] mg/kg, [redacted] mg/kg) versus placebo on the formation of new HO lesions from baseline to week 56, as determined by low-dose CT.

The primary safety objective of the study is to assess the safety and tolerability of garetosmab ([redacted] mg/kg, [redacted] mg/kg) versus placebo from baseline to week 56.

2.2. Secondary Objectives

2.2.1. Key Secondary Objectives

The key secondary objectives of the study are:

- To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on the number per patient of clinician-assessed flare-up episodes to week 56
- To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on the proportion of patients with new HO lesions as determined by CT at week 56
- To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on volume of new HO lesions as determined by CT at week 56
- To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on the occurrence of patient-reported flare-up episodes through week 56

2.2.2. Secondary Objectives

All other secondary objectives will compare the [redacted] mg/kg dose group to the placebo group and the [redacted] mg/kg dose group to the placebo group at week 28 and week 56 unless otherwise specified.

Other secondary objectives of the study are:

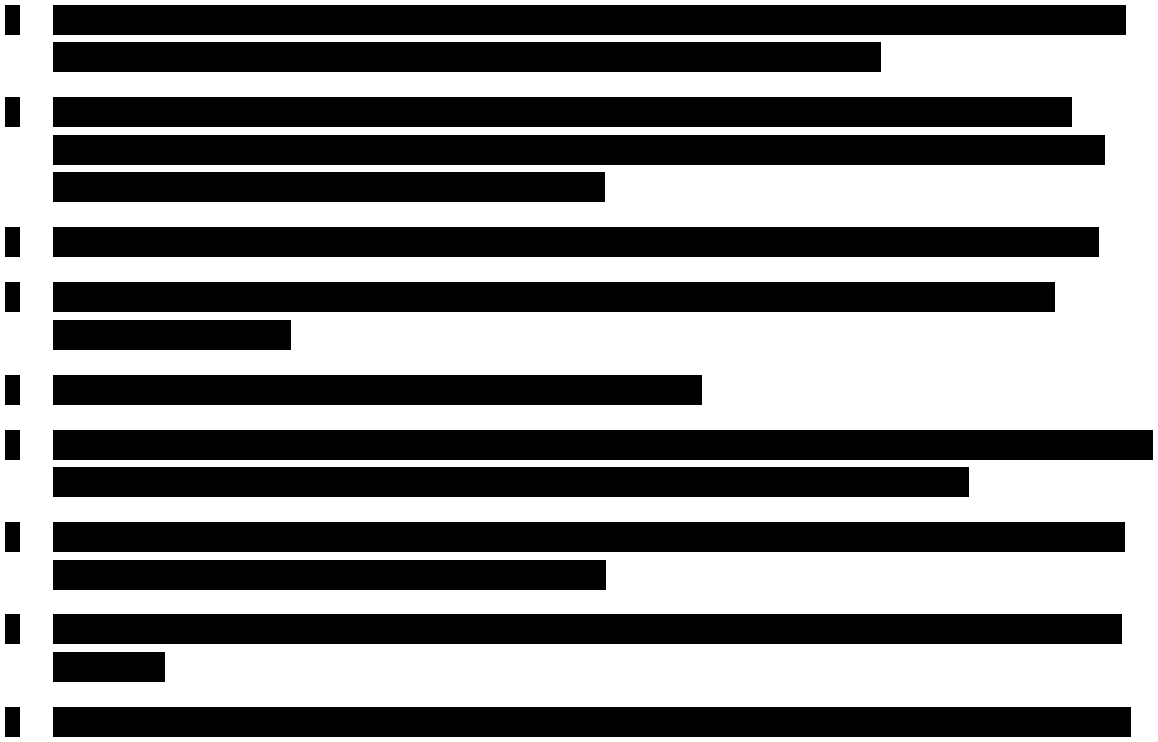
- To assess the effect of garetosmab versus placebo on the number of new HO lesions per patient from baseline to week 28 as determined by CT
- To assess the effect of garetosmab versus placebo on the number per patient of clinician-assessed flare-up episodes to week 28
- To assess the effect of garetosmab versus placebo on the proportion of patients with new HO lesions as determined by CT at week 28
- To assess the effect of garetosmab versus placebo on volume of new HO lesions as determined by CT at week 28
- To assess the effect of garetosmab versus placebo on the occurrence of patient-reported flare-up episodes-to week 28
- To assess the effect of garetosmab versus placebo on the occurrence of clinician-assessed flare-up episodes

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- To assess the effect of garetosmab versus placebo on the number per patient of patient-reported flare-up episodes
- To characterize the concentrations of total activin A
- To evaluate concentrations of garetosmab
- To assess the immunogenicity of garetosmab
- To assess the effect of garetosmab versus placebo in pulmonary function assessed by pulmonary function tests
- To assess clinical outcomes (ie, joint function [Cumulative Analog Joint Involvement Scale (CAJIS)]) at baseline and over time after the first dose of garetosmab versus placebo
- To assess the effect of garetosmab versus placebo on patient's disease severity assessed by the Patient Global Impression of Severity (PGIS)
- To assess the effect of garetosmab versus placebo on patient's change in disease assessed by the Patient's Global Impression of Change (PGIC)
- To assess the effect of garetosmab versus placebo on clinician's change in disease assessed by the Clinician's Global Impression of Change (CGIC)
- To assess the safety and efficacy of garetosmab beyond 12 months

2.3. Exploratory Objectives

The exploratory objectives of the study are:



VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Treatment with garetosmab prevents the formation of new HO lesions in patients with FOP.

3.2. Rationale

3.2.1. Rationale for Study Design

R2477-FOP-2175 is a randomized, double-blind, placebo-controlled study to confirm the efficacy and further assess the safety of garetosmab at [redacted] mg/kg in patients with FOP. In addition, the efficacy and safety of a lower dose ([redacted] mg/kg) will be evaluated to determine if efficacy can be maintained with an improved safety profile (described below). Given that FOP is an ultra-rare condition and more than 1 year has passed since the last patient received a dose in LUMINA-1, patients who were enrolled in the phase 2 study will be eligible for this phase 3 study.

Garetosmab at [redacted] mg/kg every 4 weeks (Q4W) demonstrated substantial efficacy in adult patients with FOP in the phase 2 study, LUMINA-1, including approximately 90% reduction in new HO lesions by CT and reduced incidence of flare-ups at 28 weeks; the treatment effect was maintained out to 56 weeks. Given these outcomes, combined with the wider availability of CT (as opposed to ^{18}F-NaF PET), the study will seek to show a reduction in the number of new HO lesions assessed by whole-body low-dose CT at week 56 compared to placebo.

Risks for garetosmab that were identified during LUMINA-1 included epistaxis and skin and soft tissue infections (acne, folliculitis, cellulitis, furuncle, pustular rash, carbuncle, and abscess). After the 28-week, placebo-controlled, Double-Blind Treatment Period (DBTP), during the open-label period, there were 5 deaths from causes that are typically observed in FOP patients with severe disability; No relationship between garetosmab treatment and the deaths was identified. Despite the association between garetosmab use and epistaxis, there does not appear to be an association between garetosmab use and bleeding in other organs or systems, nor between having epistaxis during garetosmab treatment and having other bleeding events. Notwithstanding, the 1-year placebo arm of R2477-FOP-2175 study will allow for additional long-term, controlled assessment of safety. Restriction of the population to those with lower likelihood of morbidity and mortality due to FOP itself (ie, lower CAJIS, exclusion of patients with known bleeding diathesis, known history of cerebral vascular malformation, know history of severe bleeding) will allow to better determine the relationship of study drug to adverse events.

The DBTP provides for 56 weeks of assigned treatment for analysis of safety and efficacy.

Patients can elect to remain blinded at week 56 and continue to receive assigned study treatment in the Extended Treatment Period (ETP). The ETP provides at least 6 additional months of assigned treatment (for a minimum total treatment duration of 18 months of study treatment). The ETP provides additional analysis of safety and efficacy beyond the DBTP.

If a patient decides not to enter the ETP, the patient will be unblinded to assigned treatment group, will no longer receive study treatment, and will enter an Observation Period. All patients that enter the Observation Period (regardless of assigned treatment in the DBTP) will be assessed by a phone call every 2 months for survival and any pertinent safety events (ie, severe bleeding).

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Thus, a patient either continues on blinded treatment until the end of study or enters the Observation Period. The ETP and Observation Period will continue until the last global patient completes week 84.

There may be an opportunity to receive garetosmab after the end of the study (Section 8.2.2.3).

3.2.2. Rationale for Dose Selection

The following dose regimens are proposed for this study in patients with FOP:

- [redacted] mg/kg IV Q4W
- [redacted] mg/kg IV Q4W

In the LUMINA-1 study, [redacted] mg/kg IV Q4W dose regimen was studied in patients with FOP and was shown to be efficacious. A second lower dose has been selected for the R2477-FOP-2175 study to determine if a lower dose can improve the benefit:risk profile.

Studies using an FOP mouse model demonstrated a dose response for reduction of HO lesions. The minimum effective dose in the mice (1 mg/kg QW) achieved a mean steady state trough concentration (C_{trough}) of approximately [redacted] mg/L (Study [redacted]). In these animals, linear elimination of garetosmab was predominant for both [redacted] mg/kg and [redacted] mg/kg QW doses. No exposure response was identified for the fatal events, epistaxis or dermatological adverse events observed with the garetosmab dose regimen of [redacted] mg/kg Q4W in LUMINA-1.

The proposed [redacted] mg/kg Q4W regimen in this clinical study is expected to achieve a steady state C_{trough} of approximately [redacted] mg/L, higher than the observed minimum effective concentration in the FOP mouse model, and hence is expected to provide a clinical benefit. Study R2477-FOP-2175 will investigate both the [redacted] mg/kg Q4W and [redacted] mg/kg Q4W dose regimens to further characterize the dose/exposure-response relationships. The higher dose ([redacted] mg/kg Q4W) will provide additional data on the efficacy and safety of garetosmab. The lower dose ([redacted] mg/kg Q4W) will provide data to inform the optimization of the benefit:risk profile for garetosmab.

3.3. Risk-Benefit

3.3.1. Risk-Benefit Assessment for Garetosmab

Potential benefit of this study and a summary of the safety and efficacy data from LUMINA-1 are described previously in Section 1 and the IB. Because patients with FOP suffer from a severe, debilitating, and ultimately fatal genetic disease, it is proposed that the potential benefit of garetosmab in reducing HO activity outweighs any potential risks previously outlined.

Five deaths were reported in the open-label period of LUMINA-1. The sponsor investigated these events extensively, and the majority of these deaths appear consistent with common causes of death in patients with FOP, and with the life expectancy in patients with FOP of similar age and disease severity as measured by the clinical staging of FOP developed by Pignolo et al (Pignolo, 2018). Thus, a clear relationship to treatment was not identified. However, as these deaths occurred in the absence of a placebo group in the open-label period of the LUMINA-1 study, the possibility of an association cannot be excluded. Therefore, this phase 3 study has been designed to further evaluate the benefit-risk profile of garetosmab in adult patients with FOP. This study will include an extended 1-year placebo arm which will allow for controlled assessment of

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

safety, while the addition of inclusion/exclusion criteria will restrict the population to those with lower likelihood of morbidity and mortality due to the disease itself (ie, lower CAJIS and less disability), and allow the sponsor to better determine the relationship of study drug to adverse events. In addition, the ETP will allow the sponsor to understand better the long-term safety profile of garetosmab.

Specific safety considerations and risk mitigation strategies for the study are described in the sections below. These measures will be described in the informed consent form (ICF).

A risk-benefit statement with respect to the overall development program is provided in the IB.

3.3.2. Risk of Epistaxis and Monitoring

Due to adverse events (AEs) of epistaxis reported during the conduct of the LUMINA-1 study, epistaxis is considered an identified risk with garetosmab.

Results from LUMINA-1 showed imbalances in TEAEs during the 28-week double-blind period, with a higher incidence of epistaxis in the garetosmab group (50.0%) compared to placebo (16.7%). Although epistaxis has been a frequently reported TEAE, the events have been predominantly mild in severity with no effect on patients' ability to receive garetosmab. Only 1 patient experienced a serious event of epistaxis, which required hospitalization for nasal packing; the patient recovered and continued in the study. Additional details are provided in the IB.

To mitigate and/or allow for a more detailed understanding of the potential risk for epistaxis, the following actions will be taken:

- Addition of the following exclusion criteria (Section 7.2.2):
  - Concomitant antiplatelet therapy (other than low-dose acetylsalicylic acid) or anticoagulants
  - Any history of severe, non-traumatic bleeding requiring transfusion or hospitalization for hemodynamic compromise (eg, severe nose bleeds requiring hospitalization, nasal packing or cauterization, menstrual bleeding that is prolonged/heavy)
  - Known pre-existing medical history of a bleeding diathesis (eg, hemophilia A, von Willebrand's Factor deficiency, platelet count $\leq 20 \times 10^9$/L)
- Screening/baseline consult with an ear-nose-throat (ENT) specialist to assess for and document possible pre-existing nasal blood vessel ectasias or other anatomic anomalies.
- The following events will be considered adverse events of special interest (AESI) (Section 10.1.3), requiring notification to sponsor within 24 hours:
  - Moderate epistaxis (defined as any episode of epistaxis lasting longer than 30 minutes or requiring professional medical intervention)
  - Severe epistaxis (based on definition of a severe AE as described in Section 10.2.5)
  - Other moderate or severe episodes of spontaneous non-traumatic bleeding

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- Screening/baseline and post-treatment assessment of coagulation parameters (including activated partial thromboplastin time, prothrombin time, international normalization ratio [INR], thrombin time) and fibrinogen levels will be performed in addition to BMP9 measurements and an assessment of platelet function via platelet flow cytometry.
  - If possible, for patients with a moderate or severe AESI of epistaxis or other non-traumatic bleeding, the investigator should attempt to obtain an unscheduled assessment of coagulation parameters and platelet flow cytometry as close as possible to the time of this AESI.
- In addition, investigators should discourage the use of anti-inflammatory drugs, to the extent possible, giving preference to COX-2 inhibitors.

3.3.3. Risk of Skin and Soft Tissue Infections and Monitoring

Due to AEs in the category of skin infection (including but not limited to folliculitis, abscesses, and cellulitis) reported in LUMINA-1, skin and soft tissue infections are considered an identified risk with garetosmab.

During the 28-week double-blind treatment period of LUMINA-1, skin infection TEAEs (including folliculitis, abscesses, cellulitis and acne) were reported in 60% of patients treated with garetosmab and 12.5% of the patients treated with placebo. None of these events was serious, severe, or led to discontinuation of study treatment. During the open-label treatment period, skin and soft-tissue infection TEAEs (including folliculitis, furuncles, abscess, carbuncle, and cellulitis) were reported in patients treated with garetosmab, including 5 patients who experienced serious events of abscess which required admission to the hospital for incision and drainage. The events resolved, and patients continued to receive garetosmab after a temporary treatment interruption.

To mitigate and/or allow for a more detailed understanding of the potential risk of skin and soft tissue infections, the following actions will be taken:

- Patients will be reminded of the importance for good hygiene practices.
- Early and proactive monitoring for potential lesions during regularly scheduled physical exams
  - Particular attention should be paid to areas with poor ventilation (eg, perineal, perianal, vulvar, axillar, and underarm areas).
- The following will be considered AESIs:
  - Skin infection/abscess that requires referral to specialist for treatment

3.3.4. Potential Risk for Reproductive Organ Adverse Events in Male Patients and Monitoring

In animal studies, garetosmab resulted in male reproductive tissue findings in both rats and monkeys. After 5 weeks of weekly treatment in rats, garetosmab-related severe inflammation was observed histologically in the epididymis and efferent ducts. After 26 weeks of weekly treatment in monkeys, whose male reproductive anatomy more closely resembles that of humans, there was a decrease in germ-cell production in the testes tissue; however, this finding did not result in

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

inflammation as seen in rats, nor did it result in decreased sperm quality based on semen analysis results.

In a clinical study in 8 healthy male subjects treated with garetosmab [redacted] mg/kg IV Q4W×2 doses (R2477-1033-HV-1621), no clinically meaningful changes were observed with respect to sperm motility, concentration, movement, count, and volume. Mean analyte values remained within normal limits. One subject reported an AE of testicular pain after the first dose. The event was mild, occurred on study day 3 and resolved on study day 10, was considered by the investigator to be related to study drug, and did not recur with a second dose. This subject did not have any abnormalities noted on scrotum ultrasounds obtained at week 2, week 12, and week 24.

In the week 28 analysis of LUMINA-1, in which patients with FOP were treated with garetosmab [redacted] mg/kg IV Q4W, no AESIs related to reproductive organs (epididymitis, orchitis, hydrocele, scrotum pain, scrotum swelling) were reported. In order to confirm these findings, the following actions will be taken in male patients in this study:

- Baseline urogenital exams, including scrotum ultrasound with doppler prior to initiation of study treatment and as follow-up for relevant AEs
- The following will be considered AESIs (Section 10.2.3):
  - Epididymitis, orchitis, hydrocele, scrotum pain, and scrotum swelling
  - Patients who experience any of these AEs will be referred for evaluation and clinical care by an appropriate specialist. Scrotum ultrasound may be performed, if clinically warranted, during follow-up of the AE.
- Finally, male patients in this study will be informed of the potential risk of developing AEs of pain and/or discomfort, swelling of the scrotum region, and decreased sperm counts, motility, and fertility.

3.3.5. Potential Risk for Embryofetal Toxicity and Pregnancy Monitoring and Prevention

Based on findings from animal studies and theoretical mechanistic considerations, garetosmab treatment in pregnant women may lead to embryofetal toxicity. Results from a reproductive and postnatal developmental toxicology study conducted in the cynomolgus monkey indicate that exposing pregnant monkeys to garetosmab results in infant malformations and infant mortality. Garetosmab has not been administered to pregnant women. In addition, while antibody drugs in the semen are normally found at extremely low levels, the level of garetosmab that may cross into the semen is unknown, given the potential for inflammation of the efferent duct associated with garetosmab treatment.

To mitigate and/or allow for a more detailed understanding of the potential risk of embryofetal toxicity, the following actions will be taken:

- Women of childbearing potential (WOCBP) will only be enrolled in the study after a negative pregnancy test, and additional urine pregnancy testing will be performed prior to each subsequent dose of study treatment.
- Monthly menstrual history will be collected, and pregnancy testing and reminders to use highly effective methods of contraception will be conducted during the study.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- Male patients with WOCBP partners will be asked to use condoms to prevent fetal exposure and to inform and ensure their female partners also use highly effective contraception measures to prevent pregnancy.
- Garetosmab will be discontinued in any patient who becomes pregnant.
  - In case pregnancy occurs, the investigator will follow the pregnancy until delivery (Section 10.1.3). If the pregnancy continues to term (delivery), the health of the infant will be followed up for a period of 3 months postnatally.

3.3.6. Potential Iatrogenic Injuries

Soft-tissue injuries, especially those involving muscle, may induce flare-ups and HO in patients with FOP. There have been anecdotal reports of flare-ups induced by phlebotomy procedures and blood pressure cuff pressure. Such events were not observed in LUMINA-1. Study personnel will be trained to minimize the risk of iatrogenic soft-tissue injuries.

3.3.7. Radiation Exposure

CT is an imaging procedure that involves ionizing radiation exposure to the patient. The ionizing radiation deposited in tissue is expressed in units of millisievert (mSv). The effective dose (ED) is a single figure that refers to the tissue-weighted radiation dose to the patient, accounting for stochastic risk effects associated with the radiation exposure. In the US, the maximum recommended allowed ED for an adult research subject (age ≥18 years) in a single year is 50 mSv (21 Code of Federal Regulations 361.1). In the European Union, the guidelines for studies intended to gain knowledge directly aimed at the prevention or cure of disease establish an ED limit of up to 20 mSv per year for adult patients (age ≥18 years). In Japan, in line with the International Commission on Radiological Protection (ICRP), the maximum recommended allowed ED for a research subject in a single year is 50 mSv, and the average of ED per year for five years is limited up to 20 mSv. In the present study, for a patient, a low-dose whole-body CT scan will result in an ED of approximately 2.9 mSv to 5.1 mSv. For the four CT scans (three CT scans for all patients and the fourth CT scan for patients continuing treatment in the ETP) planned in this study, the total ED range is approximately 11.6 mSv to 20.4 mSv over approximately 18 months and is well within the annual research exposure limit. In case the week-56 CT scan for a patient is repeated due to an image quality issue resulting in the images to be deemed inadequate for evaluation of HO lesions, an additional CT scan will be undertaken. The additional radiation dose for this repeat CT scan would be approximately 2.9 mSv to 5.1 mSv. The total radiation exposure during the entire study will be approximately or less than a single diagnostic CT scan of the chest, abdomen, and pelvis (approximately 25 mSv). Radiation risk information will be included in the ICF.

3.3.8. Study Conduct in Response to COVID-19

Recognizing that the “Coronavirus Disease 2019” (COVID-19) pandemic will have an impact on the conduct of clinical trials, the sponsor does not intend to screen any patients in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. Until then, the sponsor plans to obtain approvals from Health Authorities/Ethics Committees to enable initiation of study sites for this study, as allowed by local laws and regulations.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

For information regarding the permitted timing of COVID-19 vaccinations, see Section 7.2.2 Exclusion Criteria, criterion #23 and Section 8.8 Concomitant Medications and Procedures.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoints

4.1.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the number of new HO lesions at week 56.

4.1.1.2. Primary Safety Endpoint

The primary safety endpoint is the incidence and severity of treatment-emergent AESIs from baseline to week 56.

4.1.2. Secondary Endpoints

4.1.2.1. Key Secondary Endpoints

The key secondary endpoints are:

- Number of clinician-assessed flare-ups through week 56
- Occurrence of new HO lesions at week 56 (Yes/No)
- Total volume of new HO lesions at week 56
- Occurrence of patient-reported flare-ups through week 56 (Yes/No)

4.1.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Number of new HO lesions at week 28
- Number of clinician-assessed flare-ups through week 28
- Occurrence of new HO lesions at week 28 (Yes/No)
- Total volume of new HO lesions at week 28
- Occurrence of patient-reported flare-ups through week 28 (Yes/No)
- Occurrence of clinician-assessed flare-ups through weeks 28 and 56 (Yes/No)
- Number of patient-reported flare-ups through week 28 and 56
- Change from baseline in joint function assessment by physician to week 28 and week 56 by the CAJIS
- Change from baseline in pulmonary function as assessed by spirometry at week 28 and week 56
- Change from baseline in disease severity to week 28 and week 56 by the PGIS
- Change since the start of the study in disease severity to week 28 and week 56 by the PGIC

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- Change since the start of the study in disease severity to week 28 and week 56 by the CGIC

4.1.2.3. Other Secondary Endpoints

Other secondary endpoints are:

- Concentrations of total activin A in serum over time through week 56
- Concentrations of garetosmab in serum over time through week 56
- Incidence and titer of anti-drug antibodies (ADA) to garetosmab over time through week 56

For patients continuing extended treatment, additional other secondary efficacy endpoints are:

- Number of new HO lesions at week 84
- Occurrence of new HO lesions at week 84 (Yes/No)
- Total volume of new HO lesions at week 84
- Number of clinician-assessed flare-ups through week 84
- Occurrence of clinician-assessed flare-ups through week 84 (Yes/No)

4.1.3. Exploratory Endpoints

The exploratory endpoints are:

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

4.2. Estimands for Primary and Key Secondary Objectives

4.2.1. Estimand for Primary Efficacy Objective:

The estimand for the primary efficacy objective to assess the effect of garetosmab versus placebo on the formation of new HO lesions from baseline to week 56, as determined by low dose CT, is defined below:

Population	Patients with FOP
Endpoint	Number of new HO lesions at week 56
Treatments	Garetosmab at each dose level vs placebo
Handling of intercurrent event	The intercurrent events of interest include: • Premature discontinuation of study treatment: Treatment policy strategy will be used to address these intercurrent events, specifically, the value for the endpoint is used regardless of adherence to study treatment. [redacted]
Population-level summary and treatment comparison	The rate of new HO lesion formation, defined as the mean number of new HO lesions formed per year during the 56 weeks of DBTP, will be the population-level summary measure of treatment effect. The comparison of treatment effect will be quantified by the rate ratio, defined as the ratio of the rates of new HO lesion formation.

4.2.2. Estimands for Key Secondary Objectives:

The estimands for the following key secondary objectives are provided below:

- To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on the number per patient of clinician-assessed flare-up episodes to week 56
- To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on the proportion of patients with new HO lesions as determined by CT at week 56
- To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on volume of new HO lesions as determined by CT at week 56
- To assess the effect of garetosmab ([redacted] mg/kg and [redacted] mg/kg) versus placebo on the proportion of patient-reported flare-up episodes through week 56

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Population	Patients with FOP
Endpoint	• Number of clinician-assessed flare-ups through week 56 • Occurrence of new HO lesions at week 56 (Yes/No) • Total volume of new HO lesions at weeks 56 • Occurrence of patient-reported flare-ups through week 56 (Yes/No)
Treatments	Garetosmab at each dose level vs placebo
Handling of intercurrent event	The intercurrent events of interest include: • Premature discontinuation of study treatment: Treatment policy strategy will be used to address these intercurrent events, specifically, the value for the endpoint is used regardless of adherence to study treatment. [redacted]

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Population-level summary and treatment comparison	• Number of clinician-assessed flare-ups through week 56: The rate of clinician-assessed flare-ups, defined as the mean number of new clinician-assessed flare-ups per year during the 56 weeks of DBTP, will be the population-level summary measure of treatment effect. The comparison of treatment effect will be quantified by the risk ratio, defined as the ratio of the rates of clinician-assessed flare-ups. • Occurrence of new HO lesions at week 56 (Yes/No): Difference in the proportion of patients with new HO lesions between garetosmab dose group and placebo • Total volume of new HO lesions at week 56: Difference in mean in total volume of new HO lesions between garetosmab dose group and placebo • Occurrence of patient-reported flare-ups through week 56 (Yes/No): Difference in the proportion of patients with patient-reported flare-ups between garetosmab dose group and placebo

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

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

5.2. Efficacy Variables

HO is the key clinical feature of FOP and the primary cause of immobility, disability, pain, and early mortality. Therefore, our choices of efficacy endpoint measures are aimed at allowing a rapid and sensitive assessment of the potential drug effect of inhibiting activin A on heterotopic bone formation.

5.2.1. Quantitative Whole-Body CT

The number of new HO lesions as assessed by CT at week 56 is chosen as the primary efficacy endpoint. For consistency and comparability with the global LUMINA-1 study, similar imaging procedures, image review process, and image acquisition time points are used in this study.

Findings in LUMINA-1 showed that a treatment effect can be observed by CT in a 6-month time frame and was maintained at week 56. This study will examine the treatment effect of garetosmab on the number and volume of new HO lesions, as well as the percentage of patients with new HO lesions, as assessed by CT at 56 weeks (primary endpoint) and 28 weeks (secondary endpoint). Other characteristics of new and existing HO lesions will also be assessed throughout the study. Without treatment, active HO lesions are expected to mature and become detectable by CT. A post-hoc analysis was performed by the LUMINA-1 study imaging contract research organization (CRO) at the request of the sponsor to compare quantification of new HO lesions in the LUMINA-1 study by reading only low-dose CT images versus reading both ^{18}F-NaF PET and CT as specified in the protocol. The analysis showed that using CT as the sole method for quantifying new HO lesions performed as well as PET/CT ($p=0.75$). Combined with the wider availability of CT (as opposed to ^{18}F-NaF PET), the study will seek to show a reduction in the number of new HO lesions assessed by whole-body low-dose CT at week 56 compared to placebo. The same criteria for defining new lesions on CT in LUMINA-1 will also be applied in this study. Additional details on new HO lesion assessments can be found on the imaging charter.

5.3. Clinical Endpoint Measures

Clinical aspects of FOP disease and flare activity will be measured by the following:

- FOP Flare-up diary. This questionnaire is self-completed by the patient (or the patient responses are recorded by their caregiver, if applicable) daily. The FOP Flare-up daily diary contains 3 sections: a historical flare-up section (collected only at baseline), a Flare-up maintenance section (to capture longitudinal data on each flare-up), and a new Flare-up section that captures new flare-ups.
  - Flare-up is defined as two or more of the following: pain, swelling, joint stiffness, or decrease in movement.
- FOP clinician-assessed flare-up

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- Clinician-assessed FOP Flare-up is defined as signs and symptoms that based on the Investigator's judgement are attributed to an FOP Flare-up. Major symptoms and signs associated with FOP Flare-up to be considered by the Investigator when evaluating for a Flare-up include but are not limited to: swelling, pain, decrease in movement, joint stiffness, warmth and redness. Details regarding the Flare-up are to be collected as described in Section 9.2.3.3.
- CAJIS is a clinician assessment of 15 major joints; each major joint rated normal unaffected (0), affected (1), or completely functionally ankylosed (2). The total score ranges from 0 to 30. Instructions for the use of the CAJIS assessment is provided in the study reference manual. Physicians at all sites will undergo training for CAJIS assessment as described in the study reference manual (Kaplan, 2017).
- EQ-5D-3L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-3L is a measure of health-related quality of life (HRQoL) and defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. This questionnaire is self-completed by the patient (or their responses are recorded by their caregiver, if applicable).
- The Short Form – 36 Survey (SF-36) is a 36-item self-administered patient-reported outcome (PRO) measure assessing HRQoL concepts relevant across age, disease, and treatment group. The SF-36 will be completed by patients ages 18 years of age and older. The SF-36 assesses physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Patients answer questions assessing these concepts over the previous week using 3-, 5-, or 6point Likert scales; scores range from 0 to 100, with higher scores indicating better health. The past-week recall has been compared to the 4-week recall and is shown to have comparable properties (Keller, 1997). The SF-36 is one of the most widely used and studied PRO measures, with good psychometric properties documented across different populations.
- PGIC is a single-item, self-administered questionnaire to assess the patient's global impression of change. This endpoint will be used to assess change in disease severity over time and will be used as an anchor to assess meaningful change.
- PGIS is a single-item, self-administered questionnaire to assess the patient's global impression of severity. This endpoint will be used to assess disease severity over time and will be used as an anchor to assess meaningful change.
- CGIC is a single-item questionnaire to assess the clinician's global impression of change. This endpoint will be used to assess change in disease severity over time and will be used as an anchor to assess meaningful change.
- Spirometry will assess pulmonary function and lung volume assessments will be performed by CT.

Note: To ensure consistency of assessments, it is advised that the same clinician performs the clinician-assessed FOP flare-ups and CAJIS evaluations, at all visits for the mentioned assessments for a given patient, whenever possible.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

5.4. Biochemical Markers of Bone Formation

Biochemical markers of bone formation, bone specific alkaline phosphatase (BSAP) and alkaline phosphatase (tAP), amongst others, are elevated in some patients with FOP at levels 2- to 6-fold above those found in healthy subjects (Al Kaissi, 2016) (Kitoh, 2013). Elevations in these markers of bone formation are thought to be a reflection of the degree of ongoing HO. Suppression of HO by garetosmab may reduce the levels of these markers. Therefore, the effect of garetosmab on these biomarkers as well as on other biochemical markers of bone formation and resorption will also be assessed.

5.5. Safety Variables

Safety variables in this study include:

- TEAEs
- Vital signs
- Physical examination
- Body weight and height
- Menstrual cycle history at screening/baseline and throughout the study (for female patients)
- Electrocardiogram (ECG)
- Laboratory testing including coagulation assessments (activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT), Fibrinogen and a calculation of international normalization ratio (INR))
- Platelet count and platelet activation by flow cytometry
- ENT consultation

5.6. Pharmacokinetic and Total Target Variables

The pharmacokinetic (PK) variable is the concentration of functional garetosmab at each time point. These sampling timepoints are specified in Table 2 (screening and DBTP visits up to week 56), Table 3 (ETP visits), and Table 4 (continued ETP visits).

The total target variable is the concentration of total activin A at each time point. These sampling timepoints are specified in Table 2 (screening and DBTP visits up to week 56), Table 3 (ETP visits), and Table 4 (continued ETP visits).

Serum samples in this study will be collected using a sparse sampling schedule, eg, only small number of blood samples is collected at any single clinic visit.

5.7. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time point/visit. Samples in this study will be collected at the clinic visits specified in Table 2 (screening and DBTP visits up to week 56), Table 3 (ETP visits), and Table 4 (continued ETP visits). Samples for neutralizing antibody (NAb) may be analyzed when the NAb assay becomes available.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

5.8. Research Biomarker Variables

Change in blood levels of additional bone and cartilage biomarkers, may include, but are not limited to changes in BSAP, total procollagen type 1 N-terminal propeptide (P1NP) collagen 10, and type I collagen cross-linked C-telopeptide (CTX1). Changes in blood levels of inflammatory markers may include but are not limited to changes in high sensitivity C-reactive protein (hs-CRP). Biomarkers related to the activin A and the ACVR1 pathway including but not limited to BMP ligands or biomarkers that further elucidate the mechanism of action of garetosmab may also be explored. Samples in this study will be collected at the clinic visits specified in Table 2 (screening and DBTP visits up to week 56), Table 3 (ETP visits), and Table 4 (continued ETP visits).

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

6. STUDY DESIGN

6.1. Study Description and Duration

R2477-FOP-2175 is a phase 3, randomized, multi-center, multinational, parallel-group, placebo-controlled study to assess the efficacy of garetosmab on the reduction of heterotopic bone formation, and its safety, tolerability, and PK in FOP patients with active disease caused by any FOP-causing variant of ACVR1. Approximately 66 patients will be enrolled 1:1:1 into the 3 parallel arms of the study. The study consists of 4 periods and a Follow-up Safety Visit (Figure 1, Figure 2, and Figure 3):

- **Screening Period:** 4 weeks in duration (from study day -28 to day -1 [visit 1]). All patients will undergo an informed consent process and screening procedures. Screening procedures may be conducted over multiple days.
- **Double-Blind Treatment Period (DBTP):** 56 weeks in duration (from study day 1 [visit 2] to week 56 [visit 17]). All patients will be randomized to double-blind treatment with garetosmab [redacted] mg/kg, garetosmab [redacted] mg/kg, or placebo.
- **Extended Treatment Period (ETP):** 28+ weeks in duration (study week 56+ [visit 17+]) for those who choose to continue double-blind treatment. Patients who complete the DBTP and elect to extend double-blinded treatment continue until the last global patient reaches week 84.
- **Observation Period:** 28+ weeks in duration (study week 56+ [visit 17+]) for those who choose to discontinue from double-blind treatment. Patients who complete the DBTP and elect to go unblinded and stop treatment will be followed to assess survival and any pertinent safety events (ie, severe bleeding; Section 3.3.2) since the last contact. The Observation Period will continue until the last global patient completes their last study visit. Patients will not receive treatment and may participate in other studies.
- **Follow-Up Safety Visit:** 30 weeks from the last dose administered (study week 84+ [visit 24+]) for all patients who receive treatment, except for patients who are unblinded that were treated with placebo (placebo-treated patients unblinded at week 56 [visit 17] do not participate in the Follow-Up Safety Visit). Consists of a safety follow-up visit 30 weeks after the last study drug administration.

Efficacy assessments will include whole-body CT for HO lesions, assessment of flare-ups, CAJIS, pulmonary function tests, change in disease severity, and quality of life (EQ-5D-3L and SF-36).

Safety assessment will include AEs, vital signs, physical examination, ECGs, serum and urine laboratory testing, ENT consultation, coagulation parameters, and platelet flow cytometry.

Patients who participated in the phase 2 LUMINA-1 study can enroll if they meet the inclusion criteria and do not meet the exclusion criteria.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Figure 1: Study Flow Diagram

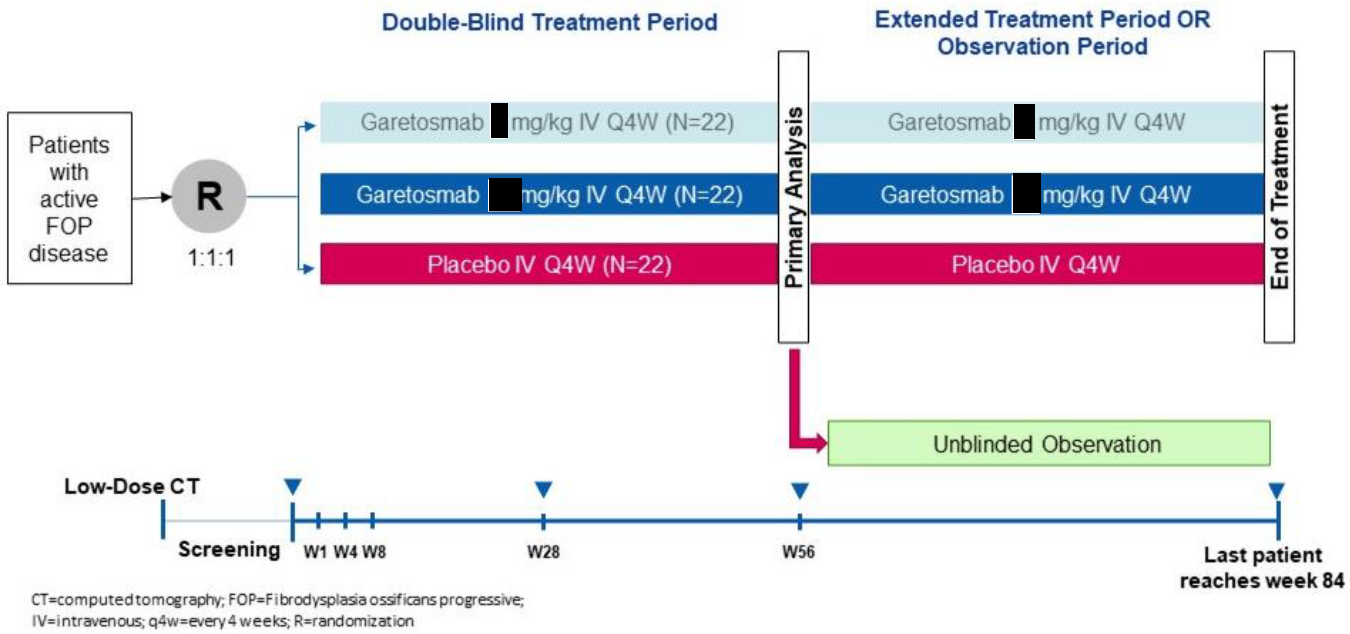
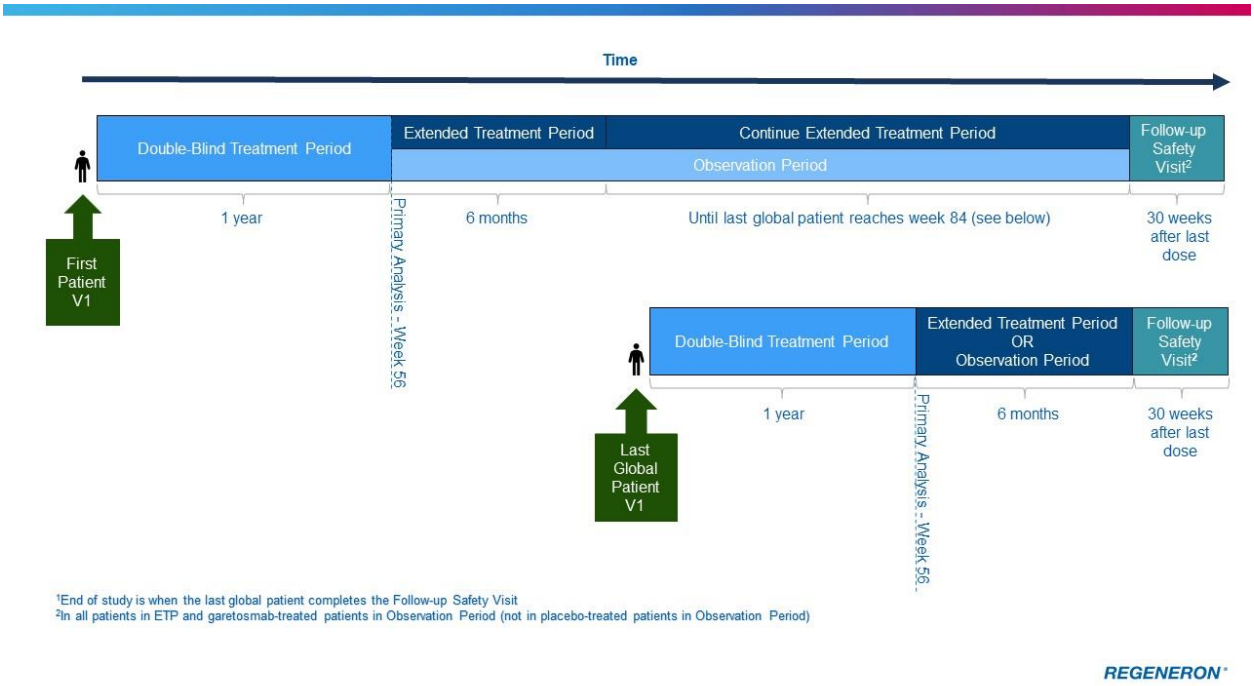
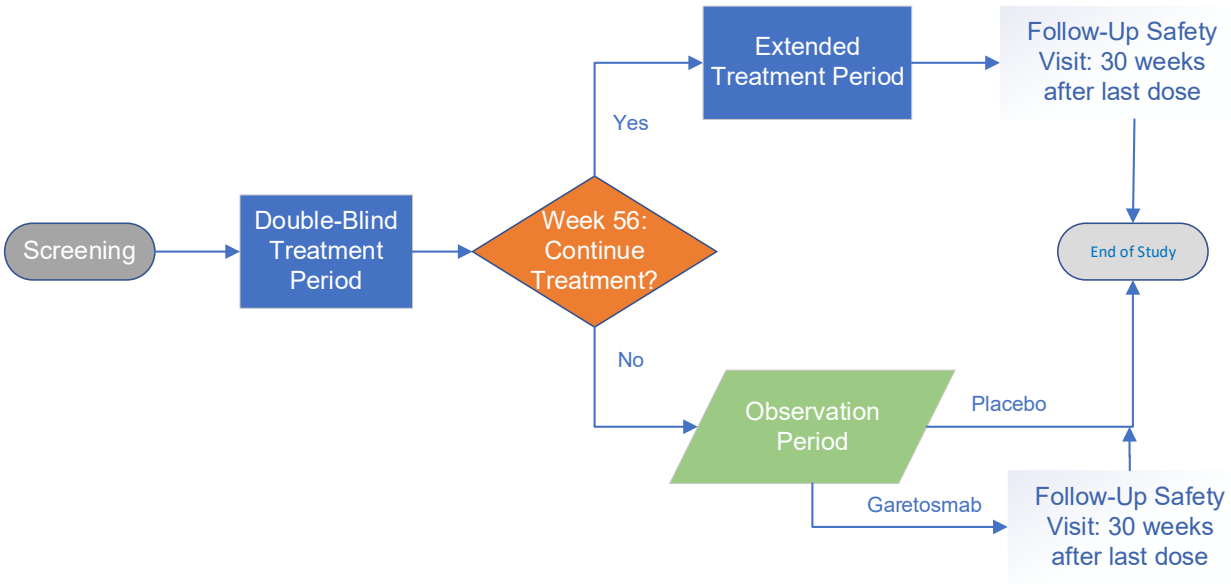


Figure 2: Study Flow Diagram from First Patient In Until End of Study[1]



VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Figure 3: Patient Decision Tree



VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

6.1.1. Screening Period

During the Screening Period (study day -28 to day -1 [visit 1]), all patients will undergo the informed consent process and screening procedures (Figure 1, Figure 2, Figure 3, and Table 2). Screening procedures may be conducted over multiple days (Screening; Table 2). Patients who have previously participated in the LUMINA-1 study or another clinical study for treatment of FOP or are using an approved treatment for FOP may be eligible for the study after a wash-out period of five half-lives.

Screening procedures will be conducted as outlined in the Schedule of Events (Table 2), including medical history, confirmation of FOP diagnosis and ACVR1 mutation, height and weight (if feasible), physical examination, including a detailed skin examination to document existing acne or skin infections and urogenital exam for male patients, laboratory testing, and other study assessments. At the time of screening, if the patient does not have documentation of what ACVR1 mutation he/she carries or if the documentation cannot be retrieved, then a blood sample for the determination of the ACVR1 mutation should be collected prior to enrollment for this purpose. **Note:** For sites in China, ACVR1 mutation in these patients will be confirmed only by prior documentation of any known ACVR1 FOP causing mutation.

Laboratory assessments and other procedures used to determine eligibility may be repeated once during the Screening Period. If the ACVR1 mutation results have not been received before randomization, the medical monitor should be contacted.

Patients who meet initial eligibility screening will have baseline procedures conducted. Baseline imaging procedures (whole-body low-dose CT) will be performed within 1 week before first study drug administration (study day 1), ie, within study day -7 to day -1, to establish a baseline for assessing new HO lesions during the course of the study. Patients must be physically able and willing to undergo CT scanning procedures to be eligible for this study. As part of screening/baseline, patients will have a consultation with an ENT specialist to assess and document pre-existing nasal blood vessel ectasias or other anatomic anomalies; this evaluation must take place before first dose of study drug.

Pre-treatment CAJIS, patient-reported FOP Flare-up diary, and other PRO questionnaires will be completed. Patients and their primary caregiver(s), if assistance is needed, will be given instructions on how to complete the FOP Flare-up diary. The baseline entry for the FOP flare-up diary will be completed on day1 before study drug administration.

For all patients, an assessment of coagulation parameters (including but not limited to aPTT, PT, TT, INR), fibrinogen, and platelet function via platelet flow cytometry will be performed at screening and baseline visit. Assessment of coagulation parameters and platelet function via flow cytometry will be performed to monitor and explore potential mechanism of epistaxis and any other non-traumatic bleeding. Countries with export restrictions of biological samples to the United States are excluded from mandatory testing if samples cannot be sent to the central lab.

Baseline samples will be collected for drug and activin A (target) concentration measurements, ADA assessment, and other biomarker concentration measurements (Table 2).

For male patients, screening scrotum ultrasound will be performed to aid detection of existing abnormality and to capture a pre-treatment baseline image.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Women of childbearing potential and male patients with WOCBP partners will be reminded at all visits to adhere to highly effective contraception (defined in Section 7.2.2 Exclusion Criteria #25 and #26). Pregnancy status and menstrual cycle history of WOCBP will be monitored through the end of the study. During screening period sex-hormones (Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol) will be measured between days 3 to 5 of the menstrual cycle in female patients with regular menstrual cycles.

6.1.2. Double-Blind Treatment Period

During DBTP from Baseline (day 1 [visit 2]) through week 56 [visit 17], enrolled patients will receive garetosmab at [redacted] mg/kg or [redacted] mg/kg or placebo administered IV Q4W through week 52 (day 365), for a total of 14 doses (Figure 1, Figure 2, Figure 3, and Table 2). At week 56 [visit 17], patients will choose to either continue to the ETP or to discontinue treatment and enter the Observation Period (Figure 3). At week 56, patients who enter the ETP will be dosed with study drug and patients who enter the Observation Period will not be dosed with study drug (Table 2).

Before the first dose of study drug the investigator should review screening lab results.

Patients will be closely monitored for a minimum of 2 hours after administration of study drug.

Efficacy and safety procedures in the DBTP will be performed as outlined in the Schedule of Events (Table 2).

New HO lesions will be assessed by analyzing the whole-body low-dose CT at week 28 (visit 10; day 197 [-7 to +15 days]) and week 56 (visit 17; day 393 [±14 days]). See Section 3.3.7 and Table 2.

Other clinical endpoints will be assessed by investigator or PRO measures at week 28 (visit 10; day 197 [-7 to +15 days]) and week 56 (visit 17; day 393 [±14 days]). The daily FOP Flare-up diary will be checked at every visit for completeness.

AEs will be assessed as described in Section 10.

If possible, for patients with a moderate or severe AESI of epistaxis and/or frequent episodes of epistaxis during the study, the investigator will obtain a consultation with an ENT specialist to assess relationship to any pre-existing anatomic anomalies and assess for possible treatments, including nasal cauterization based on the specialist's and investigator's judgment. If possible, the same ENT specialist should evaluate the patient at screening and follow-up assessments. Furthermore, for patients with a moderate or severe AESI of epistaxis or other non-traumatic bleeding, the investigator should attempt to obtain an unscheduled assessment of coagulation parameters and sample for platelet flow cytometry as close as possible to the time of this AESI.

Serum samples will be collected for the determination of garetosmab (study drug) and activin A (target) concentrations as well as assessment of ADA.

Serum samples will be collected for the determination of bone formation and mechanism of action biomarkers, including but not limited to BSAP, tAP, and P1NP, and exploratory biomarker profiling that may elucidate the mechanism of action of garetosmab. Sex-hormones (FSH, LH, estradiol) will be measured at days 3 to 5 of the menstrual cycle in female patients with regular menstrual cycle for the first 6 months of the DBTP.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

6.1.2.1. Extended Treatment Period

At the end of the DBTP (week 56 [visit 17]), patients may elect to continue to be treated monthly with their assigned, blinded treatment during the Extended Treatment Period (ETP) (Figure 3). Patients will continue to be blinded and receive their originally assigned treatment, garetosmab at [redacted] mg/kg or [redacted] mg/kg or placebo, administered IV Q4W at week 56 until the last global patient completes week 84 (Figure 1, Figure 2, Figure 3, Table 3, and Table 4).

Efficacy and safety procedures in the ETP will be performed as outlined in the Schedule of Events (Table 3 and Table 4).

6.1.2.2. Observation Period

At the end of the DBTP (week 56 [visit 17]), patients who do not elect to continue treatment will enter the Observation Period (Figure 3). Treatment will be discontinued (no drug will be administered at week 56 [visit 17]) and patients will be unblinded at the week 56 timepoint (Table 2). Patients will be followed with a phone call every 2 months after their last administered dose to assess for patient status (ie, survival) and pertinent safety events (ie, severe bleeding; Section 3.3.2) since the last contact, until the end of study (Figure 1, Figure 2, Figure 3, and Table 5). The Observation Period will continue until the last global patient completes their last study visit. During the Observation Period, patients may participate in other clinical studies and/or will be permitted to be prescribed any therapies that become approved. Patients who enter the Observation Period may not re-enter the ETP.

Safety procedures in the Observation Period will be performed as outlined in the Schedule of Events (Table 5).

6.1.3. Follow-up Safety Visit

All patients who receive garetosmab or participate in extended treatment (placebo-treated patients unblinded at week 56 do not participate in the Follow-Up Safety Visit) will have a safety follow-up visit 30 weeks after the last study drug administration (Figure 3), at which time the concentrations of garetosmab are expected to be near or below the level of quantitation (BLQ). At this visit, vital signs and AEs will be assessed, samples will be collected for laboratory assessments, serum pregnancy test (WOCBP only), drug concentration measurement, BMP-9 measurement, and ADA assessment (Table 3, Table 4, and Table 5).

6.1.4. Study Stopping Rules

6.1.4.1. Study Stopping Criteria

The independent data monitoring committee (IDMC) will monitor unblinded data on an ongoing basis to assess the risk/benefit profile of garetosmab (Section 6.3.1). If at any time the IDMC has significant concerns regarding a meaningful imbalance in serious adverse events (SAEs) and/or AESIs, the IDMC may make a recommendation to the sponsor to temporarily halt the study (screening, randomization, or dosing of study drug) for additional review. Based on the outcome of the review and discussions with investigators and if appropriate, regulatory authorities, the study may be suspended, restarted, or terminated. Further details will be provided in an IDMC charter.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

6.1.5. End of Study Definition

The end of study is defined as the date the last global patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

6.2. Planned Interim Analysis

No interim analysis is planned for this study.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

An IDMC will regularly monitor safety data and make recommendations to the sponsor. Further details will be defined in the IDMC charter.

6.3.2. Adjudication of New Heterotopic Ossification Lesions

Two radiologists will be employed for identification of new heterotopic ossification lesions. A third radiologist will serve to settle any disagreements. Further details will be defined in the imaging charter.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 66 patients will be enrolled globally.

7.2. Study Population

The study population consists of patients with FOP.

7.2.1. Inclusion Criteria

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

1. Male or female 18 years or older at screening
2. Clinical diagnosis of FOP (based on findings of congenital malformation of the great toes, episodic soft tissue swelling, and/or progressive HO)
3. Confirmation of FOP diagnosis with documentation of ACVR1 FOP causing mutation
4. FOP disease activity within 1 year of screening visit. FOP disease activity is defined as pain, swelling, stiffness, or other signs and symptoms associated with FOP flare-ups; or worsening of joint function, or radiographic progression of HO lesions (increase in size or number of HO lesions) with/without being associated with flare-up episodes
5. Willing and able to undergo CT imaging procedures and other procedures as defined in this study
6. Willing and able to comply with clinic visits and study-related procedures
7. Provide informed consent signed by study patient or legally acceptable representative
8. Able to understand study-related questionnaires

7.2.2. Exclusion Criteria

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

1. CAJIS score at screening >19
2. Patient has significant concomitant illness or history of significant illness such as but not limited to cardiac, renal, rheumatologic, neurologic, psychiatric, endocrine, metabolic, or lymphatic disease, that in the opinion of the study investigator might confound the results of the study or pose additional risk to the patient by their participation in the study
3. Previous history or diagnosis of cancer (exceptions: localized basal/squamous cell cancer that has been successfully excised; in situ cervical cancer)
4. Severely impaired renal function defined as estimated glomerular filtration rate <30 mL/min/1.73 m^2 calculated by the Modification of Diet in Renal Disease equation (1 retest is allowed)
5. Uncontrolled diabetes defined as hemoglobin A1C (HbA1c) >9% at screening (1 retest is allowed)

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

6. History of poorly controlled hypertension, as defined by:
    a. Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg at the screening visit
    b. Systolic blood pressure of 160 mm Hg to 179 mm Hg or diastolic blood pressure of 100 mm Hg to 109 mm Hg at the screening visit, AND a history of end-organ damage (including history of left-ventricular hypertrophy, heart failure, angina, myocardial infarction, stroke, transient ischemic attack, peripheral arterial disease, end-stage renal disease, and moderate-to-advanced retinopathy [hemorrhages or exudates, papilledema])
7. Known history of cerebral vascular malformation
8. Cardiovascular conditions such as New York Heart Association class III or IV heart failure, cardiomyopathy, intermittent claudication, myocardial infarction, or acute coronary syndrome within 6 months prior to screening; symptomatic ventricular cardiac arrhythmia (Note: sinus dysrhythmia, asymptomatic block or well-controlled atrial fibrillation with normal resting ventricular rate are not exclusion criteria.)
9. History of severe anemia requiring transfusion
10. Patients who are on concomitant antiplatelet therapy (eg, clopidogrel), anticoagulants (eg, warfarin, heparin, factor Xa inhibitor, or thrombin inhibitors) in the last 30 days or within 5 half-lives of the therapy, whichever is longer. Low-dose acetylsalicylic acid (aspirin ≤100 mg or ≤150 mg/day, based on local practice) is acceptable.

    (NOTE: low doses of heparin for flushing of catheters will be permitted.)
11. Patients with a history of severe, non-traumatic bleeding requiring transfusion or hospitalization for hemodynamic compromise (eg, severe nose bleeds requiring hospitalization, nasal packing or cauterization, menstrual bleeding that is prolonged/heavy)
12. Patients with a known pre-existing medical history of a bleeding diathesis (eg, hemophilia A, von Willebrand's Factor deficiency, platelet count $\leq 20 \times 10^9$/L)
13. Ongoing significant viral illness or pneumonia within 2 weeks of screening
14. History of severe respiratory compromise requiring oxygen, respiratory support (eg, bilevel positive airway pressure [biPAP] or continuous positive airway pressure [CPAP]), or a history of aspiration pneumonia requiring hospitalization
15. Known history of recent epididymitis (within 6 months of screening) or sexually transmitted diseases affecting urogenital organs
16. Prior use in the past year and concomitant use of bisphosphonates
17. Concurrent participation in another interventional clinical study or a non-interventional study with radiographic measures or invasive procedures (eg, collection of blood or tissue samples). Participation in the FOP Connection Registry or other studies in which patients complete study questionnaires is allowed
18. Treatment with another investigational drug, denosumab, imatinib or isotretinoin in the last 30 days or within 5 half-lives of the investigational drug, whichever is longer

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

19. Known hypersensitivity to garetosmab or any of its excipients
20. Positive serum human chorionic gonadotropin (hCG)/urine pregnancy test at the screening/baseline visit
21. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor
22. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
23. Has received a COVID-19 vaccination (initial series or booster) within 1 week of planned start of study medication or for which the planned COVID-19 vaccinations would not be completed 1 week prior to start of study drug
24. Pregnant or breastfeeding women
25. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception or undergo pregnancy tests prior to the initial dose, during the study, and for at least 30 weeks after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen- and progestogen-containing) hormonal contraception (oral) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening,
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS),
    c. bilateral tubal ligation/occlusion,
    d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study patient and that the vasectomized partner has obtained medical assessment of surgical success for the procedure),
    e. and/or sexual abstinence †,‡

    Pregnancy testing and contraception are required for WOCBP.

    Pregnancy testing and contraception are not required for women who are post-menopausal or permanently sterile.

    *WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial Facilitation Group (CTFG) guidance.

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

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

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

26. Male patients with WOCBP partners* who are not willing to use condoms with WOCBP partners to prevent potential fetal exposure, during the study, and for 30 weeks after the last dose. Sperm donation is prohibited during the study and for 30 weeks after the last dose of study drug.

    *Male patients with WOCBP partners will be asked to inform and ensure their female partners to use highly effective contraception measures† to prevent pregnancy.

    †Vasectomy with medical assessment of surgical success and sexual abstinence‡ are considered highly effective contraception measures.

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

7.3. Premature Withdrawal from the Study

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

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

Patients who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.5.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.2.2.

7.4. Replacement of Patients

Patients prematurely discontinued from study drug will not be replaced. All randomized patients who have received study drug will be included in the FAS (Section 11.3.1).

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Table 1: Study Interventions Administered

[redacted]

Garetosmab is supplied as a liquid drug product and will be administered IV in this study. Instructions on dose preparation are provided in the pharmacy manual.

Placebo to match garetosmab is supplied as a liquid solution without the mAb (or the protein) and will be administered IV in this study.

8.2. Dose Modification and Study Treatment Discontinuation Rules

8.2.1. Dose Modification

Dose modification for an individual patient is not allowed.

8.2.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug are encouraged to remain in the study and undergo all double-blind study visits and procedures with the exception of dosing with study drug. In case of early discontinuation before week 56, all efforts should be made to perform the week 56 assessments at week 56 per the visit schedule (Table 2).

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.5.

8.2.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Diagnosis of a malignancy during the study
- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- Specific types of liver dysfunction (eg, Hy's law is met [(FDA, 2009)])
- Patient withdraws consent
- Severe acute infusion reactions as described in Section 10.2.4.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- Serious or severe hypersensitivity reaction deemed related to study drug
- Severe bleeding episode (based on the definition of a severe AE) other than epistaxis
- Recurrence of severe epistaxis (based on the definition of a severe AE) following resolution of a first severe episode by procedural intervention

8.2.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug dosing will be temporarily discontinued in the event of:

- Moderate-to-severe scrotum pain or swelling requiring urology follow-up assessment
- Surgical procedure
- Hospitalization

After the condition leading to temporary discontinuation of study drug resolves, study drug dosing may resume. A decision to temporarily discontinue study drug and/or resume study drug dosing should be discussed with the Regeneron medical monitor.

The investigator may temporarily discontinue study drug dosing at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the Regeneron medical monitor should be contacted as soon as possible. Resumption of study drug dosing requires consultation and agreement between the investigator and the Regeneron medical monitor.

If a patient requires a prohibited medication at any time during the study, the principal investigator should contact the Regeneron medical monitor (except for illness requiring prompt treatment). Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

8.2.2.3. Continuation of Garetosmab after End of Study

The patients who complete the DBTP (up to week 56 [visit 17]) may be eligible for post-trial access to garetosmab, following the end of the study (including the ETP and Observation Period; see Section 6.1.5). The main criterion considered by Regeneron when providing post-trial access to patients who enroll in clinical studies is that the drug candidate has sufficient data to believe preliminarily that the overall risk-benefit is positive and could support registration. Patients in the ETP who continue onto a post-trial access program can omit the 30-week Follow-Up Safety Visit to allow for continuation of treatment without interruption.

8.3. Management of Acute Reactions

8.3.1. Acute Intravenous Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 10.2.4) and graded using the grading scales as instructed in Section 10.2.5.

8.3.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following AEs are observed:

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- Sustained/severe cough
- Rigors/chills
- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate provided that the symptoms are adequately managed.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

8.3.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis*
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension
- Other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc.)
- Any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

8.4. Method of Treatment Assignment

Patients will be randomized in 1:1:1 ratio to receive garetosmab [redacted] mg/kg Q4W, garetosmab [redacted] mg/kg Q4W, or placebo according to a central randomization scheme, using an interactive response technology (IRT) provided to the designated study pharmacist or qualified designee. Randomization will be stratified by baseline CAJIS score [dichotomized as ≤12; >12] and previous participation in the R2477-FOP-1623 (LUMINA-1) study [yes vs no].

8.5. Blinding

Study patients, investigators, Regeneron Study Director, medical monitor, study monitor, and any other Regeneron or contract research organization (CRO) personnel who are in regular contact with the study site will be blinded to treatment assignment during the DBTP and ETP of the study.

The CT imaging and bone biomarker data collected after randomization will not be communicated to the sites or the sponsor's study team members who may have regular interactions with the sites, until the study data is locked for primary analysis or subsequent analysis in the study.

Drug kits coded with a medication numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct. An unblinded pharmacist or qualified designee at the site will prepare the drug product prior to transferring it to study personnel involved in other study conduct. The person preparing the drug will not participate in other aspects of study conduct.

Patients may elect to enter the Observation Period at the week 56 visit. In these patients, DBTP treatment assignment will be provided to the patients by the study site. Unblinded patients will no longer receive study treatment.

8.6. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unblinded/unmasked (Section 8.2.2).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patients will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind/unmask the patient. Unblinding is performed using the Interactive Web Response Systems (IWRS)/Interactive Voice Response Systems (IVRS) which will notify Regeneron.
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient.

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. If there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.7. Treatment Logistics and Accountability

8.7.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site at a temperature of [redacted]; storage instructions will be provided in the pharmacy manual.

8.7.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed on site or returned to the sponsor or designee.

8.7.3. Treatment Accountability

All drug accountability records must be kept current.

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

- Dispensed to each patient
- Returned from each patient (if applicable), and
- Disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.7.4. Treatment Compliance

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

8.8. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

8.8.1. Prohibited Medications and Procedures

A patient may not receive any of the following during the DBTP, ETP, and Follow-Up Safety Visit (day 1 [visit 2] through End of Treatment), except palovarotene (which is prohibited from screening [visit 1] through End of Treatment]):

- Anticoagulants (eg, warfarin, heparin, factor Xa inhibitor, thrombin inhibitors); however, low doses of heparin for flushing of catheters will be permitted
- Amiodarone
- Those that may have effects on skeletal bone turnover, such as bisphosphonates (eg, etidronate, pamidronate), denosumab, imatinib, or isotretinoin (unapproved drug in Japan)
- Immunosuppressants (eg, methotrexate)
- Chemotherapies
- Radiotherapy
- Bone marrow transplantation
- Antiplatelet therapy (eg, clopidogrel)
- Herbal supplements that inhibit platelet function or are associated with increased risk of bleeding
- Palovarotene (in approved countries)

8.8.2. Permitted Medications and Procedures

Patients will be allowed to continue concomitant medications commonly prescribed for management of signs and symptoms of FOP disease activity and other acute or chronic disease. These may include

- Oral or systemic corticosteroids*
- Muscle relaxants
- Non-steroidal anti-inflammatory drugs (NSAIDs)*
- Opioid and other analgesics
- Antidepressants
- Vitamins and calcium supplements
- Over-the-counter antihistamines and decongestants
- Paracetamol
- Antibiotics
- Vaccinations
- Anti-hypertensives
- Proton pump inhibitors

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- Statins at stable dose levels (for at least 3 months) that are well tolerated and do not cause myalgia
- Oral hypoglycemic drugs
- Laxatives
- Antacids
- Low-dose acetylsalicylic acid (aspirin; ≤100 mg or ≤150 mg/day, based on local practice)

*To mitigate the potential risk for epistaxis, investigators should discourage the use of anti-inflammatory drugs that inhibit platelet function or are otherwise associated with an increased risk of bleeding, to the extent possible.

COVID-19 Vaccination

- If a patient intends to receive a COVID-19 vaccine (initial series or booster), before the start of study drug administration, day 1 of the study and the events associated with day 1 should not occur until at least 1 week after any COVID-19 vaccination dosing.
- During the treatment period, it is recommended to delay COVID-19 vaccination, either as an initial series or as a booster dose, until patients are receiving and tolerating a steady dose of study drug.
  - COVID-19 vaccination, either as an initial series or as a booster dose, received during the study, will be treated as a concomitant medication. As noted, administration of a COVID-19 vaccination should be separated from the time of administration of the investigational product (at least 72 hours, ideally by at least one week) in order to avoid confounding the effects (eg, adverse effects) of the vaccine/booster with the effects of study drug.

As this is not a comprehensive list of all potential concomitant medications, use of concomitant medications that are not listed above will be reviewed by the principal investigator and medical monitor to gain agreement.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct, and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19, are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures are presented by study period and visit in Table 2 (Screening Period and DBTP), Table 3 (ETP), Table 4 (continued ETP), and Table 5 (Observation Period).

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Table 2: Schedule of Events: Screening and DBTP (including Early Termination)

	Screening Period	DBTP																Early Termination
Study Procedure[1,2]	**V1**	**Baseline V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**End of DBTP/V17[3]**	**V**
Week	**-**	**-**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	
Day	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	
Window (day)	**-**	**1**	**±3d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**-7 to +15 d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	
Screening/Baseline																		
Inclusion/Exclusion[4]	X																	
Informed Consent (optional genomics sub-study)	X																	
Informed Consent (optional FBR sub-study)	X																	
Informed Consent	X																	
Medical/Prior medication/Surgical History[5]	X																	
Demographics	X																	
Body Height[6]	X																	
Confirm clinical FOP diagnosis including document of ACVR1 mutation[7]	X																	
Whole blood for DNA sample for ACVR1 gene sequencing[8]	X																	
Scrotum ultrasound with doppler (males only)	X																	
Blood samples for FSH (to determine post-menopausal status, if applicable)	X																	
Blood sample for HbA1c	X																	
Randomization		X																

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

	Screening Period	DBTP																Early Termination
Study Procedure[1,2]	**V1**	**Baseline V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**End of DBTP/V17[3]**	**V**
Week	**-**	**-**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	
Day	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	
Window (day)	**-**	**1**	**±3d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**-7 to +15 d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	
Treatment																		
Administer Study Drug: all patients[9]		X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Administer Study Drug: patients continuing to Extended Treatment[9]																	X[3]	
Concomitant Medications and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Endpoint Measures																		
Low-dose whole body CT[10,11]	X									X							X[12]	X[13]
Daily FOP Flare-up diary[14]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CAJIS	X									X							X	X
EQ-5D-3L	X									X							X	X
SF-36	X									X							X	X
PGIS	X									X							X	X
PGIC										X							X	X
Patient experience interview																X[15]		X
CGIC										X							X	X
Spirometry (FVC/FEV-1)[16]	X									X							X	X
FOP Clinician-assessed Flare		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety																		
Vital signs[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X									X							X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

	Screening Period	DBTP																Early Termination
Study Procedure[1,2]	**V1**	**Baseline V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**End of DBTP/V17[3]**	**V**
Week	**-**	**-**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	
Day	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	
Window (day)	**-**	**1**	**±3d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**-7 to +15 d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	
Menstrual history (female) and confirmation of contraception use (male and female)[18]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ENT consultation[19]	X		follow-up visits as needed[19]															
Laboratory Testing[20]																		
Pregnancy test (WOCBP)	serum[21]	urine		urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	serum
Hematology	X[21]	X		X	X	X	X	X		X			X				X	X
Blood chemistry	X[21]	X		X	X	X	X	X		X			X				X	X
Urinalysis[22]	X	X		X	X	X	X	X		X			X				X	X
Platelet flow cytometry[23]	X	X		X	X	X	X			X			X				X	
Blood sample for Coagulation parameters (activated partial thromboplastin time, prothrombin time, INR, thrombin time) and fibrinogen	X	X				X				X			X				X	X
Blood samples for FSH, estradiol, LH for female patients with regular menstrual cycles[24]	X	→																
PK and Immunogenicity Sampling[25]																		
Blood sample for PK/Drug concentration and activin A		X[26]	X	X	X	X	X	X		X		X	X	X	X	X	X	X
Blood sample BMP-9	X		X							X							X	X

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

	Screening Period	DBTP																Early Termination
Study Procedure[1,2]	**V1**	**Baseline V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**End of DBTP/V17[3]**	**V**
Week	**-**	**-**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	
Day	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	
Window (day)	**-**	**1**	**±3d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**-7 to +15 d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	
Blood sample for ADA sample		X				X				X							X	X
Biomarkers																		
Blood sample for biomarker samples of bone and cartilage		X		X				X				X					X	
Blood sample for biomarker samples of inflammatory markers		X		X				X				X					X	
Future Biomedical Research																		
Research biomarker serum for future use (optional)[27]		X		X		X		X						X			X	
Research biomarker plasma for future use (optional)[27]		X		X		X		X						X			X	
Pharmacogenomics																		
Whole blood DNA samples (optional)[27]		X																

ACVR1= Type I activin A receptor; ADA=Antidrug antibody; BMP-9=Bone morphogenic protein 9; CAJIS= Cumulative Analog Joint Involvement Scale; CGIC=Clinician's Global Impression of Change; CT= Computed tomography; d=Day; DBTP=Double-Blind Treatment Period; DNA=Deoxyribonucleic acid; ENT=Ear, nose, and throat; EOS=Endo f study; EQ-5D-3L= EuroQol 5 dimensions questionnaire with a 3-level scale; FBR=Future biomedical research; FEV1= Forced expiratory volume in 1 second; FOP= Fibrodysplasia ossificans progressiva; FSH=Follicle-stimulating hormone; FVC= Forced vital capacity; HbA1c=Hemoglobin A1c; INR=International normalized ratio; LH=Luteinizing hormone; PK=Pharmacokinetic; PGIC=Patient's Global Impression of Change; PGIS=Patient's Global Impression of Severity; SF-36=Short-Form 36; V=Visit; WOCBP=women of childbearing potential.

9.1.1. Footnotes for Schedule of Events for Table 2

1. Procedures other than those associated with imaging procedures may be conducted by trained study staff at or near patients' residences (ie, at-home visits).

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

2. During the study, study procedures within each visit may be conducted on different days, within the stated visit window. If conducted on the same day, vital signs and ECG will be conducted before blood sampling, and blood samples will be collected before CT procedure.
3. At the week 56 visit, patients will have a discussion with the study doctor and choose to continue blinded treatment and enter the ETP or to stop treatment, become unblinded, and enter the Observation Period. For patients that will enter the ETP, study drug is administered at visit 17 and refer to Table 3. For patients that will be unblinded, no study drug is administered at visit 17 and refer to Table 5.
4. Patients may be rescreened once for study participation.
5. Medical history footnote: Medical history should include detailed FOP history, prior medication and surgery for treatment of FOP, history of madarosis, acne, epistaxis, infections, and abscesses and previous participation in LUMINA-1 study
6. Depending upon the level of musculoskeletal compromise for a patient, the measurement of the patient's height may not be precise or sometimes not possible to be assessed.
7. Documentation of ACVR1 genotype, including classic [R206H] or different ACVR1 mutations, should be obtained for the study file for all patients. In China, this data will be collected after Human Genetic Resource Administration of China (HGRAC) approval.
8. All patients will have a whole blood sample collected for ACVR1 gene sequencing, to be analyzed at a central lab. For patients without prior documentation of ACVR1 at screening, the results from this test will be used for documentation. In China, there will be no collection of whole blood samples for ACVR1 sequencing.
9. All patients who receive study drug will be closely monitored after each study drug administration for at least 2 hours.
10. The baseline imaging assessment by low dose CT must be conducted between day-7 to day -1.
11. Any incidental findings identified through CT scans will be reported to the investigator and medical monitor. The investigator will communicate any findings to the patient.
12. The week 56 CT scan for a patient can be repeated, if needed due to an image quality issue, and if feasible (Section 3.3.7).
13. If the patient had a CT within 12 weeks prior to the early termination visit, then a CT scan is not required.
14. Daily FOP Flare-up diary will be collected as entries in a diary completed by the patient. If the patient is physically unable to or requires assistance to complete the e-diary on their own, caregivers can complete or provide assistance in completion of the e-diary. Caregivers can only physically assist with completion of the e-diary and there is to be no interpretation of patient disease activity on their part. At baseline visit, the FOP Flare-up diary should be completed before study drug administration.

15. Patient experience interviews will be conducted by an external interviewer at week 52, allowable time frame is between week 52 and week 54.
16. Forced vital capacity (FVC) and FEV1, and the ratio of FEV1/FVC, will be determined by spirometry in patients who are able to undergo this procedure.
17. On study day 1 vital signs will be collected pre-dose and post-dose at 2 hours (±30 minutes) after the end of infusion. On subsequent visits, vital signs will be collected prior to dosing.
18. Menstrual history and pregnancy status of WOCBP will be determined at the screening visit. Menstrual events and pregnancy status of WOCBP will be monitored at each visit, except visit 3. A negative result for the pregnancy test must be obtained prior to each study drug administration. For both female and male patients, contraception use will be confirmed.
19. ENT consultation is to be performed during Screening Period. Follow-up visits will be conducted for patients who experience episodes of moderate or severe epistaxis, have more than three episodes of epistaxis, or if deemed necessary by the investigator.
20. In some patients, it may not be possible to obtain venous blood samples for all tests. Serum pregnancy tests and other blood tests for determining eligibility must be obtained. Blood samples for safety labs will be prioritized. Study drug administration will be performed last at that study visit.
21. Blood sample collection for laboratory testing at the screening visit will be collected in a fasted state (after an 8-hour fast). No other blood sample collection will require fasting.
22. A routine urinalysis will be collected in all patients (male and female). In addition, a urinalysis and urine culture will be collected in male patients experiencing an AESI related to the male reproductive system (see Section 10.1.3).
23. Samples for platelet flow cytometry will be collected at screening, baseline, and at the visits specified (prior to study drug administration) to monitor any changes in platelet activity (eg, clotting capability).
24. Blood samples for FSH, estradiol, and LH will be collected between days 3 to 5 of the menstrual cycle during the Screening Period and during the first 6 months of the study for female patients with regular menstrual cycles. Additional details will be provided in the study reference manual.
25. Samples for PK, ADA, total activin A, and BMP9 analysis must be collected prior to study drug administration. In the event of a suspected SAE such hypersensitivity or anaphylaxis, additional PK and ADA samples may be collected at or near the event.
26. On day 1, a blood sample for drug concentration measurement will also be collected at the end of study drug administration (within 30 minutes after end of infusion). If unable to collect the sample or patients is unwilling to have sample collection from the opposite arm as the initial blood sample, the post administration sample may be omitted.

27. Separate consent is required for participation in the optional Future Biomedical Research and Pharmacogenomics sub-studies. The blood sample for genomic DNA should be collected on day 1 or may be collected at any visit. These optional samples will not be collected in China.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Table 3: Schedule of Events: ETP

	ETP							Follow-Up Safety Visit	Early Termination
Study Procedure[1,2]	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**End of ETP/V24[4]**	**≥V25**	**V**
Week	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**≥114**	
Day	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**≥798**	
Window (day)	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	**±14d**	
Treatment									
Administer Study Drug: all patients on Extended Treatment[3]	X	X	X	X	X	X			
Administer study drug: patients continuing Extended Treatment[3]							X[4]		
Concomitant Medications and Procedures	X	X	X	X	X	X	X		X
Clinical Endpoint Measures									
Low-dose whole body CT[5]							X		X[6]
CAJIS							X		X
EQ-5D-3L							X		X
SF-36							X		X
PGIS							X		X
PGIC							X		X
CGIC							X		X
FOP Clinician-assessed Flare	X	X	X	X	X	X	X		X
Safety									
Vital signs[7]	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X
Electrocardiogram							X		X
Adverse events	X	X	X	X	X	X	X	X	X
Menstrual history (female) and confirmation of contraception use (male and female)[8]	X	X	X	X	X	X	X	X	X
ENT consultation[9]	follow-up visits as needed[9]								
Laboratory Testing[10]									
Pregnancy test (WOCBP)	urine	urine	urine	urine	urine	urine	serum	serum	serum
Hematology			X				X	X	X
Blood chemistry			X				X	X	X

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

	ETP							Follow-Up Safety Visit	Early Termination
Study Procedure[1,2]	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**End of ETP/V24[4]**	**≥V25**	**V**
Week	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**≥114**	
Day	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**≥798**	
Window (day)	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	**±14d**	
Urinalysis[11]			X				X	X	X
Platelet flow cytometry[12]							X		
Blood sample for Coagulation parameters (activated partial thromboplastin time, prothrombin time, INR, thrombin time) and fibrinogen			X				X	X	X
PK and Immunogenicity Sampling[13]									
Blood sample for PK/Drug concentration and activin A							X	X	X
Blood sample BMP-9							X	X	X
Blood sample for ADA sample							X	X	X
Biomarkers									
Blood sample for biomarker samples of bone and cartilage							X	X	
Blood sample for biomarker samples of inflammatory markers							X	X	

ADA=Antidrug antibody; BMP-9=Bone morphogenic protein 9; CAJIS= Cumulative Analog Joint Involvement Scale; CGIC=Clinician's Global Impression of Change; CT= Computed tomography; d=Day; ENT=Ear, nose, and throat; EQ-5D-3L= EuroQol 5 dimensions questionnaire with a 3-level scale; ETP=Extended Treatment Period; FOP= Fibrodysplasia ossificans progressiva; INR=International normalized ratio; PK=Pharmacokinetic; PGIC=Patient's Global Impression of Change; PGIS=Patient's Global Impression of Severity; SF-36=Short-Form 36; V=Visit; WOCBP=women of childbearing potential

9.1.2. Footnotes for Schedule of Events for Table 3

1. Procedures other than those associated with imaging procedures may be conducted by trained study staff at or near patients' residences (ie, at-home visits).
2. During the study, study procedures within each visit may be conducted on different days, within the stated visit window. If conducted on the same day, vital signs and ECG will be conducted before blood sampling, and blood samples will be collected before CT procedure.
3. All patients who receive study drug will be closely monitored after each study drug administration for at least 2 hours.
4. All patients in the ETP will be administered study drug at week 84 (visit 24) and continue Extended Treatment (see Table 4) except the last global patient reaching week 84 who will not receive study drug at week 84 (visit 24) and will continue to the Follow-Up Safety Visit (visit 25 in Table 3).

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

5. Any incidental findings identified through CT scans will be reported to the investigator and medical monitor. The investigator will communicate any findings to the patient.
6. If the patient had a CT within 12 weeks prior to the early termination visit, then a CT scan is not required.
7. On study day 1 vital signs will be collected pre-dose and post-dose at 2 hours (±30 minutes) after the end of infusion. On subsequent visits, vital signs will be collected prior to dosing.
8. Menstrual events and pregnancy status of WOCBP will be monitored at each visit, except visit 3. A negative result for the pregnancy test must be obtained prior to each study drug administration. For both female and male patients, contraception use will be confirmed.
9. ENT follow-up visits will be conducted for patients who experience episodes of moderate or severe epistaxis, have more than 3 episodes of epistaxis, or if deemed necessary by the investigator.
10. In some patients, it may not be possible to obtain venous blood samples for all tests. Serum pregnancy tests and other blood tests for determining eligibility must be obtained. Blood samples for safety labs will be prioritized. Study drug administration will be performed last at that study visit.
11. A routine urinalysis will be collected in all patients (male and female). In addition, a urinalysis and urine culture will be collected in male patients experiencing an AESI related to the male reproductive system (see Section 10.1.3).
12. Samples for platelet flow cytometry will be collected at the visits specified (prior to study drug administration) to monitor any changes in platelet activity (eg, clotting capability).
13. Samples for PK, ADA, total activin A, and BMP9 analysis must be collected prior to study drug administration. In the event of a suspected SAE such hypersensitivity or anaphylaxis, additional PK and ADA samples may be collected at or near the event.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Table 4: Schedule of Events: Continued ETP

	ETP – Continued[1]							Follow-Up Safety Visit	Early Termination
Study Procedure[2,3]	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**End of ETP – Continued/V≥31**	**V≥32**	**V**
Week	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**≥142**	
Day	**617**	**645**	**673**	**701**	**729**	**757**	**785**	**≥994**	
Window (day)	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	**±14d**	
Treatment									
Administer Study Drug[4]	X	X	X	X	X	X			
Concomitant Medications and Procedures	X	X	X	X	X	X	X		X
Clinical Endpoint Measures									
CAJIS						X	X		X
EQ-5D-3L						X	X		X
SF-36						X	X		X
PGIS						X	X		X
PGIC						X	X		X
CGIC						X	X		X
FOP Clinician-assessed Flare	X	X	X	X	X	X	X		X
Safety									
Vital signs[5]	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X		X
Physical examination	X	X	X	X	X	X	X		X
Electrocardiogram							X		X
Adverse events	X	X	X	X	X	X	X	X	X
Menstrual history (female) and confirmation of contraception use (male and female)[6]	X	X	X	X	X	X	X	X	X
ENT consultation[7]	follow-up visits as needed[7]								
Laboratory Testing[8]									
Pregnancy test (WOCBP)	urine	urine	urine	urine	urine	urine	serum	serum	serum
Hematology						X	X	X	X
Blood chemistry						X	X	X	X
Urinalysis[9]						X	X	X	X
Blood sample for Coagulation parameters (activated partial thromboplastin time, prothrombin time, INR, thrombin time) and fibrinogen						X	X	X	X
PK and Immunogenicity Sampling[10]									
Blood sample for PK/Drug concentration and activin A								X	

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

	ETP – Continued[1]							Follow-Up Safety Visit	Early Termination
Study Procedure[2,3]	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**End of ETP – Continued/V≥31**	**V≥32**	**V**
Week	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**≥142**	
Day	**617**	**645**	**673**	**701**	**729**	**757**	**785**	**≥994**	
Window (day)	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	**±14d**	
Blood sample BMP-9								X	
Blood sample for ADA sample								X	
Biomarkers									
Blood sample for biomarker samples of bone and cartilage								X	
Blood sample for biomarker samples of inflammatory markers								X	

ADA=Antidrug antibody; BMP-9=Bone morphogenic protein 9; CAJIS= Cumulative Analog Joint Involvement Scale; CGIC=Clinician's Global Impression of Change; CT= Computed tomography; d=Day; ENT=Ear, nose, and throat; EQ-5D-3L= EuroQol 5 dimensions questionnaire with a 3-level scale; ETP=Extended Treatment Period; FOP= Fibrodysplasia ossificans progressiva; INR=International normalized ratio; PK=Pharmacokinetic; PGIC=Patient's Global Impression of Change; PGIS=Patient's Global Impression of Severity; SF-36=Short-Form 36; V=Visit; WOCBP=women of childbearing potential

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

9.1.3. Footnotes for Schedule of Events for Table 4

1. After completion of the ETP (see Table 3), patients will continue extended treatment and cycle through V25 to V30 until end of study is reached (ie, last global patient completes the last study visit).
2. Procedures other than those associated with imaging procedures may be conducted by trained study staff at or near patients' residences (ie, at-home visits).
3. During the study, study procedures within each visit may be conducted on different days, within the stated visit window. If conducted on the same day, vital signs and ECG will be conducted before blood sampling, and blood samples will be collected before CT procedure.
4. All patients who receive study drug will be closely monitored after each study drug administration for at least 2 hours.
5. On study day 1 vital signs will be collected pre-dose and post-dose at 2 hours (±30 minutes) after the end of infusion. On subsequent visits, vital signs will be collected prior to dosing.
6. Menstrual history and pregnancy status of WOCBP will be determined at the screening visit. Menstrual events and pregnancy status of WOCBP will be monitored at each visit, except visit 3. A negative result for the pregnancy test must be obtained prior to each study drug administration. For both female and male patients, contraception use will be confirmed.
7. ENT consultation is to be performed during Screening Period. Follow-up visits will be conducted for patients who experience episodes of moderate or severe epistaxis, have more than three episodes of epistaxis, or if deemed necessary by the investigator.
8. In some patients, it may not be possible to obtain venous blood samples for all tests. Serum pregnancy tests and other blood tests for determining eligibility must be obtained. Blood samples for safety labs will be prioritized. Study drug administration will be performed last at that study visit.
9. A routine urinalysis will be collected in all patients (male and female). In addition, a urinalysis and urine culture will be collected in male patients experiencing an AESI related to the male reproductive system (see Section 10.1.3).
10. Samples for PK, ADA, total activin A, and BMP-9 analysis must be collected prior to study drug administration. In the event of a suspected SAE such hypersensitivity or anaphylaxis, additional PK and ADA samples may be collected at or near the event.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Table 5: Schedule of Events: Observation Period

	Observation Period[1]				Follow-up Safety Visit[2]	Early Termination
Study Procedure	**V18[3]**	**V19**	**V20**	**End of Study/≥V21**	**V21**	V
Week	**60**	**68**	**76**	**≥84**	**82**	
Day	**421**	**477**	**533**	**≥589**	**574**	
Window (day)	**±7d**	**±7d**	**±7d**	**±14d**	**±7d**	
Clinical Endpoint Measures						
Phone contact	X	X	X	X	X[2]	X

d=Day; V=Visit

9.1.4. Footnotes for Schedule of Events for Table 5

1. After completion of the double-blind, placebo-controlled phase (see Table 2), patients who choose to become unblinded will enter the Observation Period and cycle through V18 to V20 until last global patient completes the last study visit.
2. Follow-Up Safety Visit is only required for patients randomized to garetosmab and scheduled 30 weeks after the last administered dose of garetosmab on week 52 (visit 16); refer to Follow-Up Safety Visit column in Table 3 for Study Procedures to be performed at this visit in these patients.
3. The first visit of the Observation Period (visit 18 [week 60]) will take place 2 months after the last dose administered (visit 16 [week 52]).

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

9.1.5. Early Termination Visit

Patients who are permanently withdrawn from the study before the primary endpoint visit (week 56) will be asked to return to the clinic for an early termination visit consisting of the week 56 assessments described in Table 2.

Patients who are permanently withdrawn from the study before the end of the ETP or the Observation Period will be asked to return to the clinic for an early termination visit consisting of the assessments described in Table 3, Table 4, and Table 5.

Note, patients who permanently discontinue from study drug and agree to continue follow-up do not need to be terminated from the study (see Section 8.2.2).

9.1.6. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs (eg, if bleeding event occurs [see Section 3.3.2]), or for any other reason, as warranted.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population:

- Confirmation of FOP diagnosis including documentation of ACVR1 mutation
- Blood collection for ACVR1 gene sequencing
- Assessment of a patient's ability to undergo imaging and other procedures described in the study protocol
- Demographics
- Height measurement
- Medical, prior medication, and surgical history
- HbA1c measurement
- Urogenital exam and scrotum ultrasound with Doppler (for male patients only)
- FSH (to determine postmenopausal status, if applicable)

Documentation of ACVR1 genotype, including classic [R206H] or different ACVR1 FOP-causing mutations, should be obtained for study file. If at the time of screening the patient doesn't have documentation of what ACVR1 mutation he/she carries or it cannot be retrieved, then the study site staff should collect a blood sample for the testing by central lab to determine the ACVR1 mutation prior to randomization. Note: For sites in China, ACVR1 mutation in patients will be confirmed only by prior documentation of any known ACVR1 FOP causing mutation.

All patients, except for patients in China, will have a whole blood sample collected, preferably at the screening visit, for future ACVR1 gene sequencing. Countries with export restrictions of

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

biological samples to the United States are excluded from mandatory testing if samples cannot be sent to the central lab.

Further details are provided in the study reference manual.

9.2.2. Procedures Related to Study Drug Administration

Study drug will be administered at the time points indicated in Table 2, Table 3, and Table 4. Emergency equipment and medications for the treatment of infusion reactions must be available (Section 8.3). Patients will be monitored for up to 2 hours post-dose for any adverse reactions.

9.2.3. Efficacy Procedures

9.2.3.1. Low-Dose Whole Body CT to Assess New HO Formation

All patients will undergo whole-body low dose CT to assess formation of new heterotopic bone.

The CT procedure should be performed after samples are collected for laboratory assessments. The CT scans will be performed at the time points specified in Table 2, Table 3, and Table 4. Patients will not need to fast and may take all their usual medications as permitted in the study (see Section 8.8.2). Patients should be positioned comfortably on the bed of the scanner with supportive aids (eg, pillows and blankets) as necessary to minimize involuntary movement during the scan.

In the event the week 56 CT scan has poor image quality resulting in the images to be inadequate for evaluation of HO lesions, a repeat CT scan should be performed.

In the event that a pathological finding that potentially requires medical attention (eg, suspected malignancy) is identified in the images by the investigator or imaging site, the sponsor will be informed of the finding. The investigator will communicate any findings to the patient.

Detailed descriptions of the CT procedures will be provided in the study imaging manual. Personnel at all sites will undergo training for CT acquisition procedures as described in the study imaging manual. The sponsor or its representative(s) may conduct site visits to monitor and ensure that the study is executed according to the study protocol. The CT scans will be collected, and formation of new HO analyzed using a central reading center. The scans may also be used to perform exploratory analysis of lung volume and disappearance of pre-existing HO lesions by the central readers.

The investigator will be allowed to independently read and analyze baseline CT images while blinded to subsequent study treatment. In order to avoid potential unblinding, the investigator will not be allowed to read or analyze CT images acquired from a patient randomized into the study after study drug dosing has been initiated.

9.2.3.2. Daily FOP Flare-Up Diary

The FOP Flare-up diary contains 3 sections, a historical flare-up section (baseline assessment), an ongoing flare-up section, and a new flare-up section. Assessment of FOP Flare-up including flare-up location, frequency, and duration, as well as the severity of selected FOP disease signs and symptoms, including pain, swelling, joint stiffness, and decrease in movement which will be rated by patients using a 4-point scale for each (0: no symptoms; 1: mild; 2: moderate; 3: severe).

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Patients and their caregiver (if applicable) will be trained on its use at the baseline visit and are instructed to record their scores in the e-diary each day throughout the study during the DBTP. The FOP Flare-up diary will be reviewed at the visits listed in Table 2. The baseline entry for the daily FOP Flare-up diary is day 1. Further details are provided in the study reference manual.

9.2.3.3. Clinician Flare-Up Assessment (Investigator Assessed)

In each visit outlined in the Schedule of Events (Table 2, Table 3, and Table 4) the Investigator will assess for the occurrence of new flare-ups since the last visit and record the number of new flare-ups on a dedicated eCRF. When assessing for an FOP Flare-up, major signs and symptoms to be considered by the investigator include but are not limited to swelling, pain, decrease movement, stiffness, and warmth. All FOP Flare-ups will be considered adverse events (AEs) and captured on the AE eCRF. Additional details will be collected via the eCRFs for each Flare-up AE, including the associated signs and symptoms, location, any precipitating factors, and treatment. Signs and symptoms collected in the eCRF include but not limited to pain, swelling, joint stiffness, decrease in movement, etc.

9.2.3.4. EQ-5D-3L

Patients will complete the questionnaire at time points according to Table 2, Table 3, and Table 4. The EQ-5D-3L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-3L as a measure of HRQoL defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each dimension has 3 ordinal levels of severity: absence of problems or issues with the specific dimension, eg, “no problems” (1), “some problems” (2), “severe problems” (3). Overall health state is defined as a 5-digit number. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, where 0 represents “death” and 1 represents “perfect health.” In the final part of the EQ-5D-3L, patients are asked to rate “your own health state today” from 100 (best imaginable health state) to 0 (worst imaginable health state). Further details are provided in the study reference manual.

9.2.3.5. The Short Form – 36 Survey (SF-36)

Patients will complete the survey at time points according to Table 2, Table 3, and Table 4. The SF-36 is a 36-item self-administered PRO measure assessing HRQoL concepts relevant across age, disease, and treatment group. The SF-36 will be completed by patients ages 18 years of age and older. The SF-36 assesses physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Patients answer questions assessing these concepts over the previous week using 3-, 5-, or 6-point Likert scales; scores range from 0 to 100, with higher scores indicating better health. The past-week recall has been compared to the 4-week recall and is shown to have comparable properties (Keller, 1997). The SF-36 is one of the most widely used and studied PRO measures, with good psychometric properties documented across different populations.

9.2.3.6. Cumulative Analog Joint Involvement Scale Score (CAJIS)

Physician assessment of joint involvement will be conducted using the CAJIS at the visits listed in Table 2, Table 3, and Table 4. The CAJIS is an assessment of 15 major joints; each major joint

rated normal unaffected (0), affected (1), or completely functionally ankylosed (2). The total score ranges from 0 to 30. Investigators at all sites will undergo training for CAJIS assessment. Further details are provided in the study reference manual.

9.2.3.7. Patient Global Impression of Severity (PGIS)

At the visits specified in Table 2, Table 3, and Table 4 patients will rate the severity of their flare-up activity during the study. PGIS is a single item, self-administered questionnaire to assess the patient's global impression of severity. This endpoint will be used to assess disease severity over time and will be used as an anchor to assess meaningful change. Further details are provided in the study reference manual.

9.2.3.8. Patient's Global Impression of Change (PGIC)

At the visits specified in Table 2, Table 3, and Table 4 patients will rate their impression of change in their flare-up activity during the study. PGIC is a single item, self-administered questionnaire to assess the patient's global impression of change. This endpoint will be used to assess change in disease severity over time and will be used as an anchor to assess meaningful change. Further details are provided in the study reference manual.

9.2.3.9. Clinician's Global Impression of Change (CGIC)

At the visits specified in Table 2, Table 3, and Table 4 the physician will rate their impression of the change in the patient's flare-up activity during the study. CGIC is a single-item questionnaire to assess the clinician's global impression of change. This endpoint will be used to assess change in disease severity over time and will be used as an anchor to assess meaningful change. Further details are provided in the study reference manual.

9.2.3.10. Patient Experience Interview

At week 52 of the DBTP (window for patient experience interview is week 52 to week 54) or at an early termination visit prior to week 52, patients from selected countries and where patient experience interviews (also known as exit interviews) are allowed will be interviewed on their experienced symptoms changes and overall experience with study participation. Results from patient experience interviews will also be used to contextualize findings on the clinical outcome assessments or meaningful change. Each interview will last approximately 60 minutes and will be conducted by trained external interviewers following a semi-structured interview guide.

9.2.3.11. Pulmonary Function

FVC and FEV1 and the ratio of FEV1/FVC will be determined by spirometry in patients who are able to undergo this procedure at the visits specified in Table 2. Further details are provided in the study reference manual.

9.2.4. Safety Procedures

9.2.4.1. Monitoring of Adverse Events and Concomitant Medications

AEs, including events that require expedited reporting (Section 10.1.3), are monitored continuously throughout the study as described in Section 10.

Concomitant medications (Section 8.8) are reviewed at each visit in the DBTP (Table 2) and the ETP except the Safety Follow-Up Visit (Table 3 and Table 4).

9.2.4.2. Body Weight

Body weight will be assessed using calibrated scales at visits specified in Table 2, Table 3, and Table 4. Patients should void (empty bladder) prior to weight assessment. Patients should be wearing undergarments only and no shoes during weight assessments. Body weight will be recorded to the nearest 0.1 kg.

9.2.4.3. Vital Signs

Vital signs, including temperature, blood pressure, pulse, and respiration will be collected pre-dose at time points according to Table 2, Table 3, and Table 4, and at the early termination visit, if applicable. Blood pressure will be measured from a consistent resting position. Further details are provided in the study reference manual.

9.2.4.4. Physical Examination

A thorough and complete physical examination will be performed at screening and baseline, week 56, week 84, and at early termination visit (Table 2, Table 3, and Table 4). Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history. A thorough skin examination should be performed at the screening visit to assess for the presence of folliculitis, furuncles, abscess, carbuncle, cellulitis, or other signs of skin infection. After baseline, targeted physical examinations may be performed instead of a full physical examination, if appropriate, and depending upon AEs and/or laboratory or ECG abnormalities.

Physical exams for screening may be conducted on a different day from the initial screening visit, as long as they are conducted within the screening window.

9.2.4.5. Electrocardiogram

Electrocardiograms should be performed before blood is drawn during visits requiring blood sample collection. A standard 12-lead ECG will be performed at time points according to Table 2 Table 3, and Table 4, and at the early termination visit, if applicable. The ECG should be performed prior to administration of study drug if these were to occur on the same day.

Each ECG consists of a 10-second recording of the 12 leads simultaneously, leading to a single 12-lead ECG (25 mm/s, 10 mm/mV) printout with evaluation (HR, PR, QRS, RR, QT intervals, and QTc) including date, time, number of the patient, signature of the research physician, and at least 3 complexes for each lead. The automatic reading will be used for immediate safety assessment. The investigator's medical opinion and automatic values will be recorded in the electronic case report form (CRF).

9.2.4.6. Menstrual History and Confirmation of Contraception Use

Assessment of menstrual cycle history for WOCBP will be conducted at baseline and at the visits specified in Table 2, Table 3, and Table 4 to identify any changes in occurrence, frequency, and duration following study drug treatment. Further details are provided in the study reference manual.

9.2.4.7. Ear, Nose, and Throat Consultation

As part of screening/baseline, patients will have a consultation with an ENT specialist to assess for and document possible pre-existing nasal blood vessel ectasias or other anatomic anomalies (Table 2, Table 3, and Table 4). Follow-up visits will be conducted for patients who experience episodes of moderate or severe epistaxis, have more than three episodes of epistaxis, or if deemed necessary by the investigator. Whenever possible, the same ENT specialist who conducted the screening/baseline exam should conduct the follow-up examination. Further details are provided in the study reference manual.

9.2.4.8. Platelet Flow Cytometry

Samples will be taken at screening at baseline and at the visits specified in Table 2 and Table 3 to monitor platelet activity and to monitor any changes in platelet activity (eg, clotting capability) following study drug treatment/administration. Changes in platelet activity from baseline to week 56 will be defined as the percentage of positive events in the platelet population, where a positive event is defined as a platelet determined to be either P-selectin positive or PAC-1 positive (activated GPIIb/IIIa) via flow cytometry.

Blood samples will be taken at the visits specified in Table 2 and Table 3 for platelet sample preparation as instructed and outlined in the central laboratory manual and shipped to the central lab for further processing. Results will be reported in the clinical study report (CSR).

Countries with export restrictions of biological samples to the United States are excluded from mandatory testing if samples cannot be sent to the central lab. The platelet flow cytometry assessments are not applicable for Chinese patient samples.

Further details are available in the laboratory manual.

9.2.4.9. Laboratory Testing

Blood samples for laboratory testing at the screening visit will be collected in a fasted state (after an 8-hour fast). No other blood samples will require fasting.

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are available in the laboratory manual.

Samples for laboratory testing will be collected at visits according to Table 2, Table 3, and Table 4. Tests will include:

Blood Chemistry

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

*(low-density lipoprotein [LDL] and high-density lipoprotein [HDL])

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Hematology

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

Coagulation Parameters

Activated partial thromboplastin time	International Normalized Ratio (INR)
Thrombin time	Fibrinogen
Prothrombin time	

Urinalysis

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

Other Laboratory Tests

HbA1c test at screening

ACVR1 gene sequencing at screening. DNA samples will be stored until processing.

Follicle-stimulating hormone (FSH) test in women to confirm postmenopausal status

Pregnancy test for WOCBP; urine or serum samples, as indicated

Luteinizing hormone (LH), FSH and estradiol in women with regular menstrual cycles

Countries with export restrictions of biological samples to the United States are excluded from mandatory testing if samples cannot be sent to the central lab.

Abnormal Laboratory Values and Laboratory Adverse Events

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

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

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

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

9.2.5. Drug Concentration and Activin A (Target) Measurements

Serum samples for measurement of drug concentration and total activin A concentration will be collected at visits listed in Table 2, Table 3, and Table 4. Samples will be collected before dosing on days when study drug is administered. On day 1, a blood sample for drug concentration measurement will also be collected at the end of study drug administration (within 30 minutes of end of infusion).

Any unused serum samples collected for drug concentration measurements may be used for exploratory biomarker research (Section 9.2.7) or optional future biomedical research (FBR) (Section 9.2.8).

9.2.6. Immunogenicity Measurements and Samples

Serum samples for ADA assessment will be collected at visits listed in Table 2, Table 3, and Table 4. Samples will be collected before dosing on days when study drug is administered. Samples for NAb may be analyzed when an NAb assay becomes available. Any unused serum samples collected for ADA assessments may be used for exploratory biomarker research (Section 9.2.7) or optional FBR (Section 9.2.8).

9.2.7. Exploratory Biomarker Procedures

Blood samples for analysis of biomarkers will be collected at visits according to Table 2, Table 3, and Table 4. The biomarkers studied will be ones considered to be relevant to target engagement, treatment response (efficacy and safety), and the mechanism of action of anti-activin A treatment (garetosmab).

Biomarker measurements, including those of the biochemical bone formation markers and inflammation markers, will be performed in serum or plasma samples to discover and determine effects on biomarkers of FOP or on relevant physiological and pathogenic processes of HO. Biomarkers studied may include but are not limited to biochemical bone and cartilage formation markers (eg, BSAP, P1NP, Collagen-10), and inflammation markers (eg, hs-CRP).

The list may change, as it is recognized that more relevant or novel biomarkers may be discovered during the process of this study. Investigators will be blinded to the bone biomarker data.

Biomarkers related to the activin A and the ACVR1 pathway including but not limited to BMP ligands or biomarkers that further elucidate the mechanism of action of garetosmab may also be explored.

Samples may be stored for up to 15 years after the final date of the database lock and may be used for research purposes. Any residual samples will be destroyed. Data analysis will be described in the statistical analysis plan (SAP) and results may or may not be reported in the CSR.

Countries with export restrictions of biological samples to the United States are excluded from mandatory testing if samples cannot be sent to the central lab. In China, the samples will only be sent to central lab in China or the United States after HGRAC approval.

9.2.8. Future Biomedical Research (Optional)

Patients who agree to participate in the FBR sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Additional samples will be collected for FBR at

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

visits specified in Table 2. Residual biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these future biomedical research analyses will not be presented in the CSR.

FBR samples will not be collected or banked from patients at Chinese study sites.

9.2.9. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (pre-dose) but can be collected at a later study visit. Whole blood samples for DNA extraction will be collected at time points according to Table 2. DNA will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of FOP and related diseases. These samples will be single-coded as defined by the ICH guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker responses to garetosmab, other FOP clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of FOP, as well as related HO and bone diseases, may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or FOP and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole exome sequencing, whole-genome sequencing, and DNA copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all AEs occurring during the study data collection, from the time of signing the ICF to the end of study (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. AEs may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation or dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the on-treatment period) that the investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE CRF and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

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

- **SAEs**.
- **Selected Adverse Events of Special Interest** (AESI; serious and nonserious)**:**
  - The following will be considered AESIs and will be reported to the sponsor within 24 hours using the same reporting process as that for SAE reporting:
    - Epididymitis, orchitis, hydrocele, scrotum pain and/or scrotum swelling
    - Moderate-to-severe episodes of spontaneous non-traumatic bleeding
    - Moderate epistaxis (defined as lasting longer than 30 minutes or requiring professional medical intervention).
    - Severe epistaxis (based on definition of a severe AE as described in Section 10.2.5)
    - Skin infection/abscess that requires referral to specialist for treatment
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 30 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria, must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.
- **Symptomatic Overdose of Study Drug**: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

For studies with PRO, the PRO data are generally not reportable as individual AEs and thus will not be reported or reconciled as such.

10.2.2. Serious Adverse Event

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

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

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

10.2.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 2 hours after the infusion is completed. All infusion reactions must be reported as AEs (defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.5.

10.2.5. Severity

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

Mild: Does not interfere in a significant manner with the patient normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

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

Infusion Reactions

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

Mild: Mild transient reaction; infusion interruption not indicated; intervention not indicated

Moderate: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours

Severe: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae; life-threatening consequences; urgent intervention indicated; death

10.2.6. Causality

The investigator must provide causality assessment as to whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug and same class of drugs
- Concomitant medications

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its class of drugs or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol-specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol-specified procedure and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol-specified procedure or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg,

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Global Patient Safety [GPS]; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, IECs/IRBs, and the participating investigators of any SUSARs (suspected unexpected serious adverse reactions) occurring in other study centers or other studies of the active study drug (garetosmab), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the Institutional Review Board (IRB)/Ethics Committee (EC) unless delegated to the sponsor.

Event expectedness for study drug (garetosmab) is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the CSR to health authorities and IECs/IRB as appropriate.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

11. STATISTICAL PLAN

11.1. Statistical Hypothesis

[redacted]

11.2. Justification of Sample Size

[redacted]

11.3. Analysis Sets

11.3.1. Full Analysis Set

The primary efficacy analysis set is the full analysis set (FAS), defined as all randomized patients who have received study drug. Patients in the FAS will be analyzed according to the treatment group allocated by randomization (ie, as-randomized treatment group).

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who have received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set includes all patients who received study drug and had at least 1 non-missing ADA result following the first study dose.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

11.4. Statistical Methods

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

11.4.1. Patient Disposition

The following data will be summarized:

- The total number of screened patients, defined as having signed the ICF
- The total number of randomized patients, defined as all screened patients with a double-blind treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used
- The total number of patients randomized, but not receiving study treatment
- The total number of patients randomized and receiving study treatment
- The total number of patients who completed the DBTP, defined as week 56 visit performed
- The total number of patients who prematurely discontinued study treatment during the DBTP, and the reasons for discontinuation
- The total number of patients who entered the ETP, defined as patients who received study treatment at week 56 visit
- The total number of patients who prematurely discontinued study treatment during the ETP, and the reasons for discontinuation
- The total number of patients in each analysis set

11.4.2. Demography and Baseline Characteristics

Demographic variables (eg, age, race, and gender), baseline characteristics, medical history, and prior and concomitant mediations and therapies will be summarized by treatment group for patients in the FAS. See Section 5.1 for a full list of demographic and baseline variables. No statistical hypothesis tests will be performed on these characteristics.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

[redacted]

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

[redacted]

11.4.3.2. Secondary Efficacy Analysis

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

[redacted]

11.4.3.3. Other Secondary Efficacy

[redacted]

11.4.3.4. Dose Response Analysis

Besides the primary efficacy analysis, the primary efficacy endpoint will be compared between the garetosmab [redacted] mg/kg IV Q4W (low-dose) treatment group and placebo.. The analysis will employ the same statistical method as described for the primary efficacy comparison. Graphs will be provided for the mean rates of new HO lesion formation through week 56 by treatment group.

11.4.4. Control of Multiplicity

[redacted]

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

[redacted]

11.4.5. Safety Analysis

For the DBTP and the entire study duration period, summaries of safety results will be presented by study treatment received for patients in the SAF. No formal inferential testing will be performed. Summaries will be descriptive in nature.

All safety analyses will be performed using the following common rule:

- The baseline value is defined as the last available value before the first dose of DBTP study treatment.

11.4.5.1. Adverse Events

Definitions

For safety variables, the following observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of double-blind study drug.
- The DBTP TEAE observation period is defined from the day of the first dose of double-blind study treatment to the day of week 56 visit for those patients who complete week 56, or up to their last dose date + 28 days for those patients who discontinue the study treatment before week 56.
- The on-study TEAE period is defined from the day of the first study treatment administration to the end of the study.

Adverse Event Reporting Definitions

The following adverse events definitions will be applied:

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.
- TEAEs are AEs that developed or worsened or became serious during the respective TEAE period.

Analysis

Summaries of all TEAEs by treatment group will include:

- Overview of TEAEs
- TEAEs, presented by SOC and PT
- Treatment-related TEAEs, presented by primary SOC and PT
- Treatment-emergent SAEs, presented by primary SOC and PT
- TEAEs by maximum severity (according to the grading scale outlined in Section 10.2.5), presented by primary SOC and PT
- TEAEs leading to death, presented by primary SOC and PT

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- Treatment-emergent AESIs, presented by primary SOC and PT
- Treatment-emergent AEs leading to permanent treatment discontinuation, presented by primary SOC and PT

Listing will be provided for all reported AEs. More details on the analyses of AEs will be provided in SAP.

11.4.5.2. Other Safety

Definitions

The following definitions will be applied to laboratory parameters, vital signs, and ECGs:

- The potentially clinically significant value (PCSV) criteria are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests and vital signs. PCSV criteria will be provided in the SAP.
- PCSV criteria will determine which patients had at least 1 PCSV during the respective TEAE period, taking into account all evaluations performed during the respective TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSV percentage.
- On-treatment period: The treatment period used for quantitative analysis in the on-treatment period is defined from the day of the first dose of study treatment to the day of the last dose of study treatment + 28 days.

Analysis

Summary statistics of all laboratory variables and all vital sign parameters (raw data and changes from baseline) will be calculated for each protocol-scheduled visit assessed during the treatment period. For selected parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at same time points) in each treatment group.

The incidence of PCSVs at any time during the TEAE period will be summarized regardless of the baseline level, and again according to the following baseline categories:

- Normal/missing

For laboratory parameters for which PCSV criterion is not defined, similar table(s) using the normal range will be provided.

Listings will be provided with flags indicating the laboratory values meeting PCSV criteria.

11.4.5.3. Treatment Exposure

The following treatment exposure data in DBTP will be summarized by treatment group:

- Duration of study drug exposure defined as:

  (date of last DBTP study drug administration – date of first DBTP study drug administration) + 28 days

- Total number of study treatment infusions received during DBTP by patient

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

The following treatment exposure data in the ETP will be summarized by treatment group:

- Duration of study drug exposure defined as:

(date of last ETP study drug administration – date of first ETP study drug administration) + 28 days

- Total number of study treatment infusions received during ETP by patient

For patients entering ETP, the following combined treatment exposure data in the DBTP and ETP will be summarized by treatment group:

- Combined patient duration of study treatment exposure in weeks: (date of last ETP study drug administration – date of first DBTP study drug administration + 28 days)/7.
- Combined total number of study treatment infusions by patient defined as: total number of DBTP infusions + total number of ETP infusions.
- Combined patient duration of study treatment exposure in patient-years is calculated as the patient duration in weeks multiplied by 7/365.

The durations of study treatment exposure (DBTP, ETP, and cumulative across the study), measured in weeks, will be summarized by at least; mean, median, SD, and minimum/maximum. The categorical data for number of study treatment infusions (DBTP, ETP, and cumulative across the study) will be summarized by patient counts and percentages.

11.4.5.4. Treatment Compliance

For the DBTP, compliance with protocol-defined investigational product will be calculated as follows:

Treatment compliance = (Number of infusions of study drug during exposure period)/(Number of planned infusions of study drug during exposure period on or before the time that the patient discontinues from the study) x 100%.

Treatment compliance will be presented by specific ranges for each treatment group. The ranges of interest will be specified in the SAP.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

The PK parameters may include, but are not limited to:

- C_{max}
- T_{max}
- AUC_{time}
- $t_{1/2}$
- CL
- Volume of distribution
- Mean residence time

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

The concentrations of functional garetosmab over time will be summarized by descriptive statistics for each of the treatment groups.

No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA response observed:

- Pre-existing immunoreactivity: If the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value
- Treatment-emergent ADA response: A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay
  - Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate.
- Treatment-boosted ADA response: A positive result at baseline in the ADA assay with at least one post baseline titer result ≥9-fold the baseline titer value
- Maximum ADA Titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- Samples that are positive in ADA assay may be assessed for the presence of NAb when NAb assay is available.

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers positivity presented by participant, time point, and dose group will be provided. Incidence of treatment-emergent ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

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

11.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Analyses of PD and other exploratory biomarker data are defined in the SAP. Unless specified as a secondary endpoint, the results of other biomarkers may not be presented in the CSR.

Descriptive statistics on levels of biomarkers by study visit will be generated. Levels of biomarkers including means and medians will be evaluated for change from baseline through the end of the study.

11.5. Timing of Statistical Analyses

The statistical analyses will be conducted in 2 steps. All analyses that include unblinded study treatment administration information will be conducted by the Regeneron R2477-FOP-2175 unblinded team. The members of the Regeneron unblinded team will not be involved in the conduct of the study. The unblinded team will not release individual patient identification to anyone who

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

is directly involved in the conduct of the study. The measures used to protect the blind and the integrity of the study, the communication plan, and the confidentiality agreement will be described in a separate document.

11.5.1. First Step Analysis:

The first analysis will be conducted as soon as all patients have been randomized and all data through week 56 in the DBTP has been collected and validated. This first analysis will consist of the final analysis of the primary and key secondary efficacy endpoints. The safety analysis (including platelet cytometry) will be performed on all safety data collected and validated at the time of the first analysis.

The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect. Since data collection for the double-blind primary efficacy measure and key secondary efficacy measures will have been concluded at the time of this first analysis, the significance level for each garetosmab treatment group compared to placebo in the study remains at 0.05. This first analysis may be used for the submission dossier to health authorities.

11.5.2. Second Step Analysis

The second analysis will be conducted as soon as all patients have been randomized and all data through week 84 in the ETP has been collected and validated. This second analysis will consist of remaining exploratory endpoints, and safety data collected and validated at the time of the second analysis.

The results of the second analysis will not be used to change the conduct of the ongoing study in any aspect.

11.5.3. Final Analysis

The final analysis will be conducted as soon as all patients have been randomized and all patient data collected and validated through the follow-up period. This analysis will consist of the final analyses for all remaining safety data.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

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

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

12. QUALITY CONTROL AND 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 described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

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

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

The CRF data for this study will be collected with an EDC.

12.1.2. Electronic Systems

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

- IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- SAS – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk-based approach to study monitoring and oversight, aligned with risk-based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Management (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies may include: reduced source data verification, targeted source data review, the use of onsite and remote monitoring visits (as allowed by local laws), and centralized monitoring to identify site-level risks and study-level trends. The investigator must allow study-related monitoring activities to occur.

The study monitors may perform targeted source data review to verify that data recorded in the CRF by authorized site personnel are accurate and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate, and complete.

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

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. 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.

12.3. Audits and Inspections

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

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

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/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.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

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

12.4. Study Documentation

12.4.1. 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 the patient's final CRFs that will be provided to the sponsor.

12.4.2. 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 sponsor should archive the content of the Clinical Trial Master File for at least 25 years after the end of the clinical trial, unless other union law requires archiving for longer. 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.

12.4.3. Recruitment Strategy

Potential study participants may be identified by the investigator through a variety of means, such as publicizing the trial or using existing patient lists. Recruitment resources may include, but are not limited to, recruitment flyers, brochures, social media ads, newspaper ads, radio ads, etc. A third-party vendor may assist in recruitment efforts, such as the development of recruitment materials. Patients who participated in the phase 2, R2477-FOP-1623 study (LUMINA-1) can enroll if they meet the inclusion criteria and do not meet the exclusion criteria.

All patient-facing recruitment material, including media advertising and receptionist scripts, will be reviewed and approved by the appropriate IRB/EC/authority prior to use. Resources may be in paper or electronic form. Regeneron will not access any patient identifiable information as part of recruitment efforts.

12.4.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

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 the 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, or if there are significant changes to the study procedures, 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. Patient 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.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

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.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website/registry according to applicable local guidelines and regulations. For data integrity, scientific, and statistical reasons, published results from all participants will be disclosed following end of study.

Treatment codes will be disseminated to each investigation site thereafter.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

15. PREMATURE TERMINATION OF THE STUDY OR CLOSEOUT 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 is 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. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement in accordance with local/national laws and regulations/requirements.

18. PUBLICATION POLICY

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

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

19. REFERENCES

Al Kaissi A, Kenis V, Ben Ghachem M, Hofstaetter J, Grill F, Ganger R, et al. The Diversity of the Clinical Phenotypes in Patients With Fibrodysplasia Ossificans Progressiva. Journal of clinical medicine research. 2016;8(3):246-53.

Aykul S, Corpina RA, Goebel EJ, Cunanan CJ, Dimitriou A, Kim HJ, et al. Activin A forms a non-signaling complex with ACVR1 and type II Activin/BMP receptors via its finger 2 tip loop. eLife. 2020;9.

Botman E, Raijmakers P, Yaqub M, Teunissen B, Netelenbos C, Lubbers W, et al. Evolution of heterotopic bone in fibrodysplasia ossificans progressiva: An [(18)F]NaF PET/CT study. Bone. 2019;124:1-6.

Cohen RB, Hahn GV, Tabas JA, Peeper J, Levitz CL, Sando A, et al. The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. A study of forty-four patients. J Bone Joint Surg Am. 1993;75(2):215-9.

FDA. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, Final. 2009 [cited 2018 10 Sept]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Hatsell SJ, Idone V, Wolken DM, Huang L, Kim HJ, Wang L, et al. ACVR1R206H receptor mutation causes fibrodysplasia ossificans progressiva by imparting responsiveness to activin A. Science translational medicine. 2015;7(303):303ra137.

Hino K, Ikeya M, Horigome K, Matsumoto Y, Ebise H, Nishio M, et al. Neofunction of ACVR1 in fibrodysplasia ossificans progressiva. Proceedings of the National Academy of Sciences of the United States of America. 2015;112(50):15438-43.

Huning I, Gillessen-Kaesbach G. Fibrodysplasia ossificans progressiva: clinical course, genetic mutations and genotype-phenotype correlation. Molecular syndromology. 2014;5(5):201-11.

Kaplan F, Grogan D. Palovarotene phase 2 trial: top line results. Boston, MA: FOP Drug Development Forum; 2016.

Kaplan FS, Al Mukaddam M, Pignolo RJ. A cumulative analogue joint involvement scale (CAJIS) for fibrodysplasia ossificans progressiva (FOP). Bone. 2017;101:123-8.

Kaplan FS, Pignolo RJ, Shore EM. The FOP metamorphogene encodes a novel type I receptor that dysregulates BMP signaling. Cytokine & growth factor reviews. 2009;20(5-6):399-407.

Kaplan FS, Zasloff MA, Kitterman JA, Shore EM, Hong CC, Rocke DM. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. J Bone Joint Surg Am. 2010;92(3):686-91.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Keller SD, Bayliss MS, Ware JE, Jr., Hsu MA, Damiano AM, Goss TF. Comparison of responses to SF-36 Health Survey questions with one-week and four-week recall periods. Health services research. 1997;32(3):367-84.

Kitoh H, Achiwa M, Kaneko H, Mishima K, Matsushita M, Kadono I, et al. Perhexiline maleate in the treatment of fibrodysplasia ossificans progressiva: an open-labeled clinical trial. Orphanet journal of rare diseases. 2013;8:163.

Liljesthröm M, Pignolo R, Kaplan F. Epidemiology of the Global Fibrodysplasia Ossificans Progressiva (FOP) Community. J Rare Dis Res Treat. 2020;5(2):31-6.

Pignolo RJ, Baujat G, Brown MA, De Cunto C, Di Rocco M, Hsiao EC, et al. Natural history of fibrodysplasia ossificans progressiva: cross-sectional analysis of annotated baseline phenotypes. Orphanet journal of rare diseases. 2019;14(1):98.

Pignolo RJ, Bedford-Gay C, Liljesthrom M, Durbin-Johnson BP, Shore EM, Rocke DM, et al. The Natural History of Flare-Ups in Fibrodysplasia Ossificans Progressiva (FOP): A Comprehensive Global Assessment. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2016;31(3):650-6.

Pignolo RJ, Kaplan FS. Clinical staging of Fibrodysplasia Ossificans Progressiva (FOP). Bone. 2018;109:111-4.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. The Journal of allergy and clinical immunology. 2006;117(2):391-7.

Upadhyay J, Xie L, Huang L, Das N, Stewart RC, Lyon MC, et al. The Expansion of Heterotopic Bone in Fibrodysplasia Ossificans Progressiva Is Activin A-Dependent. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2017;32(12):2489-99.

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: Phase 3 Randomized, Placebo-Controlled Study to Assess Safety, Tolerability, and Efficacy of Garetosmab in Patients with Fibrodysplasia Ossificans Progressiva 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)

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study Title: Phase 3 Randomized, Placebo-Controlled Study to Assess Safety, Tolerability, and Efficacy of Garetosmab in Patients with Fibrodysplasia Ossificans Progressiva

Protocol Number: R2477-FOP-2175

Protocol Version: Amendment 5

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 Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

VV-RIM-00367296-2.0 Approved - 24 Sep 2024 GMT-5:00

Signature Page for VV-RIM-00367296 v2.0

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