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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A RANDOMIZED, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFECTS ON HETEROTOPIC BONE FORMATION OF REGN2477 IN PATIENTS WITH FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

Compound:	REGN2477
Clinical Phase:	2
Study Name:	**LUMINA-1**
Protocol Number:	R2477-FOP-1623
Protocol Version:	R2477-FOP-1623 Amendment 6 Global Admin
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Scientific/Medical Monitor:	[redacted]

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AMENDMENT HISTORY

Amendment 6 Global Admin

The purpose of this non-substantial amendment is to correct minor errors identified in Amendment 6 Global.

Change	Rationale for Change	Section Changed
This non-substantial amendment seeks to correct the following identified minor errors: – Revised the description of access to REGN2477 after Period 3 in the synopsis to match correct description in the protocol body – Corrected footnotes #17 and #28 and linked #28 to the rows for collection of hematology, blood chemistry, and urinalysis in Schedule of Events Table 3	Correction of errors in the synopsis and the Schedule of Events footnotes for the previous Amendment 6 Global	Clinical Study Protocol Synopsis, Study Duration Table 3 Schedule of Events: Period 3 (Follow-Up Treatment Period), footnote #28 Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2, Table 3, #17, #28
– Revised the description of the change in Amendment 6 Global Amendment History Table from 'every 3 months' to 'every **6 months'** to match the statement in the protocol body : "Reduced the frequency of blood sample collection to every **6 months** after week 56 for assessments of safety and ADA	Correction of an error in the amendment history table for the previous Amendment 6 Global	Amendment History Table Amendment 6 Global (row 10)

Amendment 6 Global

The purpose of this amendment is to account for the COVID-19 pandemic and to minimize the risks to the patients in the study as well as healthcare providers by allowing flexibility in the visit schedule while social distancing suggestions are in place. Allowing for this flexibility does not increase the risk of participating in this study as there will be continued contact between the patients and study personnel despite postponement of in-person clinic visits. In addition, this amendment seeks to update the planned analysis for Period 2 (open-label treatment period; week 56) based on the primary analysis results from Period 1 (double-blind, placebo-controlled period; week 28). These data prompted definition of a separate study hypothesis to "treatment with REGN2477 prevents the formation of new HO lesion in patients with FOP" and addition of new endpoints to test this separate hypothesis for Period 2 (week 56)

Change	Rationale for Change	Section Changed
Added statements to address the impact of the COVID-19 pandemic: – That temporary, alternative mechanisms and flexibility in the visit schedule that may be used to ensure the continuity of clinical study conduct and oversight in light of the public health emergency related to COVID-19. Defined the COVID-19 modified intent-to-treat principle that will be used for the week 56 primary analysis of efficacy endpoints related to imaging	To explain the plan for ensuring continuity of clinical study activities and study oversight activities during the COVID-19 public health emergency. To address the potential impact of the COIVID-19 pandemic on the collection of imaging scans and/or missed or delayed study drug administration	Section 3.3.4 Rationale for Efficacy Endpoints (Period 2; Week 56) Section 3.4 Study-Specific Safety Considerations and Monitoring Section 5.1 Study Description and Duration Section 8.1 Schedule of Events Section 8.1.1 Footnotes for the Schedule of Events Table1, Table 2, Table 3, #26 and #27 Section 8.2.2.1 Positron Emission Tomography/Computed Tomography Procedures Section 10.4.3.2 Analysis of Efficacy Endpoints in Period 2 (Week 56)
Added a summary of the primary analysis results for efficacy and safety in Period 1 (week 28) Added a summary of risks for epistaxis and skin and soft tissue infection	To provide a high-level summary of the study results for efficacy and safety for Period 1(week 28)	Section 1 Introduction Section 3.4.3 Risk for Epistaxis and Monitoring Section 3.4.4 Risk for Skin and Soft Tissue Infection and Monitoring
Added a new hypothesis for Period 2 (week 56; open-label treatment period) based on the current understanding of the biology of FOP Added a rationale for the analyses to confirm the new hypothesis (week 56) with additional alpha of 0.1 specified for control for Type I multiplicity for Period 2 (week 56) Revised the description of the Clinical Endpoint Measures	To update the planned efficacy analysis for Period 2 (week 56; open-label treatment period) based on the primary efficacy analysis results from Period 1 (week 28; double-blind, placebo- controlled period) To specify new analyses which can handle the possibility of patients with missing week 56 imaging assessment (due to COVID-19 disruption for the study) and are consistent with regulatory guidance for analysis for rare disease patient populations.	Clinical Study Protocol Synopsis: Statistical Plan Section 1 Introduction Section 3.1 Hypothesis: Period 1 Double-Blind, Placebo-Control Treatment Period (Week 28) Section 3.2 Hypothesis: Period 2 Open-Label Period (Week 56) Section 3.3.1 Rationale for Clinical Development of REGN2477 for FOP Section 3.3.3 Rationale for Efficacy Endpoint Measures (Period 1; Week 8) Section 3.3.4 Rationale for Efficacy Endpoints (Period 2; Week 56) Section 3.3.6 Clinical Endpoint Measures Section 10.4.3.2.4 Multiplicity Considerations for Period 2 (Week 56)

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Change	Rationale for Change	Section Changed
Added new endpoints for Period 2 (week 56) to confirm the understanding of the biology of new HO bone lesions: • primary efficacy endpoint • key secondary efficacy endpoints • other secondary efficacy endpoints Added a new primary endpoint (week 56) based on low-dose CT assessment Reorganized the Study Variables section to present endpoints by Period 1 (week 28), Period 2 (week 56), and Period 3 (week 76)	To describe the added endpoints or analysis in Period 2 (open-label treatment period; Week 56) To specify a primary endpoint using an imaging assessment that may be easier to perform than the PET assessment during the COVID-19	Clinical Study Protocol Synopsis: Endpoint(s) for Period 1 (Week 28), Endpoint(s) for Period 2 (Week 56) Section 3.4.6 Radiation Exposure Section 4.2 Primary, Secondary, and Exploratory Endpoints (Period 1; Week 28) Section 4.2.4 Other Secondary Endpoints Section 4.2.5 Other Secondary Endpoints related to Clinical Pharmacology (Period 1, Period 2, Period 3) Section 4.2.6 Exploratory Endpoints (Period 1; Week 28) Section 4.3 Primary, Secondary, and Exploratory Endpoints (Period 2; Week 56) Section 4.3.1 Primary Efficacy Endpoint (Period 2 [Week 56]) Section 4.3.2 Key Secondary Efficacy Endpoints (Period 2 [Week 56]) Section 4.3.3 Other Secondary Efficacy Endpoints (Period 2 [Week 56]) Section 4.3.4 Exploratory Endpoints (Period 2 [Week 56]) Section 4.4 Exploratory Endpoints (Period 3 [Week 76]) Section 5.1.2 Period 1: Double-Blind Treatment (Week 1 [Day 1] to Week 24 [Day 169]) and End of Period 1 Assessments (Week 28 [Day 197]) Section 5.1.3 Period 2: Open-Label REGN2477 Treatment (Week 28 [Day 197]) to Week 52 [Day 365]) and End of Period 2 Assessments (Week 56 [Day 393]) Section 5.1.4 Period 3: Follow-Up Treatment Period Week 56 (Day 393) to End of Study Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2, and Table 3, #26, #27

Change	Rationale for Change	Section Changed
Added description of the new statistical analyses for efficacy in Period 2 (week 56) Updated the description of the analysis of efficacy endpoints in Period 1 (Week 28) was updated (amendment 6) to match the final SAP for Period 1 Clarified the description of drug (functional REGN2477) and target (total activin A) assessed	To specify the new statistical analyses in Period 2 (open-label treatment period; week 56) based on the primary efficacy analysis results from Period 1 (week 28; double-blind, placebo-controlled period) To be consistent with the final SAP for Period 1 (double-blind treatment period; Week 28) issued before the database lock To be consistent with the drug and target assays	Clinical Study Protocol Synopsis: Statistical Plan Section 3.3.4 Rationale for Efficacy Endpoints (Period 2; Week 56) Section 10 Statistical Plan Section 10.1.1 Statistical Hypothesis (Period 1 [Week 28]) Section 10.1.2 Statistical Hypothesis (Period 2 [Week 56]) Section 10.4.3.1 Analysis of Efficacy Endpoints in Period 1 (Week 28) Table 5 Analysis Strategy for Primary and Key Secondary Efficacy Endpoints Section 0 Primary Endpoints: Total Lesion Activity by ^{18}F-NaF PET Section 10.4.3.1.2 Primary Endpoints: Total HO Volume by CT Section 10.4.3.2 Analysis of Efficacy Endpoints in Period 2 (Week 56) Section 10.4.3.1.4 Multiplicity Considerations for Efficacy Analyses for Period 1 (Week 28) Section 10.4.3.2.1 Primary Efficacy Endpoints in Period 2 (Week 56) Section 10.4.3.2.2 Key Secondary Efficacy Endpoints in Period 2 (Week 56) Section 10.4.3.2.3 Other Secondary Efficacy Endpoints in Period 2 (Week 56) Section 10.4.3.2.4 Multiplicity Considerations for Period 2 (Week 56) Section 10.4.5 Analysis of Drug Concentration and Total Activin A Concentration Data Section 10.5 Primary and Additional Analysis
Added a description of the criteria for continued access to REGN2477 for patients who completed Period 3 (week 76)	To be consistent with our corporate policy governing access to investigational drugs in confirmatory clinical studies.	Clinical Study Protocol Synopsis: Study Design Section 5.1 Study Description and Duration Figure 1 Study Design Schematic Screening/Baseline Period (Day -28 to Day -1): Study Visit 1 Section 5.1.4 Period 3: Follow-Up Treatment Period Week 56 (Day 393) to End of Study Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2, and Table 3, #17

Change	Rationale for Change	Section Changed
Removed the requirement for a safety discussion with investigators prior to each administration of study drug after week 56. Therefore, after week 56 the need for such interactions will be decided on a case by case basis. Reduced the frequency of blood sample collection to every6 months after week 56 for assessments of safety and ADA	The safety results for Period 1 (week 28) have not identified significant safety concerns that require continued safety discussions or frequent safety laboratory assessments. The reduction in assessments for safety and ADA assessment after week 28 reduces the burden on patient.	Clinical Study Protocol Synopsis: Study Design Section 5.1.2 Period 1: Double-Blind Treatment (Week 1 [Day 1] to Week 24 [Day 169]) and End of Period 1 Assessments (Week 28 [Day 197]) Section 7.2.1 Dose Modification Section 7.2.2 Study Drug Discontinuation Table 3 Schedule of Events: Period 3 (Follow-Up Treatment Period) Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2, and Table 3, #11, #17, #28 Section 8.1.2 Early Termination Visit
Added assessments for FOP I-ADL, EQ-5D-3L, CAJIS and spirometry and collection of blood samples for measurement of drug and target, and ADA every 24 weeks after week 76.	To support assessment of safety, PK, target, and ADA.	Table 3 Schedule of Events: Period 3 (Follow-Up Treatment Period) Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2, and Table 3, #17
Will ask patients who permanently discontinue study treatment but do not withdraw from the study to return to the clinic for blood sample collection for • measurement of serum drug and target concentration, at 4 weeks, 8 weeks, and 16 weeks, and 28 weeks after the patient's last dose. • assessment of ADA at the patients last visit.	The request will support assessment of - drug elimination phase - safety assessments for follow-up of patients - assessment for potential disease rebound - assessment of ADA at the end of the study	Section 7.2.2 Study Drug Discontinuation Section 8.1.2 Early Termination Visit
Updated Pharmacovigilance and Risk Management to Global Patient Safety in various sections	Text change reflects the new organization name	Section 7.2.1.1 Individual Level Dose Modification Section 9.6 Safety Monitoring

Amendment 5 Global

Change and Rationale for Change	Section Changed
• The purpose of this amendment is to revise the description of study treatment based on a new liquid formulation. The option for subcutaneous (SC) administration is removed as the concentration of the current formulation is not suitable for SC use.	Section 7.1 Investigational and Reference Treatments

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Amendment 4 Global

Change and Rationale for Change	Section Changed
This is a non-substantial amendment to change the hierarchy order of statistical testing for the primary efficacy and key secondary endpoints in response to comments from a health authority. The order of statistical testing of the primary efficacy and key secondary endpoints is: Baseline-Active heterotopic ossification (AHO) analysis set first and Baseline-Active HO Classic ACVR1[R206H] Mutation (AHOC) analysis set second.	Clinical Study Protocol Synopsis: Endpoints, Efficacy Analysis Sets, Primary Efficacy and Key Secondary; Statistical Plan, Justification of Sample Size, Statistical Methods Section 4.2.2 Primary Efficacy Endpoints Section 4.2.3 Key Secondary Endpoints Section 10.1 Statistical Hypothesis Table 5 Analysis Strategy for Primary and Key Secondary Efficacy Endpoints Section 10.4.3.1.1 Primary Endpoints: Total Lesion Activity by 18F-NaF PET Section 10.4.3.1.2 Primary Endpoints: Total HO Volume by CT Section 10.4.3.1.3 Key Secondary Endpoints: Pain NRS-AUC Section 10.2 Justification of Sample Size Section 10.3.1 Baseline-Active HO Analysis Set Section 10.3.2 Baseline-Active HO Classic ACVR1[R206H] Mutation Analysis Set Section 10.4.3.1.4 Multiplicity Considerations
Update in Scientific/Medical Monitor title	Title Page
Typographical errors	Throughout the document

Amendment 3 Global

Change and Rationale for Change	Section Changed
The purpose of this amendment is to revise the protocol to reflect new safety information relating to a potential risk for epistaxis. In order to mitigate the potential risk for epistaxis, 3 exclusion criteria were added: • #18 Patients who are on concomitant antiplatelet therapy (egg, clopidogrel), anti-coagulants (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) is acceptable. • #19 Patients with a history of severe, non-traumatic bleeding requiring transfusion or hospitalization for hemodynamic compromise • #20 Patients with a known pre-existing medical history of a bleeding diathesis (eg, hemophilia A, von Willebrand's Factor deficiency, platelet count $\leq 20x10^9$/L). As an additional mitigation strategy, 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. Clarified the Low dose acetylsalicylic acid (aspirin; [≤100 mg/day]) To aid in the exclusion of patients who may have existing propensity for bleeding and to assess the effect of REGN2477 administration, baseline and post-treatment laboratory measures of coagulation parameters and platelet effector function were added. Added baseline exploratory research sample to explore mechanism of epistaxis and REGN2477 mechanism of action Added antiplatelet therapy, anticoagulants, and herbal supplements (that inhibit platelet function or are associated with increased risk of bleeding) to the list of prohibited medications To increase early detection of epistaxis or bleeding events, the following were added as adverse events of special interest (AESIs): • Moderate to severe episodes of non-traumatic bleeding • Moderate epistaxis (defined as any episode lasting longer than 30 minutes or requiring professional medical intervention) • Severe epistaxis (based on definition of a severe AE as per protocol)	Clinical Study Protocol Synopsis: Procedures and Assessments Section 3.3.3 Potential Risk for Epistaxis and Monitoring Section 5.1.1 Screening/Baseline Period (Day -28 to Day -1): Study Visit 1 Section 5.1.2 Period 1: Double-Blind Treatment (Week 1 [Day 1] to Week 24 [Day 169]) and End of Period 1 Assessments (Week 28 [Day 197]) Section 6.2.2 Exclusion Criteria, #18, #19, #20 Section 7.6.1 Prohibited Medications Section 7.6.2 Permitted Medications Table 1 Schedule of Events: Screening/Baseline through Period 1 (Randomized Double-Blind Treatment Period) Table 2 Schedule of Events: Period 2 (Open Label Treatment Period) Table 3 Schedule of Events: Period 3 (Follow-Up Treatment Period Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2, and Table 3, #25 Section 8.2.4.5 Laboratory Testing Section 8.2.6 Biomarker Procedures Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor

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Amendment 2 Global

Change and Rationale for Change	Section Changed
The purpose of this amendment is to add individual level dose modification criteria, clarify the study level dose modification, and specify that a pregnancy will be tracked until delivery along with a 3-month postnatal follow-up period for the infant, in response to a health authority requests.	Clinical Study Protocol Synopsis: Study Design Section 3.2.7 Rationale for Dose Selection Section 3.3.2 Potential Risk for Teratogenicity/Fetal Toxicity and Pregnancy Monitoring and Prevention Section 5.1.3 Period 2: Open-Label REGN2477 Treatment (Week 28 [Day 197]) to Week 52 [Day 365]) and End of Period 2 Assessments (Week 56 [Day 393]) Section 7.2.1 Dose Modification Section 7.2.1.1 Individual Level Dose Modification Section 7.2.1.2 Study Level Dose Modification Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor
Added 3 footnotes that had been inadvertently omitted from amendment 1 Global: • A footnote to indicate that measurement of a patient's height may not be precise or not possible to be assessed. • A footnote clarifying the urinalysis procedure. • A footnote to provide more detail about the clinical endpoint measures. Added further detail regarding study assessments.	Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2 and Table 3: Footnotes #22, #23, and #24. Section 8.2.3 Clinical Endpoint Measures Section 8.2.4.5 Laboratory Testing
Minor edits for clarification of study terminology, corrections, and minor changes: • Clarified the description of the sample size • Correct an error in description of the full analysis set in the synopsis	Clinical Study Protocol Synopsis: Study Design, Population, Endpoints, Statistical Plan Section 1 Introduction Section 3.2.2 Rationale for Study Design Section 5.1 Study Description and Duration Section 6.1 Number of Patients Planned Section 7.2.1 Dose Modification Section 7.2.1.1 Individual Level Dose Modification Section 7.2.1.2 Study Level Dose Modifications Section 10.2 Justification of Sample Size

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Amendment 1 Global

Change and Rationale for Change	Section Changed
The purpose of this amendment 1 Global is to remove the requirement that patients have the specific classic ACVR1[R206H] mutation. This change is based on in vitro studies which demonstrated that different mutations in ACVR1 receptors transduced bone morphogenic protein signaling when stimulated with Activin A. These results indicate that REGN2477 may be effective for all FOP mutations. This change expands the scope of the study to include patients with a clinical diagnosis of FOP who may have different ACVR1 mutations. To support interpretation of the study results, all patients will have their ACVR1 gene sequenced during the study (mandatory). The primary statistical analyses for the study will be based on the original study design, not the expanded study population.	Clinical Study Protocol Synopsis: Study Design, Endpoints, Statistical Plan Study Design, Target Population, Procedures and Assessments, Statistical Plan Section 1 Introduction Section 3.2.2 Rationale for Study Design Section 3.3.1 Potential Risk for Reproductive Organ Adverse Events in Male Subjects and Monitoring Section 4.1 Demographic and Baseline Characteristics Section 5.1.1 Screening/Baseline Period (Day -28 to Day -1): Study Visit 1 Section 6.2.1 Inclusion Criteria: Criterion #3 (deleted) Table 1 Schedule of Events: Screening/Baseline through Period 1 (Randomized Double-Blind Treatment Period) Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2 and Table 3: Footnotes #5 and #21 Section 8.2.1 Procedures Performed only at the Screening/Baseline visit Section 21 References: Hino, 2015
The statistical analysis was revised to address feedback from regulatory agencies, as well as addressing the changes related to inclusion of patients with ACVR1 mutations: Use a hierarchical testing procedure instead of the Hochberg procedure. Revised Statistical Plan Specify hierarchical testing of the 4 efficacy primary endpoints Specify that the baseline active HO analysis set includes all randomized patients who had active HO lesion at baseline Specify that patients will be randomized to REGN2477 or placebo in a 1:1 ratio by ACVR1 mutation (classic [R206H], other) in addition to gender and presence/absence of baseline active HO lesions. Specify that results are analyzed first in patients with the ACVR1[R206H] mutation and secondly in patients with any ACVR1 mutation. Make minor corrections to descriptions and tables	Clinical Study Protocol Synopsis: Study Design, Endpoints, Statistical Plan Section 4.2 Primary, Secondary, and Exploratory Endpoints Section 4.2.2 Primary Efficacy Endpoints Section 4.2.3 Key Secondary Endpoints Section 4.2.4 Other Secondary Endpoints Section 4.2.6 Exploratory Endpoints Section 10.1 Statistical Hypothesis Section 10.2 Justification of Sample Size Table 4 Sample Size (Total Lesion Activity by 18F-NaF PET, Total Volume of HO Lesions by CT, and SUVmax) at Week 28 for Comparisons between REGN2477 and Placebo Treatment Groups Section 10.3.1 Baseline Active HO Classic ACVR1[R206H] Mutation Analysis Set (new) Section 10.3.1 Baseline Active HO Analysis Set Section 10.3.3 Full Analysis Set Section 10.3.5 Other Analysis Sets Section 10.4.3 Efficacy Analyses Table 5 Analysis Strategy for Primary and Key Secondary Efficacy Endpoints Section 10.4.3.1.1 Primary Endpoints: Total Lesion Activity by 18F-NaF PET

Change and Rationale for Change	Section Changed
	Section 10.4.3.1.2 Primary Endpoints: Total HO Volume by CT Section 10.4.3.1.3 Key Secondary Endpoints: Pain NRS-AUC Section 10.4.3.1.4 Multiplicity Considerations
The study design was revised to allow patients who completed the open label portion of the study through week 52, to continue to receive study drug from week 56 through week 76 or beyond. Changed "the 24-week follow-up period" to the "follow-up treatment period" (Period 3). Each patient will continue to receive REGN2477 every 4 weeks during this period until they complete the week 76 visit, and all data have been collected and validated through the time when the last patient randomized into the study completes the week 28 visit (Period 1), and results of the primary analyses of safety and efficacy are available to the sponsor. If at the time patients reach the week 76 visit but data from the last patient randomized into the study through the week 28 visit have not been collected and validated, and results of the primary analyses of safety and efficacy are not yet available to the sponsor, patients will continue to receive REGN2477 every 4 weeks, beyond week 76. Patients will have the option to discontinue study medication before the beginning or at any time during Period 3, similarly to what occurs at any time during the study after patients have signed the informed consent. Treatment with REGN2477 will continue provided that no safety signals are identified during continuous monitoring of the study by the investigator, medical monitor and IDMC. In addition, all patients will be required to maintain contraception during this period. Revised footnote #17 in the Schedule of Events, Table 3, as this footnote addressed the transition from on-treatment to off- treatment which is no longer relevant to the study. The deletion of this footnote caused footnote #19 for Daily Pain NRS and Daily FOP disease activity diary from Schedule of Events, Table 1 to be changed to footnote#18. Removed the post-treatment period as the third observation period, because treatment with REGN2477 will continue during Treatment Follow-up (Period 3) through the end of the study.	Clinical Study Protocol Synopsis: Study Design, Study Duration, Statistical Plan Section 1 Introduction Section 3.2.2 Rationale for Study Design Section 5.1 Study Description and Duration Section 5.1.4 Period 3: Follow-Up Treatment Period Week 56 (Day 393) to End of Study (heading only) Figure 1 Study Design Schematic Section 7.1 Investigational and Reference Treatments Table 1 Schedule of Events: Screening/Baseline through Period 1 (Randomized Double-Blind Treatment Period) Table 3 Schedule of Events: Period 3 (Follow-Up Treatment Period) Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2, and Table 3: Footnotes #17 and #18 Section 10.4.4.1 Adverse Events Section 10.5 Primary and Additional Analysis
"End of Treatment" was removed from visit 17 of Period 2 (Open Label Treatment Period), as the end of study will occur after Period 3 (Follow-up Treatment Period).	Table 2 Schedule of Events: Period 2 (Open Label Treatment Period)

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Change and Rationale for Change	Section Changed
Schedule of Events Table 3: Addition of a new column entitled: "End of Study/Week 80" to denote the new end of study and to indicate the procedures that will be conducted during this period in the event that data from the last patient randomized into the study through the week 28 visit (Period 1) have not been collected and validated, and results of the primary analyses of safety and efficacy are not yet available to the sponsor. Reduced visit windows in Period 3 from ±14 days to ±7 days, as patients will continue to be treated with REGN2477 during this period. A new row entitled "Administer REGN2477" was added.	Table 3 Schedule of Events: Period 3 (Follow-Up Treatment Period)
Removed the sentence regarding patients entering the off-drug treatment phase after early termination as the off-drug phase was removed and the statement is no longer applicable	Section 8.1.2 Early Termination Visit
Removed the post-treatment period from the definitions of Adverse Events, as the post-treatment period is no longer relevant.	Section 10.4.4.1 Adverse Events, Definitions
Added the week 76 time point to the additional analyses of safety and efficacy data to be performed following the open-label treatment period for consistency with the planned analyses.	Section 10.5 Primary and Additional Analysis

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Change and Rationale for Change	Section Changed
Added a secondary objective and secondary endpoints for assessment of the effect of REGN2477, between week 28 and week 56, on the number, activity, and volume of HO lesions identified by ^{18}F-NaF PET or by CT in patients who switch from placebo to REGN2477 at week 28.	Clinical Study Protocol Synopsis: Objectives, Endpoints Section 2.2 Secondary Objectives Section 4.2.4 Other Secondary Endpoints
Added assessment of hs-CRP as a biomarker Added assessment of magnesium to the clinical chemistry panel Added an endpoint for FEV1 of spirometry Added measurement of height at baseline	Section 4.2.6 Exploratory Endpoints Section 5.1.2 Period 1: Double-Blind Treatment (Week 1 [Day 1] to Week 24 [Day 169]) and End of Period 1 Assessments (Week 28 [Day 197]) Section 5.1.4 Period 3: Follow-Up Treatment Period Week 56 (Day 393) to End of Study Table 3 Schedule of Events: Period 3 (Follow-Up Treatment Period): Future Biomedical Research Sample row. Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 8.2.4.5 Laboratory Testing Section 8.2.6 Biomarker Procedures Section 8.2.7 Future Biomedical Research
Provided more detail about the frequency of IDMC meetings and clarified the monitoring for potential AEs in male patients.	Section 5.1.5.1 Study Stopping Criteria Table 1 Schedule of Events: Screening/Baseline through Period 1 (Randomized Double-Blind Treatment Period) Section 8.2.1 Procedures Performed only at the Screening/Baseline Visit
To address feedback from a regulatory agency: The duration of time for patients to maintain highly effective contraception was extended to 30 weeks after the last dose of study drug to address feedback from a regulatory agency. Added an exclusion criterion “Previous history or diagnosis of cancer” and updated the SAE definition to note that “a new diagnosis or progression of a malignancy in patients enrolled in the study will also be considered a SAE” to address feedback from a regulatory agency. Deleted ‘futility’ as a reason for premature termination of the study.	Section 6.2.2 Exclusion Criteria: Criterion #16 Section 6.2.2 Exclusion Criteria: Criterion #3 Section 9.3.2 Serious Adverse Event Section 16.1 Premature Termination of the Study

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Change and Rationale for Change	Section Changed
Clarified the rationale for use of SC route of administration. Provided details on how the safety of each dose will be reviewed prior to next dose.	Clinical Study Protocol Synopsis: Study Design Section 5.1.2 Period 1: Double-Blind Treatment (Week 1 [Day 1] to Week 24 [Day 169]) and End of Period 1 Assessments (Week 28 [Day 197]) Section 7.1 Investigational and Reference Treatments Section 7.2.1 Dose Modification
Clarified the PET/CT procedures and the exploratory endpoints assessed by PET/CT.	Section 4.2.6 Exploratory Endpoints Section 8.2.2.1 Positron Emission Tomography/Computed Tomography Procedures Section 4.2.6 Exploratory Endpoints
Clarified that PET/CT scans will be read and analyzed using a blinded central reading center during the study, however at baseline, added the provision that the investigator will be allowed to independently read and analyze PET/CT images. Baseline PET/CT images will be performed before each patient is randomized into the study. As these baseline images do not contain any unblinding data, the PI may utilize these images as part of standard of care resulting in not having to duplicate the imaging assessments and thereby reducing the patients' total annual radiation exposure.	Section 8.2.2.1 Positron Emission Tomography/Computed Tomography Procedures
Added the requirement that any incidental findings identified through PET/CT scans will be reported to the investigator and medical monitor, and that the investigator will communicate any findings to the patient.	Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2, and Table 3: Footnotes #13 Section 8.2.2.1 Positron Emission Tomography/Computed Tomography Procedures
Added whole body ^{18}F-NaF PET and whole body low dose CT imaging at week 76 (day 533 [±7 days]) for a total of 5 scans during the study. This will allow for the evaluation of longer term effects of REGN2477 (ie, an additional 20 weeks of treatment) in FOP patients. As a result of the additional scan, the total ED range approximation was changed from 21 mSv to 25 mSv.	Clinical Study Protocol Synopsis: Study Design Table 3: Schedule of Events: Period 3 (Follow-Up Treatment Period) Section 3.2.4.1 18F-NaF Positron Emission Tomography Section 3.3.6 Radiation Exposure Section 4.2.6 Exploratory Endpoints Section 5.1.4 Period 3 Follow-up Treatment Period Week 56 (Day 393) to End of Study

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Change and Rationale for Change	Section Changed
Added that ECG and symptom-directed physical examination may be performed during the follow-up treatment period (Period 3, after week 56) with REGN2477 at the investigator's discretion, and that urine pregnancy testing will be performed prior to each REGN2477 dose administration, and a serum pregnancy test will be performed at the end of study visit. PK/ADA sampling will continue to be performed at all visits after week 56.	Section 8.1.1 Footnotes for the Schedule of Events: Table 1, Table 2, and Table 3: Footnotes #9, #10, and #11
Clarified that treatment with imatinib or isotretinoin is also exclusionary and are prohibited medications	Section 3.2.2 Rationale for Study Design Section 6.2.2 Exclusion Criteria: Criterion #12 Section 7.6.1 Prohibited Medications
Provide more detail about the clinical endpoint measures	Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2 and Table 3: Footnote #14 and #24 Section 8.2.3.3 FOP Independent Activity of Daily Living Section 8.2.3.4 EQ-5D-3L Questionnaire
Added that patients can be rescreened for study participation.	Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2 and Table 3: Footnote #20
Added a footnote to indicate that measurement of a patient's height may not be precise or not possible to be assessed	Section 8.1.1 Footnotes for the Schedule of Events Table 1, Table 2 and Table 3: Footnote #22
Removed futility as a reason for study termination	Section 16.1 Premature Termination of the Study
Reorganization of sections for consistency with current template, minor corrections for the content	Section 4.5 Pharmacokinetic Variables
Updated the Scientific/Medical Monitor	Protocol Title Page
Minor edits for clarification of study terminology, corrections, and minor changes: Period 1, Period 2, and Period 3 instead of "treatment period 1", "treatment period 2", or "treatment period 3" "diary" has been replaced with "e-diary". "FOP disease diary" has been replaced with "FOP disease activity diary". "Menstrual History" instead of "Menstrual Questionnaire" "FOP Independent Activities of Daily Living" instead of "Activity of Daily Living" "FCV" to "FVC" Subjects changed to patients Adding "Doppler" to scrotum ultrasound	Throughout the document

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Effects on Heterotopic Bone Formation of REGN2477 in Patients with Fibrodysplasia Ossificans Progressiva
Site Location(s)	The study will be conducted at multiple sites globally
Principal Investigator	TBD
Objective(s)	**Primary Objective:** The primary safety objective of the study is to assess the safety and tolerability of REGN2477 in male and female patients with fibrodysplasia ossificans progressiva (FOP). The primary efficacy objective of the study is to assess the effect of REGN2477 versus placebo on the change from baseline in heterotopic ossification (HO) in patients with FOP, as determined by ^{18}-NaF uptake in HO lesions by positron emission tomography (PET) and in total volume of HO lesions by computed tomography (CT). **Secondary Objectives:** The secondary objectives of the study are: • To compare the effect of REGN2477 versus placebo on pain due to FOP, as measured by the area under the curve (AUC) for pain based on daily numeric rating scale (NRS) scores • To assess the effect of REGN2477 versus placebo on the change from baseline in HO, as determined by the number of new HO lesions identified by ^{18}F-NaF PET or by CT • To assess the effect of REGN2477 versus placebo on the change from baseline in ^{18}F-NaF standardized uptake value maximum (SUV_{max}) of individual active HO site (s) by PET • To assess the effect of REGN2477, between week 28 and week 56, on the number, activity, and volume of HO lesions identified by ^{18}F-NaF PET or by CT in patients who switch from placebo to REGN2477 at week 28 versus the same patients between baseline and week 28 • To assess the effect of REGN2477 versus placebo on the change from baseline in biochemical markers of bone formation • To characterize the concentrations of total activin A at baseline and over time following the first dose of study drug • To characterize the concentration-time profile (pharmacokinetics [PK]) of REGN2477 in patients with FOP • To assess the immunogenicity of REGN2477

Study Design	This is a phase 2, randomized, placebo-controlled, 2-period study designed to evaluate the safety, tolerability, PK, and effects on heterotopic bone formation of repeated doses of 10 mg/kg REGN2477 administered intravenously (IV), every 4 weeks (Q4W) in adult patients with FOP. Up to 40 patients with FOP disease activity may be enrolled at multiple sites globally to yield approximately 24 or more patients with the classic type I activin A receptor with a R206H mutation (ACVR1[R206H]) and active HO at baseline as determined by ^{18}F-NaF PET/CT. This study consists of a screening/baseline period (day -28 to day -1), 2 treatment periods and a follow-up treatment period. The 3 treatment periods are: • **Period 1**: a 6-month randomized double-blind placebo-controlled treatment period • **Period 2**: a 6-month open-label REGN2477 treatment period • **Period 3**: a follow-up treatment period with REGN2477 continuing until patients have completed the week 76 visit, and all data have been collected and validated through the time when the last patient randomized into the study completes the week 28 visit (Period 1), and results of the primary analyses of safety and efficacy are available to the sponsor. Patients who meet initial eligibility screening will have baseline procedures conducted. In light of the public health emergency related to the COVID-19 pandemic, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of alternative 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. 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 and/or until the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites. During Period 1, patients will be randomized to receive REGN2477 at 10 mg/kg dose or matching placebo, administered IV Q4W through week 24, for a total of 7 doses. Randomization will be stratified by gender, by classic ACVR1[R206H] mutation/different ACVR1 mutations, and by presence/absence of baseline active HO lesions as determined by ^{18}F-NaF PET/CT. Index HO lesion identified at baseline and new HO lesions will be assessed by imaging endpoint measures including whole body ^{18}F-NaF PET and whole body low dose CT at week 8 (day 57 [±7 days]), and week 28 (day 197 [±7 days]). Serum samples for the determination of REGN2477 concentrations and anti-drug antibody (ADA) will be collected. To ensure safety, individual patients will be closely monitored and safety of each dose of study drug will be reviewed by the investigator and Regeneron medical monitor prior to administering the subsequent repeated dose. The safety review to be conducted by the investigator and Regeneron medical monitor prior to study drug infusions on visits 2, 5, 6 and 7 (Period 1) and visits 11, 12, 13 and 14 (Period 2) will include evaluation of laboratory test (hematology, blood chemistry and urinalysis) results collected as part of these visits. For the remaining study visits, assessment of results of hematology, blood chemistry and urinalysis tests planned for these same visits may be performed, but will not be required prior to study drug infusion. The decision

	not to wait for the results of these exams, processed at the study's central laboratory, should be made on a case-by-case basis, if the patient's clinical condition, adverse event profile, and assessment of vital signs, ECGs and previous laboratory test results indicate that the patient is suitable to receive the next dose of study drug. For the study visits after week 56 (Period 3), the need for a safety review by the investigator and Regeneron medical monitor will be decided on a case-by-case basis. In addition, the Independent Data Monitoring Committee (IDMC) will regularly monitor the unblinded safety data. In the event that a significant tolerability issue or safety concern is identified, dose modification or study drug discontinuation may be implemented. All patients who complete the Period 1 double-blind treatment will receive REGN2477 open-label in Period 2, administered IV at a dose of 10 mg/kg Q4W through week 52, for a total of 7 doses. For patients previously treated with placebo drug, week 28 (day 197) assessments will be considered as pretreatment baseline for safety and efficacy analysis of this period of the study. Serum samples for the determination of REGN2477 concentrations and ADA will be collected. Index HO lesion identified at baseline and new HO lesions will be assessed by imaging endpoint measures including whole body ^{18}F-NaF PET and whole body low dose CT at week 56 (day 393 [±7 days]), and at week 76 (day 533 [±7 days]). In light of the public health emergency related to the COVID-19 pandemic, Investigators may perform study visit 18 (week 56) imaging exam employing only whole body low-dose CT scans. Assessment of imaging endpoints without the PET scan may be implemented to mitigate the delay to acquire images due to the inaccessibility to PET/CT imaging centers and/or unavailability of the ^{18}F-NaF tracer. In addition, the timing for study visit 18 (week 56) is flexible as long as any changes are documented. This low-dose CT scan may be performed by trained staff either at study site or at other clinical sites with access to a qualified CT scanner or using a mobile qualified CT scanner at a local community healthcare setting close to patient or at a home visit, contingent upon prior concurrence and approval from the Investigator and Regeneron medical director. Individual patient dose modification will be determined on a case-by-case basis as described in the protocol. Study level dose modification will be determined by the sponsor upon recommendation of the IDMC following their review of safety, PK, and total activin A (target engagement) data available at the time. During the follow-up treatment period with REGN2477 (Period 3), from week 56 until the end of study, efficacy and safety procedures will be performed, and serum samples for the determination of REGN2477 concentrations and ADA will be collected. Each patient will continue to receive REGN2477, provided that no safety signals are identified during continuous monitoring of the study by the investigator, medical monitor and IDMC. In addition, during this period, all patients will be required to maintain contraception.
Study Duration	The duration of the double-blind treatment period (Period 1), and open-label treatment and assessment period (Period 2) for a patient is approximately 56 weeks, excluding the screening period. The follow-up treatment period will begin at week 56 and continue until patients have completed the week 76 visit (Period 3), and all data have been collected and validated through the time when the last patient randomized into the study completes the week 28 visit (Period 1), and results of the primary analyses of safety and efficacy are available to the sponsor.

	After Period 3 (week 76), patients can continue to receive REGN2477 treatment every 4 weeks until any 1 of the following occurs: clinical development of REGN2477 is terminated, the risk-benefit is deemed unfavorable in this patient population, other means of access to REGN2477 (eg, expanded access protocol) becomes available for study patients for whom the benefit-risk assessment for REGN2477 treatment remains positive, or, approval of the drug by the competent regulatory authority governing each respective country (eg, European Commission for EU Member States) with commercial availability. A limited number of assessments for safety, efficacy, and clinical pharmacology parameters will be conducted.
Population	
Sample Size:	Up to 40 patients with FOP may be enrolled at multiple sites globally to yield approximately 24 or more patients with the classic ACVR1[R206H] mutation and active HO at baseline.
Target Population:	The study population will consist of male and female adult patients aged 18 to 60 years of age, with a clinical diagnosis of FOP based on findings of congenital malformation of the great toes, episodic soft tissue swelling, and/or progressive HO, and confirmed with documentation of ACVR1 genotype, including the classic [R206H] or different ACVR1 mutations. If at the time of screening, the patient does not have documentation of what ACVR1 mutation he/she carries or it cannot be retrieved, genotyping will need to be performed prior to randomization. Patients must have had FOP disease activity within 1 year of screening visit, defined as pain, swelling, stiffness, and other signs and symptoms associated with FOP flare-ups; or worsening of joint function, or radiographic progression of HOs (increase in size or number of HO lesions) with/without being associated with flare-up episodes.

Treatment(s)	
Study Drug (Dose/Route/Schedule):	REGN2477 10 mg/kg, administered IV Q4W
Placebo (Route/Schedule):	REGN2477-matching placebo administered IV Q4W
Efficacy Analysis Sets	• Baseline-Active HO (AHO) analysis set: all randomized patients who had active HO lesion at baseline; it is based on the treatment allocated (as randomized). For analyses of change from week 28, baseline will be defined as week 28. • Baseline-Active HO Classic ACVR1[R206H] Mutation (AHOC) analysis set: all randomized patients with the classic ACVR1[R206H] mutation and who had active HO lesion at baseline; it is based on the treatment allocated (as randomized). For analyses of change from week 28, baseline will be defined as week 28. • Full Analysis Set (FAS): all randomized patients; it is based on the treatment allocated (as randomized).
Endpoint(s) for Period 1 (Week 28)	
Primary Safety Endpoint for Period 1 (Week 28):	• Incidence and severity of treatment-emergent adverse events (TEAEs) through the end of the Period 1 at week 28
Primary Efficacy Endpoints for Period 1 (Week 28):	• Time-weighted average (standardized area under the curve [AUC]) percent change from baseline in total lesion activity by ^{18}F-NaF PET over 28 weeks (AHO) • Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 (AHO) • Time-weighted average (standardized area under the curve [AUC]) percent change from baseline in total lesion activity by ^{18}F-NaF PET over 28 weeks (AHOC) • Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 (AHOC)
Secondary Endpoints for Period 1 (Week 28):	Key Secondary Endpoints: • Time-weighted average (standardized AUC) change from baseline in daily pain due to FOP, as measured using the daily NRS over 28 weeks (AHO) • Time-weighted average (standardized AUC) change from baseline in daily pain due to FOP, as measured using the daily NRS over 28 weeks (AHOC)

	Other Secondary Endpoints • Percent change from baseline in ^{18}F-NaF SUV_{max} of individual active HO site(s) by PET at week 8 (AHOC) • Percent change from baseline in ^{18}F-NaF SUV_{max} of individual active HO site(s) by PET at week 8 (AHO) • Change from baseline in number of HO lesions as assessed by ^{18}F-NaF PET at week 28 (AHOC) • Change from baseline in number of HO lesions as assessed by ^{18}F-NaF PET at week 28 (AHO) • Change from baseline in number of HO lesions as assessed by ^{18}F-NaF PET at week 28 (FAS) • Change from baseline in the number of HO lesions detectable by CT at week 28 (AHOC) • Change from baseline in the number of HO lesions detectable by CT at week 28 (AHO) • Change from baseline in the number of HO lesions detectable by CT at week 28 (FAS)
	• Time-weighted average (standardized AUC) change from baseline in daily pain due to FOP, as measured using the daily NRS over 28 weeks (FAS) • Time weighted average (standardized AUC) percent change from baseline in biomarkers of bone formation levels in serum over 28 weeks, including Total Procollagen Type 1 N-Terminal Propeptide (P1NP), bone specific alkaline phosphatase (BSAP), and total alkaline phosphatase (tAP) (FAS) • Incidence and severity of TEAEs Other Secondary Endpoints related to Clinical Pharmacology (Period 1, Period 2, Period 3) • Concentration of total activin A in serum over time • PK profile of REGN2477, assessed as concentrations of REGN2477 in serum over time • Immunogenicity of REGN2477, as determined by the incidence, titer, and clinical impact of treatment-emergent ADA to REGN2477 over time
Endpoint(s) for Period 2 (Week 56)	
Primary Efficacy Endpoint for Period 2 (Week 56):	• Number of new HO lesions as assessed by CT at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
Key Secondary Endpoints for Period 2 (Week 56):	• Total volume of new HO lesions as assessed by CT at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO) • Number of new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)

	• Total lesion activity by ^{18}F-NaF PET in new HO lesions at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after double-blind period) (AHO) • Percent of patients with new HO lesions as assessed by CT at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO) • Percent of patients with new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
Other Secondary Endpoints for Period 2 (week 56):	• Number of new HO lesions as assessed by CT only at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO) • Percent of patients with investigator-assessed flare-ups in Period 2 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO) • Percent of patients with flare-ups assessed by patient e-diary in Period 2 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO) • Number of new HO lesions as assessed by CT at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO) • Total volume in new HO lesions as assessed by CT at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO) • Percent of patients with new HO lesions as assessed by CT at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO) • Number of new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO) • Total lesion activity in new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO) • Percent of patients with new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO) • Percent change from week 28 in SUVmax to week 56 (in patients switching from placebo to REGN2477 after the double-blind period) • Percent change from baseline in SUVmax to week 56 (in patients who continue REGN2477 after the double-blind period) (AHO) • Percent change from week 28 in total lesion activity as assessed by ^{18}F-NaF PET to week 56 (in patients switching from placebo to REGN2477 after the double-blind period) versus the same patients between baseline and week 28 (AHO) • Percent change from baseline in total lesion activity as assessed by ^{18}F-NaF PET to week 56 (in patients who continue REGN2477 after the double-blind period) (AHO)

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	• Percent change from week 28 in the total volume of HO lesions as assessed by CT to week 56 (in patients switching from placebo to REGN2477 after the double-blind period) versus the same patients between baseline and week 28 (AHO) • Percent change from baseline in the total volume of HO lesions as assessed by CT to week 56 (in patients who continue REGN2477 after the double-blind period) (AHO) • Change from week 28 in number of HO lesions (target and new lesions relative to baseline) as assessed by ^{18}F-NaF PET to week 56 (in patients switching from placebo to REGN2477 in double-blind period and who have active HO lesions at week 28) versus the same patients between baseline and week 28 (AHO) • Change from week 28 in number of HO lesions (target and new lesions relative to baseline) as assessed by CT to week 56 (in patients switching from placebo to REGN2477 in double-blind period and who have active HO lesions at week 28) versus the same patients between baseline and week 28 (AHO)
Procedures and Assessments	**Safety Assessments** Safety procedures and assessments will include vital signs assessment, physical examination, a menstrual cycle history, electrocardiogram, and laboratory testing. **ACVR1 Gene Sequencing** A blood sample for future ACVR1 gene sequencing will be preferably collected from patients at the screening/baseline visit. However, it can be collected at any time during the study period, as the result of this test it is not to be used for assessment of study eligibility. **Imaging Procedures** Positron emission tomography with ^{18}F-NaF and volumetric CT will be used to measure the change in heterotopic bone formation. **Clinical Endpoint Measures** Clinical endpoint measures will include the NRS categorical scale of pain, the FOP disease activity assessment via patient diary, the patient reported FOP Independent Activity of Daily Living (FOP I-ADL) Questionnaire based on the Patient Reported Outcomes Measurement Information System (PROMIS), the Europol 5 dimensions questionnaire with a 3-level scale (EQ-5D-3L), the physician assessment of cumulative analog joint involvement scale (CAJIS) and spirometry assessment of pulmonary function. **Biomarker Procedures** Blood will be collected for the analysis and discovery of biomarkers, including but not limited to biochemical bone formation markers (BSAP, tAP and P1NP), hs-CRP, as well as mechanism based biomarkers related to the activin A and activin receptor pathway including but not limited to Activin and BMP ligands or markers that may elucidate the mechanism of action of REGN2477, and whole blood RNA analysis. 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.

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	Pharmacokinetic and Anti-Drug Antibody Assessments Serum samples for measurements of drug concentration, activin A concentration, and ADA will be collected. Any unused serum samples may be used for exploratory biomarker research or future biomedical research.
Statistical Plan	**Justification of Sample Size** Randomization will be stratified by the presence/absence of active HO lesions at baseline, to allow analyses of efficacy endpoint measures defined solely for patients with active HO at baseline. Patients without active HO lesions at baseline will contribute to the assessment of safety and other endpoint measures. Randomization will also be stratified by gender and classic ACVR1[R206H] mutation/different ACVR1 mutations. The sample size estimation for at least 24 patients (12 patients per treatment group) with active HO at baseline and classic ACVR1[R206H] mutation is based on statistical considerations for the following efficacy endpoints: percent change from baseline in (1) total lesion activity by ^{18}F-NaF PET over 28 weeks, (2) total HO volume by CT at week 28, and (3) ^{18}F-NaF SUV_{max} at week 8. Accounting for a 20% dropout rate at week 28, the sample size would yield approximately 10 patients per treatment group for week-28 analyses. This sample size will provide 80% power at a 2-sided 0.05 significance level in allowing the detection of an observed treatment difference in the order of 57%, 65%, and 40% reduction in the total lesion activity by ^{18}F-NaF PET, the total HO volume by CT, and the ^{18}F-NaF SUV_{max}, respectively, if the measure variability in FOP patients is similar to that observed in other bone diseases and the FOP mouse model. Recent in vitro studies demonstrated that different mutations in the ACVR1 receptor transduced BMP signaling when stimulated with activin A. These results suggest that REGN2477 may provide beneficial clinical impact on HO in patients with FOP, irrespective of the underlying ACVR1 mutation. **Statistical Hypotheses** **Hypothesis (Period 1 [Week 28])** The following null and alternative hypotheses will be tested sequentially for the primary and secondary efficacy endpoints respectively: **H0:** No treatment difference between REGN2477 and placebo **H1:** There is a treatment difference between REGN2477 and placebo **Hypothesis (Period 2 [Week 56])** For the Period 2 (week 56) analyses, the following primary and key secondary null hypotheses will be tested: **$H_{1,1}$:** There is no difference in number of new (relative to week 28 scan) HO lesions as assessed by CT per patient at week 56 compared to the number of new (relative to baseline scan) HO lesions as assessed by CT per patient at week 28 in placebo/REGN2477 group in AHO (primary) **$H_{2,1}$:** There is no difference in total volume of new (relative to week 28 scan) HO lesions per patient as assessed by CT at week 56 compared to the total volume of new (relative to baseline scan) HO lesions per patient as assessed by CT at week 28 in placebo/REGN2477 group in AHO (key secondary) **$H_{2,2}$:** There is no difference in number of new (relative to week 28 scan) HO lesions per patient as assessed by ^{18}F-NaF PET at week 56 compared to the number of new (relative to baseline scan) HO lesions per patient by ^{18}F-NaF PET at week 28 in placebo/REGN2477 group in AHO (key secondary)

$\mathbf{H}_{2,3}$: There is no difference in total lesion activity per patient by ^{18}F-NaF PET in new (relative to week 28 scan) lesions at week 56 compared to the total lesion activity per patient by ^{18}F-NaF PET in new (relative to baseline scan) lesions at week 28 in placebo/REGN2477 group in AHO (key secondary)

$\mathbf{H}_{2,4}$: There is no difference in percent of patients with new HO lesions as assessed by CT at week 56 relative to week 28 scan in placebo/REGN2477 group in AHO (key secondary)

$\mathbf{H}_{2,5}$: There is no difference in percent of patients with new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to week 28 scan in placebo/REGN2477 group in AHO (key secondary)

Statistical Methods

Efficacy Analysis for Period 1 (Week 28)

Percent change from baseline in targeted total lesion activity 18F-NaF PET at week 8 and 28 weeks will be analyzed in AHO or AHOC using a mixed-effect model with repeated measures (MMRM) model. The model will include treatment, gender, ACVR1 mutation type (AHO analysis set only) as fixed effects, time point, and treatment-by-time point interaction, as well as, the continuous fixed covariates of baseline value and baseline value-by-time point interaction. An unstructured covariance matrix can be used in this model to account for within-patient correlation. Time weighted average over 28 weeks will be estimated from the model. Different parameterization of MMRM model will be utilized if at least 1 patient is missing all post-baseline values. Because all the patients in AHO or AHOC have active HO at baseline, the stratification factor for baseline HO status will not be included in the model.

Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 will be analyzed in AHO or AHOC using MMRM model. The model will include treatment, gender, ACVR1 mutation type as fixed effects, time point, and treatment-by-time point interaction, as well as, the continuous fixed covariates of baseline value and baseline value-by-time point interaction. An unstructured covariance matrix can be used in this model to account for within-patient correlation. Different parameterization of MMRM model will be utilized if at least 1 patient is missing all post-baseline values.

Analysis of Time-weighted average (standardized AUC) change from baseline in daily pain due to FOP by the daily NRS over 28 weeks will be performed in AHO or AHOC using the ANCOVA with treatment, gender, ACVR1 mutation type (AHO analysis set only) as factors, and the baseline value as continuous covariate.

In order to handle multiple testing of the 4 primary and 2 key secondary efficacy endpoints, hierarchical testing procedure will be applied at a 2-sided 5% significance level. Hypothesis for the primary and key secondary efficacy endpoint will be formally tested only if hypothesis for the preceding endpoint is significant at the 2-sided 5% level. The order of testing sequence for primary and key secondary efficacy endpoints is as follows:

Time-weighted average (standardized AUC) of the percent change from baseline in total lesion activity by ^{18}F-NaF PET over 28 weeks in AHO

↓

Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 in AHO

↓

Time-weighted average (standardized AUC) of the percent change from baseline in total lesion activity ^{18}F-NaF PET over 28 weeks in AHOC

↓

Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 in AHOC

↓

Time-weighted average (standardized AUC) of the change from baseline in daily pain due to FOP, as measured using the daily NRS over 28 weeks in AHO

↓

Time-weighted average (standardized AUC) of the change from baseline in daily pain due to FOP, as measured using the daily NRS over 28 weeks in AHOC

No further multiplicity adjustments will be made for testing other secondary efficacy endpoints and exploratory endpoints where nominal p-values will be provided for descriptive purpose.

Efficacy Analysis for Period 2 (Week 56)

These analyses are new and independent from that of Period 1 and warrant their own overall 2-sided type I error rate of 10% (alpha of 0.1) which is consistent with regulatory guidance for studies in rare diseases. The small inflation of alpha is also necessary to handle the possibility of patients with missing week 56 imaging assessment due to COVID-19.

The type-I error rate will be controlled at 0.10 for the primary and key secondary null hypotheses in Period 2 (week 56). To control the type-I error rate for the primary and key secondary endpoints in Period 2 (week 56), a hierarchical testing procedure will be applied at a 2-sided 10% significant level to test the above hypotheses in the specified order. The key secondary efficacy endpoints will be tested only if statistical significance is established for the primary endpoint. No further adjustments will be made for other secondary and exploratory endpoints in Period 2 (week 56), for which estimates, 95% CI, and/or nominal p-values will be provided for descriptive purpose.

The COVID-19 pandemic has affected the conduct of the study mainly by causing delay in dose administration, delay in the collection of the PET/CT scans due to site closure, and unavailability of ^{18}F-NaF due to interruption of tracer production. Some patients may not be able to complete their week 56 scans within the protocol-specified visit window and may only be able complete their scans using CT-only modality.

The week 56 efficacy analyses of imaging endpoints will be conducted using COVID-19 modified Intent-To-Treat (COVID-19 mITT) principle which will analyze only those patients for whom:

- at least 1 post-week 28 scan is collected and,
- the time period between any 2 consecutive doses is less than 9 weeks (63 days) in Period 2 and,
- no more than 1 dose was missed in Period 2

This will ensure that primary analyses for imaging endpoints will include patients with continuous saturating levels of REGN2477. For patients whose week 56 scans are delayed, the first delayed scan available after the week 28 scan will be used to impute the week 56 data in the primary analyses. In the absence of a PET/CT scan, data from available CT-only scans will be used to analyze the primary endpoint and other secondary imaging endpoints, if applicable. This imputation ensures that the estimation of the treatment effect will not be biased by the COVID-19 pandemic.

The number of new HO lesions as assessed by CT at week 56 relative to week 28 scan will be summarized for the placebo/REGN2477 group. Wilcoxon signed rank test will be used for the within group comparison in the placebo/REGN2477 group to compare the number of new HO lesions by CT at week 56 relative to week 28 scan with the number of new HO lesions by CT at week 28 relative to baseline scan.

The total volume associated with new HO lesions as assessed by CT at week 56 relative to week 28 scan will be summarized for the placebo/REGN2477 group. Wilcoxon signed rank test will be used for the within group comparison in the placebo/REGN2477 group to compare the total volume at week 56 associated with new HO lesions by CT relative to week 28 scan with the total volume associated with new HO lesions by CT at week 28 relative to baseline scan.

The number of new HO lesions by ^{18}F-NaF PET at week 56 relative to week 28 scan will be summarized for the placebo/REGN2477 group. Wilcoxon signed rank test will be used for the within group comparison in the placebo/REGN2477 group to compare the number of new HO lesions as assesses by PET at week 56 relative to week 28 scan with the number of new HO lesions by PET at week 28 relative to baseline scan.

The total lesion activity associated with new HO lesions by PET at week 56 relative to week 28 scan will be summarized for the placebo/REGN2477 group. Wilcoxon signed rank test will be used for the within group comparison in the placebo/REGN2477 group to compare the total lesion activity associated with new HO lesions by PET at week 56 relative to week 28 scan with the total lesion activity associated with new HO lesions by PET at week 28 relative to baseline scan.

Number and percent of patients with new HO lesions by CT at week 56 relative to week 28 will be provided for the placebo/REGN2477 group. The within group comparison to compare the percent of patients with new HO lesions by CT at week 56 relative to week 28 scan with the percent of patients with new HO lesions by CT at week 28 relative to baseline scan will be performed using McNemar's test in placebo/REGN2477 group.

Number and percent of patients with new HO lesions by PET at week 56 relative to week 28 scan will be provided for the placebo/REGN2477 group. The within group comparison to compare the percent of patients with new HO lesions by PET at week 56 relative to week 28 scan with the percent of patients

with new HO lesions by PET at week 28 relative to baseline scan will be performed using McNemar's test in placebo/REGN2477 group.

The type-I error rate will be controlled at 0.10 for the primary and key secondary null hypotheses in Period 2 (week 56).

To control the type-I error rate for the primary and key secondary endpoints in Period 2 (week 56), a hierarchical testing procedure will be applied at a 2-sided 10% significant level to test the above hypotheses in the specified order. The key secondary efficacy endpoints will be tested only if statistical significance is established for the primary endpoint.

No further adjustments will be made for other secondary and exploratory endpoints in Period 2 (week 56), for which estimates, 95% CI, and/or nominal p-values will be provided for descriptive purpose.

The results obtained for the REGN2477/REGN2477 group (patients who continue receiving REGN2477 beyond week 28) will be analyzed for persistence of efficacy.

In the REGN2477/REGN2477 group, the estimates of treatment effects at week 56 will be provided with 95% confidence interval on the endpoints related to new HO lesions (new relative to baseline scan).

Estimates of the treatment effects with 95% confidence interval on the endpoints related to new HO lesions from Period 1 (new relative to baseline scan) in the REGN2477/REGN2477 group patients will be descriptively compared with the estimates from Period 2 (new relative to week 28) in the placebo/REGN2477 group.

Primary and Additional Analysis

No interim analysis is planned for this study.

Primary analysis of safety and efficacy data of the randomized double-blind placebo-controlled period (Period 1) of the study will be performed once all data have been collected and validated through the end of this period (Period 1, week 28; database lock [DBL] 1). Additional analyses of safety and efficacy data will be performed following the open-label REGN2477 period (Period 2; week 56; DBL 2), and at the end of the follow-up treatment period at week 76 (Period 3, Week 76; DBL 3). Since the key efficacy measure data collection for Period 1 will have been concluded at the time of the first analysis (Period 1, week 28; DBL 1) and the radiographic data for subsequent periods had not been read nor entered into the database, the final analysis for Period 1 is not considered an interim analysis for subsequent periods and no multiplicity adjustments are needed.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACTH	Adrenocorticotropic hormone
ACVR1	Type I activin A receptor
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AHOC	Baseline active HO classic ACVR1[R206H] mutation analysis set
AHO	Baseline active HO analysis set (AHO)
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BMP	Bone morphogenic protein
BSAP	Bone specific alkaline phosphatase
BUN	Blood urea nitrogen
CAJIS	Cumulative Analog Joint Involvement Scale
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CT	Computed tomography
DBL	Database lock
EC	Ethics Committee
ECG	Electrocardiogram
ED	Effective dose
EDC	Electronic data capture
EQ-5D-3L	EuroQol 5 dimensions questionnaire with a 3-level scale
FAS	Full analysis set
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FIH	First in human
^{18}F-NaF	Fluorine-18-labelled sodium fluoride
FOP	Fibrodysplasia ossificans progressiva

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FOP I-ADL	FOP Independent Activities of Daily Living
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GH	Growth hormone
GLP	Good Laboratory Practice
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
hs-CRP	High sensitivity C-reactive protein
HO	Heterotopic ossification
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
INR	International Normalised Ratio
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous
Ki	Incorporation rate
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NOAEL	No-observed-adverse-effect-level
NRS	Numeric rating scale
P1NP	Total Procollagen Type 1 N-Terminal Propeptide
PET	Positron emission tomography
PK	Pharmacokinetic
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Preferred term
Q4W	Every 4 weeks

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RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SUV_{max}	Standardized uptake value (maximum)
T4	Thyroxine
tAP	Total alkaline phosphatase
^{99m}Tc	Technetium-99 methylene diphosphonate
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
WBC	White blood cell
WoCBP	Woman of child bearing potential

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1. INTRODUCTION

REGN2477 is a fully human monoclonal antibody that specifically binds to and blocks signaling of activin A. REGN2477 is being developed for the treatment of fibrodysplasia ossificans progressiva (FOP), an ultra-rare genetic disorder affecting approximately 800 patients worldwide. Characteristics of FOP include progressive heterotopic ossification (HO) of skeletal muscle, ligaments, tendons, and fascia, which leads to joint immobility, significant disability, pain and premature death (Kaplan 2010, Aleman-Meunch 2012, Hüning 2014). There is no approved treatment for the prevention or reversal of HO associated with FOP. Fibrodysplasia ossificans progressiva appears to be caused by mutations in the region encoding for the intracellular domain of type I activin A receptor (ACVR1) with the most common mutation observed in patients being ACVR1[R206H] (Hüning 2014). Recent studies in a conditional-inducible mouse model of FOP have demonstrated that the ACVR1[R206H] variant drives HO by conferring to the receptor the abnormal ability to recognize activin A as an agonistic ligand resulting in abnormal bone formation similar to the clinical condition (Hatsell 2015). In this model, exogenous activin A drives exuberant HO activity and REGN2477 administration dramatically halts heterotopic bone formation. In vitro studies demonstrated that different mutations in the ACVR1 receptor transduced bone morphogenic protein (BMP) signaling when stimulated with activin A (Hino 2015). These results indicate that REGN2477 may suppress HO for patients with FOP who have ACVR1 mutations other than ACVR1[R206H]. Taken together, these data suggest that REGN2477 may be an effective treatment for FOP irrespective of the underlying ACVR1 mutation.

This study (R2477-FOP-1623 LUMINA-1) is designed to test the hypotheses that 1) REGN2477 is generally well tolerated and 2) REGN2477 inhibits HO in patients with FOP. Positron emission tomography (PET) with ^{18}F-NaF and volumetric computed tomography (CT) will be used to measure the change in heterotopic bone formation. ^{18}F-NaF PET has been shown in several other disease settings to provide a sensitive, specific, and whole body quantitative measure of bone mineralization activity. The use of ^{18}F-NaF PET and other imaging modalities, such as Technetium-99 (^{99m}Tc) bone scan, are able to detect HO lesions in FOP patients (Eekhoff 2016, Fang 1986, Herford 2003, Trikha 2005, Tulchinsky 2007). In the Regeneron mouse model of inducible FOP, HO lesions have been shown to be detectable by ^{18}F-NaF PET and HO activities in these lesions are markedly diminished following treatment with REGN2477 (see the Investigator's Brochure [IB]). It is hypothesized that use of ^{18}F-NaF PET may allow an assessment of treatment effect in a relatively small number of patients as early as 8 weeks after treatment initiation and may be the most sensitive modality to quantify total change in HO activity during the 6-month treatment time planned for Period 1 of this study. Because this modality has not been previously studied in patients with FOP, this study also plans an assessment of change in the total volume of HO (as assessed by quantitative CT) over the 6 month treatment interval as well as a change in the number of new lesions during this period (as assessed by ^{18}F-NaF PET and CT). Additional endpoints captured in this study will include changes in biochemical biomarkers of bone turnover and changes in clinical measures for joint function and patient reported disease activity and activities of daily living. Patients with FOP describe pain associated with their disease, at times refractory to analgesic treatments. Pain severity will be assessed daily in this study through the Pain Numeric Rating Scale (NRS).

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This study plans to enroll up to 40 adult male and female FOP patients to ensure inclusion of approximately 24 or more patients with the classic [R206H] ACVR1 mutation and active HO lesion detectable by ^{18}F-NaF PET at baseline to allow the assessment of change from baseline treatment effects on key efficacy endpoints of heterotopic bone formation. The protocol amendment 1 expands the scope of patient eligibility by opening enrollment to patients with a FOP diagnosis and documentation of any ACVR1 mutation. During the study, all patients will have their ACVR1 gene sequenced as part of the study. The study will consist of 3 treatment periods. The first period (Period 1) will be a 6-month randomized, double-blind, placebo-controlled treatment period evaluating changes from baseline in HO by ^{18}F-NaF PET and CT at 8 weeks and 6 months. The second period (Period 2) will be a 6-month open-label treatment period, during which all patients in the study will be treated with REGN2477. Patients previously treated with placebo will be crossed over to REGN2477 to allow for an assessment of a 6-month treatment effect; patients previously on REGN2477 will be treated with REGN2477 for an additional 6 months to allow for an assessment of a 12-month treatment effect. The third period (Period 3) will be a follow-up treatment period during which all patients in the study will continue to be treated with REGN2477 at monthly visits until the patients have completed the week 76 visit, and all data have been collected and validated through the time when the last patient randomized into the study completes the week 28 visit (Period 1), and results of the primary analyses of safety and efficacy are available to the sponsor. The patients who reach the week 76 visit will continue REGN2477 treatment consistent with Regeneron corporate policy governing access to investigational drugs in confirmatory clinical studies (Section 5.1.4). Patients will have the option to discontinue study medication before the beginning or at any time during Period 3, similarly to what occurs at any time during the study. The proposed dose regimen is 10 mg/kg, given intravenously (IV) every 4 weeks (Q4W).

The LUMINA-1 study is currently ongoing, and all patients have completed Period 1 (double-blind, placebo-controlled period; see the IB). The results from the primary analysis of efficacy in Period 1 of the LUMINA-1 study demonstrated clinical benefit of REGN2477 for the treatment of FOP by markedly reducing the number of new heterotopic bone lesions as assessed by both^{18}F-NaF PET and CT (see Section 3.3.1). These results refined our understanding of the pathophysiology of FOP and the role of activin A in the disease. Together with the understanding of the genetics of this disease and with the complementary preclinical animal model data, the clinical data from the primary analysis of LUMINA-1 indicate that activin A is required for the formation of new lesions in patients with FOP but does not seem to play a major role in the progression of existing lesions by PET or CT. Moreover, these data demonstrate that REGN2477 provides improvement on clinically meaningful endpoints, ie, formation of new HO bone lesions and inhibition of flare-up episodes for this disease.

Treatment with REGN2477 demonstrated an acceptable safety profile (see the IB). During Period 1 (the 28-week double-blind treatment period), the majority of treatment-emergent adverse events (TEAEs) were mild to moderate in severity. Notable imbalances in TEAEs for the REGN2477 group included Epistaxis, Acne, Madarosis, and a composite of skin and soft tissue infections including Abscess, Folliculitis, and Cellulitis. A pathophysiologic explanation for these adverse events (AEs) has not been identified, although with respect to epistaxis, data to date suggest that REGN2477 does not inhibit platelet number, function, or clotting activity (see Section 3.4.3 and Section 3.4.4).

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The results from the 2 first-in-human (FIH) studies (R2477-HV-1525 and R2477-1033-HV-1621) which evaluated REGN2477 showed that REGN2477 doses up to 10 mg/kg (single-dose) and 10 mg/kg Q4W for 4 doses were generally well-tolerated (see the IB).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary safety objective of the study is to assess the safety and tolerability of REGN2477 in male and female patients with FOP.

The primary efficacy objective of the study is to assess the effect of REGN2477 versus placebo on the change from baseline in HO in patients with FOP, as determined by ^{18}F-NaF uptake in HO lesions by PET and in total volume of HO lesions by CT.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To compare the effect of REGN2477 versus placebo on pain due to FOP, as measured by the area under the curve (AUC) for pain based on daily pain NRS scores
- To assess the effect of REGN2477 versus placebo on the change from baseline in HO, as determined by the number of new HO lesions identified by ^{18}F-NaF PET or by CT
- To assess the effect of REGN2477 versus placebo on the change from baseline in ^{18}F-NaF standardized uptake value maximum (SUV_{max}) of individual active HO site(s) by PET
- To assess the effect of REGN2477, between week 28 and week 56, on the number, activity, and volume of HO lesions identified by ^{18}F-NaF PET or by CT in patients who switch from placebo to REGN2477 at week 28 versus the same patients between baseline and week 28
- To assess the effect of REGN2477 versus placebo on the change from baseline in biochemical markers of bone formation
- To characterize the concentrations of total activin A at baseline and over time following the first dose of study drug
- To characterize the concentration-time profile (pharmacokinetic [PK]) profile of REGN2477 in patients with FOP
- To assess the immunogenicity of REGN2477

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To explore the effects of REGN2477 versus placebo on change from baseline on clinical endpoints such as the following: FOP disease activity, joint function, and patient reported activities of daily living, and glucocorticoids and pain medication use
- To explore the effect of REGN2477 versus placebo on normal bone metabolic activity as determined by change from baseline in ^{18}F-NaF PET uptake in skeletal bone
- To explore the effect of REGN2477 on the plasma concentration profile of ^{18}F-NaF
- To explore the effect of REGN2477 vs. placebo on the total dose of corticosteroids used over the treatment phase of the study
- To explore the correlation between change from baseline in ^{18}F-NaF PET signal of SUV_{max} at 8 weeks with change from baseline in volumetric CT evaluation of HO at 28 weeks
- To explore the effects of REGN2477 on lesion progression from PET detectable lesions to CT detectable lesions

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis: Period 1 Double-Blind, Placebo-Control Treatment Period (Week 28)

Prior to the conduct of this LUMINA-1 study, the hypothesis was that activin A is required for the formation and progression of new and existing active HO. By blocking activin A, there was an expectation that compared to placebo, REGN2477 would show a marked reduction of HO (on both existing target lesions identified at baseline and new lesions that might develop after baseline). This effect would be evidenced by decreases in ^{18}F-NaF PET uptake into existing active lesions and inhibition of the growth of heterotopic bone lesions by volumetric CT.

The hypotheses were:

1. REGN2477 is generally well-tolerated in patients with FOP
2. Treatment with REGN2477 reduces HO in patients with FOP

3.2. Hypothesis: Period 2 Open-Label Period (Week 56)

Results from the prespecified primary efficacy analysis from Period 1 (28-week, double-blind period) have indicated that REGN2477 prevents occurrence of new HO lesions (see the IB).

Upon analysis of the results of time weighted average of percent change from baseline in total lesion activity by PET through week 28 and percent change from baseline in total volume of HO by CT at week 28, it became clear that the overall reduction of these measures observed in patients treated with the REGN2477 compared to those treated with placebo was mainly driven by an approximately 90% decrease in the number of new lesions, as detected by both PET and CT. The quantification of new lesions by each modality was highly concordant with one another.

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These results support a new hypothesis:

1. Treatment with REGN2477 prevents the formation of new HO in patients with FOP

3.3. Rationale

3.3.1. Rationale for Clinical Development of REGN2477 for FOP

Fibrodysplasia ossificans progressiva is a devastating ultra-rare autosomal dominant genetic disease for which there is no effective treatment currently. It is caused by mutations in the ACVR1 gene (also known as ALK2, Shore 2006). Preclinical data generated at Regeneron Pharmaceuticals, Inc. (Regeneron) provide strong rationale for evaluating REGN2477, an anti-activin A antibody, for the treatment of this disease.

The FOP disease is characterized by childhood onset and life-long episodic and progressive HO in soft tissues, which can lead to joint immobility, skeletal deformity, and severe disability. Early mortality is common, often in the fifth decade, principally due to cardiorespiratory failure from thoracic insufficiency syndrome. Disease flare-up episodes, often reported by patients as acute onset of painful or non-painful soft tissue swelling, joint stiffness, or loss of joint mobility, are not predictable in their occurrence, are variable in severity and duration (from days to many months), and do not always result in HO (Pignolo 2016, Kaplan 2016). Pain associated with FOP disease activity may be severe and even refractory to opioid analgesics. Heterotopic bone formation and disability may develop insidiously without acute flare-up symptoms (Pignolo 2016). Bone scintigraphy and the more sensitive and specific ^{18}F-NaF PET method readily detect multiple focal HO lesions with abnormally high uptake of bone homing tracers in body regions where patients with FOP report experiencing flare-up symptoms and in regions without symptoms (Fang 1986, Herford 2003, Trikha 2005, Tulchinsky 2007, Eekhoff 2016). There are currently no effective treatments to prevent or inhibit HO in patients with FOP. Surgical attempts to remove the heterotopic bone in patients with FOP result in more aggressive episodes of HO and are rarely conducted. Disease flare-ups are typically treated with high doses of glucocorticoids or non-steroidal anti-inflammatory medications; however, these agents have not been shown to affect the course of HO.

Regeneron has developed a murine model of FOP that conditionally expresses the most common mutation variant of ACVR1, ACVR1[R206H], which is seen in patients with FOP, and recreates key features of the human disease. This animal model displays heterotopic bone formation in soft tissues, spontaneously or following tissue injury, and exacerbation following surgical resection of bony lesions. In this model, blockade of activin A by REGN2477 not only prevented the onset of HO if given prophylactically prior to induction of HO, but also halted the progression of pre-existing HO if given as a treatment after HO has been induced (Hatsell 2015, see IB). Recent in vitro studies demonstrated that different mutations in the ACVR1 receptor transduced BMP signaling when stimulated with activin A (Hino 2015). These data indicate that REGN2477 may suppress HO for patients with FOP who have ACVR1 mutations other than ACVR1[R206H]. Taken together, these results suggest that REGN2477 may provide beneficial clinical impact on HO in patients with FOP, irrespective of the underlying ACVR1 mutation. Preclinical imaging data support the use of both ^{18}F-NaF PET and CT to follow disease progression and treatment.

The LUMINA-1 study is currently ongoing, and all patients have completed Period 1 (double-blind, placebo-controlled period). The study database for the analysis of Period 1 was locked (19 Nov 2019 for clinical results and 13 Dec 2019 for imaging results). The results of the primary efficacy and safety analysis for Period 1, after adult patients received 7 monthly infusions of either REGN2477 or placebo with at least 28 weeks of follow-up, showed that REGN2477 reduced average total lesion activity (by ^{18}F-NaF PET) from baseline over 28 weeks by approximately 25% (LS mean difference) compared to placebo (p=0.0741; see IB for details). Correspondingly, there was an approximate 25% (LS mean difference) decrease in bone lesion volume (both new and existing lesions) compared to placebo as measured by CT (p=0.373). These results were largely driven by marked decreases of nearly 90% in the incidence of new lesions irrespective of imaging modality (p<0.01). The percent of patients who developed 1 or more new HO lesions as assessed by PET was lower in the REGN2477 treatment group (3 of 20 patients [15%]) as compared to placebo (11 of 24 patients [45.8%]) through week 28 (prespecified p=0.050). Similarly, the percent of patients who developed new HO lesions as assessed by CT was again lower in the REGN2477 treatment group (3 of 20 patients [15%]) compared to placebo (11 of 24 patients [45.8%]) through week 28 (post-hoc p=0.050). The identification of lesions as "new" versus "existing" at baseline was specified in the imaging charter. Taken together, these results indicate that while REGN2477 has a relatively modest treatment effect on the attenuation of existing lesions, there was a large effect preventing the occurrence of new lesions.

In addition, an analysis to compare low-dose CT-only and PET/CT reads on new HO lesions from the LUMINA-1 study was performed by the Sponsor. Low-dose CT-only reads (ie, in the absence of PET scan) were performed by 2 new independent blind readers and a new blinded adjudicator. The readers and adjudicator assessments were entered into a separate electronic data capture (EDC) system. The CT-only reads and lesion quantification were carried out following the same procedures described in the Imaging Review Charter.

This analysis to compare the performance between PET/CT and low-dose CT-only showed there was no marked difference detected in the performance between PET/CT and CT reads (p=0.75). Specifically, the CT-only reading methodology reconfirmed the REGN2477 treatment effects on number or percentage of patients with new lesions, total number of new lesions, and volume of new lesions seen by the primary PET/CT reading methodology. Thirty-eight new lesions were identified by the CT-only reads and 30 new lesions were identified by the PET/CT reads. Only 1 lesion out of 38 new lesions identified by the CT-only reads was in REGN2477 group, and 3 out of 30 new lesions identified by the PET/CT reads were in REGN2477 group.

Additional to the data indicating that activin A mostly serves to initiate the biologic events that ultimate result in heterotopic bone formation, the incidence of patient-reported flare ups was also reduced by 50% (prespecified p=0.032), while investigator-reported AEs of flare ups were 10% for REGN2477 and 42% for placebo (post-hoc p=0.039). A favorable trend for reduced daily average pain as measured by NRS was seen in the REGN2477 groups compared to placebo.

These data have prompted the definition of separate study hypotheses for the open-label treatment period (week 28 to week 56; Section 3.2) and addition of endpoints consistent with these hypotheses to confirm the efficacy of REGN2477 in preventing the formation of new HO and reducing flare-ups (Section 4.3).

Further details of REGN2477 clinical data and preclinical data to support clinical development may be found in the IB.

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3.3.2. Rationale for Study Design

The study population will consist of adult male and female patients with FOP who are 18 to 60 years old with documentation of any ACVR1 mutation and a recent history of active disease or HO progression as assessed by their treating physician within the last year. All patients with FOP who enroll in the study will have a blood sample collected for sequencing of their ACVR1 gene during the study. This information will support interpretation of the study results.

Up to 40 FOP patients with or without current flare-up activities may be enrolled and randomized 1:1 to REGN2477 or placebo treatment initially. We estimate that at least 60% of FOP patients will have at least 1 active HO lesion, detected by ^{18}F-NaF PET/CT at baseline. Enrollment of up to 40 patients is expected to yield approximately 24 or more patients with the classic ACVR1[R206H] mutation and active HO at baseline. Randomization will be stratified by presence/absence of baseline active HO lesions, to allow change from baseline analyses of key efficacy endpoint measures such as ^{18}F-NaF uptake in HO lesions. Patients without baseline active HO lesions will contribute to the assessment of safety and other endpoint measures such as development of new HO lesions. Randomization will also be stratified by gender and classic ACVR1[R206H] mutation/different ACVR1 mutations.

As there is no effective treatment for this severe rare disease, which often has a variable and insidious course, a placebo-controlled study is appropriate and will allow longitudinal documentation of disease activity and progression in both treatment groups in a blinded fashion to rigorously assess efficacy and safety of REGN2477. The 1:1 randomization ratio serves to minimize potential erroneous conclusions due to imbalance between the 2 treatment groups, and limits the number of patients exposed to REGN2477 until initial safety is established.

No active comparator is being considered because there is no effective therapy for this disease. Patients in both groups will be allowed to receive standard of care therapies, including glucocorticoids and analgesics as needed for symptomatic management of the disease. Treatment difference in use of glucocorticoids and analgesics will be exploratory endpoints in this study. Bisphosphonates, which are sometime prescribed to patients with FOP, will not be allowed during the study, as these drugs are known to affect bone biomarkers and ^{18}F-NaF uptake by the normal skeleton. Also, denosumab, imatinib and isotretinoin should not be prescribed to study patients as these drugs may affect skeletal bone turnover.

This study is designed as a 3-period study, with an initial 6-month randomized double-blind placebo-controlled treatment period (Period 1), a subsequent 6-month open-label REGN2477 treatment period (Period 2) for all patients in the study, and a follow-up treatment period (Period 3) with continued use of REGN2477.

The 6-month duration of Period 1 was chosen based on our current knowledge of HO progression in FOP as assessed by the co-primary and key secondary imaging endpoints measures. Cross-Sectional and longitudinal ^{18}F-NaF PET data in a small number of FOP patients showed abnormally high levels of ^{18}F-NaF uptake at multiple heterotopic locations and that detection of new HO lesions by PET was highly sensitive and preceded that by CT. In these patients, PET detectable lesions progressed to CT detectable calcified bony lesions in approximately 6 months, and often resulted in functional limitations (Eekhoff 2016; for more details see Section 3.3.3.1). Based upon observation of ^{99m}Tc bone scans as well as^{18}F-NaF PET from FOP patients, it is anticipated that a majority of the patients (more than 60%) in this planned study will have at least

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1 active lesion which will demonstrate increased ^{18}F-NaF uptake (as measured by maximum SUV_{max}) at baseline. Without treatment, ^{18}F-NaF uptake in an individual lesion decreases within 6 months, as bone fully calcifies and becomes visible on CT. Therefore, to observe a change from baseline treatment effect of lesions active by PET at baseline, we chose an early time point of 8 weeks post-treatment. This early time point is expected to allow sufficient time for drug action in tissue, while permitting a distinction of the effect of the drug from that of the natural HO bone maturation process. It is expected, however, that HO is a dynamic process in these patients and that without treatment, patients would have a number of lesions which would wax and wane during a 6-month period of time whereas an effective therapy which inhibits HO activity would decrease this activity. For this reason, a co-primary endpoint measure in this study will be the Total Lesion Activity (sum of ^{18}F-NaF uptake in all active HO lesions by PET) from baseline through 6 months to allow for detection of treatment effects on both existing lesions and new lesions. Volumetric assessment of HO lesions by CT over 6 months will also allow assessment of growth of HO lesions and transition of PET detectable lesions to CT detectable mature HO lesions.

Based on patient reports, FOP patients experience an average of 2 flare-ups per year, with a subset of flare-ups leading to HO. However, HO has also been reported without being preceded by flare-ups (Pignolo 2016). Therefore, we anticipate that, in the absence of treatment, a number of new HO lesions will develop over the 6-month treatment period. The Total Lesion Activity (sum of ^{18}F-NaF uptake in all active HO lesions by PET) from baseline through 6 months allows detection of treatment effects on both existing lesions and new lesions.

After completion of Period 1 (the 6-month double-blind placebo controlled period), patients will enter Period 2, during which all patients will be treated open-label for 6 months with REGN2477 but will remain blinded to their previous treatment assignment. Those patients who had been in the placebo group in Period 1 will be crossed over to REGN2477 treatment in Period 2, thereby allowing all patients participating in this study to contribute to the evaluation of REGN2477 safety and efficacy. Patients who had been in the REGN2477 group in Period 1 will be treated with REGN2477 for an additional 6 months in Period 2 to provide an assessment of a 12-month treatment effect.

At the end of the Period 2, patients will continue to be treated with REGN2477 monthly during the follow-up treatment period (Period 3) until patients have completed the week 76 visit, and all data have been collected and validated through the time when the last patient randomized into the study completes the week 28 visit (Period 1), and results of the primary analyses of safety and efficacy are available to the sponsor. If at the time patients reach the week 76 visit data from the last patient randomized into the study through the week 28 visit have not been collected and validated, and results of the primary analyses of safety and efficacy are not yet available to the sponsor, patients will continue to receive REGN2477 Q4W beyond week 76. During this follow-up treatment period (Period 3), each patient will continue to receive REGN 2477 provided that no safety signals are identified during continuous monitoring of the study by the investigator, medical monitor and Independent Data Monitoring Committee (IDMC). In addition, during this period, all patients will be required to maintain contraception use. Patients will have the option to discontinue study medication at any time during Period 3, similarly to what occurs at any time during the study after patients have signed the informed consent.

3.3.3. Rationale for Efficacy Endpoint Measures (Period 1; Week 28)

Heterotopic ossification 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.

3.3.3.1. ^{18}F-NaF Positron Emission Tomography

The ^{18}F-NaF PET imaging will be utilized in this study to assess active HO lesions (lesions with rapid mineralization in a period of active growth compared to normotopic skeleton and HO lesions that have matured and no longer grow) at baseline, week 8, week 28, week 56, and week 76. The inherent quantitative nature of this imaging modality and our understanding of the biology of HO progression in FOP provide the rationale and we intend to qualify this endpoint measure during this study.

^{18}F-NaF is a Food and Drug Administration (FDA)-approved PET tracer widely used to detect abnormal osteogenic activity in several bone pathologies such as Paget's disease, ankylosing spondylitis, and osteoblastic bone metastases (Grant 2008). When combined with CT, ^{18}F-NaF PET has a sensitivity and specificity of >90% for the detection of osteoblastic metastases (Even-Sapir 2006). Following IV administration, ^{18}F-NaF is rapidly cleared from the plasma into the skeleton and binds to bone at a high rate, leading to an elevated target-to-background ratio signal (Blake 2012, Even-Sapir 2006). Uptake of ^{18}F-NaF is concentrated at sites of high osteoblastic activity where the ^{18}F ions bind to the newly mineralizing bone in a manner proportional to the apposition rate of bone, as shown by double tetracycline labeling studies in a porcine model (Piert 2001). Due to the inherent quantitative capability of PET, ^{18}F-NaF imaging provides an objective, non-invasive measure that is proportional to the rate of bone formation.

^{18}F-NaF PET/CT has been used in monitoring treatment effects on bone in other diseases. For example, in a study of 14 patients with Paget's disease, the SUV_{max} and tracer bone incorporation rate (K_i) were found to be significantly higher in Pagetic bone than in normal bone (35.07±23.86 vs. 7.15±4.76 and 0.114±0.115 vs. 0.014±0.008 mL/min/mL, respectively, mean ± standard deviation [SD], $p<0.05$ for both measures). Following treatment with bisphosphonates under various regiments from single IV injection to daily oral administration significant reduction of PET signal in Pagetic bone was observed compared to baseline (-27.84±24.59 at 1 month and -44.64±23.61% at 6 months, $p<0.05$ at both time points) (Installe 2005).

Pilot studies (Eekhoff 2016) in a small number (N=4) of FOP patients evaluated by whole body ^{18}F-NaF PET scan showed all patients had metabolically active HO lesions, with elevated ^{18}F-NaF uptake above the background levels of surrounding soft tissue and normal mature bone (Win 2014). Though there is limited data with this specific imaging modality, other bone scan data using ^{99m}Tc, which also detects bone mineralization, have demonstrated uptake in areas of HO in patients with FOP (Fang 1986, Herford 2003, Trikha 2005, Tulchinsky 2007). Collectively, these results are consistent with those observed in the FOP mouse model with the ACVR1[R206H] mutation, which showed that the areas of active HO demonstrate abnormally high uptake of ^{18}F-NaF on PET. In these mice, administration of REGN2477 inhibits heterotopic bone formation and markedly decreases ^{18}F-NaF PET uptake in HO lesions (see IB). It is thus hypothesized that normalization in ^{18}F-NaF uptake in pre-existing active HO lesions or a reduction in the number of

new active HO lesions in patients treated with REGN2477, compared with those treated with placebo, can provide evidence of a "proof of concept" for the treatment effect of REGN2477 on HO activity and that eventually this effect will translate into a reduction in HO lesions as detected by CT. Time-weighted percent change (AUC analysis) from baseline in Total Lesion Activity by ^{18}F-NaF PET to week 28 compared to placebo is chosen as 1 of the co-primary efficacy endpoints to assess the drug effect on heterotopic bone formation activity in existing and new lesions.

3.3.3.2. Quantitative Whole Body CT

Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 compared to placebo is chosen as another of the co-primary efficacy endpoints, to allow assessment of growth of HO lesions.

In the FOP mouse model, microCT was also used to demonstrate the treatment effects of REGN2477. In this model, REGN2477 prevented new HO lesion development and halted progression of existing HO lesions (see the IB for more detail). Although there are no published longitudinal natural history data on the change of HO lesion volume, it is known that new areas of HO in patients with FOP are detectable by CT in 3 to 6 months following tissue trauma, flare-up, or surgical procedures (Eekhoff 2016, Kaplan 2016, Kitoh 2013). Thus, it is anticipated that a treatment effect may be observed by CT in a 6-month time-frame. This study will also assess the treatment effect of REGN2477, as compared with placebo, on number of new HO lesions, in addition to changes in HO lesion volume by CT at 28 weeks. Without treatment, active HO lesions that are detectable by the very sensitive ^{18}F-NaF PET measure at baseline are expected to coalesce over time into mature HO lesions that will be detectable by CT. Therefore, a treatment effect may be discernable by comparing the number of new CT detectable HO lesions in REGN2477-treated patients versus placebo-treated patients.

3.3.4. Rationale for Efficacy Endpoints (Period 2; Week 56)

All patients remaining in the study have transitioned to the open-label REGN2477 treatment periods, Periods 2 (Section 5.1.3) and Period 3 (Section 5.1.4).

The switch of patients in the placebo group to REGN2477 treatment will allow the confirmation of the study hypothesis for Period 2 (Section 3.2) that REGN2477 treatment leads to the prevention of new heterotopic bone formation compared to control. The "control" is the experience of these same patients during the preceding placebo treatment period (Period 1). New HO related primary endpoint and key secondary endpoints will be evaluated in Period 2 (week 56; Section 4.3). These analyses are new and independent from that of Period 1 and warrant their own overall type I error rate of 10% (alpha of 0.1) which is consistent with regulatory guidance for studies in rare diseases. The small inflation of alpha is also necessary to handle the possibility of patients with missing week 56 imaging assessment due to COVID-19 (Section 10.4.3.2.4). The previously specified HO related secondary endpoints will also be assessed in Period 2 (week 56). Additionally, assessment of the patients who continue REGN2477 treatment from Period 1 (double-blind period) will allow the confirmation of the persistence of effect of REGN2477 in reducing new heterotopic bone formation with the continued REGN2477 treatment.

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In light of the public health emergency related to the COVID-19 pandemic, announced by the World Health Organization on 11 March 2020, Investigators may perform study visit 18 (week 56) and/or visit 23 (week 76) imaging exams employing only whole-body low-dose CT scans. Assessment of the imaging endpoints without the PET scan may be implemented to mitigate the delay to acquire images due to the inaccessibility to PET/CT imaging centers and/or unavailability of the ^{18}F-NaF tracer. The analysis to compare the performance between PET/CT and CT in Period 1 (week 28) showed there was no marked difference detected in the performance between PET/CT and CT reads (details in Section 3.3.1). Specifically, the CT-only reading method reconfirmed the REGN2477 treatment effects on number or percentage of patients with new lesions, total number of new lesions, and volume of new lesions seen by PET/CT method primary read. Based on this finding, the CT-only reading method will also be used to analyse all week 56 endpoints.

The effect of REGN2477 on 'flare-up' will be evaluated in Period 2 with a new endpoint based on investigator-assessed flare-ups' and the previously specified endpoint based on patient-assessed flare-up (by patient e-diary; Section 4.3.3) which will be analyzed in patients who switch from placebo in Period 1 to REGN2477 in Period 2 (Section 10.4.3.2.3).

3.3.5. Biochemical Markers of Bone Formation

Biochemical markers of bone formation, bone specific alkaline phosphatase (BSAP) and total alkaline phosphatase (tAP), 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 due to HO activity. REGN2477 may depress the levels of these markers if they are elevated, compared with the levels in patients who receive placebo. Therefore, the effect of REGN2477 on these biomarkers as well as on other biochemical markers of bone formation and resorption will also be assessed.

3.3.6. Clinical Endpoint Measures

We plan to measure clinical aspects of FOP disease activity (number and duration of flare-ups, location and severity of FOP disease signs and symptoms) via a daily diary completed by patients, physician assessment of joint involvement using the Cumulative Analog Joint Involvement Scale (CAJIS; Kaplan 2017), investigator-assessed flare-ups, patient reported quality of life assessments using the EuroQol 5 dimensions questionnaire with a 3-level scale (EQ-5D-3L), additional questions relevant to Independent Activities of Daily Living for FOP patients from the Patient Reported Outcomes Measurement Information System (PROMIS) (collectively called the FOP I-ADL Questionnaire), and spirometry assessment of pulmonary function. These measures will allow us to explore the correlation between the longitudinal change in disease activities and the change in HO activities detected by imaging and biochemical measures of heterotopic bone formation. Patients with FOP describe pain associated with their disease, at times refractory to analgesic treatments. Pain severity will be assessed daily in this study using a NRS, via the e-diary.

3.3.7. Rationale for Dose Selection

The dose and dose regimen proposed for this study is 10 mg/kg IV Q4W. In the FIH single-dose study, 10 mg/kg of REGN2477 was generally well-tolerated and demonstrated saturation of target over the proposed dosing interval. Therefore, it was chosen to initiate this proof of concept study in FOP. The rationale for this dose and dose regimen is further discussed below.

The clinical data from the FIH study of REGN2477 have demonstrated that single doses of 10 mg/kg IV appear to be generally well-tolerated. In this study, single doses of REGN 2477 were administered IV and subcutaneous (SC) in healthy women not of child bearing potential. This study has been completed and database lock (DBL) occurred on 14 February 2017. A total of 40 healthy subjects have received placebo or REGN2477 in a 1:3 ratio, with REGN2477 administered at 0.3, 1, 3, or 10 mg/kg IV and 300 mg SC doses. Top line analysis of the final unblinded safety data indicates that all dose levels have been well-tolerated, and no safety signals have been identified. Top line PK and total activin A (a measure of target engagement) data from the FIH study demonstrate that 10 mg/kg dose will likely saturate the target over the Q4W dosing interval selected for this study, but that 3 mg/kg and lower doses may be subsaturating (see more detail in the IB).

Preclinical efficacy data in FOP mice indicate that, in a prophylactic prevention model, significant reduction in heterotopic bone formation was observed following 1 mg/kg given IV every week, and maximal effects were seen with 10 mg/kg and 25 mg/kg doses given SC every week. At the 1 mg/kg dose, the trough concentration of REGN2477 in these mice was approximately 5 mg/L. Preliminary pharmacokinetics and activin A target engagement data from the FIH study suggest that a 10 mg/kg dose level, when administered Q4W, is likely to saturate the activin A target and to achieve, at 1 month, trough drug levels above the pharmacologically active drug level observed in the FOP mouse model. It is unknown, however, what concentrations of REGN2477 will be required to demonstrate a treatment effect in FOP patients with active HO. Given the severity of the disease and rarity of FOP patient, it is proposed that the 10 mg/kg dose given Q4W is likely to provide target coverage and is justified with appropriate close monitoring (see Section 3.4.1 and Section 3.4.2).

Results from a chronic non-human primate preclinical toxicology study support this planned study in patients with FOP. A 26-week good laboratory practice (GLP) -compliant toxicology study was conducted in cynomolgus monkeys. This study had a 12-week recovery period. There have been no adverse effects seen after 26 weeks of dosing in this study at dosages up to and including 50 mg/kg/week. Therefore, the no-observed-adverse-event-level (NOAEL) in this study was 50 mg/kg, the highest dose tested. Based on systemic drug exposures in this toxicology study, the selected human dose of 10 mg/kg Q4W provides sufficient safety margin (exposure multiple) of approximately 5-fold for the current study design.

In 5-week GLP studies in rats, a 50 mg/kg NOAEL was established in female rats. In male rats, however, REGN2477 related severe inflammation was observed histologically in the epididymis and efferent ducts, resulting in a NOAEL of 0.2 mg/kg/week. At dose levels above 0.2 mg/kg, decreases in sperm motility and counts were observed, which recovered after drug washout.

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Though the rat has been identified as the most sensitive species for the epididymal/testicular toxicity, 2 additional GLP 5-week toxicity studies were conducted in 2 additional non- human primate species, green monkeys and marmoset monkeys, in order to better understand the potential effect of REGN2477 in humans. Animals in these studies received REGN2477 once weekly for 5 weeks. Preliminary results of these ongoing studies have identified minimal inflammation and sperm stasis within a portion of the efferent ducts, with no findings in the epididymis. The severe effects on sperm quality (decreases in sperm motility and counts) observed in the rat studies were not observed in the short-term or long-term primate studies. Marked differences in the magnitude of inflammation seen in rats versus nonhuman primates are considered to reflect species differences in the respective anatomy of the epididymis and efferent ducts (Foley 2001, La 2012). Nevertheless, epididymal toxicity will be considered a potential risk for anti-activin A treatment pending further clinical experience.

Patients in this proof of concept study will be closely monitored and safety data will be carefully reviewed by an IDMC (see Section 5.3.1) for any tolerability issues or safety signals. In the event that significant tolerability issues or safety signals were to be identified, the dose level may be adjusted downward. Dose modification and study drug treatment discontinuations rules are described in detail in Section 7.2).

3.4. Study-Specific Safety Considerations and Monitoring

A benefit versus risk assessment of REGN2477 is described in the IB.

Study Conduct in Response to COVID-19

Included in this amendment are measures to account for the COVID-19 pandemic and to minimize the risks to the patients in the study as well as healthcare providers by allowing flexibility in the visit schedule while social distancing suggestions are in place. Allowing for this flexibility does not increase the risk of participating in this study as there will be continued contact between the patients and study personnel despite postponement of in-person clinic visits.

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

As stated above, it is unclear whether the male reproductive organ findings from the rat will translate into clinically meaningful changes in the humans. Because patients with FOP suffer from a severe, debilitating, and ultimately fatal autosomal dominant genetic disease and because there is no approved treatment available, it is proposed that the potential benefit of REGN2477 in reducing HO activity may outweigh the potential risk of male reproductive changes.

Male patients in this study will be informed of the potential risk of developing AEs of pain and/or discomfort, and swelling of the scrotum region, and decreased sperm counts, motility, and fertility. Sperm banking as a mitigating strategy for the potential risk of reduced fertility following treatment should be discussed with male patients. If requested, sperm banking procedures may be conducted as directed by the patient's own physician before the start of study drug treatment and will not be a study procedure. Baseline urogenital exams, including scrotum ultrasound with Doppler, will be conducted prior to initiation of treatment and patients will be followed for relevant AEs. Specifically, complaints of epididymitis, orchitis, hydrocele, scrotum pain, or scrotum swelling will be followed as adverse events of special interest (AESIs, see Section 9.4.3). Patients

who experience any of these AEs will be evaluated by a study urologist, and will be referred for clinical care by an appropriate specialist. Scrotum ultrasound may be performed, if clinically warranted, during follow-up of the AE. Biomarkers of testicular injury (serum concentrations of testosterone, follicle stimulating hormone [FSH], and luteinizing hormone [LH]) will be monitored throughout the study.

3.4.2. Potential Risk for Teratogenicity/Fetal Toxicity and Pregnancy Monitoring and Prevention

Results in an ongoing enhanced pre/postnatal development study of REGN2477 in cynomolgus monkeys showed a potential risk for teratogenicity/fetal toxicity. REGN2477 has had no abortifacient effects thus far, nor has it resulted in any maternal toxicity. However, treatment with REGN2477 resulted in some early births, infant malformations, a stillbirth, and infant mortality (for detailed description of the study, see IB). In the 50 mg/kg group, none of the pregnancies resulted in a normal birth; all had severe total body alopecia, and died shortly after birth or were stillborn. The cause of death has not yet been established. Exposure to 5 mg/kg did not result in severe alopecia or mortality; however, some of these animals had adverse findings of teeth abnormalities and neurological deficiencies during their functional observation battery. Data collection from this study's remaining in-life phase is still incomplete.

Strict measures will be taken to avoid giving REGN2477 to pregnant women. Women of child bearing potential (WoCBP) will only be enrolled in this study after the results of a pregnancy test are negative. Pregnancy testing will be performed and a negative pregnancy result will be confirmed prior to each subsequent dose administration. Monthly menstrual history will be collected, and pregnancy testing and reminders for contraception use will be conducted during the study and during the follow-up period. In addition, WoCBP and male patients with WoCBP partners will be instructed to use highly effective methods of contraception throughout the study. While the level of antibody drugs in the semen are normally found at extremely low levels, the levels of REGN2477 that may cross into the semen is unknown, given the potential for inflammation of the efferent duct associated with REGN2477 treatment. Therefore, a more conservative approach to contraception requirements will be applied to male patients enrolled in this study. Male patients with WoCBP partners will be asked to use condom to prevent fetal exposure and to inform and ensure their female partners to use highly effective contraception measures to prevent pregnancy. In case pregnancy occurs, the investigator will follow the pregnancy until delivery (Section 9.4.3). If the pregnancy continues to term (delivery), the health of the infant will be followed-up for a period of 3-months postnatally.

3.4.3. Risk for Epistaxis and Monitoring

Due to AEs of epistaxis reported during the conduct of the R2477-FOP-1623 study through 30 Jan 2019, epistaxis was considered a potential risk with REGN2477. Results from R2477-FOP-1623 safety analysis during the 28-week double blind treatment period (Period 1) and up to data cut-off date of 17 Sep 2019 showed imbalances in TEAEs, with higher incidence of epistaxis in the REGN2477group (50.0%) compared to placebo (16.7%). When patients in the placebo group transitioned to REGN2477in the ongoing open-label period (Period 2), epistaxis was reported in a total of 9 (20.9%) patients, including 5 (20.8%) patients who received placebo during the double-blind treatment period and 4 (21.1%) patients who received REGN2477during the double-blind treatment period. Although epistaxis has been a frequently reported TEAE, the

reported events have been predominantly mild in severity with no effect on patients' ability to receive REGN2477. Only 1 patient experienced a serious event of epistaxis. The study is ongoing, and patients are in the open-label period (Period 2) or the follow-up treatment period (Period 3).

In toxicology studies with monkey and rats, REGN2477 50 mg/kg/week treatment (26-weeks for monkeys, 5-weeks for rats) did not result in epistaxis findings, other bleeding events, or abnormalities in coagulation test results in either species.

In the completed R2477-HV-1525 study which evaluated a single-dose administration of REGN2477 10 mg/kg IV, there were no episodes of epistaxis or other bleeding episodes. In the completed R2477-1033-HV-1621, 6 subjects received REGN2477 alone (10 mg/kg IV) and 24 subjects received REGN2477 (1 mg/kg, 3 mg/kg, or 10 mg/kg) in combination with REGN1033 (6 mg/kg REGN1033). One 1 episode of mild epistaxis occurred in 1 subject who received the 10 mg/kg REGN2477 + 6 mg/kg REGN1033 combination (high dose). This epistaxis AE occurred 3 days after administration of study drug, was considered mild, and was assessed by the investigator as related to the study drug.

In order to mitigate the potential risk for patients, 3 exclusion criteria were added to this protocol: 1) concomitant antiplatelet therapy (other than low dose acetylsalicylic acid) or anticoagulants, 2) any history of severe, non-traumatic bleeding requiring transfusion or hospitalization for hemodynamic compromise, 3) known preexisting medical history of a bleeding diathesis (Section 6.2.2). In addition, investigators should discourage the use of anti-inflammatory drugs, to the extent possible.

In order to monitor the occurrence of epistaxis or other important bleeding episodes, moderate epistaxis (defined as any episode lasting longer than 30 minutes or requiring professional medical intervention), severe epistaxis (based on definition of a severe AE as described in Section 9.5.1), and other AEs of moderate to severe non-traumatic bleeding will be followed as adverse events of special interest (AESIs, see Section 9.4.3).

Baseline and post-treatment assessment of coagulation parameters (activated partial thromboplastin time, prothrombin time, international normalization ratio [INR], thrombin time), fibrinogen, and platelet effector function will be performed. For all patients who are currently enrolled in the study, the assessment of coagulation parameters (including, but not limited to activated partial thromboplastin time, prothrombin time, INR) and platelet effector function will be performed at their next evaluation, unless these tests have been performed in the past year. 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 assessments of coagulation parameters and platelet effector function as close as possible to the time of this AESI.

3.4.4. Risk for Skin and Soft Tissue Infection and Monitoring

During the double-blind treatment period (Period 1) of the ongoing R2477-FOP-1623 study, skin infection TEAEs (including folliculitis, abscesses, cellulitis, and pustular rash) were reported in patients treated with REGN2477 and none of the patients treated with placebo. None of these events were serious, severe, or led to discontinuation of study treatment.

During the open-label treatment period (Period 2/3) of R2477-FOP-1623 study, skin and soft tissue infection TEAEs (including folliculitis, furuncles, abscess, carbuncle, and cellulitis) were reported in patients treated with REGN2477, including patients treated with placebo and patients treated

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with REGN2477during Period 1. Two patients experienced serious abscesses which required admission to the hospital for incision and drainage. The events resolved, and the patients continued to receive REGN2477 after a temporary treatment interruption.

In the completed R2477-HV-1525 study, no TEAEs involving skin and soft tissue infections were reported. In the completed R2477-1033-HV-1621 study, acne was reported in 1 (12.5%) patient and skin infection in 1 patient (12.5%).

Special attention should be directed towards early detection of skin and soft tissue infections. Good hygiene and early and proactive monitoring for potential lesions is recommended. Particular attention should be paid to areas with poor ventilation, such as the perigenital and underarm areas.

3.4.5. 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. Study personnel will be trained to minimize the risk of iatrogenic soft tissue injuries.

3.4.6. Radiation Exposure

Positron emission tomography/CT is an imaging procedure that involves ionizing radiation exposure to the patient. The ionizing radiation deposited in tissue is expressed in units of mSv. The effective dose (ED) is a single figure that refers to the tissue-weighted radiation dose to the subject, accounting for stochastic risk effects associated with the radiation exposure. In the US, the maximum recommended allowed ED for an adult research subject in a single year is 50 mSv (CFR 21, vol. 5, 2015). 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 subjects. In the present study, for an adult patient each dose of ^{18}F-NaF will result in an annual ED of approximately 2.4 mSv to 8.9 mSv, while a CT scan will result in an ED of approximately 2.9 mSv to 5.1 mSv, for a cumulative ED range of 16 mSv to 42 mSv. For all 5 scans planned for the study, the total ED range is approximately 25 mSv to 56 mSv. In selected cases, a single low-dose CT scan may change the total ED range to 29 mSv to 60 mSv. The total radiation exposure during the entire study could be up to the equivalent of 3 diagnostic CT scans of the chest, abdomen, and pelvis. Radiation risk information will be included in the informed consent form.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will include standard demographic and disease characteristics including detailed FOP disease (HO status, ACVR1 mutation type), medical history and comorbidities, and medication/surgical history for each patient.

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4.2. Primary, Secondary, and Exploratory Endpoints (Period 1; Week 28)

There are 3 analysis sets defined for analysis of efficacy in this study: Baseline-Active HO Classic ACVR1[R206H] Mutation (AHOC) analysis set, Baseline-Active HO (AHO) analysis set, and full analysis set (FAS) (for a complete description, see Section 10.3).

4.2.1. Primary Safety Endpoint

- Incidence and severity of TEAEs through the end of the Period 1 at week 28

4.2.2. Primary Efficacy Endpoints

- Time-weighted average (standardized AUC) of the percent change from baseline in total lesion activity by ^{18}F-NaF PET over 28 weeks (AHO)
- Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 (AHO)
- Time-weighted average (standardized AUC) of the percent change from baseline in total lesion activity by ^{18}F-NaF PET over 28 weeks (AHOC)
- Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 (AHOC)

4.2.3. Key Secondary Endpoints

- Time-weighted average (standardized AUC) of the change from baseline in daily pain due to FOP, as measured using the daily NRS over 28 weeks (AHO)
- Time-weighted average (standardized AUC) of the change from baseline in daily pain due to FOP, as measured using the daily NRS over 28 weeks (AHOC)

4.2.4. Other Secondary Endpoints

- Percent change from baseline in ^{18}F-NaF SUV_{max} of individual active HO site(s) by PET at week 8 (AHOC)
- Percent change from baseline in ^{18}F-NaF SUV_{max} of individual active HO site(s) by PET at week 8 (AHO)
- Change from baseline in number of HO lesions as assessed by ^{18}F-NaF PET at week 28 (AHOC)
- Change from baseline in number of HO lesions as assessed by ^{18}F-NaF PET at week 28 (AHO)
- Change from baseline in number of HO lesions as assessed by ^{18}F-NaF PET at week 28 (FAS)
- Change from baseline in number of HO lesions detectable by CT at week 28 (AHOC)
- Change from baseline in number of HO lesions detectable by CT at week 28 (AHO)
- Change from baseline in number of HO lesions detectable by CT at week 28 (FAS)

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- Time-weighted average (standardized AUC) of the change from baseline in daily pain due to FOP, as measured using the daily NRS over 28 weeks (FAS)
- Time weighted average (standardized AUC) of the percent change from baseline in biomarkers of bone formation levels in serum over 28 weeks, including Total Procollagen Type 1 N-Terminal Propeptide (P1NP), bone specific alkaline phosphatase (BSAP), and total alkaline phosphatase (tAP) (FAS)
- Incidence and severity of TEAEs

4.2.5. Other Secondary Endpoints Related to Clinical Pharmacology (Period 1, Period 2, Period 3)

These secondary endpoints will be analyzed for all 3 study periods: Period 1 (week 28), Period 2 (week 56) and Period 3 (week 76).

- Concentration of total activin A in serum over time
- PK profile of REGN2477, assessed as concentrations of REGN2477 in serum over time
- Immunogenicity of REGN2477, as determined by the incidence, titer, and clinical impact of treatment-emergent ADA to REGN2477 over time

4.2.6. Exploratory Endpoints (Period 1; Week 28)

These exploratory endpoints may be analyzed for any of the defined analysis sets (AHOC, AHO, FAS). This will be described in the SAP.

The exploratory endpoints are:

- Joint function assessment by physician at baseline and week 28 by the CAJIS
- Patient-reported quality of life by EQ-5D-3L at baseline and week 28
- Patient-reported assessment of activities of daily living by FOP I-ADL at baseline and week 28
- FOP disease activity assessed by patient e-diary over time during Period 1
  - Number and duration of flare-ups (defined in this study as experiencing at least 2 of the following: new onset of pain, swelling, joint stiffness, decrease in movement, or detection of HO)
  - Location and severity of FOP disease signs and symptoms including 1) pain, 2) swelling, 3) joint stiffness, 4) decreased movement, each scored using a 4-point scale (0: no symptom; 1: mild; 2: moderate; 3: severe)
- Total dosage of glucocorticoids use over time during Period 1
- Number of patients with new HO lesions as assessed by ^{18}F-NaF PET through week 28
- Percent change from baseline of mean SUV_{mean} of selected normal bones (eg, lumbar spine and femoral heads) as assessed by PET/CT at week 8 and week 28
- Change in number of lesions that are only ^{18}F-NaF PET detectable at baseline to CT detectable lesions at week 28

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- Change from baseline in the FEV1 of spirometry at week 28
- Time-weighted average (standardized AUC) change from baseline in the levels of hs-CRP over 28 weeks

4.3. Primary, Secondary, and Exploratory Endpoints (Period 2; Week 56)

All patients in the placebo treatment group who completed Period 1 (double-blind treatment period; week 28) were switched to receive REGN2477 10 mg/kg Q4W through week 56 (placebo/REGN2477 treatment group) in the Period 2 (open-label treatment period) (Section 5.1.3). The imaging and clinical assessments at week 28 serve as the baseline for the week 56 efficacy endpoints.

The primary, key secondary, other secondary, and exploratory endpoints will be assessed in the AHO population (Section 10.3) and also in the AHOC population. A separate analysis of the FAS will not be performed as the FAS is the same as the AHO set because all patients in the study had active HO lesions at baseline.

4.3.1. Primary Efficacy Endpoint (Period 2 [Week 56])

The primary efficacy endpoint in Period 2 is:

- Number of new HO lesions as assessed by CT at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)

4.3.2. Key Secondary Efficacy Endpoints (Period 2 [Week 56])

The key secondary efficacy endpoints for Period 2 analyses (in AHO) are:

- Total volume of new HO lesions as assessed by CT at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Number of new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to week 28 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Total lesion activity by^{18}F-NaF PET in new HO lesions at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after double-blind period) (AHO)
- Percent of patients with new HO lesions as assessed by CT at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Percent of patients with new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)

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4.3.3. Other Secondary Efficacy Endpoints (Period 2 [Week 56])

The other secondary efficacy variables for Period 2 analyses (all in AHO) are:

- Number of new HO lesions as assessed by CT only at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Percent of patients with investigator-assessed flare-ups in Period 2 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Percent of patients with flare-ups assessed by patient e-diary in Period 2 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Number of new HO lesions as assessed by CT at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)
- Total volume in new HO lesions as assessed by CT at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)
- Percent of patients with new HO lesions as assessed by CT at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)
- Number of new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)
- Total lesion activity in new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)
- Percent of patients with new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)
- Percent change from week 28 in SUV_{max} to week 56 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Percent change from baseline in SUV_{max} to week 56 (in patients who continue REGN2477 after the double-blind period) (AHO)
- Percent change from week 28 in total lesion activity as assessed by ^{18}F-NaF PET to week 56 (in patients switching from placebo to REGN2477 after the double-blind period) versus the same patients between baseline and week 28 (AHO)
- Percent change from baseline in total lesion activity as assessed by ^{18}F-NaF PET to week 56 (in patients who continue REGN2477 after the double-blind period) (AHO)
- Percent change from week 28 in the total volume of HO lesions as assessed by CT to week 56 (in patients switching from placebo to REGN2477 after the double-blind period) versus the same patients between baseline and week 28 (AHO)
- Percent change from baseline in the total volume of HO lesions as assessed by CT to week 56 (in patients who continue REGN2477 after the double-blind period) (AHO)

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- Change from week 28 in number of HO lesions (target and new lesions relative to baseline) as assessed by ^{18}F-NaF PET to week 56 (in patients switching from placebo to REGN2477 in double-blind period) versus the same patients between baseline and week 28 (AHO)
- Change from week 28 in number of HO lesions (target and new lesions relative to baseline) as assessed by CT to week 56 (in patients switching from placebo to REGN2477 in double-blind period) versus the same patients between baseline and week 28 (AHO)

4.3.4. Exploratory Endpoints (Period 2 [Week 56])

The exploratory endpoints are (all in AHO):

- Joint function assessment by physician at week 56 by the CAJIS
- Patient-reported quality of life by EQ-5D-3L at week 56
- Patient-reported assessment of activities of daily living by FOP I-ADL at week 56
- FOP disease activity assessed by patient e-diary during Period 2
  - Number and duration of flare-ups (defined in this study as experiencing at least 2 of the following: new onset of pain, swelling, joint stiffness, decrease in movement, or detection of HO)
  - Location and severity of FOP disease signs and symptoms including 1) pain, 2) swelling, 3) joint stiffness, 4) decreased movement, each scored using a 4-point scale (0: no symptom; 1: mild; 2: moderate; 3: severe)
- Total dosage of glucocorticoids use during Period 2
- Change from baseline in number of HO lesions (target and new lesions relative to baseline) as assessed by ^{18}F-NaF PET at week 56
- Change from baseline in number of HO lesions (target and new lesions relative to baseline) detectable by CT at week 56
- Number of patients with new HO lesions as assessed by ^{18}F-NaF PET through week 56 relative to baseline scan
- Percent change from baseline of mean SUV_{mean} of selected normal bones (eg, lumbar spine and femoral heads) as assessed by PET/CT at week 56
- Percent change from baseline of ratio of mean SUV_{mean} of selected normal bones (eg, lumbar spine and femoral heads) to venous plasma SUV during PET as assessed by PET/CT at week 56
- Percent change from baseline in venous plasma clearance ^{18}F-NaF SUV at week 56
- Percent change from baseline in ^{18}F-NaF incorporation rate (K_i) in individual active HO lesion(s) at week 56
- Percent change from baseline of ratio of SUV_{max} of individual active HO lesion(s) to venous plasma SUV during PET scan at week 56

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- Change from baseline in the FEV1 of spirometry at week 56
- Change from week 28 in the FEV1 of spirometry at week 56

4.4. Exploratory Endpoints (Period 3 [Week 76])

The exploratory endpoints for Period 3 analyses are:

- Number of new HO lesions as assessed by CT at week 76 relative to week 28 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Total volume of new HO lesions as assessed by CT at week 76 relative to week 28 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Number of new HO lesions as assessed by ^{18}F-NaF PET at week 76 relative to week 28 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Total lesion activity by ^{18}F-NaF PET in new lesions at week 76 relative to week 28 (in patients switching from placebo to REGN2477 after double-blind period) (AHO)
- Percent of patients with new HO lesions as assessed by CT at week 76 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Percent of patients with new HO lesions as assessed by ^{18}F-NaF PET at week 76 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Percent of patients with investigator-assessed flare-ups in Period 3 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Percent of patients with flare-ups assessed by patient e-diary in Period 3 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Number of new HO lesions as assessed by CT at week 76 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)
- Total volume in new HO lesions as assessed by CT at week 76 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)
- Percent of patients with new HO lesions as assessed by CT at week 76 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)
- Number of new HO lesions as assessed by ^{18}F-NaF PET at week 76 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)
- Total lesion activity in new HO lesions by ^{18}F-NaF PET at week 76 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)
- Percent of patients with new HO lesions as assessed by ^{18}F-NaF PET at week 76 relative to baseline scan (in patients who continue REGN2477 after the double-blind period) (AHO)

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- Percent change from week 28 in SUV_{max} to week 76 (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)
- Percent change from baseline in SUV_{max} to week 76 (in patients who continue REGN2477 after the double-blind period) (AHO)
- Percent change from baseline in total lesion activity by ^{18}F-NaF PET to week 76 (in patients who continue REGN2477 after the double-blind period) (AHO)
- Percent change from baseline in the total volume of HO lesions as assessed by CT to week 76 (in patients who continue REGN2477 after the double-blind period)
- Joint function assessment by physician at week 76 by the CAJIS
- Patient-reported quality of life by EQ-5D-3L at week 76
- Patient-reported assessment of activities of daily living by FOP I-ADL at week 76
- FOP disease activity assessed by patient e-diary during Period 3
  - Number and duration of flare-ups (defined in this study as experiencing at least 2 of the following: new onset of pain, swelling, joint stiffness, decrease in movement, or detection of HO)
  - Location and severity of FOP disease signs and symptoms including 1) pain, 2) swelling, 3) joint stiffness, 4) decreased movement, each scored using a 4-point scale (0: no symptom; 1: mild; 2: moderate; 3: severe)
- Total dosage of glucocorticoids use during Period 3
- Change from baseline in the FEV1 of spirometry at week 76
- Change from week 28 in the FEV1 of spirometry at week 76

4.5. Biomarker Variables

- Research biomarker outcome measures are: to explore transcription changes in whole blood that may be related to activin pathway modulation or FOP disease activity
- Change in blood levels of additional bone and cartilage biomarkers, which may include osteocalcin, Total Procollagen Type 1 C-Terminal Propeptide (P1CP), matrix metalloproteinase 13, Procollagen type II, C-terminal telopeptide and cartilage-derived retinoic acid-sensitive protein
- Change in circulating levels of Activin pathway regulatory molecules, such as follistatin, inhibin A, and inhibin B

4.6. Pharmacokinetic Variables

The PK variable is the concentration of functional REGN2477 at each time point.

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4.7. Anti-Drug Antibody Variables

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

- Total number of patients whose response in the ADA assay is negative at all time points analyzed
- Pre-existing immunoreactivity: defined either as a positive ADA assay response at baseline with all post-dose ADA assay results negative, or a positive assay response at baseline with all post-dose ADA assay responses less than 9-fold over baseline titer levels
- Treatment-emergent: defined as any positive ADA assay response when baseline results are negative or missing. Treatment-emergent responses are further classified as:
  - Persistent: treatment-emergent positive ADA response detected in at least 2 consecutive post baseline samples separated by at least a 12-week post baseline period (based on actual sampling time), with no ADA-negative samples in-between, regardless of any missing samples or a positive response at the last ADA sampling time point,
  - Indeterminate: a positive response at the last collection time point only, regardless of any missing samples, or
  - Transient: not persistent or indeterminate, regardless of any missing samples, ie, may be positive over less than a 12-week post baseline period, and not positive on the last ADA sampling time point.
- Treatment-boosted: defined as any post-dose positive ADA assay response that has titer ≥9-fold over the baseline titer when baseline results are positive
- Titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

5. STUDY DESIGN

5.1. Study Description and Duration

This is a phase 2, randomized, placebo-controlled, study designed to evaluate the safety, tolerability, PK, and effects on heterotopic bone formation of repeated doses of 10 mg/kg IV REGN2477 Q4W in adult patients with FOP. Patients may be enrolled at multiple sites globally. Up to 40 FOP patients may be enrolled to yield approximately 24 or more patients with the classic ACVR1[R206H] mutation and with active HO at baseline as determined by ^{18}F-NaF PET/CT.

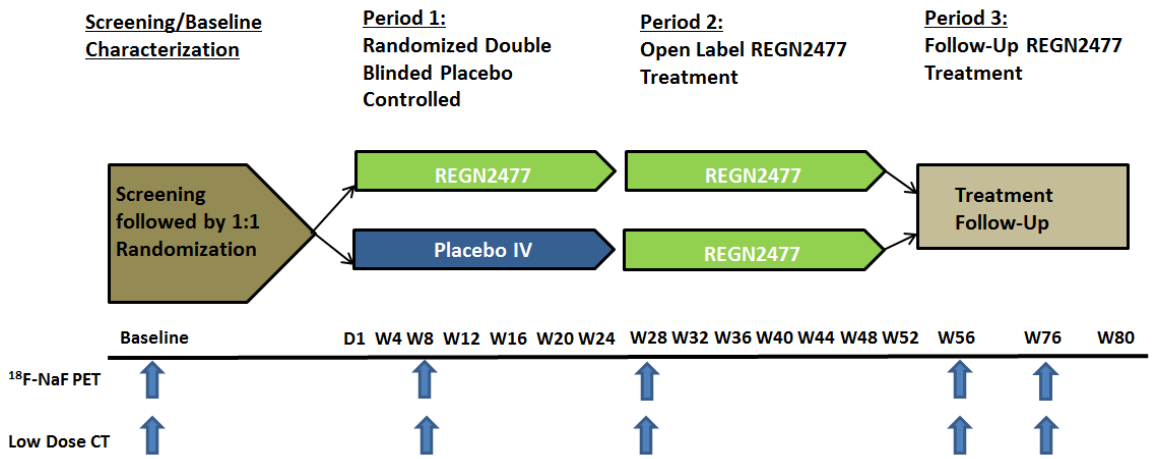
As depicted in the study design schematics (Figure 1), this study consists of a screening/baseline period (day -28 to day -1), two 6-month treatment periods, and a follow-up treatment period (Period 3). The 3 treatment periods are:

- Period 1: a 6-month randomized double-blind placebo-controlled treatment period
- Period 2: a 6-month open-label REGN2477 treatment period
- Period 3: a follow-up treatment period with REGN2477 continuing until patients have completed the week 76 visit, and all data have been collected and validated through the time when the last patient randomized into the study completes the week 28 visit (Period 1)

After Period 3 (week 76), patients can continue to receive REGN2477 treatment Q4W based on details described in Section 5.1.4. A limited number of assessments for safety, efficacy, and clinical pharmacology parameters will be conducted.

In light of the public health emergency related to COVID-19, study procedures, including study drug administration, may be conducted by trained staff at or near patients' residences (ie, at home visits) or at alternative sites established to minimize study patient to exposure to the SARS-CoV-2.

Figure 1: Study Design Schematic Screening/Baseline Period (Day -28 to Day -1): Study Visit 1



Note: The patients who completed through study week 76 may continue REGN2477 treatment beyond week 80 (described in Section 5.1.4).

5.1.1. Screening/Baseline Period (Day -28 to Day -1): Study Visit 1

During the screening/baseline period, all patients will undergo the informed consent process and screening/baseline procedures. Procedures during this visit may be conducted on different days (Table 1).

The following screening procedures will be conducted: review of medical/surgical history and prior/concomitant medications, physical exams, confirmation of clinical diagnosis of FOP and documentation of ACVR1 genotype, including the classic [R206H] or different ACVR1 mutations, laboratory assessments, vital signs, ECG, and the study physician's assessment of a patient's ability to undergo imaging and other procedures described in the study protocol. 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 determination of the ACVR1 mutation prior to randomization. Laboratory assessments and other procedures used to determine eligibility may be repeated once during the screening period. Patients and their primary caregiver(s), if assistance is needed, will be given instructions on how to complete the FOP disease activity diary and the pain NRS. For male patients, baseline urogenital exams will be conducted by the study urologist and scrotum ultrasound will be performed to aid detection of existing abnormality and to capture pretreatment baseline image. For all patients, an assessment of coagulation parameters (including, but not limited to activated partial thromboplastin time, prothrombin time, INR, thrombin time), fibrinogen, and platelet effector function will be performed at baseline visit for newly enrolled patients and prior to next administration of study drug for enrolled patients. In addition, assessment of coagulation parameters and platelet effector function will be performed at several visits during Period 1 and Period 2 to explore mechanism of epistaxis and REGN2477 mechanism of action (Table 1 and Table 2). 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 effector function as close as possible to the time of this AESI.

Patients who meet initial eligibility screening will have baseline procedures conducted. Baseline imaging procedures (whole body ^{18}F-PET, low dose CT) will be performed within 1 week of study drug administration (study day 1), ie, within study day -7 to day -1, to identify and characterize index HO lesions. Patients must be physically able and willing to undergo both PET and CT measures to be eligible for this study. Pre-dose baseline PK, anti-drug antibody, activin A, and other biomarker samples will be collected. Pretreatment CAJIS, daily pain NRS, patient reported FOP disease activity diary, and other patient reported outcome questionnaires will be completed. The baseline entry for both the daily pain NRS and the daily FOP disease diary will be on day -1. A blood sample will be collected from all patients for future ACVR1 gene sequencing.

Women of child bearing potential and male patients with WoCBP partners will be reminded at all visits to adhere to highly effective contraception (defined in exclusion criteria 16 and 17). Pregnancy status and menstrual cycle history of WoCBP will be monitored through the end of the study.

5.1.2. Period 1: Double-Blind Treatment (Week 1 [Day 1] to Week 24 [Day 169]) and End of Period 1 Assessments (Week 28 [Day 197])

Patients will be randomized to receive REGN2477 at 10 mg/kg dose or matching placebo, administered IV Q4W through week 24, for a total of 7 doses, as outlined in the schedule of events (Table 1). Randomization will be stratified by gender, classic ACVR1[R206H] mutation/different ACVR1 mutations, and by presence/absence of baseline active HO lesions as determined by ^{18}F-NaF PET/CT. Baseline imaging data will be reviewed by a central imaging analysis vendor and Regeneron Clinical Imaging Director prior to randomization.

Patients will be closely monitored for a minimum of 120 minutes after administration of study drug.

To ensure safety of this approach, individual patients will be closely monitored and safety of each dose will be reviewed by the investigator and the Regeneron medical monitor prior to administering the subsequent repeated dose. The safety review to be conducted by the investigator

and Regeneron medical monitor prior to study drug infusions on visits 2, 5, 6 and 7 (Period 1) and visits 11, 12, 13 and 14 (Period 2) will include evaluation of laboratory test (hematology, blood chemistry and urinalysis) results collected as part of these visits (see Section 8.1). For the remaining study visits, assessment of results of hematology, blood chemistry and urinalysis tests planned for these same visits may be performed, but will not be required prior to study drug infusion. The decision not to wait for the results of these exams, processed at the study's central laboratory, should be made on a case-by-case basis, if the patient's clinical condition, TEAE profile, and assessment of vital signs, ECGs and previous laboratory test results indicate that the patient is suitable to receive the next dose of study drug. For the study visits after week 56 (Period 3), the need for a safety review by the investigator and Regeneron medical monitor will be decided on a case-by-case basis. In addition, the IDMC (see Section 5.3.1) will regularly monitor the unblinded study-level safety data.

In the event that a significant tolerability issue or safety concern is identified, dose modification or study drug discontinuation may be implemented according to Section 7.2.

Efficacy and safety procedures will be performed as outlined in the schedule of events (Table 1). Adverse events will be assessed as described in Section 9.4. Index HO lesion identified at baseline and new HO lesions will be assessed by imaging endpoint measures including whole body ^{18}F-NaF PET and whole body low dose CT at week 8 (day 57 [±7 days]), and week 28 (day 197 [±7 days]). Clinical endpoints will be assessed by investigator or patient reported outcome measures at week 28 (day 197 [±7 days]). The daily pain NRS and FOP disease activity diary will be checked at every visit for completeness.

Serum samples for the determination of REGN2477 concentration and ADA will be collected.

Serum samples for the determination of bone formation and mechanism of action biomarkers, BSAP, tAP, and P1NP, inflammation biomarker, hs-CRP, as well as markers related to the Activin A and Activin receptor pathway including but not limited to Activin and BMP ligands or markers that may elucidate the mechanism of action of REGN2477 will be collected.

Additional biomarker samples will be collected as described in the schedule of events (Table 1).

5.1.3. Period 2: Open-Label REGN2477 Treatment (Week 28 [Day 197]) to Week 52 [Day 365]) and End of Period 2 Assessments (Week 56 [Day 393])

All patients who complete the double-blind treatment period will receive REGN2477 administered IV at a dose of 10 mg/kg Q4W through week 52, for a total of 7 doses as outlined in the schedule of events (Table 2).

Efficacy and safety procedures will be performed as outlined in the schedule of events (Table 2). For patients previously treated with placebo drug, week 28 (day 197) assessments will be considered as pretreatment baseline for safety and efficacy analysis of this period of the study.

Index HO lesion identified at baseline and new HO lesions will be assessed by imaging endpoint measures including whole body ^{18}F-NaF PET and whole body low dose CT at week 56 (day 393 [±14 days]). Clinical endpoints will be assessed by investigator or patient reported outcome measures at week 56 (day 393 [±14 days]). The daily pain NRS and FOP disease activity diary will be checked at every visit for completeness.

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In light of the public health emergency related to the COVID-19 pandemic, Investigators may perform study visit 18 (week 56) imaging exam employing only whole body low-dose CT scans. Assessment of imaging endpoints without the PET scan may be implemented to mitigate the delay to acquire images due to the inaccessibility to PET/CT imaging centers and/or unavailability of the ^{18}F-NaF tracer. In addition, the timing for study visit 18 (week 56) is flexible as long as any changes are documented. This low-dose CT scan may be performed by trained staff either at study site or at other clinical sites with access to a qualified CT scanner or using a mobile qualified CT scanner at a local community healthcare setting close to patient or at a home visit, contingent upon prior concurrence and approval from the Investigator and Regeneron medical director (Section 3.3.4).

Serum samples for the determination of REGN2477 concentrations and ADA will be collected.

Additional biomarker samples will be collected as described in the schedule of events (Table 2).

5.1.4. Period 3: Follow-Up Treatment Period Week 56 (Day 393) to End of Study

The patients who completed the open-label portion of the study, through week 52, will continue to receive study drug from week 56 through week 76 or beyond.

REGN2477 treatment will continue after week 76 until any 1 of the following occurs:

- Clinical development of REGN2477 for the indication described in this study protocol is discontinued
- Clinical development of REGN2477 is terminated
- Risk/benefit of REGN2477 in this patient population is deemed unfavorable
- 3 years of REGN2477 treatment from the start of Period 3
- Other means of access to REGN2477 (eg, expanded access protocol) becomes available for study patients for whom the benefit-risk assessment for REGN2477 treatment remains positive
- Approval of the drug by the competent regulatory authority governing each respective country (eg, European Commission for EU Member States) with commercial availability

Efficacy and safety procedures will be performed as outlined in the schedule of events (Table 3).

Index HO lesion identified at baseline and new HO lesions will be assessed by imaging endpoint measures including whole body ^{18}F-NaF PET and whole body low dose CT at week 76 (day 533 [±7 days]).

In light of the public health emergency related to the COVID-19 pandemic, Investigators may perform study visit 23 (week 76) imaging exam employing only whole body low-dose CT scans. Assessment of imaging endpoints without the PET scan may be implemented to mitigate the delay to acquire images due to the inaccessibility to PET/CT imaging centers and/or unavailability of the ^{18}F-NaF tracer. In addition, the timing for study visit 23 (week 76) is flexible as long as any changes are documented. This low-dose CT scan may be performed by trained staff either at study site or at other clinical sites with access to a qualified CT scanner or using a mobile qualified CT scanner at a local community healthcare setting close to patient or at a home visit, contingent upon

prior concurrence and approval from the Investigator and Regeneron medical director (Section 3.3.4).

The daily pain NRS and FOP disease activity diary will be checked at every visit for completeness.

Additional biomarker samples will be collected as described in the schedule of events (Table 3).

Serum samples for the determination of REGN2477 concentrations and ADA will be collected.

5.1.5. Study Stopping Rules

5.1.5.1. Study Stopping Criteria

The emerging benefit-risk profile of REGN2477 treatment will be closely monitored by an IDMC. The IDMC (defined in Section 5.3.1) will monitor unblinded data on an ongoing basis to assess the risk/benefit profile of REGN2477. The IDMC will meet to review the unblinded safety data after 6 patients have completed 4 weeks of study drug treatment and safety data has become available, and monthly thereafter. As the study progresses, based upon the enrollment rate, the cumulative review of safety data, and at the discretion of the IDMC members, the IDMC may choose to meet on a quarterly basis.

If at any time the IDMC has significant concerns regarding a meaningful imbalance in SAEs and 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. In the event of a study restart after a temporary halt, dose modification, if needed, will be determined as described in Section 7.2.1.

The IDMC will not conduct any formal efficacy analyses, other than in their oversight of safety and evaluation of risk benefit profile. There are no formal early stopping criteria for efficacy.

5.1.5.2. Individual Patient Stopping Rule

Dosing in an individual patient may be temporarily or permanently stopped according to Section 7.2.2.

5.1.6. End of Study Definition

The end of study for this study is defined as the last visit of the last patient.

5.2. Planned Interim Analysis

No interim analysis is planned.

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

An IDMC, composed of members who are independent from the sponsor and the study investigators, will monitor patient safety by conducting formal reviews of cumulative unblinded safety data. If requested, the IDMC may have access to any other data for the purposes of a risk-benefit assessment.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the IDMC are described in the IDMC charter.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Up to 40 patients with FOP may be enrolled at multiple sites globally to yield approximately 24 or more patients with the classic ACVR1[R206H] mutation and active HO at baseline.

6.2. Study Population

Male and female adult patients with a clinical diagnosis of FOP aged 18 to 60 years of age and with documentation of ACVR1 mutation.

6.2.1. Inclusion Criteria

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

1. Male or female 18 to 60 years of age 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 any ACVR1 mutation
4. FOP disease activity within 1 year of screening visit. FOP disease activity is defined as pain, swelling, stiffness, and other signs and symptoms associated with FOP flare-ups; or worsening of joint function, or radiographic progression of HOs (increase in size or number of HO lesions) with/without being associated with flare-up episodes
5. Provide signed informed consent
6. Willing and able to attend and comply with study visits and study related activities
7. Willing and able to undergo PET and CT imaging procedures and other procedures as defined in this study
8. Able to understand and complete study-related questionnaires and diaries (assistance from caregivers are allowed)

6.2.2. Exclusion Criteria

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

1. 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

2. Previous history or diagnosis of cancer
3. 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)
4. Uncontrolled diabetes defined as hemoglobin A1C (HbA1c) >9% at screening (1 retest allowed)
5. 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)
6. Ongoing significant viral illness or pneumonia within 2 weeks of screening
7. Severe anemia requiring transfusion
8. History of severe respiratory compromise requiring oxygen, respiratory support (example bilevel positive airway pressure [biPAP] or continuous positive airway pressure [CPAP]) or a history of aspiration pneumonia requiring hospitalization
9. Known history of recent epididymitis (within 6 months of screening), TB, or sexually transmitted diseases affecting urogenital organs
10. Use of bisphosphonate within 1 year of screening
11. 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 are allowed
12. 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
13. History of hypersensitivity to doxycycline or other tetracycline antibiotics, vaccines, or other biologics
14. Positive serum human chorionic gonadotropin (hCG)/urine pregnancy test at the screening/baseline visit
15. Pregnant or breastfeeding women
16. Women of child bearing potential[*] who are unwilling to practice highly effective contraception[**] or undergo pregnancy tests prior to the initial dose, during the study, and for 30 weeks after the last dose.

    [*] Pregnancy testing and contraception are not required for women not of child bearing potential, including postmenopausal women or those with documented hysterectomy or bilateral oophorectomy.

    Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of child bearing potential. Postmenopausal status will be confirmed by measurement of FSH.

** Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence***.

*** 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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

17. 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 24 weeks after the last dose. Sperm donation is prohibited during the study and for 24 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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

18. Patients who are on concomitant antiplatelet therapy (eg, clopidogrel), anti-coagulants (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 (≤100 mg/day) acetylsalicylic acid (aspirin) is acceptable.
19. Patients with a history of severe, non-traumatic bleeding requiring transfusion or hospitalization for hemodynamic compromise
20. 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).

6.3. Premature Withdrawal from the Study

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

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

Patients who are withdrawn prematurely from the study will be asked to complete the study assessments, as described in Section 8.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.2.2.

6.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

REGN2477 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 matching REGN2477 is prepared in the same formulation as REGN2477, without the addition of protein.

During the randomized double-blind placebo-controlled treatment period (Period 1), each patient will receive REGN2477 or placebo IV in a double-blinded fashion.

During the open-label REGN2477 treatment period (Period 2), each patient will receive REGN2477.

During the follow-up treatment period (Period 3), each patient will continue to receive open label REGN2477.

7.2. Dose Modification and Study Treatment Discontinuation Rules

7.2.1. Dose Modification

Dose modification will be allowed if emerging safety signals indicates the need for a reduction of dose level according to the criteria set out below. Dose modification will imply a reduction from 10 mg/kg to 3 mg/kg IV Q4W in patients with FOP.

To ensure safety of this approach, individual patients will be closely monitored and safety of each dose will be reviewed by the investigator and Regeneron medical monitor prior to administering the subsequent repeated dose. The blinded safety review to be conducted by the investigator and Regeneron medical monitor prior to study drug infusions on visits 2, 5, 6 and 7 (Period 1) and visits 11, 12, 13 and 14 (Period 2) will include evaluation of laboratory test (hematology, blood chemistry and urinalysis) results collected as part of these visits (see Section 8.1). For the remaining study visits, assessment of results of hematology, blood chemistry and urinalysis tests planned for these same visits may be performed, b performed, but will not be required prior to study drug infusion. The decision not to wait for the results of these exams, processed at the study's central laboratory, should be made on a case-by-case basis, if the patient's clinical condition, TEAE profile, and assessment of vital signs, ECGs and previous laboratory test results indicate that the patient is suitable to receive the next dose of study drug. For the study visits after week 56 (Period 3), the need for a safety review by the investigator and Regeneron medical monitor prior to infusion of REGN2477 will be decided on a case-by-case basis.

7.2.1.1. Individual Level Dose Modification

Individual patient dose modification will be determined on a case-by-case basis based on the discussion between the investigator and Regeneron medical monitor, Regeneron Global Patient Safety, and approved by the Vice President Early Clinical Development or his/her designee.

If 1 of the following occurs, individual dose modification will be considered;

- Occurrence of 1 severe AE deemed to be related to the study drug.
- Moderate to severe scrotum pain or swelling not otherwise justified by an alternate etiology after urology follow up assessment.

The following AEs will not be considered as meeting the dosing modification rule:

- Any AE that has a clear alternative causation
- Episodes of flare-up or worsening of signs and symptoms of FOP

After individual level dose reduction and depending upon the patient's clinical evolution following 1 or more infusions of 3 mg/kg IV of Q4W study drug, the investigator may consider resuming the original 10 mg/kg IV Q4W dosing regimen. The investigator will communicate with Regeneron medical monitor before resuming the original dose. Prior to resuming the original dose, the Regeneron medical monitor will discuss with Regeneron Global Patient Safety and obtain approval by the Vice President Early Clinical Development or his/her designee.

Any individual level dose modification that occurs will be communicated by Regeneron medical monitor to the IDMC in a timely manner.

7.2.1.2. Study Level Dose Modification

The IDMC (see Section 5.3.1) will regularly monitor the unblinded safety data and, based on significant concerns regarding a meaningful imbalance in the frequency and/or severity of AEs or altered laboratory results, may make recommendations to the sponsor to consider dose modification.

Study level dose modification will be determined by the sponsor upon recommendation of the IDMC following their review of safety, PK, and total activin A (target engagement) data available at the time.

7.2.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule and for blood sample collection for measurement of serum drug and target, and ADA: at 4 weeks, 8 weeks, 16 weeks, and 28 weeks after the last dose of study drug. Safety lab exams (ie, hematology, blood chemistry and urinalysis) may also be collected during these visits at the investigator's discretion. A blood sample collection for assessment of ADA will occur at the patient's last visit.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.2.

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7.2.2.1. 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
- Severe acute infusion reactions as described in Section 9.5.1
- Serious or severe hypersensitivity reaction deemed related to study drug

7.2.2.2. 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

7.3. Management of Acute Reactions

7.3.1. Acute 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 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

7.3.1.1. Interruption of the Infusion

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

- 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.

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7.3.1.2. Termination of the 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 discontinuation of the infusion

7.4. Method of Treatment Assignment

Patients will be randomly assigned to receive REGN2477 or placebo in a 1:1 ratio (REGN2477: placebo) on study day 1. Patients will be randomized according to a central randomization scheme, using an interactive response technology (IRT) provided to the designated study pharmacist or qualified designee.

7.4.1. 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 double-blind treatment period of the study.

The PET and 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.

7.4.2. 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).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.

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- Only the affected patient 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 the patient.
- The investigator will notify Regeneron and/or designee before unblinding the patient, whenever possible.

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist/designee (when applicable), at any time during the conduct of the study, except in the case of a true emergency. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

7.5. Treatment Logistics and Accountability

7.5.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label the 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 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

7.5.2. 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 returned to the sponsor or designee.

7.5.3. 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 (if approved by sponsor) 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.

7.5.4. Treatment Compliance

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

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7.6. Concomitant Medications

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.

7.6.1. Prohibited Medications

Prohibited medications are:

- Amiodarone
- Those that may have effects on skeletal bone turnover, such as bisphosphonates (eg, etidronate, pamidronate), denosumab, imatinib, or isotretinoin
- Immunosuppressants (eg, methotrexate)
- Chemotherapies
- Radiotherapy
- Bone marrow transplantation
- Antiplatelet therapy (eg, clopidogrel)
- Anticoagulants (eg, warfarin, heparin, factor Xa inhibitor, thrombin inhibitors)
- Herbal supplements that inhibit platelet function or are associated with increased risk of bleeding

7.6.2. Permitted Medications

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
- NSAIDs*
- Opioid and other analgesics
- Antidepressants
- Vitamins and calcium supplements
- Over-the-counter antihistamines and decongestants
- Paracetamol
- Antibiotics
- Vaccinations
- Anti-hypertensives
- Proton pump inhibitors

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- 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/day])

*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.

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 Regeneron medical monitor to gain agreement.

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

In light of the public health emergency related to the COVID-19 pandemic, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of alternative mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, noninvasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. 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 and/or until the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites.

Study assessments and procedures are presented by study period and visit in Table 1, Table 2, and Table 3).

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Table 1: Schedule of Events: Screening/Baseline through Period 1 (Randomized Double-Blind Treatment Period)

		Period 1 (Randomized Double-Blind Treatment)								
Visit[1]	**Screening/ Baseline Period**	**Visit 2**	**Visit 3[2]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Day ± visit window (d)	**-28 to -1**	**1**	**2**	**7 ±1d**	**29 ±3d**	**57 ±7d**	**85 ±7d**	**113 ±7d**	**141 ±7d**	**169 ±7d**
Week		**1**	**1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**
Screening/Baseline[3, 20]:										
Informed consent	X									
Informed consent (optional genomic sub-study)	X									
Inclusion/Exclusion	X									
Medical/Prior Medication/Surgical history[4]	X									
Urogenital exam (male patients only)	X									
Scrotum ultrasound with Doppler (male patients only)	X									
Blood sample for HbA1c measurement	X									
Confirm clinical FOP diagnosis, including documentation of ACVR1 mutation[5]	X									
Whole blood DNA sample for ACVR1 gene sequencing[21]	X									
Demographics	X									
Treatment:										
Study enrollment randomization		X								
Administer Study Drug (REGN2477 or placebo)[6, 8, 9]		X			X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Safety:										
Adverse events	X	X	X	X	X	X	X	X	X	X
Height (if feasible)[22]	X									
Body Weight	X	X			X	X	X	X	X	X
Vital signs[7, 8]	X	X[8]	X	X	X	X	X	X	X	X
Electrocardiogram[7, 9]	X	X[9]	X		X	X				X
Physical examination	X									
Menstrual history, pregnancy status reporting and confirmation of contraception use[10]	X	X			X	X	X	X	X	X
Laboratory Testing[3]:										
Hematology[7, 11]	X	X	X		X	X	X	X	X	X
Blood chemistry[7, 11]	X	X	X		X	X	X	X	X	X
Urinalysis[7, 23]	X	X	X		X	X	X	X	X	X

		Period 1 (Randomized Double-Blind Treatment)								
Visit[1]	**Screening/ Baseline Period**	**Visit 2**	**Visit 3[2]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Day ± visit window (d)	**-28 to -1**	**1**	**2**	**7 ±1d**	**29 ±3d**	**57 ±7d**	**85 ±7d**	**113 ±7d**	**141 ±7d**	**169 ±7d**
Week		**1**	**1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**
Blood samples for FSH[7, 11]	X	X			X	X				
Blood samples for ACTH, GH, cortisol, TSH, free T4, testosterone (total and free; male patients only), estradiol, LH, amylase, and lipase[7, 11]		X			X	X				
Blood sample for coagulation parameters (activated partial thromboplastin time, prothrombin time, INR, thrombin time), fibrinogen, and platelet effector function	X[25]				X		X			
Pregnancy test (WoCBP)[7, 10, 11]	serum	urine			urine	urine	urine	urine	urine	urine
Imaging Assessments:										
^{18}F-NaF PET[7, 12, 13]	X					X				
Blood sample for ^{18}F-NaF tracer concentration (optional)[7, 11, 12, 13]	X									
Low dose CT[7, 12]	X					X				
Clinical Endpoint Measures[24]										
Daily Pain NRS[14, 18]	X	X	X	X	X	X	X	X	X	X
Daily FOP disease activity e-diary[14, 18]	X	X	X	X	X	X	X	X	X	X
FOP I-ADL	X									
EQ-5D-3L	X									
Joint function (CAJIS)	X									
Pulmonary function by spirometry (FVC, FEV1)	X									
Biochemical Bone Formation and Mechanism based Biomarkers										
Blood samples for BSAP and P1NP[7, 11]	X	X		X	X	X		X		
Blood samples for mechanism of action or safety	X									
PK/Drug Concentration and ADA Samples:										
PK/Drug conc. and activin A sample[7, 11]		X		X	X	X	X	X	X	
ADA sample[7, 11]		X						X		
Biomarker Procedures:										
Whole blood for RNA gene expression[7, 11]		X	X	X	X					
Future Biomedical Research Samples										
Research biomarker serum and biomarker plasma[7, 11]	X	X		X	X	X	X	X		
Optional Genomic Study: DNA Analysis										

		Period 1 (Randomized Double-Blind Treatment)								
Visit[1]	**Screening/ Baseline Period**	**Visit 2**	**Visit 3[2]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Day ± visit window (d)	**-28 to -1**	**1**	**2**	**7 ±1d**	**29 ±3d**	**57 ±7d**	**85 ±7d**	**113 ±7d**	**141 ±7d**	**169 ±7d**
Week		**1**	**1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**
Whole blood DNA sample (optional)[7, 15]		X								

Table 2: Schedule of Events: Period 2 (Open-Label Treatment Period)

	Period 2 (Open-Label REGN2477 Treatment)						
Visit[1]	**Visit 11[16]**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**
Day ± visit window (d)	**197 -7d/+15d**	**225 ±7d**	**253 ±7d**	**281 ±7d**	**309 ±7d**	**337 ±7d**	**365 ±7d**
Week	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Treatment:							
Administer REGN2477[6, 8, 9]	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Safety:							
Adverse events	X	X	X	X	X	X	X
Body Weight	X	X	X	X	X	X	X
Vital signs[7, 8]	X	X	X	X	X	X	X
Electrocardiogram[7, 9]	X[9]			X			
Physical examination	X						
Menstrual history, pregnancy status reporting and confirmation of contraception use[10]	X	X	X	X	X	X	X
Laboratory Testing:							
Hematology[7, 11]	X	X	X	X	X	X	X
Blood chemistry[7, 11]	X	X	X	X	X	X	X
Urinalysis[7, 23]	X	X	X	X	X	X	X
Blood samples for ACTH, GH, cortisol TSH, free T4, testosterone (total and free; male patients only), FSH, estradiol, LH, amylase, and lipase[7, 11]	X	X		X			
Blood sample for coagulation parameters (activated partial thromboplastin time, prothrombin time, INR, thrombin time), fibrinogen, and platelet effector function	X	X		X			
Pregnancy test (WoCBP)[7, 10]	urine	urine	urine	urine	urine	urine	urine
Imaging and Other Assessments:							
^{18}F-NaF PET[7, 13]	X						
Low dose CT[7, 13]	X						

	Period 2 (Open-Label REGN2477 Treatment)						
Visit[1]	**Visit 11[16]**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**
Day ± visit window (d)	**197 -7d/+15d**	**225 ±7d**	**253 ±7d**	**281 ±7d**	**309 ±7d**	**337 ±7d**	**365 ±7d**
Week	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Clinical Endpoint Measures[24]							
Daily Pain NRS[14]	X	X	X	X	X	X	X
Daily FOP disease activity e-diary[14]	X	X	X	X	X	X	X
FOP I-ADL	X						
EQ-5D-3L	X						
Joint function (CAJIS)	X						
Pulmonary function by spirometry (FVC, FEV1)	X						
Biochemical Bone Formation and Mechanism based Biomarkers							
Blood samples for BSAP and P1NP[7, 11]	X	X	X		X		X
Blood samples for mechanism of action or safety	X						
PK/Drug Concentration and ADA Samples:							
PK/Drug conc. and activin A sample[7, 11]	X	X	X	X	X	X	X
ADA sample[7, 11]	X			X			X
Future Biomedical Research Samples							
Research biomarker serum and biomarker plasma[7, 11]	X	X			X		X

Table 3: Schedule of Events: Period 3 (Follow-Up Treatment Period)

	Period 3 (Follow-Up Treatment Period)					End of Study[17]	
Visit[1]	**Visit 18[19]/ Early Termination Visit**	**Visit 19**	**Visit 20**	**Visit 21**	**Visit 22**	**Visit 23**	**≥Visit 24**
Day ± visit window (d)	**393 ±14d**	**421 ±7d**	**449 ±7d**	**477 ±7d**	**505 ±7d**	**533 ±7d**	561 ±7d
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80[17]**
Treatment:							
Administer REGN2477[6, 8, 9, 26]	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Safety:							
Adverse events	X	X	X	X	X	X	X
Vital signs[7, 8]	X	X	X	X	X	X	X
Electrocardiogram[7, 9]	X	X	X	X	X	X	X
Physical examination[9]	X	X	X	X	X	X	X
Menstrual history, pregnancy status reporting and confirmation of contraception use[10]	X	X	X	X	X	X	X
Laboratory Testing:							
Hematology[7, 11,]	X						X[17,28]
Blood chemistry[7, 11]	X						X[17,28]
Urinalysis[7, 23]	X						X[17,28]
Blood samples for ACTH, GH, cortisol TSH, free T4, testosterone (total and free; male patients only), FSH, estradiol, LH, amylase, and lipase[7, 11]	X					X	
Pregnancy test (WoCBP)[7, 10, 11]	urine	urine	urine	urine	urine	serum	urine/serum[17]
Imaging and Other Assessments:							
^{18}F-NaF PET[7, 13]	X[27]					X[27]	
Blood sample for ^{18}F-NaF tracer concentration (optional)[7, 11, 13]	X						
Low dose CT[7, 13]	X					X	

	Period 3 (Follow-Up Treatment Period)					End of Study[17]	
Visit[1]	**Visit 18[19]/ Early Termination Visit**	**Visit 19**	**Visit 20**	**Visit 21**	**Visit 22**	**Visit 23**	**≥Visit 24**
Day ± visit window (d)	**393 ±14d**	**421 ±7d**	**449 ±7d**	**477 ±7d**	**505 ±7d**	**533 ±7d**	561 ±7d
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80[17]**
Clinical Endpoint Measures[24]							
Daily Pain NRS[14]	X	X	X	X	X	X	
Daily FOP disease activity e-diary[14]	X	X	X	X	X	X	
FOP I-ADL	X					X	X[17]
EQ-5D-3L	X					X	X[17]
Joint function (CAJIS)	X					X	X[17]
Pulmonary function by spirometry (FVC, FEV1)	X					X	X[17]
Biochemical Mechanism based Biomarkers							
Blood samples for mechanism of action or safety	X						
Future Biomedical Research Samples							
Research biomarker serum and biomarker plasma[7, 11]	X					X	
PK/Drug Concentration and ADA Samples:							
PK/Drug conc. and activin A sample[7, 11]	X	X	X	X	X	X	X[17]
ADA sample[7, 11]	X			X			X[17]

8.1.1. Footnotes for the Schedule of Events Table 1, Table 2, and Table 3

1. Procedures other than those associated with drug administration and imaging procedures may be conducted by trained study staff at or near patients' residences (ie, at home visits).
2. Study visit 3 (day 2) will be conducted in the clinic following the first dose of study drug, although no study drug administration or imaging procedure is conducted at this visit.
3. Procedures may be conducted on different days during the screening/baseline period, if needed. Blood draws for laboratory testing at the screening visit will be collected in a fasted state (after an 8-hour fast). No other blood draw will require fasting.
4. Medical history should include detailed FOP history, and prior medication and surgery for treatment of FOP.
5. Documentation of ACVR1 genotype, including classic [R206H] or different ACVR1 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 the investigator to determine the ACVR1 mutation prior to randomization. This testing, which will be performed on an as needed basis, is separate from the mandatory whole blood collection described in footnote #21.
6. All patients who receive study drug will be closely monitored after each study drug administration for at least 2 hours.
7. 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 (except ^{18}F-NaF tracer concentrations) will be collected before imaging procedures. Study drug administration will be performed last at that study visit.
8. On study day 1 (Period 1) and on study day 197 (Period 2), vital signs will be collected pre-dose and post-dose at 1 hour and 4 hours after the end of infusion. On subsequent visits, vital signs will be collected prior to dosing.
9. On study day 1 (Period 1) and on study day 197 (Period 2), ECG will be conducted pre-dose and post-dose 1 hour and 4 hours after the end of infusion. On subsequent visits, ECG will be conducted prior to dosing. ECG and symptom-directed physical examination may be performed during Period 3 at the investigator's discretion.
10. 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 and visit 4. For all patients, contraception use will be confirmed. A negative result for the pregnancy test must be obtained prior to each study drug administration. After week 56, urine pregnancy testing will be performed prior to each REGN2477 dose administration. A serum pregnancy test will be performed at the patient's end of study visit.
11. 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.

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12. The baseline imaging assessments by ^{18}F-NaF PET and low dose CT must be conducted between day-7 to day -1.
13. The ^{18}F-NaF PET may be performed at a separate location than the study clinic, within the visit window, before study drug administration. Blood samples for the determination of the tracer concentration in plasma will be collected for baseline and week 56 imaging sessions from a subset of patients who will undergo an optional dynamic PET scan. Any incidental findings identified through PET/CT scans will be reported to the investigator and medical monitor. The investigator will communicate any findings to the patient.
14. Daily pain NRS score and FOP disease activity will be collected as entries in a diary completed by. 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.
15. Separate consent is required for participation in the optional genomic DNA sub-study and collection of blood sample (DNA). The blood sample for genomic DNA should be collected on day 1 or may be collected at any visit.
16. Patients will undergo end of double-blind treatment (Period 1) assessments at the week 28 visit (Period 1), which is the first visit in the open-label treatment (Period 2) with administration of open-label REGN2477.
17. The week 80 column illustrates additional visits and procedures to be performed Q4W (study drug administration, concomitant medications, and safety assessments) and every 24 weeks (laboratory testing, clinical endpoint measures, PK/drug concentration and ADA samples). The first collection of the assessments conducted every 24 weeks would be at week 100 (visit 29). The serum pregnancy test should only be required when the patient is performing the last visit in the study and thereafter will not receive additional infusions of REGN2477. The criteria for continued administration of REGN2477 after week 76 is described in Section 5.1.4.
18. The baseline entry for both the daily pain NRS and the daily FOP disease activity diary will be on day -1.
19. Patients will undergo end of open-label treatment (Period 2) assessments at the week 56 visit, which is the first visit of the follow-up treatment period (Period 3).
20. Patients can be rescreened for study participation.
21. All patients will have a whole blood sample collected, preferably at the screening/baseline visit, for future ACVR1 gene sequencing. However, the sample can be collected at any time during the study period, as the result of this test is not to be used for assessment of study eligibility.
22. 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.
23. A urinalysis and culture will be collected/performed if there is an AESI (only applicable to male patients).

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24. With the exception of the Daily Pain NRS and FOP disease activity e-diary, if a study questionnaire is not available in a patient's native language at the time of enrollment that questionnaire will not be part of the required study procedures for that patient.
25. For patients already enrolled in the study, the blood sample for these assessments will be collected at their next visit, unless these assessments have been performed in the past year. These assessments will be conducted locally.
26. Study drug to be administered IV by trained nursing staff either at study site or in local community healthcare setting close to patient or at a home visit.
27. A low-dose CT only scan may be performed if ^{18}F-NaF tracer or PET/CT scanner is unavailable during a scheduled visit (Section 5.1.3, Section 5.1.4). This low-dose CT scan may be performed by trained staff either at study site, at other clinical sites with access to a CT scanner, or using a mobile qualified CT scanner at a local community healthcare setting close to patient or at a home visit.
28. After the week 56 visit, samples for hematology, blood chemistry and urinalysis will be collected every 24 weeks. After the week 80 visit (visit 24) samples will continue to be collected as outlined in footnote 17 with the next sample collection at week 100 (visit 29). Although blood for safety will be collected approximately every 6 months, at the discretion of the study physician, additional blood and urine samples may be collected if a safety concern arises.

8.1.2. Early Termination Visit

Patients who are permanently withdrawn from the study drug will be asked to return to the clinic for an early termination visit consisting of week 56 study assessments. Patients who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule and for blood sample collection for measurement of serum drug and target, and ADA: at 4 weeks, 8 weeks, 16 weeks, and 28 weeks after the last dose of study drug. Safety lab exams (ie, hematology, blood chemistry and urinalysis) may also be collected during these visits at the investigator's discretion (Section 7.2.2). A blood sample collection for assessment of ADA will occur at the patient's last visit.

8.1.3. 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, or for any other reason, as warranted.

8.2. Study Procedures

8.2.1. 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: medical, prior medication, and surgical history, urogenital exam and scrotum ultrasound with Doppler (for male patients only), confirmation of FOP diagnosis including documentation of ACVR1 mutation, blood collection for ACVR1 gene

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sequencing, height measurement, HbA1c measurement, and assessment of a patient's ability to undergo imaging and other procedures described in the study protocol.

8.2.2. Imaging Procedures

8.2.2.1. Positron Emission Tomography/Computed Tomography Procedures

Positron emission tomography with ^{18}F-NaF and volumetric CT will be used to measure the change in heterotopic bone formation. The PET/CT scans will be performed at the time points specified in Section 8.1. PET/CT scans will be used to assess changes to the uptake of ^{18}F-NaF in suspected active HO lesions as well as uptake into new lesions over time. A PET/CT scanner will be used to acquire dynamic and/or static emission and CT images from patients with FOP. All patients will undergo whole body static emission ^{18}F-NaF PET scan. An optional dynamic emission ^{18}F-NaF PET scans may be performed in a subset of patients, based on sites' capabilities and patients' consent, over a predefined region of the body using a single-bed position. Static emission PET scans will be performed in the same session after the dynamic scan is completed. Static emission PET scans axial field of view will be specified in the imaging manual. Low-dose CT acquisitions will be performed contemporaneously and will cover similar regions as those of the static emission PET scan. Blood samples will be collected for assessment of ^{18}F-NaF concentration in plasma from the subset of patients who will consent and undergo dynamic emission ^{18}F-NaF PET scans.

Patients will not need to fast, and may take all their usual medications as permitted by the study (see Section 7.6). Patients should be well hydrated to promote rapid excretion of the tracer to decrease radiation dose and to improve image quality. 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.

Detailed descriptions of the PET/CT procedures and the criteria for identifying active HO lesions will be provided in the study imaging manual. Personnel at all sites will undergo training for PET/CT acquisition procedures as described in the study imaging manual. The sponsor or its representative(s) will conduct site visits to monitor and ensure that the study is executed according to the study protocol. The PET/CT scans will be read and analyzed using a blinded central reading center. The investigator will be allowed to independently read and analyze baseline PET/CT images while blinded to subsequent study treatment. In order to avoid potential unblinding, the investigator will not be allowed to read or analyze PET/CT images acquired from a patient randomized into the study after study drug dosing has been initiated.

In the event that a pathological finding that potentially requires medical attention (eg, suspected malignancy) is identified, the sponsor and the investigator will be informed of the finding. The imaging data may be provided to the investigator upon discussion with the sponsor. The investigator will communicate any findings to the patient.

In light of the public health emergency related to the COVID-19 pandemic, Investigators may perform study visit 18 (week 56) and/or visit 23 (week 76) imaging exams employing only whole-body low-dose CT scans. Assessment of imaging endpoints without the PET scan may be implemented to mitigate the delay to acquire images due to the inaccessibility to PET/CT imaging centers and/or unavailability of the ^{18}F-NaF tracer. In addition, the window for the week 56 imaging assessments can be flexible (eg, as soon as feasible or later when possible) to respond to COVID-19 related travel restrictions. This low-dose CT scan may be performed by trained staff

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either at study site, at other clinical sites with access to a qualified CT scanner, or using a mobile qualified CT scanner at a local community healthcare setting close to patient or at a home visit, contingent upon prior concurrence and approval from the Investigator and Regeneron medical director.

8.2.3. Clinical Endpoint Measures

With the exception of the Daily Pain NRS and FOP disease activity e-diary, if a study questionnaire is not available in a patient's native language at the time of enrollment that questionnaire will not be part of the required study procedures for that patient.

8.2.3.1. Numeric Rating Scale Pain Evaluation

The NRS is a categorical rating scale used by patients to rate their pain associated with FOP. Patients will be asked to rate their pain on a scale that ranges from "0" (no pain) to "10" (worst possible pain). The NRS measurements will be performed at the screening and baseline visits, and daily throughout the study and the results recorded in the e-diary device. Patients and their caregiver (if applicable) will be trained on its use at the screening/baseline visit (Section 8.1) and are instructed to record their current, least, and worst pain scores in the e-diary each day throughout the study. The average of the 3 ratings will be used to represent the patient's level of pain over the previous 24 hours (McCaffery 1989). Completion of the Daily Pain NRS will be reviewed at the visits listed in Section 8.1. The baseline entry for the daily pain NRS diary is day-1.

8.2.3.2. FOP Disease Activity Assessment

Assessment of FOP disease activity, 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 symptom; 1: mild; 2: moderate; 3: severe).

Patients and their caregiver (if applicable) will be trained on its use at the screening/baseline visit (Section 8.1) and are instructed to record their scores in the e-diary each day throughout the study. The FOP disease activity diary will be reviewed at the visits listed in Section 8.1. The baseline entry for the daily FOP disease activity diary is day -1.

8.2.3.3. FOP Independent Activities of Daily Living

Patient reported ability to independently perform activities of daily living (I-ADL) will be assessed via a questionnaire, FOP I-ADL. Questions in the FOP I-ADL are selected from the PROMIS bank of questions. For questions 1 to 24, each activity is rated from (1) "unable to do" to (5) "without any difficulty", and for questions 25 to 28, each activity is rated from (1) "cannot do" to (5) "not at all". The FOP I-ADL will be reviewed at baseline and at the visits listed in Section 8.1. For languages where the FOP I-ADL questionnaire is not currently available in a validated form, patients will not complete this assessment during the course of the study.

8.2.3.4. EQ-5D-3L Questionnaire

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 health related quality of life, 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, participants are asked to rate "your own health state today" from 100 (best imaginable health state) to 0 (worst imaginable health state). Patients will complete the questionnaire at time points according to Section 8.1. For languages where the EQ-5D-3L questionnaire is not currently available in a validated form, patients will not complete this assessment during the course of the study.

8.2.3.5. Cumulative Analog Joint Involvement Scale

Physician assessment of joint involvement will be conducted using the CAJIS at the visits listed in Section 8.1. The CAJIS is an assessment of 15 major joints; each major joint rated normal unaffected (0), affected (1), or completely functionally ankylosed (2) (Kaplan 2017). The total score ranges from 0 to 30. Physicians at all sites will undergo training for CAJIS assessment.

8.2.3.6. Pulmonary Function by Spirometry

Forced vital capacity [FVC] and FEV1 [forced expiratory volume in 1 second] and the ratio of FEV1/FVC will be determined by spirometry in patients who are able to undergo this procedure at baseline, week 28, week 56, and week 76.

8.2.4. Safety Procedures

8.2.4.1. Vital Signs

Vital signs, including body temperature, blood pressure, heart rate, pulse, and respiration, will be collected at the visits specified in Section 8.1, and at the early termination visit, if applicable. Blood pressure will be measured from a consistent resting position.

8.2.4.2. Physical Examination

A thorough and complete physical examination will be performed at the visits specified in Section 8.1, and at the early termination visit, if applicable. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history. Targeted physical examinations may be performed, if appropriate, depending upon AEs and/or laboratory or ECG abnormalities.

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

8.2.4.3. Menstrual History

Assessment of menstrual cycle history for WoCBP will be conducted at baseline and at the visits specified in Section 8.1 to identify any changes in occurrence, frequency, duration following study drug treatment.

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8.2.4.4. Electrocardiogram

Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at the visits specified in Section 8.1 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).

8.2.4.5. Laboratory Testing

Blood draws for laboratory testing at the screening visit will be collected in a fasted state (after an 8-hour fast). No other blood draw will require fasting. Hematology, chemistry, and urinalysis testing samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are located in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to Section 8.1. Tests will include:

Blood Chemistry

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

Hematology and Coagulation

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils
Activated partial thromboplastin time	Prothrombin time
Thrombin Time	International Normalized Ratio (INR)
Platelet effector function	Fibrinogen

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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

Blood samples will be collected during screening to measure HbA1c and for DNA isolation for ACVR1 gene sequencing (the DNA samples will be stored until sequencing is performed).

Blood samples will be collected at the visits specified in Section 8.1 to measure adrenocorticotropic hormone (ACTH), growth hormone (GH), testosterone (total and free; male patients only), LH, FSH, estradiol, thyroid stimulating hormone (TSH) and free thyroxine (T4), amylase, and lipase.

Blood or urine samples will be collected from female patients at the visits specified in Table 1 for a pregnancy test before study drug administration.

A urinalysis and culture will be collected/performed if there is an AESI (only applicable to male patients).

Blood samples will be collected at baseline and various timepoints (Table 1 and Table 2) for measurement of coagulation parameters (including, but not limited to activated partial thromboplastin time, prothrombin time, INR, thrombin time), fibrinogen, and platelet effector function. For all patients who are currently enrolled in the study, blood samples will be collected prior to next administration of study drug for measurement of coagulation parameters (activated partial thromboplastin time, prothrombin time, INR, thrombin time), fibrinogen, and platelet effector function, unless these tests have been performed in the past year. These assessments will be conducted locally. 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 effector function as close as possible to the time of this AESI.

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 monitor 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 9.4.5.

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8.2.5. Pharmacokinetic and Anti-Drug Antibody Procedures

8.2.5.1. Drug Concentration and Total Activin A Concentration Measurements and Samples

Serum samples for measurement of drug concentration and total activin A concentration will be collected at visits listed in Section 8.1. Samples will be collected before dosing on days when study drug is administered.

Any unused serum samples collected for drug concentration measurements may be used for exploratory biomarker research (Section 8.2.6) or future biomedical research (see Section 8.2.7).

8.2.5.2. Anti-Drug Antibody Measurements and Samples

Serum samples for ADA assessment will be collected at visits listed in Section 8.1. Samples will be collected before dosing on days when study drug is administered. Any unused serum samples collected for ADA assessments may be used for exploratory biomarker research (Section 8.2.6) or future biomedical research (see Section 8.2.7).

8.2.6. Biomarker Procedures

Blood samples for analysis of biomarkers and whole blood for RNA analysis will be collected at visits according to Section 8.1. The biomarkers studied will be ones considered to be relevant to the pathophysiology of FOP, target engagement, safety and the mechanism of action of anti-activin A treatment.

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. Biomarkers studied may include but need not be limited to biochemical bone and cartilage formation markers (BSAP, osteocalcin, P1NP), Total Procollagen Type 1 C-Terminal Propeptide, matrix metalloproteinase 13, and type IIA procollagen amino terminal propeptide or inflammation markers (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.

Markers related to the Activin A and the Activin receptor pathway including but not limited to Activin and BMP ligands may be explored to understand the impact to other ligands that signal through mutant ACVR1 and that may be impacted by REGN2477.

RNA may be isolated from whole blood to evaluate the gene expression relating to the activin A pathway, FOP disease, other bone diseased related to HO, and anti-activin A treatment using methods that may include transcriptome sequencing.

The RNA samples will be double-coded as defined by the International Council for Harmonisation (ICH) guideline E15.

Samples (biomarker or RNA) 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.

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8.2.7. Future Biomedical Research

Additional serum and plasma will be banked for future biomedical research to further explore hormonal levels, biomarkers associated with FOP, bone and cartilage formation, and inflammation as specified in Section 8.2.6, and with anti-activin A inhibition by REGN2477 (Section 8.1), and in the event that additional biomarkers are discovered in the field of FOP research. These biomarkers may be evaluated following completion of the study and will not be reported in the clinical study report.

The 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. The samples may be utilized for future biomedical research of FOP, and bone diseases related to HO. No additional samples will be collected for future biomedical research. After 15 years, any residual samples will be destroyed.

8.2.7.1. Optional Genomic Study: DNA Analysis

Patients who agree to participate in the optional genomics sub-study will be required to sign a separate informed consent form (ICF) before collection of the sample. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study. Blood samples for DNA extraction should be collected on day 1/baseline (pre-dose), but may be collected at any study visit after screening.

The DNA sample for the sub-study will be double-coded as defined by the ICH guideline E15. Sub-study samples will be stored for up to 15 years after the final date of the database lock and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker responses, other clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of FOP as well as other 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 REGN2477 or FOP, and other HO and bone 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, 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. The results of these analyses will be reported separately from the clinical study results.

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, regardless of assessed causality.

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9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, IRBs/EC as appropriate, and to the investigators.

Any AE not listed as an expected event in the IB or in this protocol will be considered unexpected. Any worsening of or new onset of symptoms related to FOP that occur during the screening/washout period prior to study drug administration will be considered expected.

In addition, the sponsor will report in an expedited manner all SAEs that are expected and at least reasonably related to the study drug to the health authorities, according to local regulations.

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

9.3. Definitions

9.3.1. 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.

An AE also includes any 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.

9.3.2. 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**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than 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**

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- 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).

Note: In addition to the criteria above, a new diagnosis or progression of a malignancy in patients enrolled in the study will also be considered a SAE.

Criteria for reporting SAEs must be followed for these events. See Section 9.4 for more information on recording and reporting SAEs.

9.3.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 9.4.3)

9.3.4. Infusion Reactions

Infusion reactions are defined as any 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 9.3) and graded using the grading scales as instructed in Section 9.5.1.

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study. Refer to the study reference manual for the procedures to be followed.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manual for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study or within 113 days of last study drug administration if the patient was terminated early from the study: the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit: only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

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

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.

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. The investigator will be provided a pregnancy tracking form and follow the pregnancy until delivery. If the pregnancy continues to term (delivery), the health of the infant will be followed-up for a period of 3-months postnatally.

Adverse Events of Special Interest: All AESI, serious and non-serious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 9.4.2.

AESI for this program at current time are:

- Epididymitis
- Orchitis (inflammation of the testicles)
- Hydrocele (fluid buildup around 1 or both testicles)
- Scrotum pain
- Scrotum swelling
- Moderate to severe episodes of non-traumatic bleeding
- Moderate epistaxis (defined as any episode lasting longer than 30 minutes or requiring professional medical intervention)
    - Severe epistaxis (based on definition of a severe AE as described in Section 9.5.1)

Refer to the study manual for the procedures to be followed.

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the study reference manual for the procedures to be followed.

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

9.4.6. Follow-up

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

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

- **Mild:** Does not interfere in a significant manner with the patient's 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.

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

The relationship of AEs to study drug will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

A list of factors to consider when assessing the relationship of AEs to study drug is provided in Appendix 1.

The investigator should justify the causality assessment of each SAE.

Relationship of Adverse Events to Study Conduct:

The relationship of AEs to study conduct will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by study conduct?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by study conduct

Related: There is a reasonable possibility that the event may have been caused by study conduct

A list of factors to consider when assessing the relationship of AEs to study conduct is provided in Appendix 1.

The investigator should justify the causality assessment of each SAE.

Relationship of Adverse Events to Injection Procedure:

The relationship of AEs to injection procedure will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the injection procedure?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the injection procedure

Related: There is a reasonable possibility that the event may have been caused by the injection procedure

A list of factors to consider in assessing the relationship of AEs to injection procedure is provided in Appendix 1.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

9.6. Safety Monitoring

The investigator will monitor the safety of study patients 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 monitor will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Global Patient Safety; 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.

9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the IB or this protocol, and has a reasonable suspected causal relationship to the medicinal/study drug).

10. STATISTICAL PLAN

This Section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP for Period 1 (double-blind treatment period; week 28) was issued before the database was locked (19 Nov 2019 for clinical results and 13 Dec 2019 for imaging results). No changes have been made to the SAP with regard to the specified Period 1 analyses as those analyses have already been conducted.

Prior to the DBL for Period 2 (open-label treatment period; week 56), an SAP amendment will be issued to present the definition of the separate study hypothesis for the open-label treatment period (week 28 to week 56; Period 2) and the new analyses to test efficacy of REGN2477 in preventing the formation of new HO lesions.

Analysis variables are listed in Section 4.

10.1. Statistical Hypotheses

10.1.1. Statistical Hypothesis (Period 1 [Week 28])

The primary efficacy endpoints of the study are

- Time-weighted average (standardized area under the curve [AUC]) of the percent change from baseline in total lesion activity by ^{18}F-NaF PET over 28 weeks in AHO
- Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 in AHO
- Time-weighted average (standardized area under the curve [AUC]) of the percent change from baseline in total lesion activity by ^{18}F-NaF PET over 28 weeks in AHOC
- Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 in AHOC

The key secondary efficacy endpoints are

- Time-weighted average (standardized AUC) of the change from baseline in daily pain due to FOP, as measured using the daily NRS over 28 weeks in AHO
- Time-weighted average (standardized AUC) of the change from baseline in daily pain due to FOP, as measured using the daily NRS over 28 weeks in AHOC

The following null and alternative hypotheses will be tested for efficacy endpoints respectively:

H0: No treatment difference between REGN 2477 and placebo

H1: There is a treatment difference between REGN 2477 and placebo

Testing of the primary and key secondary efficacy endpoints will follow a hierarchical testing procedure to address multiplicity at an overall 2-sided alpha=0.05 significance level. Testing of the key secondary efficacy endpoints will follow a hierarchical testing sequence only if statistical significance is established for all primary endpoints. The order of testing sequence for primary and key secondary efficacy endpoints is detailed in Section 10.4.3.1.4. No further adjustments will be made for other secondary and exploratory endpoints, for which nominal p-values will be provided for descriptive purpose only.

10.1.2. Statistical Hypothesis (Period 2 [Week 56])

For the efficacy analyses in Period 2 (week 56), the key statistical comparisons will be based on within group (placebo/REGN2477) comparisons for the patients who were randomized to placebo in the double-blind period and switch to REGN 2477 in the open-label period (Period 2).

For the Period 2 (week 56) analyses, the following primary and key secondary null hypotheses will be tested:

- $H_{1,1}$: There is no difference in number of new (relative to week 28 scan) HO lesions as assessed by CT per patient at week 56 compared to the number of new (relative to baseline scan) HO lesions as assessed by CT per patient at week 28 in placebo/REGN2477 group in AHO (primary)
- $H_{2,1}$: There is no difference in total volume of new (relative to week 28 scan) HO lesions per patient as assessed by CT at week 56 compared to the total volume of new (relative to baseline scan) HO lesions per patient as assessed by CT at week 28 in placebo/REGN2477 group in AHO (key secondary)
- $H_{2,2}$: There is no difference in number of new (relative to week 28 scan) HO lesions per patient as assessed by ^{18}F-NaF PET at week 56 compared to the number of new (relative to baseline scan) HO lesions per patient by ^{18}F-NaF PET at week 28 in placebo/REGN2477 group in AHO (key secondary)
- $H_{2,3}$: There is no difference in total lesion activity per patient by ^{18}F-NaF PET in new (relative to week 28 scan) lesions at week 56 compared to the total lesion activity per patient by ^{18}F-NaF PET in new (relative to baseline scan) lesions at week 28 in placebo/REGN2477 group in AHO (key secondary)
- $H_{2,4}$: There is no difference in percent of patients with new HO lesions as assessed by CT at week 56 relative to week 28 scan in placebo/REGN2477 group in AHO (key secondary)
- $H_{2,5}$: There is no difference in percent of patients with new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to week 28 scan in placebo/REGN2477 group in AHO (key secondary)

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To control the type-I error rate at 0.10 for the primary and key secondary null hypotheses in Period 2, a hierarchical testing procedure will be applied at a 2-sided 10% significant level as detailed in Section 10.4.3.2.4. No further adjustments will be made for other secondary and exploratory endpoints in Period 2, for which estimates, 95% CI, and/or nominal p-values will be provided for descriptive purpose.

10.2. Justification of Sample Size

Randomization will be stratified by the presence/absence of active HO lesions at baseline, to allow analyses of efficacy endpoint measures defined solely for patients with active HO at baseline (Section 10.3.1). Patients without active HO lesions at baseline will contribute to the assessment of safety and other endpoint measures (Section 10.3.4, Section 10.3.3). Randomization will also be stratified by gender and classic ACVR1[R206H] mutation/different ACVR1 mutations.

The sample size estimation for at least 24 patients (12 patients per treatment group) with active HO at baseline and classic ACVR1[R206H] mutation is based on statistical considerations for the following efficacy endpoints: percent change from baseline in (1) total lesion activity by ^{18}F-NaF PET over 28 weeks, (2) total volume of HO lesion by CT at week 28, and (3) ^{18}F-NaF SUV_{max} at week 8. Accounting for a 20% dropout rate at week 28, the sample size would yield approximately 10 patients per treatment group for week-28 analyses. This sample size will provide 80% power at a 2-sided 0.05 significance level in allowing the detection of an observed treatment difference in the order of 57%, 65%, and 40% reduction in the total lesion activity by ^{18}F-NaF PET, the total volume of HO lesion by CT, and the ^{18}F-NaF SUV_{max}, respectively, if the measure variability in FOP patients is similar to that observed in other bone diseases and the FOP mouse model (Table 4). Recent in vitro studies demonstrated that different mutations in the ACVR1 receptor transduced BMP signaling when stimulated with activin A (Hino 2015). These results suggest that REGN2477 may provide beneficial clinical impact on HO in patients with FOP, irrespective of the underlying ACVR1 mutation.

No prior published data on treatment effects in patients with FOP using these endpoints are available; however, numerous case reports show positive ^{99m}Tc methylene diphosphonate (MDP) bone scan, as well as an abnormally high ^{18}F-NaF PET signal in a small cohort of patients with FOP at the site of flare-up and "asymptomatic" locations.

There is no precedent in patients with FOP to allow estimation of variance or clinically meaningful effect sizes for these endpoints. Based on studies in other bone diseases in human and in the FOP mice, changes are estimated at a magnitude of 73% for the total lesion activity by ^{18}F-NaF PET, 65% for the total volume of HO lesion by CT, and 50% for ^{18}F-NaF SUV_{max} PET.

There are ^{18}F-NaF PET (SUV_{max}) data available from a bisphosphonate treatment study of 14 patients with Paget's disease (Installe 2005). In this study, ^{18}F-NaF PET/CT was used to monitor treatment effects on bone. The SUV_{max} and bone influx constants (Ki) were found to be significantly higher in Pagetic bone than normal bone (mean±SD are 35.07±23.86 vs. 7.15±4.76 and 0.114±0.115 vs. 0.014±0.008 mL/min/mL, respectively, where $p<0.05$ for both measures). Following treatment with bisphosphonates, a significant reduction of PET signal in Pagetic bone was observed compared to baseline (-27.84±24.59% at 1 month and -44.64±23.61% at 6 months, $P<0.05$ at both time points (Installe 2005). These data yielded a log-scale SD~0.36 for 1-month change. Assuming a 50% reduction by REGN2477 versus placebo in total lesion activity by ^{18}F-NaF SUV_{max} PET and a log-scale SD~0.36, the sample size required for week-28 analysis

assuming the effect size of 1.9 is 6 patients with active lesion per arm for 80% power at a 2-sided 0.05 significance level.

Prior data for total lesion activity by ^{18}F-NaF PET and total volume of HO lesion by CT in FOP are available only in mice.

REGN2477 treatment yielded an effect size of 2.2 and a log-scale SD of approximately 0.60 in reducing induced HO total lesion activity in mice as measured by ^{18}F-NaF PET AUC. Assuming an effect size of 2.2, the sample size required for week-28 analysis is 5 patients with active lesion per arm for 80% power at a 2-sided 0.05 significance level.

Effect sizes for total volume of HO by CT ranged 0.9 to 1.4 with a log-scale SD of 0.75 to 1.0. Assuming larger effect size of 1.4 and smaller log-scale SD of 0.75, the required sample size for week-28 analysis is 10 patients with active lesion per arm for 80% power at a 2-sided 0.05 significance level.

Considering that FOP is a rare disease and the robust preclinical efficacy of REGN2477, in the interest of maintaining smallest reasonable sample size, larger target effect sizes are used to compute power for potential sample size for this study. The calculations, which were carried out on log-scale (ie, ln[post/pre]) and back-transformed to express differences in percent change scale, are summarized in Table 4.

Table 4: Sample Size (Total Lesion Activity by ^{18}F-NaF PET, Total Volume of HO Lesions by CT, and SUV_{max}) at Week 28 for Comparisons between REGN2477 and Placebo Treatment Groups

Endpoint	Sample Size[a]	TRUE Underlying Difference	Log-Scale SD	TRUE Effect Size
Time-weighted average (standardized AUC) percent change in total lesion activity by ^{18}F-NaF PET over 28 weeks	5	73% reduction	0.60	2.2
	10	57% reduction	0.60	1.4
Percent change in total volume of HO lesions by CT at week 28	10	65% reduction	0.75	1.4
	12	60% reduction	0.75	1.2
Percent change in ^{18}F-NaF SUV_{max} at week 8	6	50% reduction	0.36	1.9
	10	40% reduction	0.36	1.4

[a] N / treatment group for 80% power to yield statistically significant difference (alpha=0.05, 2-sided)

10.3. Analysis Sets

10.3.1. Baseline-Active HO Analysis Set

The baseline active HO analysis set (AHO) includes all randomized patients who had active HO lesion at baseline; it is based on the treatment allocated (as randomized). For analyses of change

from week 28, baseline will be defined as week 28. The endpoints that will be analyzed using the AHO set are listed in Section 4.2.

10.3.2. Baseline-Active HO Classic ACVR1[R206H] Mutation Analysis Set

The baseline active HO classic ACVR1[R206H] mutation analysis set (AHOC) includes all randomized patients with the classic ACVR1[R206H] mutation and who had active HO lesion at baseline; it is based on the treatment allocated (as randomized). For analyses of change from week 28, baseline will be defined as week 28. The endpoints that will be analyzed using the AHOC set are listed in Section 4.2.

10.3.3. Full Analysis Set

The full analysis set (FAS) includes all randomized patients; it is based on the treatment allocated (as randomized). The endpoints that will be analyzed using the FAS set are listed in Section 4.2.

10.3.4. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who 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.

10.3.5. Other Analysis Sets

The pharmacokinetic analysis set included all treated patients who received any REGN2477 or placebo and who had at least 1 non-missing analyte measurement following the first dose of REGN2477 or placebo.

The ADA analysis set included all treated patients who had received any amount of REGN2477 or placebo and had at least 1 non-missing post-dose anti-drug antibody result following the first dose of REGN2477 or placebo.

10.4. Statistical Methods

For continuous variables, descriptive statistics by treatment group will include the following information: the number of patients reflected in the calculation (n), mean or geometric mean, median, SD or log-scale SD, Q1, Q3, minimum, and maximum.

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

10.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria and exclusion regarding the target indication and signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set

- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

10.4.3. Efficacy Analyses

10.4.3.1. Analysis of Efficacy Endpoints in Period 1 (Week 28)

This section was updated (amendment 6) to match the final SAP for Period 1 (double-blind treatment period; week 28) issued before the DBL. In the final SAP, the planned statistical method for the primary endpoint was changed from mixed model repeated measures (MMRM) to analysis of covariance (ANCOVA) to address feedback from a health authority.

The analysis strategy used for the primary and key secondary efficacy endpoints is presented in Table 5.

Table 5: Analysis Strategy for Primary and Key Secondary Efficacy Endpoints

Endpoint (Description, Time Point)	Primary versus Supportive Approach	Statistical Method	Analysis Set
Primary Efficacy Endpoints			
TWA of PCFB in total lesion activity by ^{18}F-NaF PET over 28 weeks	P	ANCOVA	AHO
PCFB in the total volume of HO lesions as measured by CT at week 28	P	MMRM	AHO
TWA of PCFB in total lesion activity by ^{18}F-NaF PET over 28 weeks	P	ANCOVA	AHOC
PCFB in the total volume of HO lesions as measured by CT at week 28	P	MMRM	AHOC
Key Secondary Efficacy Endpoints			
TWA of CFB in daily pain due to FOP, as measured using the daily NRS over 28 weeks	P	ANCOVA	AHO
TWA of CFB in daily pain due to FOP, as measured using the daily NRS over 28 weeks	P	ANCOVA	AHOC

AHOC=active HO with classic ACVR1 mutation; AHO=active HO; ANCOVA=analysis of covariance; CFB=change from baseline; MMRM=mixed model with repeated measures; PCFB=percentage change from baseline; TWA=Time-weighted average (standardized area under the curve [AUC]).
The MMRM model will include treatment, gender, ACVR1 mutation type (AHO analysis set only) as fixed effects, time point, and treatment-by-time point interaction, as well as, the continuous fixed covariates of baseline value. In case of substantial imbalance at baseline in the number of patients in the randomization strata: gender, ACVR1 mutation type, strata factor(s)may be excluded from the model. An unstructured covariance matrix can be used in this model to account for within-patient correlation. Different parameterization of MMRM model will be utilized if at least 1 patient is missing all post-baseline values.
The ANCOVA model contains treatment, gender, ACVR1 mutation type (AHO analysis set only) as factor, and the baseline value as continuous covariate.

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10.4.3.1.1. Primary Endpoints: Total Lesion Activity by ^{18}F-NaF PET

For ^{18}F-NaF uptake at HO site, measured by SUV, the following analysis is planned:

- All active HO lesions per patient will be identified and indexed at baseline. Up to 7 lesions will be identified as target lesions, and their associated ^{18}F-NaF SUV_{mean}, SUV_{max} by PET, and their volume by CT will be derived. These index lesions will be assessed again on the post-dose treatment period visit scans. New lesions that arise during the post-dose treatment period will be assessed similarly.
- Total lesion activity by PET per patient will be derived for each time point as the sum of individual target HO lesion SUV_{mean} x metabolic volume. Percent time weighted average (standardized AUC, ie, AUC divided by 28) of percent change from baseline will be calculated for each patient as the AUC of percent change from baseline in total lesion activity by ^{18}F-NaF PET over 28 weeks divided by 28. The ANCOVA model will be used to analyze time weighted average of percent change over 28 weeks. The model will include treatment, gender, ACVR1 mutation type (classic, nonclassic) and baseline total lesion activity as a covariate. In case of substantial imbalance at baseline in the number of patients in the randomization strata: gender, ACVR1 mutation type, strata factor(s) may be excluded from the model. If both imaging scans at week 8 and 28 are missing, then mean of percent changes of placebo group at week 8 and 28 will be used for imputation. If imaging scan for only week 8 is missing, linear interpolation of percent change between the baseline and week 28 will be used to calculate AUC. If imaging scan for week 28 is missing, percent change at week 8 will be carried forward to week 28 for calculating AUC.

10.4.3.1.2. Primary Endpoints: Total HO Volume by CT

- Total HO volume by CT in each patient will be derived for each time point as the Sum of all individual HO lesion volume
- Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 will be analyzed in AHO or AHOC using MMRM model. The model will include treatment, gender, ACVR1 mutation type as fixed effects, time point, and treatment-by-time point interaction, as well as, the continuous fixed covariates of baseline value. In case of substantial imbalance at baseline in the number of patients in the randomization strata: gender, ACVR1 mutation type, strata factor(s) may be excluded from the model. An unstructured covariance matrix can be used in this model to account for within-patient correlation. Different parameterization of MMRM model will be utilized if at least 1 patient is missing all post-baseline values.

10.4.3.1.3. Key Secondary Endpoints: Pain NRS-AUC

Analysis of Time-weighted average (standardized AUC) of the change from baseline in daily pain due to FOP by the daily NRS over 28 weeks will be performed in AHO or AHOC using the ANCOVA with treatment, gender, ACVR1 mutation type (analysis set only) as fixed factors, and the baseline value as continuous covariate.

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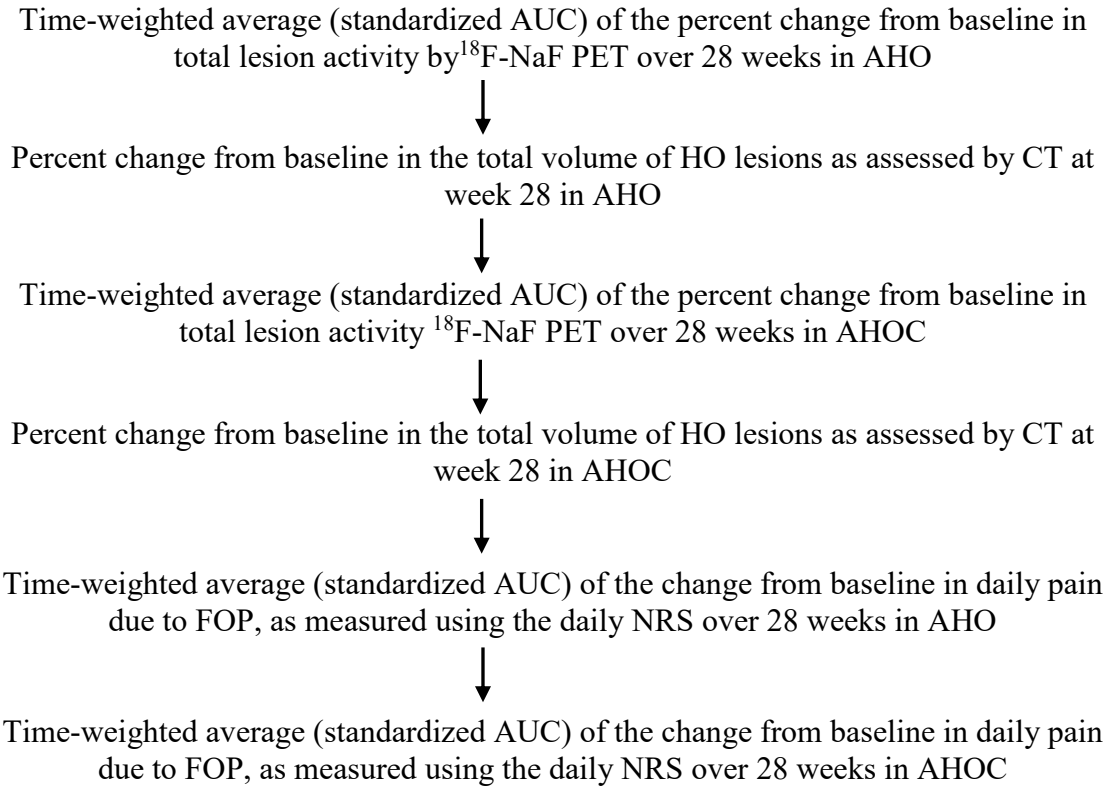
10.4.3.1.4. Multiplicity Considerations for Efficacy Analyses for Period 1 (Week 28)

In order to handle multiple testing of the 4 primary and 2 key secondary efficacy endpoints, a hierarchical testing procedure will be applied at a 2-sided 5% significance level. Key secondary efficacy endpoints will be tested in a (hierarchical order after all primary efficacy endpoints achieve statistical significance at an overall 2-sided alpha=0.05 significance level. The testing sequence is as follows:



No further multiplicity adjustments will be made for testing other secondary efficacy and exploratory week-28 endpoints where nominal p-values will be provided for descriptive purpose.

Sensitivity analyses will be performed for the primary and key secondary efficacy endpoints when misclassification of ACVR1 mutation type occurs.

10.4.3.2. Analysis of Efficacy Endpoints in Period 2 (Week 56)

In the placebo/REGN2477 group (placebo patients who switch to REGN2477 after the double-blind period), efficacy analyses will focus on the within group statistical comparisons of Period 1 versus Period 2.

The COVID-19 pandemic has affected the conduct of the study mainly by causing delay in dose administration, delay in the collection of the PET/CT scans due to site closure, and unavailability of ^{18}F-NaF due to interruption of tracer production. Some patients may not be able to complete their week 56 scans within the protocol-specified visit window and may only be able complete their scans using CT-only modality.

The week 56 efficacy analyses of imaging endpoints will be conducted using COVID-19 modified Intent-To-Treat (COVID-19 mITT) principle which will analyze only those patients for whom:

- at least 1 post-week 28 scan is collected and,
- the time period between any 2 consecutive doses is less than 9 weeks (63 days) in Period 2 and,
- no more than 1 dose was missed in Period 2

This will ensure that primary analyses for imaging endpoints will include patients with continuous saturating levels of REGN2477. For patients whose week 56 scans are delayed, the first delayed scan available after the week 28 scan will be used to impute the week 56 data in the primary analyses. In the absence of a PET/CT scan, data from available CT-only scans will be used to analyze the primary endpoint and other secondary imaging endpoints, if applicable. This imputation ensures that the estimation of the treatment effect will not be biased by the COVID-19 pandemic.

In the REGN2477/REGN2477 group (patients who continue receiving REGN2477 beyond week 28), the estimates of treatment effects at week 56 will be provided with 95% confidence interval on the endpoints related to new HO lesions (new relative to baseline scan).

Estimates of the treatment effects with 95% confidence interval on the endpoints related to new HO lesions from Period 1 (new relative to baseline scan) in the REGN2477/REGN2477 group patients will be descriptively compared with the estimates from Period 2 (new relative to week 28) in the placebo/REGN2477 group.

The missing data handling rules used for the Period 2 (open-label treatment period) analyses will be specified in the final SAP (week 56).

10.4.3.2.1. Primary Efficacy Endpoints in Period 2 (Week 56)

Number of new HO lesions as assessed by CT at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) in AHO

The number of new HO lesions as assessed by CT at week 56 relative to week 28 scan will be summarized for the placebo/REGN2477 group. Wilcoxon signed rank test will be used for the within group comparison in the placebo/REGN2477 group to compare the number of new HO lesions by CT at week 56 relative to week 28 scan with the number of new HO lesions by CT at week 28 relative to baseline scan.

The number of new HO lesions as assessed by CT at week 56 relative to week 28 scan in the placebo/REGN2477 group will also be descriptively compared with the number of new HO lesions as assessed by CT at week 28 relative to baseline scan in the REGN2477/REGN2477 group.

10.4.3.2.2. Key Secondary Efficacy Endpoints in Period 2 (Week 56)

Total volume of new HO lesions as assessed by CT at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) in AHO

The total volume associated with new HO lesions as assessed by CT at week 56 relative to week 28 scan will be summarized for the placebo/REGN2477 group. Wilcoxon signed rank test will be used for the within group comparison in the placebo/REGN2477 group to compare the total

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volume at week 56 associated with new HO lesions relative to week 28 scan with the total volume associated with new CT lesions at week 28 relative to baseline scan.

The total volume associated with new HO lesions by CT at week 56 relative to week 28 scan in the placebo/REGN2477 group will be descriptively compared with the total volume associated with new HO lesions by CT at week 28 relative to baseline scan in the REGN2477/REGN2477 group.

Number of new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) in AHO

The number of new HO lesions at week 56 relative to week 28 scan will be summarized for the placebo/REGN2477 group. Wilcoxon signed rank test will be used for the within group comparison in the placebo/REGN2477 group to compare the number of new HO lesions as assessed by PET at week 56 relative to week 28 scan with the number of new HO lesions at week 28 relative to baseline scan.

The number of new HO lesions by PET at week 56 relative to week 28 scan in placebo/REGN2477 group will also be descriptively compared with the number of new HO lesions by PET at week 28 relative to baseline scan in the REGN2477/REGN2477 group

Total lesion activity by ^{18}F-NaF PET in new HO lesions at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) in AHO

The total lesion activity associated with new HO lesions by PET at week 56 relative to week 28 scan will be summarized for the placebo/REGN2477 group. Wilcoxon signed rank test will be used for the within group comparison in the placebo/REGN2477 group to compare the total lesion activity associated with new HO lesions by PET at week 56 relative to week 28 scan with the total lesion activity associated with new HO lesions by PET at week 28 relative to baseline scan.

The total lesion activity associated with new HO lesions by PET at week 56 relative to week 28 scan in the placebo/REGN2477 group will be descriptively compared with the total lesion activity associated with new HO lesions by PET at week 28 relative to baseline scan in the REGN2477/REGN2477 group.

Percent of patients with new HO lesions as assessed by CT at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)

Number and percent of patients with new HO lesions by CT at week 56 relative to week 28 will be provided for the placebo/REGN2477 group. The within group comparison to compare the percent of patients with new HO lesions by CT at week 56 relative to week 28 scan with the percent of patients with new HO lesions by CT at week 28 relative to baseline scan will be performed using McNemar's test in placebo/REGN2477 group.

The percent of patients with new HO lesions by CT at week 56 relative to week 28 scan in the placebo/REGN2477 group will be descriptively compared with the percent of patients with new HO lesions by CT at week 28 relative to baseline scan in the REGN2477/REGN2477 group.

Percent of patients with new HO lesions as assessed by ^{18}F-NaF PET at week 56 relative to week 28 scan (in patients switching from placebo to REGN2477 after the double-blind period) (AHO)

Number and percent of patients with new HO lesions by PET at week 56 relative to week 28 scan will be provided for the placebo/REGN2477 group. The within group comparison to compare the percent of patients with new HO lesions by PET at week 56 relative to week 28 scan with the percent of patients with new HO lesions by PET at week 28 relative to baseline scan will be performed using McNemar's test in placebo/REGN2477 group.

The percent of patients with new HO lesions by PET at week 56 relative to week 28 scan in the placebo/REGN2477 group will be descriptively compared with the percent of patients with new HO lesions by PET at week 28 relative to baseline scan in the REGN2477/REGN2477 group.

10.4.3.2.3. Other Secondary Efficacy Endpoints in Period 2 (Week 56)

Percent of patients with new investigator-assessed flare-ups in Period 2 (in patients switching from placebo to REGN2477 after the double-blind period)

Number and percent of patients with new investigator-assessed flare-ups in the open-label period (Period 2; week 56) will be provided for the placebo/REGN2477 group. The within group comparison to compare the percent of patients with investigator-assessed flare-ups during the double-blind period (Period 1) with the percent of patients with new investigator-assessed flare-ups in the open-label period (Period 2; week 56) will be performed using McNemar's test in placebo/REGN2477 group.

The percent of patients with new investigator-assessed flare-ups in Period 2 (week 56) of the placebo/REGN2477 group will be descriptively compared with the percent of patients with new investigator-assessed flare-ups in Period 1 of the REGN2477/REGN2477 group.

Percent of patients with new flare-ups (using patient diary) in Period 2 (in patients switching from placebo to REGN2477 after the double-blind period)

Number and percent of patients with new flare-ups (using patient e-diary) in the open-label period (period 2; week 56) will be provided for the placebo/REGN2477 group. The within group comparison to compare the percent of patients with flare-ups (using patient e-diary) during the double-blind period with the percent of patients with new flare-ups (using patient e-diary) in the open-label period (period 2; week 56) will be performed using McNemar's test in placebo/REGN2477 group.

The percent of patients with new flare-ups (by patient e-diary) in Period 2 (week 56) of the placebo/REGN2477 group will be descriptively compared with the percent of patients with new flare-ups (by patient e-diary) in Period 1 of the REGN2477/REGN2477 group.

10.4.3.2.4. Multiplicity Considerations for Period 2 (Week 56)

The type-I error rate will be controlled at 0.10 for the primary and key secondary null hypotheses in Period 2 (week 56) (described in Section 3.3.4).

To control the type-I error rate for the primary and key secondary endpoints in Period 2 (week 56), a hierarchical testing procedure will be applied at a 2-sided 10% significant level to test the above hypotheses in the specified order. The key secondary efficacy endpoints will be tested only if statistical significance is established for the primary endpoint.

No further adjustments will be made for other secondary and exploratory endpoints in Period 2 (week 56), for which estimates, 95% CI, and/or nominal p-values will be provided for descriptive purpose.

10.4.4. Safety Analysis

10.4.4.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to the time before the first dose of study drug.
- Double blind period is defined as day 1 from start of administration of the first dose of study drug through week 28 of the double-blind period
- Open label and follow-up period is defined as from date of first dose of open label to date of last visit of the follow-up period.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

10.4.4.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a potentially clinically significant value at any post-randomization time point will be summarized for each clinical laboratory test.

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

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

10.4.4.3. Treatment Exposure

The treatment duration during the study will be presented by treatment and calculated as: (date of last study drug administration – date of first study drug administration) + 28. The observation period will be presented by treatment group and calculated as: (date of the last study visit – date of first study drug administration) +1. The number (%) of patients randomized and exposed to double-blind study drug will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP. In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, means, SD, minimums, medians, and maximums. A summary of the number of doses by treatment group will be provided.

10.4.4.4. Treatment Compliance

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

Treatment compliance = (Number of injections of study drug during exposure period)/(Number of planned injections 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.

10.4.5. Analysis of Drug Concentration and Total Activin A Concentration Data

Drug and total target concentrations at each sampling time will be summarized using descriptive statistics. Summary of drug and total target concentrations will be presented by nominal time point (ie, the time points specified in the protocol). Individual data will be presented by actual time. Plots of the concentrations of functional REGN2477 and total activin A will be presented over time (linear and log scales). When the scale is linear, concentrations below the lower limit of quantification (LLOQ) will be set to zero. In the log-scaled figures, concentrations below the LLOQ will be imputed as LLOQ/2.

10.4.6. Analysis of Anti-Drug Antibody Data

Listings of ADA positivity and titers presented by patient, time point, and treatment group will be provided. Prevalence of treatment-emergent and treatment-boosted ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by treatment group.

The impact of treatment-emergent and treatment-boosted ADAs on drug and total activin A concentration-time profiles will be evaluated. The impact of treatment-emergent and treatment-boosted ADA on efficacy and safety will also be evaluated.

10.4.7. Analysis of Quality of Life Data

Quality of life data will be summarized descriptively by study visit and treatment group. Change from baseline in quality of life data through the end of the study will be similarly summarized.

10.4.8. Analysis of Biomarker Data

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

Biomarker endpoints may be further assessed using an MMRM based on log-transformed data. Results will be back-transformed and expressed as percent change from baseline for each treatment. Time weighted average (standardized AUC) may be compared between treatments if appropriate.

10.5. Primary and Additional Analysis

Primary analysis of safety and efficacy data of the randomized double-blind placebo-controlled period (Period 1) of the study will be performed once all data have been collected and validated through the end of this period (Period 1, week 28; DBL 1). Additional analyses of safety and efficacy data will be performed following the open-label REGN2477 treatment (Period 2, week 56; DBL 2), and at the end of the follow-up treatment period at week 76 (Period 3, week 76; DBL 3). Since the key efficacy measure data collection for Period 1 will have been concluded at the time of the first analysis (Period 1, week 28; DBL 1) and the radiographic data for subsequent periods had not been read nor entered into the database, the final analysis for Period 1 for subsequent periods is not considered an interim analysis and no multiplicity adjustments are needed.

10.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

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

General rules for handling missing safety data:

- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

10.7. 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 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

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

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

The CRF data for this study will be collected with an EDC tool, Medidata RAVE.

11.2. Electronic Systems

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

- IRT system – randomization, study drug supply,
- Medidata RAVE- EDC system, data capture
- Statistical Analysis System – statistical review and analysis
- ARGUS – a pharmacovigilance and clinical safety software system for collection and reporting of safety data Study Monitoring

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12. STUDY MONITORING

12.1. Monitoring of Study Sites

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

12.2. Source Document Requirements

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

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

12.3. 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 patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

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

13. 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

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pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

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

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. 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.

14.2. Informed Consent

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

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

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

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

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

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

14.3. 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 their 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.

14.4. 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 patients, 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.

15. PROTOCOL AMENDMENTS

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

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

16.1. Premature Termination of the Study

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

16.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

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

17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents 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 and the relevant records will be transferred to a mutually agreed-upon destination.

18. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

19. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

20. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

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22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: "A Randomized, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Effects on Heterotopic Bone Formation of REGN2477 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)

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APPENDIX 1. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG AND STUDY CONDUCT

Is there a reasonable possibility that the event may have been caused by the study drug or study conduct?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- do not reappear or worsen when dosing with study drug is resumed
- are not a suspected response to the study drug based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug
- resolve or improve after discontinuation of study drug
- reappear or worsen when dosing with study drug is resumed
- are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

NOTE: This list is not exhaustive.

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study Title: "A Randomized, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Effects on Heterotopic Bone Formation of REGN2477 in Patients with Fibrodysplasia Ossificans Progressiva"

Protocol Number: R2477-FOP-1623

Protocol Version: R2477-FOP-1623 Protocol Amendment 6 Global Admin

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00123469 v1.0

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