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

Published: 04-07-2017
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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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON50623

Source
ToetsingOnline

Brief title
LUMINA-1 (0456/0113)

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
Fibrodysplasia ossificans progressiva (FOP); "fibrous tissue that is being progressively converted into bone tissue"

Research involving
Human

Sponsors and support

Primary sponsor: Regeneron Pharmaceuticals, Inc.
Source(s) of monetary or material Support: The study sponsor as completed in section B7

Intervention

Keyword: Fibrodysplasia ossificans progressiva, Phase 2, Randomized placebo-controlled trial, REGN2477

Outcome measures

Primary outcome

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 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 18F-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 18F-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)

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)

Secondary outcome

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 18F-NaF SUVmax of individual active HO site(s) by PET at week 8 (AHOC)

* Percent change from baseline 18F-NaF SUVmax of individual active HO site(s) by PET at week 8 (AHO)

* Change from baseline in number of HO lesions as assessed by 18F-NaF PET at week 28 (AHOC)

* Change from baseline in number of HO lesions as assessed by 18F-NaF PET at week 28 (AHO)

* Change from baseline in number of HO lesions as assessed by 18F-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

Please refer to the protocol for the secundairy endpoints for period 2 (week

56).

Study description

Background summary

Fibrodysplasia ossificans progressive (FOP) 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 heterotopic ossification (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 18F-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 18F-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 18F-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.

Study objective

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 18F-NaF PET or by CT
- To assess the effect of REGN2477 versus placebo on the change from baseline in 18F-NaF standardized uptake value maximum (SUVmax) 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 18F-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 concentration 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 18F-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 18F-NaF PET/CT. Index HO lesion identified at baseline and new HO lesions will be assessed by imaging endpoint measures including whole body 18F-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 18F-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 18F-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.

Intervention

REGN2477 10 mg/kg, administered IV Q4W or REGN2477-matching placebo,

administered IV Q4W

Study burden and risks

Please refer to appendix C of the subject information sheet for an overview of the side effects and possible risks of the study.

Contacts

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Scientific
Regeneron Pharmaceuticals, Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Men and women 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 heterotopic

ossification).
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 heterotopic ossifications (increase in site or number of HO lesions) with/without being associated with flare-up episodes.
5. Willing and able to undergo PET and CT imaging procedures and other procedures as defined in this study.

Exclusion criteria

1. 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. Use of bisphosphonate within 1 year of screening.
3. 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.
4. Pregnant or breastfeeding women.
5. Male and women of childbearing potential patients who are unwilling to practice highly effective contraception.
6. 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.
7. Patients with a history of severe, non-traumatic bleeding requiring transfusion or hospitalization for hemodynamic compromise
8. Patients with a known pre-existing medical history of a bleeding diathesis (eg, hemophilia A, von Willebrand*s Factor deficiency, platelet count *20x10^9/L).

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-04-2018
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Garetosmab
Generic name:	REGN2477

Ethics review

Approved WMO Date:	04-07-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-05-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-005035-33-NL
CCMO	NL60850.029.17