Clinical trial results:
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

Summary

EudraCT number	2016-005035-33
Trial protocol	GB NL IT ES
Global end of trial date	16 September 2021

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022

Trial information

Trial identification

Sponsor protocol code	R2477-FOP-1623

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03188666
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, NY, United States, 10591
Public contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc, 001 8447346643, clinicaltrials@regeneron.com
Scientific contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc, 001 8447346643, clinicaltrials@regeneron.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary safety objective of the study is to assess the safety and tolerability of REGN2477 in male and female subjects 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 subjects 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).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	44
EEA total number of subjects	30

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	44
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 48 participants were screened, out of which, 44 participants were randomized and treated.

Pre-assignment

Screening details:

This three-period study consisted of a 28 week, randomized, double-blind placebo-controlled treatment period (Period 1) followed by 28 weeks, open-label treatment (Period 2) and 20-weeks follow-up treatment (Period 3). Participants could continue receiving REGN2477 every 4 weeks beyond week 76 provided that no safety signals were identified.

Period 1

Period 1 title	Period 1 (28 weeks double-blind)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received a single dose of placebo matched to REGN2477 intravenous (IV) infusion every 4 weeks (Q4W) for up to 28 weeks during Period 1.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received placebo matched to REGN2477 IV infusion Q4W in period 1

Arm title	REGN2477 10 mg/kg Q4W

Arm description:

Participants received a single dose of REGN2477 10 milligrams per kilogram (mg/kg) IV infusion every 4 weeks (Q4W) for up to 28 weeks during Period 1.

Arm type	Experimental
Investigational medicinal product name	REGN2477
Investigational medicinal product code	
Other name	garetosmab
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received REGN2477 10 mg/kg IV infusion Q4W

Number of subjects in period 1	Placebo	REGN2477 10 mg/kg Q4W
Started	24	20
Completed	24	19
Not completed	0	1
Adverse event, non-fatal	-	1

Period 2

Period 2 title	Period 2 (28 weeks open-label)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/REGN2477 10 mg/kg Q4W

Arm description:

Participants who were in the placebo group in Period 1 crossed over to receive a single dose of REGN2477 IV infusion Q4W for additional 28 weeks during Period 2.

Arm type	Experimental
Investigational medicinal product name	REGN2477
Investigational medicinal product code	
Other name	garetosmab
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received REGN2477 10 mg/kg IV infusion Q4W in Period 2

Arm title	REGN2477/REGN2477 10 mg/kg Q4W

Arm description:

Participants who were in the REGN2477 group in Period 1 continued treatment with a single dose of REGN2477 IV infusion Q4W for additional 28 weeks during Period 2.

Arm type	Experimental
Investigational medicinal product name	REGN2477
Investigational medicinal product code	
Other name	garetosmab
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received REGN2477 10 mg/kg IV infusion Q4W in Period 2

Number of subjects in period 2	Placebo/REGN2477 10 mg/kg Q4W	REGN2477/REGN2477 10 mg/kg Q4W
Started	24	19
Completed	24	18
Not completed	0	1
Adverse event, serious fatal	-	1

Period 3

Period 3 title	Period 3 and beyond to EOS
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/REGN2477 10 mg/kg Q4W

Arm description:

Participants who were in the placebo group in Period 1 crossed over and received Q4W IV infusions of REGN2477 for additional 28 weeks during Period 2 followed by 20 weeks during Period 3. Participants could continue receiving REGN2477 every 4 weeks beyond week 76 provided that no safety signals were identified. *Note: One death was reported for a participant that continued receiving REGN2477 beyond week 76. See Adverse Events section for Total # of Deaths (all causes).

Arm type	Experimental
Investigational medicinal product name	REGN2477
Investigational medicinal product code	
Other name	garetosmab
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received REGN2477 10 mg/kg IV infusion Q4W in Period 3

Arm title	REGN2477/REGN2477 10 mg/kg Q4W

Arm description:

Participants who were in the REGN2477 group in Period 1 continued treatment with a single dose of REGN2477 IV infusion Q4W for additional 28 weeks during Period 2 followed by 20 weeks during Period 3. Participants could continue receiving REGN2477 every 4 weeks beyond week 76 provided that no safety signals were identified.

Arm type	Experimental
Investigational medicinal product name	REGN2477
Investigational medicinal product code	
Other name	garetosmab
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received REGN2477 10 mg/kg IV infusion Q4W in Period 3

Number of subjects in period 3	Placebo/REGN2477 10 mg/kg Q4W	REGN2477/REGN2477 10 mg/kg Q4W
Started	24	18
Completed week 76	21	16
Completed	20	16
Not completed	4	2
Adverse event, serious fatal	1	2
Consent withdrawn by subject	2	-
AE, serious fatal (occurred after week 76)*	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received a single dose of placebo matched to REGN2477 intravenous (IV) infusion every 4 weeks (Q4W) for up to 28 weeks during Period 1.	
Reporting group title	REGN2477 10 mg/kg Q4W
Reporting group description:	
Participants received a single dose of REGN2477 10 milligrams per kilogram (mg/kg) IV infusion every 4 weeks (Q4W) for up to 28 weeks during Period 1.	

Reporting group values	Placebo	REGN2477 10 mg/kg Q4W	Total
Number of subjects	24	20	44
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	24	20	44
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	27.8	27.3	
standard deviation	± 8.54	± 8.67	-
Sex: Female, Male Units: Participants			
Female	14	11	25
Male	10	9	19
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	24	20	44
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	2	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	22	17	39
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Fibrodysplasia Ossificans Progressiva			

(FOP) Genetic Mutation Units: Subjects			
Active HO classic ACVR1 (R206H)	22	20	42
Other	2	0	2
Total Lesion Activity (TLA) at Baseline as Assessed by 18 F-NaF PET (AHO)			
Fluorine-18 sodium fluoride 18^F-NaF PET is used to assess lesion and disease activity. The baseline-Active Heterotopic ossification (AHO) analysis set included all randomized participants who had at least one active HO lesion at baseline; it is based on the treatment allocated (as randomized).			
Units: g.			
arithmetic mean	473.40	418.18	
standard deviation	± 348.373	± 372.801	-
Total Volume of HO Lesions at Baseline as Assessed by Computed Tomography (CT) (AHO)			
The baseline-Active Heterotopic ossification (AHO) analysis set includes all randomized participants who had at least one active HO lesion at baseline; it is based on the treatment allocated (as randomized).			
Units: cubic centimeter (cm^3)			
arithmetic mean	235.78	251.43	
standard deviation	± 253.329	± 327.881	-
Total Lesion Activity at Baseline as Assessed by 18F-NaF PET (AHOC)			
The baseline-active HO classic ACVR1 [R206H] mutation analysis set (AHOC) includes all randomized participants with the classic ACVR1 [R206H] mutation and who had at least one active HO lesion(s) at baseline, as defined by 18F-NaF PET positivity; it is based on the treatment allocated (as randomized).			
Units: g.			
arithmetic mean	464.27	418.18	
standard deviation	± 350.479	± 372.801	-
Total Volume of HO Lesions at Baseline as Assessed by CT (AHOC)			
The baseline-active HO classic ACVR1 [R206H] mutation analysis set (AHOC) includes all randomized participants with the classic ACVR1 [R206H] mutation and who had at least one active HO lesion(s) at baseline, as defined by 18F-NaF PET positivity; it is based on the treatment allocated (as randomized).			
Units: cubic centimeter (cm^3)			
arithmetic mean	239.72	251.43	
standard deviation	± 263.813	± 327.881	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received a single dose of placebo matched to REGN2477 intravenous (IV) infusion every 4 weeks (Q4W) for up to 28 weeks during Period 1.	
Reporting group title	REGN2477 10 mg/kg Q4W
Reporting group description:	
Participants received a single dose of REGN2477 10 milligrams per kilogram (mg/kg) IV infusion every 4 weeks (Q4W) for up to 28 weeks during Period 1.	
Reporting group title	Placebo/REGN2477 10 mg/kg Q4W
Reporting group description:	
Participants who were in the placebo group in Period 1 crossed over to receive a single dose of REGN2477 IV infusion Q4W for additional 28 weeks during Period 2.	
Reporting group title	REGN2477/REGN2477 10 mg/kg Q4W
Reporting group description:	
Participants who were in the REGN2477 group in Period 1 continued treatment with a single dose of REGN2477 IV infusion Q4W for additional 28 weeks during Period 2.	
Reporting group title	Placebo/REGN2477 10 mg/kg Q4W
Reporting group description:	
Participants who were in the placebo group in Period 1 crossed over and received Q4W IV infusions of REGN2477 for additional 28 weeks during Period 2 followed by 20 weeks during Period 3. Participants could continue receiving REGN2477 every 4 weeks beyond week 76 provided that no safety signals were identified. *Note: One death was reported for a participant that continued receiving REGN2477 beyond week 76. See Adverse Events section for Total # of Deaths (all causes).	
Reporting group title	REGN2477/REGN2477 10 mg/kg Q4W
Reporting group description:	
Participants who were in the REGN2477 group in Period 1 continued treatment with a single dose of REGN2477 IV infusion Q4W for additional 28 weeks during Period 2 followed by 20 weeks during Period 3. Participants could continue receiving REGN2477 every 4 weeks beyond week 76 provided that no safety signals were identified.	
Subject analysis set title	Placebo/REGN2477 10 mg/kg Q4W (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set (SAF) included all randomized participants who received any study drug and were analyzed as treated.	
Subject analysis set title	REGN2477/REGN2477 10 mg/kg Q4W (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The SAF included all randomized participants who received any study drug and were analyzed as treated.	
Subject analysis set title	Period 1: Placebo (AHO)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The active heterotopic ossification analysis set (AHO) included all randomized participants who had at least one active HO lesion at baseline; and was based on the treatment allocated (as randomized). Participants received a single dose of placebo matched to REGN2477 IV infusion Q4W for up to 28 weeks during Period 1.	
Subject analysis set title	Period 1: REGN2477 10 mg/kg Q4W (AHO)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The AHO analysis set included all randomized participants who had at least one active HO lesion at baseline; and was based on the treatment allocated (as randomized). Participants received a single dose of REGN2477 10 mg/kg IV infusion Q4W for up to 28 weeks during Period 1.	
Subject analysis set title	Period 1: Placebo (AHOC)

Subject analysis set type	Sub-group analysis

Subject analysis set description:

The active HO classic ACVR1 (R206H) mutation analysis set (AHOC) included all randomized participants with the classic ACVR1 (R206H) mutation and who had at least one AHO at baseline, as defined by 18^F-NaF PET positivity; and was based on the treatment allocated (as randomized). Participants received a single dose of placebo matched to REGN2477 IV infusion Q4W for up to 28 weeks during Period 1.

Subject analysis set title	Period 1: REGN2477 10 mg/kg Q4W (AHOC)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The AHOC analysis set included all randomized participants with the classic ACVR1 (R206H) mutation and who had at least one AHO at baseline, as defined by 18^F-NaF PET positivity; and was based on the treatment allocated (as randomized). Participants received a single dose of REGN2477 10 mg/kg IV infusion Q4W for up to 28 weeks during Period 1.

Subject analysis set title	Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The COVID-19 modified intent-to-treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan. Participants who were in the placebo group in Period 1 crossed over to receive a single dose of REGN2477 IV infusion Q4W for additional 28 weeks (up to Week 56) during Period 2.

Subject analysis set title	Period 2: REGN2477/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The COVID-19 mITT included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan. Participants who were in the REGN2477 group in Period 1 continued treatment with a single dose of REGN2477 IV infusion Q4W for additional 28 weeks (up to Week 56) during Period 2.

Subject analysis set title	REGN2477 10 mg/kg Q4W (PK)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic (PK) analysis set included all treated participants who received any study drug and who had at least 1 non-missing drug concentration following the first dose of study drug. Concentrations were merged from both treatment groups, REGN2477/REGN2477 and placebo/REGN2477, by nominal time after active REGN2477 treatment. The pre-dose for treatment group placebo/REGN2477 was Week 28 before active dosing sample.

Subject analysis set title	Placebo/REGN2477 10 mg/kg Q4W (ADA)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The anti-drug antibody (ADA) analysis set included all treated patients who received any amount of study drug (active or placebo [safety analysis set]) and had at least one non-missing anti-REGN2477 antibody result following the first dose of study drug or placebo. The ADA analysis set was based on the actual treatment received (as treated) rather than as randomized.

Subject analysis set title	REGN2477/REGN2477 10 mg/kg Q4W (ADA)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The ADA analysis set included all treated participants who received any amount of study drug (active or placebo [safety analysis set]) and had at least one non-missing anti-REGN2477 antibody result following the first dose of study drug or placebo. The ADA analysis set was based on the actual treatment received (as treated) rather than as randomized.

Primary: Period 1: Number of Participants with Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Period 1: Number of Participants with Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs[1]

End point description:

Treatment-emergent adverse events are adverse events not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period. A serious TEAE was defined as any untoward medical occurrence that resulted in any of following outcomes not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period: death, life-threatening, required initial/prolonged in-participant hospitalization, persistent/significant disability/incapacity, congenital anomaly/birth defect/considered as medically important event. Number of participants with TEAEs and Serious TEAEs are reported. Safety analysis set (SAF) included all randomized participants who received any study drug and were analyzed as treated.

End point type	Primary

End point timeframe:

Up to Week 28

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data were planned to be analyzed.

End point values	Placebo	REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	20		
Units: Participants				
Participants with at least one TEAE	24	20		
Participants with at least one serious TEAE	2	4		

Statistical analyses

No statistical analyses for this end point

Primary: Period 1: Number of Participants with TEAEs by Severity

End point title	Period 1: Number of Participants with TEAEs by Severity[2]

End point description:

Severity of TEAEs were graded as follows: Mild: Does not interfere in a significant manner with the participant'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 participants. Moderate: Produces some impairment of functioning but is not hazardous to health. It was uncomfortable or an embarrassment. Treatment for symptom may be needed. Severe: Produces significant impairment of functioning or incapacitation and was a definite hazard to the participant's health. Treatment for symptom may be given and/or participants hospitalized. Number of participants with TEAEs by severity is reported. Safety analysis set (SAF) included all randomized participants who received any study drug and was analyzed as treated.

End point type	Primary

End point timeframe:

Up to Week 28

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data were planned to be analyzed.

End point values	Placebo	REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	20		
Units: Participants				
Participants with at least one Mild TEAE	9	7		
Participants with at least one Moderate TEAE	12	10		
Participants with at least one Severe TEAE	3	3		

Statistical analyses

No statistical analyses for this end point

Primary: Period 1: Time-Weighted Average (Standardized Area Under the Curve [AUC]) of the Percent Change From Baseline in Total Lesion Activity by Fluorine-18-labeled Sodium Fluoride (18^F-NaF) Positron Emission Tomography (PET) over 28 weeks (AHO)

End point title	Period 1: Time-Weighted Average (Standardized Area Under the Curve [AUC]) of the Percent Change From Baseline in Total Lesion Activity by Fluorine-18-labeled Sodium Fluoride (18^F-NaF) Positron Emission Tomography (PET) over 28 weeks (AHO)

End point description:

18^F-NaF PET is used to assess lesion and disease activity. 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 analysis set is reported. Active Heterotopic Ossification analysis set (AHO) included all randomized participants who had at least one active HO lesion at baseline; and was based on the treatment allocated (as randomized).

End point type	Primary

End point timeframe:

Week 28

End point values	Period 1: Placebo (AHO)	Period 1: REGN2477 10 mg/kg Q4W (AHO)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	20		
Units: Percent Change				
least squares mean (standard error)	13.7 (± 12.49)	-11.1 (± 14.28)		

Statistical analyses

Statistical analysis title	LS Mean Difference vs. Placebo
Comparison groups	Period 1: Placebo (AHO) v Period 1: REGN2477 10 mg/kg Q4W (AHO)

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0758 [3]
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-24.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.3
upper limit	2.7

Notes:

[3] - p-Value vs. Placebo; Mixed Model Repeated Measures

Primary: Period 1: Percent Change from Baseline in the Total Volume of HO Lesions as Assessed by Computed Tomography (CT) at Week 28 (AHO)

End point title	Period 1: Percent Change from Baseline in the Total Volume of HO Lesions as Assessed by Computed Tomography (CT) at Week 28 (AHO)

End point description:

CT is a diagnostic imaging test used to create detailed images of internal organs, bones, soft tissue and blood vessels. Percent change from baseline in the total volume of HO lesions as assessed by CT during Period 1 at Week 28 is reported. AHO included all randomized participants who had at least one active HO lesion at baseline; and was based on the treatment allocated (as randomized).

End point type	Primary

End point timeframe:

Week 28

End point values	Period 1: Placebo (AHO)	Period 1: REGN2477 10 mg/kg Q4W (AHO)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	20		
Units: Percent Change				
least squares mean (standard error)	30.7 (± 19.30)	5.5 (± 21.28)		

Statistical analyses

Statistical analysis title	LS Mean Difference vs. Placebo
Comparison groups	Period 1: Placebo (AHO) v Period 1: REGN2477 10 mg/kg Q4W (AHO)

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3676 [4]
Method	Mixed models analysis
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-25.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-81.1
upper limit	30.6

Notes:

[4] - p-Value vs. Placebo; Mixed Model Repeated Measures (MMRM)

Primary: Period 2: Number of New HO Lesions as Assessed by CT at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)

End point title	Period 2: Number of New HO Lesions as Assessed by CT at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)[5]

End point description:

HO detectable by CT that developed after baseline are referred to as "new HO lesions." Number of new HO lesions as assessed by CT at Week 56 relative to Week 28 scan is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT): All AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses is less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Primary

End point timeframe:

Week 28, Week 56

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The REGN2477/REGN2477 arm was reported in a different end point.

End point values	Placebo	Placebo/REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: New HO Lesions				
New lesions	22	0		

Statistical analyses

Statistical analysis title	Placebo/REGN2477 10 mg/kg Q4W

Statistical analysis description:

Compared number of new lesions per participant by CT at week 28 (relative to baseline) and week 56 (relative to week 28).

Comparison groups	Placebo v Placebo/REGN2477 10 mg/kg Q4W

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0039 [6]
Method	Wilcoxon signed rank test

Notes:

[6] - Week 56 vs. Week 28

Primary: Period 1: Time-weighted Average (Standardized AUC) of the Percent Change From Baseline in Total Lesion Activity Assessed by 18^F-NaF PET over 28 weeks (AHOC)

End point title	Period 1: Time-weighted Average (Standardized AUC) of the Percent Change From Baseline in Total Lesion Activity Assessed by 18^F-NaF PET over 28 weeks (AHOC)

End point description:

18^F-NaF PET is used to assess lesion and disease activity. Time-weighted average (Standardized AUC) of the percent change from baseline in total lesion activity as assessed by 18^F-NaF PET in Active HO Classic ACVR1 Mutation (AHOC) analysis set over 28 weeks is reported. Active HO classic ACVR1 (R206H) mutation analysis set (AHOC) included all randomized participants with the classic ACVR1 (R206H) mutation and who had at least one AHO at baseline, as defined by 18^F-NaF PET positivity; and was based on the treatment allocated (as randomized).

End point type	Primary

End point timeframe:

Week 28

End point values	Period 1: Placebo (AHOC)	Period 1: REGN2477 10 mg/kg Q4W (AHOC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	20		
Units: Percent Change				
least squares mean (standard error)	17.6 (± 9.73)	-8.0 (± 10.14)		

Statistical analyses

Statistical analysis title	REGN2477 10 mg/kg Q4W vs. Placebo
Comparison groups	Period 1: Placebo (AHOC) v Period 1: REGN2477 10 mg/kg Q4W (AHOC)
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0756
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-25.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.9
upper limit	2.8

Primary: Period 1: Percent Change from Baseline in the Total Volume of HO Lesions as Assessed by CT at Week 28 (AHOC)

End point title	Period 1: Percent Change from Baseline in the Total Volume of HO Lesions as Assessed by CT at Week 28 (AHOC)

End point description:

Percent change from baseline in the total volume of HO lesions was assessed by CT at Week 28 in AHOC analysis set is reported. Active HO classic ACVR1 (R206H) mutation analysis set (AHOC) included all randomized participants with the classic ACVR1 (R206H) mutation and who had at least one AHO at baseline, as defined by 18^F-NaF PET positivity; and was based on the treatment allocated (as randomized).

End point type	Primary

End point timeframe:

Week 28

End point values	Period 1: Placebo (AHOC)	Period 1: REGN2477 10 mg/kg Q4W (AHOC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	20		
Units: Percent Change				
least squares mean (standard error)	34.9 (± 19.90)	7.0 (± 20.87)		

Statistical analyses

Statistical analysis title	REGN2477 10 mg/kg Q4W vs. Placebo
Comparison groups	Period 1: Placebo (AHOC) v Period 1: REGN2477 10 mg/kg Q4W (AHOC)
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3407
Method	Mixed Model with Repeated Measure (MMRM)
Parameter estimate	Least Square Mean Difference
Point estimate	-27.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-86.1
upper limit	30.5

Secondary: Period 1: Time-weighted Average (Standardized AUC) of the Change from Baseline in Daily Pain due to Fibrodysplasia Ossificans Progressiva (FOP) Assessed by Daily Numeric Rating Scale (NRS) over 28 weeks (AHO)

End point title	Period 1: Time-weighted Average (Standardized AUC) of the Change from Baseline in Daily Pain due to Fibrodysplasia Ossificans Progressiva (FOP) Assessed by Daily Numeric Rating Scale (NRS) over 28 weeks (AHO)

End point description:

The pain NRS is a patient reported outcome (PRO) used by participants to rate their pain associated with FOP. Participants were asked to rate their pain on a scale that ranges from "0" (no pain) to "10" (worst possible pain), where the highest score indicated worst outcome. Time-weighted average (Standardized AUC) of the change from baseline in daily pain due to FOP assessed by daily NRS over 28 weeks in AHO analysis set is reported. Active Heterotopic Ossification analysis set (AHO) included all randomized participants who had at least one active HO lesion at baseline; and was based on the treatment allocated (as randomized). "Number of participants analyzed" are the participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 28

End point values	Period 1: Placebo (AHO)	Period 1: REGN2477 10 mg/kg Q4W (AHO)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	18		
Units: Score on a Scale				
least squares mean (standard error)	-0.27 (± 0.373)	-0.63 (± 0.444)		

Statistical analyses

Statistical analysis title	LS Mean Difference vs. Placebo
Comparison groups	Period 1: Placebo (AHO) v Period 1: REGN2477 10 mg/kg Q4W (AHO)
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2546 [7]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.27

Notes:

[7] - p-Value vs. Placebo

Secondary: Period 1: Time-weighted Average (Standardized AUC) of the Change from Baseline in Daily Pain due to FOP, Assessed by Daily NRS over 28 weeks (AHOC)

End point title	Period 1: Time-weighted Average (Standardized AUC) of the Change from Baseline in Daily Pain due to FOP, Assessed by Daily NRS over 28 weeks (AHOC)

End point description:

The pain NRS is a PRO used by participants to rate their pain associated with FOP. Participants were asked to rate their pain on a scale that ranges from "0" (no pain) to "10" (worst possible pain), where the highest score indicated worst outcome. Time-Weighted average (standardized AUC) of the change from baseline in daily pain due to FOP assessed by daily NRS over 28 weeks in AHOC analysis set is reported. AHOC analysis set included all randomized participants with the classic ACVR1 [R206H] mutation and who had at least one AHO at baseline, as defined by 18^F-NaF PET positivity; and was based on the treatment allocated (as randomized).

End point type	Secondary

End point timeframe:

Week 28

End point values	Period 1: Placebo (AHOC)	Period 1: REGN2477 10 mg/kg Q4W (AHOC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	18		
Units: Score on a Scale				
least squares mean (standard deviation)	-0.12 (± 0.221)	-0.48 (± 0.237)		

Statistical analyses

Statistical analysis title	REGN2477 10 mg/kg Q4W vs. Placebo
Comparison groups	Period 1: Placebo (AHOC) v Period 1: REGN2477 10 mg/kg Q4W (AHOC)
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2651
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.29

Secondary: Period 1: Percent Change from Baseline in 18^F-NaF SUVmax of Individual Active HO Site(s) assessed by 18^F-NaF PET at Week 8 (AHOC)

End point title	Period 1: Percent Change from Baseline in 18^F-NaF SUVmax of Individual Active HO Site(s) assessed by 18^F-NaF PET at Week 8 (AHOC)

End point description:

Standardized uptake value max (SUVmax) was a measurement of the maximum radiopharmaceutical uptake within the volume of interest. Relative accuracy of a particular radiotracer in a particular tissue is determined by expressing the absolute accuracy (obtained in the primary outcome measure) in terms of percent difference between SUVmax values obtained from PET/CT. Percent Change in 18^F-NaF SUVmax of Individual Active HO Site(s) assessed by 18^F-NaF PET in AHOC analysis set is reported. AHOC analysis set included all randomized participants with the classic ACVR1 [R206H] mutation and who had at least one AHO at baseline, as defined by 18^F-NaF PET positivity; and was based on the treatment allocated (as randomized).

End point type	Secondary

End point timeframe:

Week 8

End point values	Period 1: Placebo (AHOC)	Period 1: REGN2477 10 mg/kg Q4W (AHOC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	20		
Units: Percent Change				
least squares mean (standard error)	-11.6 (± 3.47)	-33.7 (± 3.61)		

Statistical analyses

Statistical analysis title	LS Mean Difference vs. Placebo
Comparison groups	Period 1: Placebo (AHOC) v Period 1: REGN2477 10 mg/kg Q4W (AHOC)
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-22.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.3
upper limit	-12

Secondary: Period 1: Percent Change from Baseline in 18^F-NaF SUVmax of Individual Active HO Site(s) as assessed by 18^F-NaFPET at Week 8 (AHO)

End point title	Period 1: Percent Change from Baseline in 18^F-NaF SUVmax of Individual Active HO Site(s) as assessed by 18^F-NaFPET at Week 8 (AHO)

End point description:

Percent change in 18^F-NaF SUVmax of individual active HO site(s) as assessed by 18^F-NaF PET at Week 8 in AHO analysis set is reported. Active Heterotopic Ossification analysis set (AHO) included all randomized participants who had at least one active HO lesion at baseline; and was based on the treatment allocated (as randomized).

End point type	Secondary

End point timeframe:

Week 8

End point values	Period 1: Placebo (AHO)	Period 1: REGN2477 10 mg/kg Q4W (AHO)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	20		
Units: Percent Change				
least squares mean (standard error)	-6.6 (± 3.70)	-22.3 (± 4.02)		

Statistical analyses

Statistical analysis title	LS Mean Difference vs. Placebo
Comparison groups	Period 1: Placebo (AHO) v Period 1: REGN2477 10 mg/kg Q4W (AHO)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0065 [8]
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-15.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.8
upper limit	-4.6

Notes:

[8] - p-Value vs. Placebo

Secondary: Period 1: Change from Baseline in Number of HO lesions as Assessed by 18^F-NaF PET at Week 28 (AHOC)

End point title	Period 1: Change from Baseline in Number of HO lesions as Assessed by 18^F-NaF PET at Week 28 (AHOC)

End point description:

Change from baseline in number of HO lesions was assessed by 18^F-NaF PET at Week 28 in AHOC analysis set is reported. AHOC analysis set included all randomized participants with the classic ACVR1 [R206H] mutation and who had at least one AHO at baseline, as defined by 18^F-NaF PET positivity; and was based on the treatment allocated (as randomized).

End point type	Secondary

End point timeframe:

Week 28

End point values	Period 1: Placebo (AHOC)	Period 1: REGN2477 10 mg/kg Q4W (AHOC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	20		
Units: HO Lesions				
arithmetic mean (standard deviation)	-1.0 (± 2.66)	-2.3 (± 2.24)		

Statistical analyses

Statistical analysis title	Median Difference vs. Placebo
Comparison groups	Period 1: Placebo (AHOC) v Period 1: REGN2477 10 mg/kg Q4W (AHOC)
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2351 [9]
Method	ANCOVA
Parameter estimate	Median Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	1

Notes:

[9] - p-Value vs. Placebo; ANCOVA model on ranked response

Secondary: Period 1: Change from Baseline in Number of HO Lesions as Assessed by 18^F-NaF PET at Week 28 (AHO)

End point title	Period 1: Change from Baseline in Number of HO Lesions as Assessed by 18^F-NaF PET at Week 28 (AHO)

End point description:

Change from baseline in number of HO lesions was assessed by 18^F-NaF PET in AHO analysis set is reported. Active Heterotopic Ossification analysis set (AHO) included all randomized participants who had at least one active HO lesion at baseline; and was based on the treatment allocated (as randomized).

End point type	Secondary

End point timeframe:

Week 28

End point values	Period 1: Placebo (AHO)	Period 1: REGN2477 10 mg/kg Q4W (AHO)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	20		
Units: HO Lesions				
arithmetic mean (standard deviation)	-1.0 (± 2.59)	-2.3 (± 2.24)		

Statistical analyses

Statistical analysis title	Median Difference vs. Placebo
Comparison groups	Period 1: Placebo (AHO) v Period 1: REGN2477 10 mg/kg Q4W (AHO)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1746 [10]
Method	ANCOVA
Parameter estimate	Median Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0

Notes:

[10] - p-Value vs. Placebo; ANCOVA model on ranked response

Secondary: Period 1: Change from Baseline in Number of HO Lesions Detectable by CT at Week 28 (AHOC)

End point title	Period 1: Change from Baseline in Number of HO Lesions Detectable by CT at Week 28 (AHOC)

End point description:

Change from baseline in number of HO lesions was detectable by CT using AHOC analysis set is reported. AHOC analysis set included all randomized participants with the classic ACVR1 [R206H] mutation and who had at least one AHO at baseline, as defined by 18^F-NaF PET positivity; and was based on the treatment allocated (as randomized).

End point type	Secondary

End point timeframe:

Week 28

End point values	Period 1: Placebo (AHOC)	Period 1: REGN2477 10 mg/kg Q4W (AHOC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	20		
Units: HO Lesions				
arithmetic mean (standard deviation)	1.2 (± 2.00)	-0.3 (± 1.34)		

Statistical analyses

Statistical analysis title	Median Difference vs. Placebo
Comparison groups	Period 1: Placebo (AHOC) v Period 1: REGN2477 10 mg/kg Q4W (AHOC)
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0153 [11]
Method	ANCOVA
Parameter estimate	Median Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Notes:

[11] - p-Value vs. Placebo; ANCOVA model on ranked response

Secondary: Period 1: Change from Baseline in Number of HO Lesions Detectable by CT at Week 28 (AHO)

End point title	Period 1: Change from Baseline in Number of HO Lesions Detectable by CT at Week 28 (AHO)

End point description:

Change from baseline in number of HO lesions detectable by CT at Week 28 in AHO analysis set is reported. Active Heterotopic Ossification analysis set (AHO) included all randomized participants who had at least one active HO lesion at baseline; and was based on the treatment allocated (as randomized).

End point type	Secondary

End point timeframe:

Week 28

End point values	Period 1: Placebo (AHO)	Period 1: REGN2477 10 mg/kg Q4W (AHO)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	20		
Units: HO Lesions				

arithmetic mean (standard deviation)	1.2 (± 1.93)	-0.3 (± 1.34)		

Statistical analyses

Statistical analysis title	Median Difference vs. Placebo
Comparison groups	Period 1: Placebo (AHO) v Period 1: REGN2477 10 mg/kg Q4W (AHO)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0153 [12]
Method	ANCOVA
Parameter estimate	Median Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Notes:

[12] - p-Value vs. Placebo; ANCOVA model on ranked response

Secondary: Period 2: Number of New HO Lesions as Assessed by 18^F-NaF PET at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)

End point title	Period 2: Number of New HO Lesions as Assessed by 18^F-NaF PET at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)[13]

End point description:

Number of new HO lesions as assessed by 18^F-NaF PET at Week 56 Relative to Week 28 Scan is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28, Week 56

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The REGN2477/REGN2477 arm was reported in a different end point.

End point values	Placebo	Placebo/REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: New HO lesions				
New lesions	23	1		

Statistical analyses

Statistical analysis title	Placebo/REGN2477 10 mg/kg Q4W

Statistical analysis description:

Compared number of new lesions per patient by PET at week 28 (relative to baseline) and week 56 (relative to week 28).

Comparison groups	Placebo v Placebo/REGN2477 10 mg/kg Q4W
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0039 [14]
Method	Wilcoxon signed rank test

Notes:

[14] - Week 56 vs. Week 28

Secondary: Period 2: Percentage of Participants With New HO Lesions as Assessed by CT at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)

End point title	Period 2: Percentage of Participants With New HO Lesions as Assessed by CT at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)[15]

End point description:

Percentage of participants with new HO lesions as assessed by CT at Week 56 Relative to Week 28 Scan is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28, Week 56

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The REGN2477/REGN2477 arm was reported in a different end point.

End point values	Placebo	Placebo/REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Percentage of Participants				
number (not applicable)				
% of participants with new lesions	40.9	0.0		

Statistical analyses

Statistical analysis title	Placebo/REGN2477 10 mg/kg Q4W

Statistical analysis description:

Compared percent of participants with new lesions by CT at week 28 (relative to baseline) and week 56 (relative to week 28).

Comparison groups	Placebo v Placebo/REGN2477 10 mg/kg Q4W
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0027 [16]
Method	Mcnemar

Notes:

[16] - Week 56 vs. Week 28

Secondary: Period 2: Percentage of Participants With New HO Lesions as Assessed by 18^F-NaF PET at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)

End point title	Period 2: Percentage of Participants With New HO Lesions as Assessed by 18^F-NaF PET at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)[17]

End point description:

Percentage of participants with new HO lesions as assessed by 18^F-NaF PET at Week 56 using AHO analysis set is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28, Week 56

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The REGN2477/REGN2477 arm was reported in a different end point.

End point values	Placebo	Placebo/REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Percentage of Participants				
number (not applicable)				
% of participants with new lesions	40.9	4.5		

Statistical analyses

Statistical analysis title	Placebo/REGN2477 10 mg/kg Q4W

Statistical analysis description:

Compared percent of participants with new lesions by PET at week 28 (relative to baseline) and week 56 (relative to week 28).

Comparison groups	Placebo v Placebo/REGN2477 10 mg/kg Q4W

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047 [18]
Method	Mcnemar

Notes:

[18] - Week 56 vs. Week 28

Secondary: Period 2: Number of New HO Lesions as Assessed by CT Only at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)

End point title	Period 2: Number of New HO Lesions as Assessed by CT Only at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)

End point description:

Number of new HO lesions as assessed by CT only at week 56 relative to week 28 using AHO analysis set is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28, Week 56

End point values	Period 1: Placebo (AHO)	Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: New HO lesions				
New lesions	22	0		

Statistical analyses

Statistical analysis title	Week 56 vs. Week 28
Comparison groups	Period 1: Placebo (AHO) v Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0039
Method	Wilcoxon signed rank test

Secondary: Period 2: Percentage of Participants With New HO Lesions as Assessed by CT Only at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)

End point title	Period 2: Percentage of Participants With New HO Lesions as

	Assessed by CT Only at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)

End point description:

Percentage of participants with new HO lesions as assessed by CT only at Week 56 using AHO is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28, Week 56

End point values	Period 1: Placebo (AHO)	Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: Percentage of Participants				
number (not applicable)				
% of participants with new HO lesions	45.5	9.1		

Statistical analyses

Statistical analysis title	Week 56 vs. Week 28
Comparison groups	Period 1: Placebo (AHO) v Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0209
Method	Mcnemar

Secondary: Period 2 vs. Period 1: Change From Week 28 in Number of Active HO Lesions as Assessed by 18^F-NaF PET to Week 56 (Period 2) Versus the Same Participants Between Baseline and Week 28 (Period 1) (AHO COVID-19 mITT)

End point title	Period 2 vs. Period 1: Change From Week 28 in Number of Active HO Lesions as Assessed by 18^F-NaF PET to Week 56 (Period 2) Versus the Same Participants Between Baseline and Week 28 (Period 1) (AHO COVID-19 mITT)

End point description:

Change from Week 28 to Week 56 as assessed by 18^F-NaF PET versus from Baseline to Week 28; COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28, Week 56

End point values	Period 1: Placebo (AHO)	Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: g.				
arithmetic mean (standard deviation)	1.1 (± 1.93)	-0.2 (± 0.61)		

Statistical analyses

Statistical analysis title	Period 2 vs. Period 1
Statistical analysis description:	
Difference of Change from Week 28 to Week 56 versus from Baseline to Week 28	
Comparison groups	Period 1: Placebo (AHO) v Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [19]
Method	Wilcoxon signed rank test

Notes:

[19] - Period 2 vs. Period 1

Secondary: Period 2 vs. Period 1: Change From Week 28 in Number of Active HO Lesions as Assessed by CT Scan at Week 56 (Period 2) Versus the Same Participants Between Baseline and Week 28 (Period 1) (AHO COVID-19 mITT)

End point title	Period 2 vs. Period 1: Change From Week 28 in Number of Active HO Lesions as Assessed by CT Scan at Week 56 (Period 2) Versus the Same Participants Between Baseline and Week 28 (Period 1) (AHO COVID-19 mITT)

End point description:

Change from Week 28 to Week 56 as assessed by CT Scan versus from Baseline to Week 28 is reported; COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28, Week 56

End point values	Period 1: Placebo (AHO)	Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: Cubic centimeter (cm^3)				
arithmetic mean (standard deviation)	1.1 (± 1.93)	-0.2 (± 0.61)		

Statistical analyses

Statistical analysis title	Period 2 vs. Period 1
Statistical analysis description:	
Difference of Change from Week 28 to Week 56 versus from Baseline to Week 28	
Comparison groups	Period 1: Placebo (AHO) v Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [20]
Method	Wilcoxon signed rank test

Notes:

[20] - Period 2 vs. Period 1

Secondary: Period 2: Percentage of Participants with New HO Lesions as Assessed by CT at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point title	Period 2: Percentage of Participants with New HO Lesions as Assessed by CT at Week 56 Relative to Baseline (AHO COVID-19 mITT)
End point description:	
Percentage of participants with new HO lesions as assessed by CT at week 56 relative to baseline were reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.	
End point type	Secondary
End point timeframe:	
Week 56	

End point values	Period 2: REGN2477/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percentage of Participants				
number (not applicable)	11.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Number of New HO Lesions as Assessed by CT Only at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point title	Period 2: Number of New HO Lesions as Assessed by CT Only at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point description:

Number of new HO lesions as assessed by CT only at week 56 relative baseline is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 56

End point values	Period 2: REGN2477/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: New HO Lesions	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Number of New HO Lesions as Assessed by CT at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point title	Period 2: Number of New HO Lesions as Assessed by CT at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point description:

Number of new HO lesions as assessed by CT at Week 56 relative to baseline. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Baseline, Week 56

End point values	Period 2: REGN2477/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: New HO Lesions	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Total Volume of New HO Lesions as Assessed by CT at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)

End point title	Period 2: Total Volume of New HO Lesions as Assessed by CT at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)[21]

End point description:

Total volume of new HO lesions as assessed by CT at Week 56 relative to Week 28 scan. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28, Week 56

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The REGN2477/REGN2477 arm was reported in a different end point.

End point values	Placebo	Placebo/REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Cubic centimeter (cm^3)				
arithmetic mean (standard deviation)				
Volume of new lesions	9.3 (± 19.66)	0.0 (± 0.21)		

Statistical analyses

Statistical analysis title	Placebo/REGN2477 10 mg/kg Q4W

Statistical analysis description:

Compared total new lesion volume per participant by CT at week 28 (relative to baseline) and week 56 (relative to week 28)

Comparison groups	Placebo v Placebo/REGN2477 10 mg/kg Q4W
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0039 [22]
Method	Wilcoxon signed rank test

Notes:

[22] - Week 56 vs. Week 28

Secondary: Period 2: Percentage of Participants With New HO Lesions as Assessed by 18^F-NaF PET at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point title	Period 2: Percentage of Participants With New HO Lesions as Assessed by 18^F-NaF PET at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point description:

Percentage of participants with new HO lesions as assessed by 18^F-NaF PET at week 56 relative to baseline. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 56

End point values	Period 2: REGN2477/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percentage of Participants				
number (not applicable)	5.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Number of New HO Lesions as Assessed by 18^F-NAF PET at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point title	Period 2: Number of New HO Lesions as Assessed by 18^F-NAF PET at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point description:

Number of new HO lesions as assessed by 18^F-NAF PET at week 56 relative to baseline is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 56

End point values	Period 2: REGN2477/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: New HO Lesions	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Total Lesion Activity (TLA) Assessed by 18^F-NaF PET in New HO Lesions at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)

End point title	Period 2: Total Lesion Activity (TLA) Assessed by 18^F-NaF PET in New HO Lesions at Week 56 Relative to Week 28 Scan (AHO COVID-19 mITT)[23]

End point description:

TLA is a measure of participant-level cumulative burden of metabolically active HO. Activity of individual HO lesions was calculated as the product of SUVmean and the PET volume of the active HO lesion. TLA was derived for each participant at each time point as the sum of HO lesion activity of individual target and new active HO lesions. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28, Week 56

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The REGN2477/REGN2477 arm was reported in a different end point.

End point values	Placebo	Placebo/REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: g.				
arithmetic mean (standard deviation)				
TLA in new lesions	204.4 (± 442.35)	13.2 (± 61.89)		

Statistical analyses

Statistical analysis title	Placebo/REGN2477 10 mg/kg Q4W

Statistical analysis description:

Compared total lesion activity per participant in new lesions by PET at week 28 (relative to baseline) and week 56 (relative to week 28)

Comparison groups	Placebo v Placebo/REGN2477 10 mg/kg Q4W
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0273 [24]
Method	Wilcoxon signed rank test

Notes:

[24] - Week 56 vs. Week 28

Secondary: Period 2 vs. Period 1: Percent Change From Week 28 in TLA as Assessed by 18^F-NaF PET to Week 56 (Period 2) Versus the Same Participants Between Baseline and Week 28 (Period 1) (AHO COVID-19 mITT)

End point title	Period 2 vs. Period 1: Percent Change From Week 28 in TLA as Assessed by 18^F-NaF PET to Week 56 (Period 2) Versus the Same Participants Between Baseline and Week 28 (Period 1) (AHO COVID-19 mITT)

End point description:

Percent Change from Week 28 to Week 56 versus from Baseline to Week 28 is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28, Week 56

End point values	Period 1: Placebo (AHO)	Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: Percent Change				
arithmetic mean (standard deviation)	48.2 (± 156.17)	-16.4 (± 33.81)		

Statistical analyses

Statistical analysis title	Period 2 vs. Period 1

Statistical analysis description:

Difference of Percent Change from Week 28 to Week 56 versus from Baseline to Week 28

Comparison groups	Period 1: Placebo (AHO) v Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2123 [25]
Method	Wilcoxon signed rank test

Notes:

[25] - Period 2 vs. Period 1

Secondary: Period 2 vs. Period 1: Percent Change From Week 28 in the Total Volume of HO Lesions as Assessed by CT to Week 56 (Period 2) Versus the Same Participants Between Baseline and Week 28 (Period 1) (AHO COVID-19 mITT)

End point title	Period 2 vs. Period 1: Percent Change From Week 28 in the Total Volume of HO Lesions as Assessed by CT to Week 56 (Period 2) Versus the Same Participants Between Baseline and Week 28 (Period 1) (AHO COVID-19 mITT)

End point description:

Percent Change from Week 28 to Week 56 versus from Baseline to Week 28 is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28, Week 56

End point values	Period 1: Placebo (AHO)	Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: Percent Change				
arithmetic mean (standard deviation)	34.0 (± 129.39)	2.2 (± 13.66)		

Statistical analyses

Statistical analysis title	Period 2 vs. Period 1

Statistical analysis description:

Difference of Percent Change from Week 28 to Week 56 versus from Baseline to Week 28

Comparison groups	Period 1: Placebo (AHO) v Period 2: Placebo/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1528 [26]
Method	Wilcoxon signed rank test

Notes:

[26] - Period 2 vs. Period 1

Secondary: Period 2: TLA in New HO Lesions as Assessed by 18^F-NaF PET at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point title	Period 2: TLA in New HO Lesions as Assessed by 18^F-NaF PET at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point description:

Total Lesion Activity (TLA) is a measure of participant-level cumulative burden of metabolically active HO. TLA in New (Relative to Baseline) Lesions at Week 56 is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 56

End point values	Period 2: REGN2477/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: g.				
arithmetic mean (standard deviation)	0.7 (± 2.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Total Volume of New HO Lesions as Assessed by CT Only at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point title	Period 2: Total Volume of New HO Lesions as Assessed by CT Only at Week 56 Relative to Baseline (AHO COVID-19 mITT)

End point description:

Total volume of new HO lesions as assessed by CT only at week 56 relative to baseline were reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 56

End point values	Period 2: REGN2477/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Cubic centimeter (cm^3)				
arithmetic mean (standard deviation)	0.0 (± 0.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Percent Change From Baseline in the Total Volume of HO Lesions as Assessed by CT to Week 56 (AHO COVID-19 mITT)

End point title	Period 2: Percent Change From Baseline in the Total Volume of HO Lesions as Assessed by CT to Week 56 (AHO COVID-19 mITT)

End point description:

Percent change from baseline in the total volume of HO lesions as assessed by CT to Week 56 were reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 56

End point values	Period 2: REGN2477/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percent Change				
arithmetic mean (standard deviation)	2.6 (± 10.18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Percent Change From Baseline in TLA as Assessed by 18^F-NaF PET to Week 56 (AHO COVID-19 mITT)

End point title	Period 2: Percent Change From Baseline in TLA as Assessed by 18^F-NaF PET to Week 56 (AHO COVID-19 mITT)

End point description:

Percent change from baseline in TLA as assessed by 18^F-NaF PET to week 56 were reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 56

End point values	Period 2: REGN2477/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Percent Change				
arithmetic mean (standard deviation)	-16.4 (± 53.10)			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Percent Change From Week 28 in SUVmax as Assessed by 18^F-NaF to Week 56 (AHO COVID-19 mITT)

End point title	Period 2: Percent Change From Week 28 in SUVmax as Assessed by 18^F-NaF to Week 56 (AHO COVID-19 mITT)[27]

End point description:

Percent Change from Week 28 to Week 56 is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28 to Week 56

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The REGN2477/REGN2477 arm was reported in a different end point.

End point values	Placebo	Placebo/REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: Percent Change				
arithmetic mean (standard deviation)	-16.8 (± 19.52)	-30.3 (± 15.03)		

Statistical analyses

Statistical analysis title	Period 2 vs. Period 1
Statistical analysis description: Compared percent change from week 28 to week 56 and from baseline to week 28	
Comparison groups	Placebo v Placebo/REGN2477 10 mg/kg Q4W
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0209
Method	Wilcoxon signed rank test

Secondary: Period 2: Percent Change From Baseline in 18^F-NaF PET SUVmax to Week 56 (AHO COVID-19 mITT)

End point title	Period 2: Percent Change From Baseline in 18^F-NaF PET SUVmax to Week 56 (AHO COVID-19 mITT)
End point description: Percent change from baseline in 18^F-NaF PET SUVmax to week 56. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.	
End point type	Secondary
End point timeframe: Baseline, Week 56	

End point values	Period 2: REGN2477/REGN2477 10 mg/kg Q4W (AHO COVID-19 mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Percent Change				
arithmetic mean (standard deviation)	-41.9 (± 29.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Daily Average Pain due to FOP Measured Using the Daily NRS (AHO COVID-19 mITT)

End point title	Period 2: Daily Average Pain due to FOP Measured Using the Daily NRS (AHO COVID-19 mITT)[28]

End point description:

The pain NRS was a patient reported outcome used by participants to rate their pain associated with FOP. Participants were asked to rate their pain on a scale that ranges from "0" (no pain) to "10" (worst possible pain), where the highest score indicated worst outcome. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28 up to Week 56

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The REGN2477/REGN2477 arm was reported in a different end point.

End point values	Placebo	Placebo/REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Score on a Scale				
arithmetic mean (standard deviation)	1.79 (± 2.106)	1.60 (± 1.969)		

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Percentage of Participants With Flare-ups Assessed by Participant E-diary (AHO COVID-19 mITT)

End point title	Period 2: Percentage of Participants With Flare-ups Assessed by Participant E-diary (AHO COVID-19 mITT)[29]

End point description:

Percentage of participants with flare-ups starting between week 28 and week 56 as assessed by participant E-diary is reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28 to Week 56

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The REGN2477/REGN2477 arm was reported in a different end point.

End point values	Placebo	Placebo/REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Percentage of Participants				
number (not applicable)	68.2	13.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Percentage of Participants With Investigator-assessed Flare-ups (AHO COVID-19 mITT)

End point title	Period 2: Percentage of Participants With Investigator-assessed Flare-ups (AHO COVID-19 mITT)[30]

End point description:

Percentage of participants with investigator-assessed flare-ups were reported. COVID-19 Modified Intent-to-Treat set (COVID-19 mITT) included all AHO participants who received a treatment in Period 2 for whom at least 1 post-Week 28 scan was collected and the period between any consecutive doses was less than 9 weeks (63 days) before the 1st post-week 28 scan.

End point type	Secondary

End point timeframe:

Week 28 to Week 56

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The REGN2477/REGN2477 arm was reported in a different end point.

End point values	Placebo	Placebo/REGN2477 10 mg/kg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Percentage of Participants				
number (not applicable)	45.5	13.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Periods 1, 2, and 3: Concentration of Total Activin A in Serum

End point title	Periods 1, 2, and 3: Concentration of Total Activin A in Serum

End point description:

Concentration of total activin A in serum over time is reported. The pharmacokinetic (PK) analysis set included all treated participants who received any study drug and who had at least 1 non-missing drug concentration following the first dose of study drug. "Overall number of participants analyzed" are the participants who were evaluable for this outcome measure

End point type	Secondary

End point timeframe:

Week 28, Week 56, Week 76

End point values	REGN2477 10 mg/kg Q4W (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: Milligrams per Liter (mg/L)				
arithmetic mean (standard deviation)				
Week 28 (n=38)	0.0550 (± 0.0147)			
Week 56 (n=31)	0.0505 (± 0.0175)			
Week 76 (n=16)	0.0496 (± 0.0148)			

Statistical analyses

No statistical analyses for this end point

Secondary: Periods 1, 2, and 3: Concentrations of Functional REGN2477 in Serum

End point title	Periods 1, 2, and 3: Concentrations of Functional REGN2477 in Serum

End point description:

Concentrations of REGN2477 capable of target binding were measured (functional drug). The pharmacokinetic (PK) analysis set included all treated participants who received any study drug and who had at least 1 non-missing drug concentration following the first dose of study drug. "Overall number of participants analyzed" are the participants who were evaluable for this outcome measure

End point type	Secondary

End point timeframe:

Week 28, Week 56, Week 76

End point values	REGN2477 10 mg/kg Q4W (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: mg/L				
arithmetic mean (standard deviation)				
Week 28 (n=38)	114 (± 40.0)			
Week 56 (n=31)	113 (± 44.9)			
Week 76 (n=16)	115 (± 25.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Periods 1, 2, and 3: Number of Participants with Clinical Impact of Treatment-Emergent Anti-drug Antibodies (ADA) to REGN2477

End point title	Periods 1, 2, and 3: Number of Participants with Clinical Impact of Treatment-Emergent Anti-drug Antibodies (ADA) to REGN2477

End point description:

Immunogenicity was characterized by ADA responses & titers. Responses categories: Negative - ADA negative response at all time points, regardless of missing samples; Pre-existing immunoreactivity - ADA positive response at baseline with all post first dose negative results or positive response at baseline with all post first dose ADA responses < 9-fold over baseline titer levels; Treatment-boosted response - positive response in the assay post first dose, >= 9-fold over baseline titer levels, when baseline results are positive; Treatment-emergent response - ADA positive response in the REGN2477 ADA assay post first dose when baseline results = negative or missing. The Anti-Drug Antibody (ADA) analysis set included all participants who received study drug and had at least 1 non-missing ADA result following the first study dose. "Overall number of participants analyzed" are the participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Up to Week 76

End point values	Placebo/REGN2477 10 mg/kg Q4W (ADA)	REGN2477/REGN2477 10 mg/kg Q4W (ADA)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	19		
Units: Participants				
Negative	0	0		
Pre-existing Immunoreactivity	0	0		
Treatment-Boosted Response	0	0		
Treatment-Emergent Response	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of study drug to end of study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Placebo
Reporting group description: Participants received a single dose of placebo matched to REGN2477 intravenous (IV) infusion every 4 weeks (Q4W) for up to 28 weeks during Period 1.	
Reporting group title	REGN2477/REGN2477 10 mg/kg Q4W
Reporting group description: Participants who were in the REGN2477 group in Period 1 continued treatment with a single dose of REGN2477 IV infusion Q4W for additional 28 weeks during Period 2 followed by 20 weeks during Period 3. Participants could continue receiving REGN2477 every 4 weeks beyond week 76 provided that no safety signals were identified.	
Reporting group title	Placebo/REGN2477 10 mg/kg Q4W
Reporting group description: Participants who were in the placebo group in Period 1 crossed over to receive a single dose of REGN2477 IV infusion Q4W for additional 28 weeks during Period 2 followed by 20 weeks during Period 3. Participants could continue receiving REGN2477 every 4 weeks beyond week 76 provided that no safety signals were identified.	
Reporting group title	REGN2477 10 mg/kg Q4W
Reporting group description: Participants received a single dose of REGN2477 10 milligrams per kilogram (mg/kg) IV infusion every 4 weeks (Q4W) for up to 28 weeks during Period 1.	

Serious adverse events	Placebo	REGN2477/REGN2477 10 mg/kg Q4W	Placebo/REGN2477 10 mg/kg Q4W
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)	7 / 19 (36.84%)	6 / 24 (25.00%)
number of deaths (all causes)	0	3	2
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Skull fracture			

subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic rupture			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			

subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 24 (4.17%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abscess			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 24 (4.17%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perineal abscess			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	REGN2477 10 mg/kg Q4W		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skull fracture			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Splenic rupture			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Epistaxis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal colic				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Joint swelling				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Gastroenteritis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abscess				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abscess limb				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perineal abscess				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perirectal abscess				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection viral				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				

subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	REGN2477/REGN2477 10 mg/kg Q4W	Placebo/REGN2477 10 mg/kg Q4W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)	18 / 19 (94.74%)	24 / 24 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Uterine leiomyoma			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 24 (8.33%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	2	1	0
Hypertension			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	1 / 24 (4.17%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	3 / 24 (12.50%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	3	1	1
Pain			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	1	1	1
Malaise			

subjects affected / exposed	1 / 24 (4.17%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	2 / 24 (8.33%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Vessel puncture site bruise			
subjects affected / exposed	1 / 24 (4.17%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	2
Chest discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Feeling hot			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Inflammation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Infusion site pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Medical device site bruise			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Pyrexia			

subjects affected / exposed	0 / 24 (0.00%)	7 / 19 (36.84%)	5 / 24 (20.83%)
occurrences (all)	0	8	8
Swelling			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	1 / 24 (4.17%)
occurrences (all)	0	6	1
Reproductive system and breast disorders			
Acquired phimosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Endometrial thickening			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Menstruation irregular			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	3
Ovarian cyst			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	3 / 24 (12.50%)
occurrences (all)	0	0	3
Perineal cyst			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Prostatitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	4 / 24 (16.67%)	5 / 19 (26.32%)	10 / 24 (41.67%)
occurrences (all)	7	45	34
Cough			
subjects affected / exposed	2 / 24 (8.33%)	3 / 19 (15.79%)	3 / 24 (12.50%)
occurrences (all)	2	3	3
Dyspnoea			
subjects affected / exposed	2 / 24 (8.33%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	4	0	0
Oropharyngeal pain			

subjects affected / exposed	2 / 24 (8.33%)	2 / 19 (10.53%)	1 / 24 (4.17%)
occurrences (all)	2	2	1
Nasal congestion			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	1	1	1
Atelectasis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 24 (0.00%)	3 / 19 (15.79%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Sinus congestion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Upper-airway cough syndrome			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 24 (8.33%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	5	0	3

Somatic symptom disorder			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Investigations			
Crystal urine present			
subjects affected / exposed	1 / 24 (4.17%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Platelet function test abnormal			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 24 (12.50%)	2 / 19 (10.53%)	3 / 24 (12.50%)
occurrences (all)	11	2	5
Extraskeletal ossification			
subjects affected / exposed	2 / 24 (8.33%)	1 / 19 (5.26%)	2 / 24 (8.33%)
occurrences (all)	2	1	2
Head injury			
subjects affected / exposed	1 / 24 (4.17%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	2
Post-traumatic pain			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	6 / 24 (25.00%)
occurrences (all)	3	1	11
Animal bite			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Arthropod bite			

subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Back injury			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Joint injury			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	3 / 24 (12.50%)
occurrences (all)	0	1	3
Limb injury			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Lower limb fracture			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	3 / 24 (12.50%)
occurrences (all)	0	0	4
Post vaccination syndrome			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Traumatic haematoma			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Vascular access site swelling			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Gilbert's syndrome			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Sebaceous naevus			

subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 24 (29.17%)	8 / 19 (42.11%)	6 / 24 (25.00%)
occurrences (all)	14	47	50
Dizziness			
subjects affected / exposed	2 / 24 (8.33%)	2 / 19 (10.53%)	3 / 24 (12.50%)
occurrences (all)	2	5	4
Paraesthesia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	6	0	3
Presyncope			
subjects affected / exposed	2 / 24 (8.33%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Neuralgia			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	1	2	0
Cervical radiculopathy			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Burning sensation			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	20	0
Head discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	2	0

Post-traumatic headache			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Increased tendency to bruise			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Lymph node pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Lymphadenitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Microcytic anaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Conductive deafness			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Ear discomfort			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Ear pruritus			

subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Hyperacusis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
Tinnitus			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Ocular hypertension			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Dry eye			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Photophobia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 24 (8.33%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	6 / 24 (25.00%)	2 / 19 (10.53%)	5 / 24 (20.83%)
occurrences (all)	8	8	8
Nausea			
subjects affected / exposed	2 / 24 (8.33%)	2 / 19 (10.53%)	5 / 24 (20.83%)
occurrences (all)	4	3	6
Abdominal pain			

subjects affected / exposed	1 / 24 (4.17%)	2 / 19 (10.53%)	2 / 24 (8.33%)
occurrences (all)	1	2	2
Abdominal pain lower			
subjects affected / exposed	1 / 24 (4.17%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	6
Abdominal pain upper			
subjects affected / exposed	1 / 24 (4.17%)	2 / 19 (10.53%)	2 / 24 (8.33%)
occurrences (all)	1	2	3
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 24 (4.17%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	2
Mouth ulceration			
subjects affected / exposed	1 / 24 (4.17%)	2 / 19 (10.53%)	0 / 24 (0.00%)
occurrences (all)	2	13	0
Abdominal discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	3 / 24 (12.50%)
occurrences (all)	0	7	3
Dental caries			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Dry mouth			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Dysphagia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			

subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Glossodynia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Gingival pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Inguinal hernia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Irritable bowel syndrome			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Lip blister			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Noninfective gingivitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Oral disorder			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Oral discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Vomiting			

subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	3 / 24 (12.50%)
occurrences (all)	0	1	6
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 24 (16.67%)	2 / 19 (10.53%)	4 / 24 (16.67%)
occurrences (all)	8	3	16
Acne			
subjects affected / exposed	3 / 24 (12.50%)	4 / 19 (21.05%)	12 / 24 (50.00%)
occurrences (all)	3	5	17
Erythema			
subjects affected / exposed	2 / 24 (8.33%)	1 / 19 (5.26%)	3 / 24 (12.50%)
occurrences (all)	2	1	4
Decubitus ulcer			
subjects affected / exposed	1 / 24 (4.17%)	2 / 19 (10.53%)	0 / 24 (0.00%)
occurrences (all)	2	2	0
Alopecia			
subjects affected / exposed	1 / 24 (4.17%)	3 / 19 (15.79%)	5 / 24 (20.83%)
occurrences (all)	1	3	6
Dry skin			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	2 / 24 (8.33%)
occurrences (all)	1	1	2
Skin lesion			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	3 / 24 (12.50%)
occurrences (all)	1	1	3
Pruritus			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Hyperkeratosis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	1	1	1
Acne cystic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Ecchymosis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1

Dermal cyst			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Blister			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Eczema			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Hirsutism			
subjects affected / exposed	0 / 24 (0.00%)	3 / 19 (15.79%)	1 / 24 (4.17%)
occurrences (all)	0	3	1
Hyperhidrosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Intertrigo			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hypertrichosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	4 / 24 (16.67%)
occurrences (all)	0	0	4
Nail bed bleeding			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	14	0
Madarosis			
subjects affected / exposed	0 / 24 (0.00%)	8 / 19 (42.11%)	13 / 24 (54.17%)
occurrences (all)	0	9	13
Onychalgia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Perioral dermatitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Papule			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0

Onycholysis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Petechiae			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Rash vesicular			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Rash pruritic			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 24 (12.50%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	3	1	1
Nephrolithiasis			
subjects affected / exposed	3 / 24 (12.50%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	3	0	2
Dysuria			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Proteinuria			

subjects affected / exposed	2 / 24 (8.33%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	2	2	0
Pollakiuria			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 24 (37.50%)	9 / 19 (47.37%)	8 / 24 (33.33%)
occurrences (all)	13	24	16
Pain in extremity			
subjects affected / exposed	9 / 24 (37.50%)	8 / 19 (42.11%)	6 / 24 (25.00%)
occurrences (all)	19	22	18
Myalgia			
subjects affected / exposed	3 / 24 (12.50%)	3 / 19 (15.79%)	1 / 24 (4.17%)
occurrences (all)	3	4	4
Neck pain			
subjects affected / exposed	3 / 24 (12.50%)	4 / 19 (21.05%)	2 / 24 (8.33%)
occurrences (all)	5	13	2
Muscle swelling			
subjects affected / exposed	2 / 24 (8.33%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	5	0	0
Back pain			
subjects affected / exposed	1 / 24 (4.17%)	6 / 19 (31.58%)	7 / 24 (29.17%)
occurrences (all)	1	13	9
Joint swelling			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	1	1	1
Spinal pain			
subjects affected / exposed	1 / 24 (4.17%)	4 / 19 (21.05%)	1 / 24 (4.17%)
occurrences (all)	4	10	3
Calcification of muscle			

subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Arthritis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Flank pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Exostosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Coccydynia			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	1 / 24 (4.17%)
occurrences (all)	0	3	1
Inguinal mass			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	1 / 24 (4.17%)
occurrences (all)	0	3	1
Muscular weakness			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Joint noise			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			

subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	2 / 24 (8.33%)
occurrences (all)	0	2	3
Pain in jaw			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Tendon pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 24 (20.83%)	9 / 19 (47.37%)	5 / 24 (20.83%)
occurrences (all)	7	14	6
Urinary tract infection			
subjects affected / exposed	3 / 24 (12.50%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	4	0	2
Gastroenteritis			
subjects affected / exposed	1 / 24 (4.17%)	2 / 19 (10.53%)	2 / 24 (8.33%)
occurrences (all)	1	2	2
Influenza			
subjects affected / exposed	1 / 24 (4.17%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Pharyngitis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	1	1	1
Sinusitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Abdominal abscess			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Abscess			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Abscess limb			
subjects affected / exposed	0 / 24 (0.00%)	3 / 19 (15.79%)	4 / 24 (16.67%)
occurrences (all)	0	24	4

Anorectal cellulitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Anal abscess			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	3 / 24 (12.50%)
occurrences (all)	0	3	4
Abscess rupture			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
COVID-19			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Folliculitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	3 / 24 (12.50%)
occurrences (all)	0	2	3
Conjunctivitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Cellulitis orbital			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Furuncle			
subjects affected / exposed	0 / 24 (0.00%)	3 / 19 (15.79%)	1 / 24 (4.17%)
occurrences (all)	0	13	1
Groin abscess			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Hordeolum			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Infected bite			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Infected dermal cyst			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	2

Otitis externa			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Otitis media acute			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	3	1
Paronychia			
subjects affected / exposed	0 / 24 (0.00%)	3 / 19 (15.79%)	1 / 24 (4.17%)
occurrences (all)	0	4	1
Perirectal abscess			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Pustule			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Skin bacterial infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
Rhinitis			
subjects affected / exposed	0 / 24 (0.00%)	3 / 19 (15.79%)	2 / 24 (8.33%)
occurrences (all)	0	7	3
Subcutaneous abscess			
subjects affected / exposed	0 / 24 (0.00%)	3 / 19 (15.79%)	0 / 24 (0.00%)
occurrences (all)	0	6	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	2 / 24 (8.33%)
occurrences (all)	0	1	2

Tooth infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Tooth abscess			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Vaginal infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Vulval abscess			
subjects affected / exposed	0 / 24 (0.00%)	2 / 19 (10.53%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Vulvitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 19 (5.26%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 24 (8.33%)	0 / 19 (0.00%)	2 / 24 (8.33%)
occurrences (all)	2	0	2
Hypercholesterolaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 19 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	REGN2477 10 mg/kg Q4W		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		

Uterine leiomyoma			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Hot flush			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Vessel puncture site bruise			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Chest pain			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Inflammation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infusion site pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Medical device site bruise			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	7		
Swelling			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Acquired phimosis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Endometrial thickening			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Menstruation irregular			

subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Ovarian cyst				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Perineal cyst				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Prostatitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Respiratory, thoracic and mediastinal disorders				
Epistaxis				
subjects affected / exposed	10 / 20 (50.00%)			
occurrences (all)	32			
Cough				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Dyspnoea				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Oropharyngeal pain				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Nasal congestion				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Atelectasis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Haemoptysis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	5			
Nasal dryness				

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oropharyngeal discomfort			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Sinus congestion			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Upper-airway cough syndrome			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Somatic symptom disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Investigations			
Crystal urine present			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Fibrin D dimer increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Platelet function test abnormal			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
White blood cell count increased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Extraskeletal ossification			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Head injury			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Post-traumatic pain			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Animal bite			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Arthropod bite			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Back injury			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Limb injury			

subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Lower limb fracture subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Skin laceration subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Post vaccination syndrome subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Tooth fracture subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Traumatic haematoma subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Vascular access site swelling subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Congenital, familial and genetic disorders			
Gilbert's syndrome subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Sebaceous naevus subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	10 / 20 (50.00%) 28		
Dizziness subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 7		
Paraesthesia			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Neuralgia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Cervical radiculopathy			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Burning sensation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	8		
Head discomfort			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Post-traumatic headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Increased tendency to bruise			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0			
Lymph node pain subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0			
Lymphadenitis subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0			
Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1			
Microcytic anaemia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0			
Ear and labyrinth disorders Conductive deafness subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0			
Ear pain subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0			
Ear discomfort subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0			
Ear pruritus subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0			
Hyperacusis subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1			
Hypoacusis subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0			
Tinnitus				

subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Eye disorders			
Ocular hypertension			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Photophobia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	7		
Abdominal pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Abdominal pain lower			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Mouth ulceration				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	3			
Abdominal discomfort				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Aphthous ulcer				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Dental caries				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Dry mouth				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Dysphagia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Flatulence				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Gastrointestinal disorder				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Gastrointestinal pain				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Glossodynia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Gingival pain				

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Inguinal hernia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Irritable bowel syndrome			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Lip blister			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Noninfective gingivitis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Oral disorder			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Oral discomfort			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Acne			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	6		

Erythema				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Decubitus ulcer				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	2			
Alopecia				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	3			
Dry skin				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Skin lesion				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Pruritus				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Hyperkeratosis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Acne cystic				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Ecchymosis				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Dermal cyst				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Blister				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	3			
Eczema				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	3			

Hirsutism				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Hyperhidrosis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Intertrigo				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	2			
Hypertrichosis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Nail bed bleeding				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Madarosis				
subjects affected / exposed	6 / 20 (30.00%)			
occurrences (all)	6			
Onychalgia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Perioral dermatitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Papule				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Onycholysis				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Petechiae				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Rash vesicular				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			

Rash pruritic subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Rash papular subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Skin exfoliation subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Urticaria subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Skin ulcer subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Dysuria subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Proteinuria subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Pollakiuria subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Urinary retention subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Musculoskeletal and connective tissue disorders			

Arthralgia				
subjects affected / exposed	7 / 20 (35.00%)			
occurrences (all)	8			
Pain in extremity				
subjects affected / exposed	5 / 20 (25.00%)			
occurrences (all)	6			
Myalgia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Neck pain				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	5			
Muscle swelling				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Back pain				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	4			
Joint swelling				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Spinal pain				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Calcification of muscle				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Arthritis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Temporomandibular joint syndrome				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Flank pain				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			

Exostosis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Coccydynia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Inguinal mass			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Joint noise			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal discomfort			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pain in jaw			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Tendon pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	5			
Urinary tract infection				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Influenza				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Abdominal abscess				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Abscess				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Abscess limb				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	3			
Anorectal cellulitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Anal abscess				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Abscess rupture				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
COVID-19				

subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Folliculitis				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	4			
Conjunctivitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	2			
Cellulitis orbital				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Furuncle				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Groin abscess				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Hordeolum				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Infected bite				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Infected dermal cyst				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Otitis externa				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Otitis media acute				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Paronychia				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Perirectal abscess				

subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Respiratory tract infection				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Pustule				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Skin infection				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Skin bacterial infection				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	5			
Subcutaneous abscess				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Tooth infection				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Tooth abscess				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Vaginal infection				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Viral upper respiratory tract infection				

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Vulval abscess			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Vulvitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Hypercholesterolaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2018	Protocol Amendment 1: The purpose of this amendment 1 Global was to remove the requirement that subjects have the specific classic ACVR1[R206H] mutation. This change was 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 indicated that REGN2477 may be effective for all FOP mutations. This change expands the scope of the study to include subjects with a clinical diagnosis of FOP who may have different ACVR1 mutations. To support interpretation of the study results, all subjects will have their ACVR1 gene sequenced during the study (mandatory). The primary statistical analyses for the study was based on the original study design, not the expanded study population.
29 November 2018	Protocol Amendment 2: The purpose of this amendment was 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.
15 February 2019	Protocol Amendment 3: The purpose of this amendment was to revise the protocol to reflect new safety information relating to a potential risk for epistaxis. To mitigate the potential risk for epistaxis, exclusion criteria were added.
21 June 2019	Protocol Amendment 4: 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.
25 October 2019	Protocol Amendment 5: The purpose of this amendment was 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.
22 May 2020	Protocol Amendment 6: The purpose of this amendment was 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).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Dosing of garetosmab (REGN2477) was put on hold on 30 Oct 2020. Study participants continued to be followed for safety until end of study on 16 Sep 2021.

Notes: