Clinical trial results:
ASCEND GO 2: A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled Study of RVT 1401 for the Treatment of Patients with Active, Moderate to Severe Graves' Ophthalmopathy

Summary

EudraCT number	2018-004676-35
Trial protocol	DE ES IT
Global end of trial date	15 April 2021

Results information

Result version number	v1 (current)
This version publication date	09 September 2022
First version publication date	09 September 2022

Trial information

Trial identification

Sponsor protocol code	RVT-1401-2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03938545
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Immunovant Sciences GmbH
Sponsor organisation address	Viaduktstrasse 8, Basel, Switzerland, 4051
Public contact	Central Study Contact, Immunovant Sciences GmbH, +1 800-797-0414, clinicaltrials@immunovant.com
Scientific contact	Central Study Contact, Immunovant Sciences GmbH, +1 800-797-0414, clinicaltrials@immunovant.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	23 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2021
Global end of trial reached?	Yes
Global end of trial date	15 April 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study was to examine the effects of RVT-1401 versus placebo on proptosis responder rate at Week 13 and to assess the safety and tolerability of RVT-1401 in participants with active, moderate to severe Graves' Ophthalmopathy (GO)

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Council for Harmonisation (ICH) guidelines, and all of the applicable basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998. These standards were consistent with the requirements of the European Community Directive 2001/20/EC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	65
EEA total number of subjects	44

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)	63
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 96 participants were screened, of which 65 participants were enrolled and randomized into the study. The total duration of the study was up to 20 weeks.

Period 1

Period 1 title	Overall Study (overall period)
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	RVT-1401 680 mg/week

Arm description:

Participants received a RVT-1401 680 milligram (mg) subcutaneous (SC) injection weekly for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	batoclimab
Investigational medicinal product code	RVT-1401
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 680 mg. Doses were prepared by an unblinded pharmacist or designee. Doses were administered to participants by pre-identified unblinded clinic staff or designee.

Arm title	RVT-1401 340 mg/week

Arm description:

Participants received a RVT-1401 340 mg SC injection weekly for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	batoclimab
Investigational medicinal product code	RVT-1401
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 340 mg. Doses were prepared by an unblinded pharmacist or designee. Doses were administered to participants by pre-identified unblinded clinic staff or designee.

Arm title	RVT-1401 255 mg/week

Arm description:

Participants received a RVT-1401 255 mg SC injection weekly for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	batoclimab
Investigational medicinal product code	RVT-1401
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 255 mg. Doses were prepared by an unblinded pharmacist or designee. Doses were administered to participants by pre-identified unblinded clinic staff or designee.

Arm title	Placebo

Arm description:

Participants received a matching placebo SC injection weekly for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received matched placebo. Doses were prepared by an unblinded pharmacist or designee. Doses were administered to participants by pre-identified unblinded clinic staff or designee.

Number of subjects in period 1	RVT-1401 680 mg/week	RVT-1401 340 mg/week	RVT-1401 255 mg/week
Started	18	19	10
Completed	10	14	7
Not completed	8	5	3
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	1	-	-
Study Terminated By Sponsor	6	4	2
Pregnancy	1	-	-
Non-Compliance With Study Drug	-	-	1
Lost to follow-up	-	-	-

Number of subjects in period 1	Placebo
Started	18
Completed	13
Not completed	5
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Study Terminated By Sponsor	4
Pregnancy	-
Non-Compliance With Study Drug	-
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	RVT-1401 680 mg/week
Reporting group description:	
Participants received a RVT-1401 680 milligram (mg) subcutaneous (SC) injection weekly for 12 weeks.	
Reporting group title	RVT-1401 340 mg/week
Reporting group description:	
Participants received a RVT-1401 340 mg SC injection weekly for 12 weeks.	
Reporting group title	RVT-1401 255 mg/week
Reporting group description:	
Participants received a RVT-1401 255 mg SC injection weekly for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received a matching placebo SC injection weekly for 12 weeks.	

Reporting group values	RVT-1401 680 mg/week	RVT-1401 340 mg/week	RVT-1401 255 mg/week
Number of subjects	18	19	10
Age categorical Units:			
Age continuous Units: Years			
arithmetic mean	46.6	52.4	44.3
standard deviation	± 9.03	± 8.08	± 12.61
Gender categorical Units: Subjects			
Female	15	13	8
Male	3	6	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	17	18	10
More than one race	0	0	0
Unknown or Not Reported	1	1	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	2	0
Not Hispanic or Latino	17	17	10
Unknown or Not Reported	0	0	0
Mean Proptosis Units: Millimeters (mm)			
arithmetic mean	22.7	23.0	22.3
standard deviation	± 3.10	± 3.97	± 2.95
Mean Clinical Activity Score (CAS)			

The CAS (7-item scale) measured the acute signs of inflammation like pain, redness, swelling, and impaired function in Graves' Ophthalmology (GO). One point was given for the presence of each of the parameters assessed. The CAS ranged from 0 to 7. Active GO was defined as a CAS of ≥4. Baseline was the last available assessment prior to time of the first dose unless it was specified otherwise and was identified as Day 1. A negative change from baseline represented clinical improvement.			
Units: Units on a scale			
arithmetic mean	4.8	5.1	4.9
standard deviation	± 0.86	± 0.94	± 0.99

Reporting group values	Placebo	Total	
Number of subjects	18	65	
Age categorical			
Units:			
Age continuous			
Units: Years			
arithmetic mean	46.1		
standard deviation	± 12.47	-	
Gender categorical			
Units: Subjects			
Female	14	50	
Male	4	15	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	18	63	
More than one race	0	0	
Unknown or Not Reported	0	2	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	3	
Not Hispanic or Latino	18	62	
Unknown or Not Reported	0	0	
Mean Proptosis			
Units: Millimeters (mm)			
arithmetic mean	22.7		
standard deviation	± 2.70	-	
Mean Clinical Activity Score (CAS)			
The CAS (7-item scale) measured the acute signs of inflammation like pain, redness, swelling, and impaired function in Graves' Ophthalmology (GO). One point was given for the presence of each of the parameters assessed. The CAS ranged from 0 to 7. Active GO was defined as a CAS of ≥4. Baseline was the last available assessment prior to time of the first dose unless it was specified otherwise and was identified as Day 1. A negative change from baseline represented clinical improvement.			
Units: Units on a scale			
arithmetic mean	5.2		
standard deviation	± 1.04	-	

End points

End points reporting groups

Reporting group title	RVT-1401 680 mg/week
Reporting group description:	
Participants received a RVT-1401 680 milligram (mg) subcutaneous (SC) injection weekly for 12 weeks.	
Reporting group title	RVT-1401 340 mg/week
Reporting group description:	
Participants received a RVT-1401 340 mg SC injection weekly for 12 weeks.	
Reporting group title	RVT-1401 255 mg/week
Reporting group description:	
Participants received a RVT-1401 255 mg SC injection weekly for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received a matching placebo SC injection weekly for 12 weeks.	

Primary: Percentage of participants with proptosis response at Week 13

End point title	Percentage of participants with proptosis response at Week 13
End point description:	
Proptosis was assessed using an exophthalmometer. A proptosis response was defined as having at least a 2 millimeter (mm) reduction in study eye proptosis without a deterioration (at least a 2 mm increase) in the fellow eye at the same visit. The study eye was defined as the most severely affected eye at the baseline visit. The analysis was performed in Intent-to-Treat (ITT) Population: All randomized participants who received at least one dose of RVT-1401 or placebo and had 1 post-baseline visit. Participants with proptosis assessment at Week 13 were included in the analysis.	
End point type	Primary
End point timeframe:	
Baseline; Week 13	

End point values	RVT-1401 680 mg/week	RVT-1401 340 mg/week	RVT-1401 255 mg/week	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	13	6	12
Units: Percentage of participants				
number (not applicable)	30.0	30.8	0	8.3

Statistical analyses

Statistical analysis title	Risk Difference: RVT 1401 680 mg/week vs Placebo
Statistical analysis description:	
The risk difference was obtained from a weighted average of the difference within each stratum using Cochran Mantel-Haenszel weights.	
Comparison groups	RVT-1401 680 mg/week v Placebo

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1993 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	21.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	54.1

Notes:

[1] - p-values were obtained from a Mantel-Haenszel test stratified by smoking status at baseline comparing RVT-1401 680 mg/Week group to placebo.

Statistical analysis title	Risk Difference: RVT 1401 340 mg/week vs Placebo

Statistical analysis description:

The risk difference was obtained from a weighted average of the difference within each stratum using Cochran Mantel-Haenszel weights.

Comparison groups	RVT-1401 340 mg/week v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1016 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	24.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	53.2

Notes:

[2] - p-values were obtained from a Mantel-Haenszel test stratified by smoking status at baseline comparing RVT-1401 340 mg/Week group to placebo.

Statistical analysis title	Risk Difference: RVT 1401 255 mg/week vs Placebo

Statistical analysis description:

The risk difference was obtained from a weighted average of the difference within each stratum using Cochran Mantel-Haenszel weights.

Comparison groups	RVT-1401 255 mg/week v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2963 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-8.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24
upper limit	7.3

Notes:

[3] - p-values were obtained from a Mantel-Haenszel test stratified by smoking status at baseline comparing RVT-1401 255 mg/Week group to placebo.

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

End point title	Number of Participants with Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (SAEs)[4]

End point description:

AEs - any untoward medical occurrences in a participant, temporally associated with use of a medicinal product, whether or not considered related to the product. Clinically significant changes determined by the Investigator such as vital signs, ECGs, and clinical laboratory values were also reported as AEs. TEAE is defined as an AE that starts on or after the first dose of the study drug and before 30 days after the last dose of the study drug. SAEs were defined as any untoward medical occurrences that: resulted in death; were life-threatening; required hospitalization or prolongation of existing hospitalization; resulted in disability/incapacity; were congenital anomaly/birth defects; were important medical events that may have jeopardized the participant or may have required medical or surgical intervention; invasive or malignant cancers; and development of drug dependency or drug abuse.

End point type	Primary

End point timeframe:

From Baseline up to Week 20

Notes:

[4] - 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 analysis was performed for this safety endpoint.

End point values	RVT-1401 680 mg/week	RVT-1401 340 mg/week	RVT-1401 255 mg/week	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[5]	19	10	18
Units: Participants				
number (not applicable)				
TEAEs	16	16	8	16
SAEs	0	0	1	0

Notes:

[5] - Safety Population: All randomized participants who received at least 1 dose of RVT-1401 or placebo.

Statistical analyses

No statistical analyses for this end point

Secondary: Least Square Mean Percent Change From Baseline in Binding Anti-thyroid-stimulating Hormone Receptor (TSHR) Antibody Levels to Week 13

End point title	Least Square Mean Percent Change From Baseline in Binding Anti-thyroid-stimulating Hormone Receptor (TSHR) Antibody Levels to Week 13

End point description:

Binding Anti-TSHR antibody serum levels are directly associated with GO clinical features. Baseline was the last available assessment prior to the time of the first dose unless it was specified otherwise and was identified as Day 1. A negative change from baseline in binding anti-TSHR antibody levels indicated therapeutic benefit. The analysis was performed in ITT Population. Participants with anti-TSHR serum

assessments at Week 13 were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	RVT-1401 680 mg/week	RVT-1401 340 mg/week	RVT-1401 255 mg/week	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	13	6	12
Units: Percent change				
least squares mean (confidence interval 95%)	-64.605 (-87.006 to -42.205)	-69.663 (-89.272 to -50.054)	-41.843 (-70.070 to -13.616)	-4.520 (-25.580 to 16.539)

Statistical analyses

Statistical analysis title	LSM Difference: RVT 1401 680 mg/week vs Placebo
Comparison groups	RVT-1401 680 mg/week v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-60.085
Confidence interval	
level	95 %
sides	2-sided
lower limit	-88.857
upper limit	-31.313

Notes:

[6] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	LSM Difference: RVT 1401 340 mg/week vs Placebo
Comparison groups	RVT-1401 340 mg/week v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-65.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	-91.927
upper limit	-38.358

Notes:

[7] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	LSM Difference: RVT 1401 255 mg/week vs Placebo
Comparison groups	RVT-1401 255 mg/week v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0284 [8]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-37.323
Confidence interval	
level	95 %
sides	2-sided
lower limit	-70.455
upper limit	-4.19

Notes:

[8] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Secondary: Least Square Mean Percent Change From Baseline in Total IgG Levels

End point title	Least Square Mean Percent Change From Baseline in Total IgG Levels

End point description:

Blood samples we collected to determine total IgG levels. Baseline was the last available assessment prior to the time of the first dose unless it was specified otherwise and was identified as Day 1. A negative change from baseline in the IgG levels indicated therapeutic benefit. The analysis was performed in ITT Population: Participants with evaluable data were included for the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	RVT-1401 680 mg/week	RVT-1401 340 mg/week	RVT-1401 255 mg/week	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	13	6	12
Units: Grams per liter (g/L)				
least squares mean (confidence interval 95%)	-79.101 (-86.444 to -71.757)	-65.103 (-71.687 to -58.519)	-57.934 (-67.216 to -48.651)	-6.098 (-12.948 to 0.753)

Statistical analyses

Statistical analysis title	Week 13: RVT-1401 680 mg/Week, Placebo
Comparison groups	RVT-1401 680 mg/week v Placebo

Number of subjects included in analysis	22
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-73.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.309
upper limit	-63.697

Statistical analysis title	Week 13: RVT-1401 340 mg/Week, Placebo
Comparison groups	Placebo v RVT-1401 340 mg/week
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-59.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.821
upper limit	-50.19

Statistical analysis title	Week 13: RVT-1401 255 mg/Week, Placebo
Comparison groups	Placebo v RVT-1401 255 mg/week
Number of subjects included in analysis	18
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-51.836
Confidence interval	
level	95 %
sides	2-sided
lower limit	-62.66
upper limit	-41.012

Secondary: Least Square Mean Percent Change From Baseline in IgG Subclasses 1,

2, 3 and 4

End point title	Least Square Mean Percent Change From Baseline in IgG Subclasses 1, 2, 3 and 4

End point description:

Blood samples were collected to determine IgG 1,2,3 and 4 levels. Baseline was the last available assessment prior to the time of the first dose unless it was specified otherwise and was identified as Day 1. A negative change from baseline in the IgG levels indicated therapeutic benefit. The analysis was performed in ITT Population. Participants with evaluable data were included for the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	RVT-1401 680 mg/week	RVT-1401 340 mg/week	RVT-1401 255 mg/week	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	12	5	9
Units: g/L				
least squares mean (confidence interval 95%)				
IgG1	-82.040 (-90.757 to -73.323)	-68.141 (-75.721 to -60.561)	-67.784 (-79.273 to -56.294)	-0.550 (-9.307 to 8.207)
IgG2	-75.346 (-84.395 to -66.297)	-53.678 (-62.077 to -45.280)	-53.879 (-65.648 to -42.110)	-0.481 (-9.392 to 8.431)
IgG3	-88.260 (-98.901 to -77.619)	-65.211 (-74.336 to -56.085)	-66.182 (-79.856 to -52.508)	0.503 (-9.907 to 10.914)
IgG4	-68.559 (-77.456 to -59.663)	-55.391 (-63.131 to -47.651)	-52.916 (-64.774 to -41.059)	0.163 (-9.167 to 9.493)

Statistical analyses

Statistical analysis title	IgG1: RVT-1401 680 mg/Week, Placebo
Comparison groups	RVT-1401 680 mg/week v Placebo
Number of subjects included in analysis	18
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [9]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-81.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-93.203
upper limit	-69.777

Notes:

[9] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	IgG1: RVT-1401 340 mg/Week, Placebo
Comparison groups	RVT-1401 340 mg/week v Placebo
Number of subjects included in analysis	21
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [10]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-67.591
Confidence interval	
level	95 %
sides	2-sided
lower limit	-78.562
upper limit	-56.62

Notes:

[10] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	IgG1: RVT-1401 255 mg/Week, Placebo
Comparison groups	RVT-1401 255 mg/week v Placebo
Number of subjects included in analysis	14
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [11]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-67.233
Confidence interval	
level	95 %
sides	2-sided
lower limit	-81.073
upper limit	-53.394

Notes:

[11] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	IgG2: RVT-1401 680 mg/Week, Placebo
Comparison groups	RVT-1401 680 mg/week v Placebo
Number of subjects included in analysis	18
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [12]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-74.865

Confidence interval	
level	95 %
sides	2-sided
lower limit	-86.898
upper limit	-62.832

Notes:

[12] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	IgG2: RVT-1401 340 mg/Week, Placebo
Comparison groups	RVT-1401 340 mg/week v Placebo
Number of subjects included in analysis	21
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [13]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-53.198
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64.799
upper limit	-41.596

Notes:

[13] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	IgG2: RVT-1401 255 mg/Week, Placebo
Comparison groups	RVT-1401 255 mg/week v Placebo
Number of subjects included in analysis	14
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [14]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-53.398
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.552
upper limit	-39.245

Notes:

[14] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	IgG3: RVT-1401 680 mg/Week, Placebo
Comparison groups	RVT-1401 680 mg/week v Placebo

Number of subjects included in analysis	18
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [15]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-88.764
Confidence interval	
level	95 %
sides	2-sided
lower limit	-103.039
upper limit	-74.489

Notes:

[15] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	IgG3: RVT-1401 340 mg/Week, Placebo
Comparison groups	RVT-1401 340 mg/week v Placebo
Number of subjects included in analysis	21
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [16]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-65.714
Confidence interval	
level	95 %
sides	2-sided
lower limit	-78.742
upper limit	-52.686

Notes:

[16] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	IgG3: RVT-1401 255 mg/Week, Placebo
Comparison groups	RVT-1401 255 mg/week v Placebo
Number of subjects included in analysis	14
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [17]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-66.685
Confidence interval	
level	95 %
sides	2-sided
lower limit	-83.157
upper limit	-50.214

Notes:

[17] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	IgG4: RVT-1401 680 mg/Week, Placebo

Comparison groups	RVT-1401 680 mg/week v Placebo
Number of subjects included in analysis	18
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [18]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-68.722
Confidence interval	
level	95 %
sides	2-sided
lower limit	-80.877
upper limit	-56.568

Notes:

[18] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	IgG4: RVT-1401 340 mg/Week, Placebo
Comparison groups	RVT-1401 340 mg/week v Placebo
Number of subjects included in analysis	21
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [19]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-55.554
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.182
upper limit	-43.926

Notes:

[19] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Statistical analysis title	IgG4: RVT-1401 255 mg/Week, Placebo
Comparison groups	RVT-1401 255 mg/week v Placebo
Number of subjects included in analysis	14
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [20]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-53.079
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.948
upper limit	-38.21

Notes:

[20] - The model included baseline value of the corresponding parameter, smoking stratum, and treatment group as covariates.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to Week 20

Adverse event reporting additional description:

TEAE is defined as an AE that starts on or after the first dose of the study drug and before 30 days after the last dose of the study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	RVT-1401 680 mg/week

Reporting group description:

Participants received a RVT-1401 680 milligram (mg) subcutaneous (SC) injection weekly for 12 weeks.

Reporting group title	RVT-1401 340 mg/week

Reporting group description:

Participants received a RVT-1401 340 mg SC injection weekly for 12 weeks.

Reporting group title	RVT-1401 255 mg/week

Reporting group description:

Participants received a RVT-1401 255 mg SC injection weekly for 12 weeks.

Reporting group title	Placebo

Reporting group description:

Participants received a matching placebo SC injection weekly for 12 weeks.

Serious adverse events	RVT-1401 680 mg/week	RVT-1401 340 mg/week	RVT-1401 255 mg/week
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Eye disorders			
Optic neuropathy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Eye disorders			
Optic neuropathy			
subjects affected / exposed	0 / 18 (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	RVT-1401 680 mg/week	RVT-1401 340 mg/week	RVT-1401 255 mg/week
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 18 (88.89%)	16 / 19 (84.21%)	8 / 10 (80.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	5 / 18 (27.78%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	5	0	0
Influenza like illness			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Injection site urticaria			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nodule			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pyrexia			

subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Injection site pain			
subjects affected / exposed	1 / 18 (5.56%)	3 / 19 (15.79%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
Chills			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Injection site bruising			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Injection site pruritus			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	0 / 18 (0.00%)	2 / 19 (10.53%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Injection site swelling			
subjects affected / exposed	1 / 18 (5.56%)	4 / 19 (21.05%)	1 / 10 (10.00%)
occurrences (all)	1	4	1
Injection site erythema			
subjects affected / exposed	9 / 18 (50.00%)	9 / 19 (47.37%)	3 / 10 (30.00%)
occurrences (all)	9	9	3
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Menorrhagia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dysmenorrhoea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Investigations			
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Thyroxine decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Thyroxine increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Tri-iodothyronine decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Tri-iodothyronine increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 18 (0.00%)	2 / 19 (10.53%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Vitamin D decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Intraocular pressure increased			
subjects affected / exposed	2 / 18 (11.11%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural			

complications			
Accident			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Back injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Paresis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tension headache			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dyspraxia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Headache			

subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Parosmia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	2 / 18 (11.11%)	5 / 19 (26.32%)	1 / 10 (10.00%)
occurrences (all)	2	5	1
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blepharitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Optic neuropathy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 18 (5.56%)	2 / 19 (10.53%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Abdominal pain			

subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 18 (0.00%)	2 / 19 (10.53%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	4 / 19 (21.05%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Neurodermatitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	1 / 18 (5.56%)	3 / 19 (15.79%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
Pain in extremity			

subjects affected / exposed	1 / 18 (5.56%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Osteoarthritis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Infections and infestations			
Gastrointestinal viral infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Groin abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Erythema migrans			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Fungal skin infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Herpes zoster			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Corona virus infection			
subjects affected / exposed	1 / 18 (5.56%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0

Urinary tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 18 (88.89%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		

Influenza like illness				
subjects affected / exposed	0 / 18 (0.00%)			
occurrences (all)	0			
Injection site urticaria				
subjects affected / exposed	0 / 18 (0.00%)			
occurrences (all)	0			
Nodule				
subjects affected / exposed	0 / 18 (0.00%)			
occurrences (all)	0			
Pain				
subjects affected / exposed	0 / 18 (0.00%)			
occurrences (all)	0			
Pyrexia				
subjects affected / exposed	0 / 18 (0.00%)			
occurrences (all)	0			
Injection site pain				
subjects affected / exposed	0 / 18 (0.00%)			
occurrences (all)	0			
Chills				
subjects affected / exposed	0 / 18 (0.00%)			
occurrences (all)	0			
Injection site bruising				
subjects affected / exposed	0 / 18 (0.00%)			
occurrences (all)	0			
Injection site pruritus				
subjects affected / exposed	0 / 18 (0.00%)			
occurrences (all)	0			
Fatigue				
subjects affected / exposed	0 / 18 (0.00%)			
occurrences (all)	0			
Injection site swelling				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Injection site erythema				
subjects affected / exposed	3 / 18 (16.67%)			
occurrences (all)	3			

Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Menorrhagia			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Dysmenorrhoea			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Investigations			
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Thyroxine decreased			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Thyroxine increased			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Tri-iodothyronine decreased			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Tri-iodothyronine increased			

subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Blood cholesterol increased			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Vitamin D decreased			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Intraocular pressure increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Back injury			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Tooth fracture			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Paresis			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Dysgeusia			

subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Tension headache			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Dyspraxia			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Migraine			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Parosmia			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Lethargy			
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Blepharitis			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Optic neuropathy			

subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Aphthous ulcer			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Neurodermatitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Infections and infestations			
Gastrointestinal viral infection			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Groin abscess			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Erythema migrans			

subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Fungal skin infection			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Herpes zoster			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Corona virus infection			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Herpes simplex			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Hyperlipidaemia			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2019	The following items were updated: • Definition for proptosis responder was updated to remove subjects with < 3 mm proptosis at baseline. • Additional details on method for primary analysis was added. • Additional information to note that the first interim analysis will be blinded was added. •To simplify the CAS administration, this was changed from the 10-item to the 7-item CAS. As a result, proptosis and motility assessments have been added. Other administrative changes were also made.
09 August 2019	The following items were updated: • Dosing was extended from 6 to 12 weeks. • The follow up period was shortened from 12 weeks to 8 weeks. • Associated changes related to the updated study design have also been made to the objectives and endpoints, entry criteria, and the timing of assessments in the Time and Events Table. • Additional laboratory tests were also included. • Repeat CT scans will only be completed for week 13 proptosis responders instead of for all participants. Other administrative changes were also made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 February 2021	The study was halted due to a safety finding (hypercholesterolemia) and not resumed.	-

Notes:

Limitations and caveats

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

The study was terminated early due to a safety finding (hypercholesterolemia).

Notes: