Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Multi-center Study of the Safety and Efficacy of 3-month Subcutaneous REGN1033 Treatment in Patients with Sarcopenia

Summary

EudraCT number	2013-003134-33
Trial protocol	ES NL
Global end of trial date	27 February 2015

Results information

Result version number	v1 (current)
This version publication date	01 May 2018
First version publication date	01 May 2018

Trial information

Trial identification

Sponsor protocol code	R1033-SRC-1239

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01963598
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, United States, 10591
Public contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc., 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	15 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of multiple doses of REGN1033 administered subcutaneously (SC) for 12 weeks on total lean body mass (LBM), as measured by dual energy X-ray absorptiometry (DXA) in subjects with sarcopenia.

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 Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 December 2013
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: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 244
Worldwide total number of subjects	253
EEA total number of subjects	9

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)	0

From 65 to 84 years	221
85 years and over	32

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 56 centers in 4 countries between 30 December 2013 and 27 February 2015. A total of 939 subjects were screened in the study, of whom, 686 were screen failures.

Pre-assignment

Screening details:

A total of 253 subjects were randomized in 1:1:1:1 ratio to Placebo (for REGN1033) every 2 weeks (q2w), REGN1033 100 mg q2w, REGN1033 300 mg every 4 weeks (q4w) and REGN1033 300 mg q2w arms.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Single SC injection of Placebo q2w for 12 weeks

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

Dosage and administration details:

SC injection in separate abdominal quadrants for all doses.

Arm title	REGN1033 100 mg q4w

Arm description:

Single SC injection of REGN1033 100 mg q4w alternating with placebo q4w for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Trevogrumab
Investigational medicinal product code	REGN1033
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

SC injection in separate abdominal quadrants for all doses.

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

Dosage and administration details:

SC injection in separate abdominal quadrants for all doses.

Arm title	REGN1033 300 mg q4w

Arm description:	
Single SC injection of REGN1033 300 mg q4w alternating with placebo q4w for 12 weeks.	
Arm type	Experimental
Investigational medicinal product name	Trevogrumab
Investigational medicinal product code	REGN1033
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
SC injection in separate abdominal quadrants for all doses.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
SC injection in separate abdominal quadrants for all doses.	
Arm title	REGN1033 300 mg q2w
Arm description:	
Single SC injection of REGN1033 300 mg q2w for 12 weeks.	
Arm type	Experimental
Investigational medicinal product name	Trevogrumab
Investigational medicinal product code	REGN1033
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
SC injection in separate abdominal quadrants for all doses.	

Number of subjects in period 1	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w
Started	65	63	65
Completed	64	60	61
Not completed	1	3	4
Consent withdrawn by subject	-	-	1
Adverse events	1	3	2
Adverse event, non-fatal	-	-	-
Death	-	-	-
Lost to follow-up	-	-	1

Number of subjects in period 1	REGN1033 300 mg q2w
Started	60
Completed	56
Not completed	4
Consent withdrawn by subject	1
Adverse events	-

Adverse event, non-fatal	2
Death	1
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Single SC injection of Placebo q2w for 12 weeks	
Reporting group title	REGN1033 100 mg q4w
Reporting group description:	
Single SC injection of REGN1033 100 mg q4w alternating with placebo q4w for 12 weeks.	
Reporting group title	REGN1033 300 mg q4w
Reporting group description:	
Single SC injection of REGN1033 300 mg q4w alternating with placebo q4w for 12 weeks.	
Reporting group title	REGN1033 300 mg q2w
Reporting group description:	
Single SC injection of REGN1033 300 mg q2w for 12 weeks.	

Reporting group values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w
Number of subjects	65	63	65
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	78.5	77.3	77.7
standard deviation	± 6.02	± 4.94	± 5.1
Gender categorical Units: Subjects			
Female	33	33	35
Male	32	30	30

Reporting group values	REGN1033 300 mg q2w	Total	
Number of subjects	60	253	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	77.7		
standard deviation	± 6.32	-	
Gender categorical Units: Subjects			
Female	31	132	
Male	29	121	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Single SC injection of Placebo q2w for 12 weeks	
Reporting group title	REGN1033 100 mg q4w
Reporting group description:	
Single SC injection of REGN1033 100 mg q4w alternating with placebo q4w for 12 weeks.	
Reporting group title	REGN1033 300 mg q4w
Reporting group description:	
Single SC injection of REGN1033 300 mg q4w alternating with placebo q4w for 12 weeks.	
Reporting group title	REGN1033 300 mg q2w
Reporting group description:	
Single SC injection of REGN1033 300 mg q2w for 12 weeks.	

Primary: Percent Change in Total Lean Body Mass by DXA From Baseline to Week 12

End point title	Percent Change in Total Lean Body Mass by DXA From Baseline to Week 12
End point description:	
Lean body mass, a measurement of body composition, was assessed by DXA scan. Full analysis set (FAS): includes all randomized subjects who received any study medication, had a baseline assessment and at least one post-baseline primary efficacy assessment. Here "Number of subjects analyzed" = subjects with lean body mass assessment at specified time-points.	
End point type	Primary
End point timeframe:	
Baseline to Week 12	

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	62	62	56
Units: percent change				
least squares mean (standard error)	-0.474 (± 0.4377)	1.191 (± 0.4441)	1.308 (± 0.442)	1.816 (± 0.4662)

Statistical analyses

Statistical analysis title	REGN1033 300mg q2w vs. Placebo
Statistical analysis description:	
Null and alternative hypotheses were tested as: H0: no treatment difference between REGN1033 group and placebo; H1: treatment difference between REGN1033 group and placebo. Multiplicity was controlled for the primary endpoint using hierarchical testing procedure from highest dose (REGN1033 300 mg q2w) to lowest dose (REGN1033 100 mg q4w). Hierarchical testing sequence continued only if the null hypothesis was rejected for the higher dose tested at 0.05 level.	
Comparison groups	REGN1033 300 mg q2w v Placebo

Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0004 [2]
Method	Mixed models Repeated Measures (MMRM)
Parameter estimate	Least square (LS) mean difference
Point estimate	2.289
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.042
upper limit	3.537
Variability estimate	Standard error of the mean
Dispersion value	0.6333

Notes:

[1] - Analysis was performed using mixed-effect repeated measures model (MMRM) with treatment,visit, treatment-by-visit interaction, stratification factors (i.e. sex and body mass index (BMI >27.4 or ≤27.4) as fixed effect and relevant baseline value as a covariate.
[2] - Threshold for significance at 0.05 level.

Statistical analysis title	REGN1033 300mg q4w vs. Placebo

Statistical analysis description:

Hierarchical testing sequence continued only if the null hypothesis was rejected for the higher dose tested previously at 0.05 level.

Comparison groups	REGN1033 300 mg q4w v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0043 [3]
Method	Mixed models Repeated Measures (MMRM)
Parameter estimate	LS mean difference
Point estimate	1.781
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.565
upper limit	2.998
Variability estimate	Standard error of the mean
Dispersion value	0.6175

Notes:

[3] - Threshold for significance at 0.05 level.

Statistical analysis title	REGN 1033 100mg q4w vs. Placebo

Statistical analysis description:

Hierarchical testing sequence continued only if the null hypothesis was rejected for the higher dose tested previously at 0.05 level.

Comparison groups	Placebo v REGN1033 100 mg q4w

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0077 [4]
Method	Mixed models Repeated Measures (MMRM)
Parameter estimate	LS mean difference
Point estimate	1.664
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.445
upper limit	2.884
Variability estimate	Standard error of the mean
Dispersion value	0.6191

Notes:

[4] - Threshold for significance at 0.05 level.

Secondary: Percent Change in Appendicular Lean Body Mass from Baseline to Week 6, 10, 12 and 20

End point title	Percent Change in Appendicular Lean Body Mass from Baseline to Week 6, 10, 12 and 20

End point description:

Appendicular lean body mass was assessed by DXA scan. Percent change: (Appendicular lean body mass at visit minus Appendicular lean body mass at baseline) divided by Appendicular lean body mass at baseline, multiplied by 100. Analysis was performed on FAS population. Here "n" signifies number of subjects with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	63	65	60
Units: Percent Change				
least squares mean (standard error)				
Change at Week 6 (n= 63, 62, 64, 58)	-0.749 (± 0.5501)	1.725 (± 0.5573)	0.926 (± 0.5503)	1.449 (± 0.5798)
Change at Week 10 (n= 61, 62, 62, 55)	-0.923 (± 0.5631)	2.441 (± 0.5654)	1.736 (± 0.5635)	2.127 (± 0.598)
Change at Week 12 (n= 63, 62, 62, 56)	-0.249 (± 0.5605)	2.162 (± 0.5678)	2.033 (± 0.5668)	2.502 (± 0.599)
Change at Week 20 (n= 63, 60, 60, 56)	0.054 (± 0.7284)	2.039 (± 0.7465)	2.693 (± 0.7467)	2.487 (± 0.7764)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Total Lean Mass from Baseline to Week 6, 10, 12, and 20

End point title	Percent Change in Total Lean Mass from Baseline to Week 6, 10, 12, and 20

End point description:

Total lean mass, was assessed by DXA scan. Percent change: (Total lean mass at visit minus total lean mass at baseline) divided by total lean mass at baseline, multiplied by 100. Analysis was performed on FAS population. Here "Number of subjects analyzed" = Number of subjects evaluated for this outcome measure and"n" signifies number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	62	64	59
Units: Percent Change				
least squares mean (standard error)				
Change at Week 6 (n= 63, 62, 64, 58)	-0.54 (± 0.4299)	1.167 (± 0.4362)	0.755 (± 0.4299)	1.058 (± 0.4523)
Change at Week 10 (n= 61, 62, 62, 55)	-0.538 (± 0.4576)	1.65 (± 0.4601)	1.242 (± 0.4575)	1.62 (± 0.4845)
Change at Week 12 (n= 63, 62, 62, 56)	-0.474 (± 0.4377)	1.191 (± 0.4441)	1.308 (± 0.442)	1.816 (± 0.4662)
Change at Week 20 (n= 63, 60, 60, 56)	-0.137 (± 0.61)	1.28 (± 0.6249)	2.401 (± 0.6243)	1.775 (± 0.6488)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Total and Regional (Android and Gynoid) Fat Mass from Baseline to Week 6, 10, 12, and 20

End point title	Percent Change in Total and Regional (Android and Gynoid) Fat Mass from Baseline to Week 6, 10, 12, and 20

End point description:

Total and regional (Android and Gynoid) fat mass, was assessed by DXA scan. Annual percent change: (Total mass at visit minus total mass at baseline) divided by total mass at baseline, multiplied by 100. Analysis was performed on FAS population. Here "n" signifies number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	63	65	60
Units: Percent Change				
least squares mean (standard error)				
Total fat mass:Change at Week 6(n= 63,62,64,58)	0.621 (± 0.6447)	-0.335 (± 0.6525)	-1.383 (± 0.6552)	-0.831 (± 0.6769)
Total fat mass:Change at Week 10(n= 61,62,62,55)	0.049 (± 0.7172)	-0.237 (± 0.7214)	-2.377 (± 0.7273)	-1.321 (± 0.7574)
Total fat mass:Change at Week 12(n= 63,62,62,56)	-0.076 (± 0.7077)	-0.077 (± 0.7167)	-2.666 (± 0.7232)	-0.947 (± 0.7503)
Total fat mass:Change at Week 20(n= 63,60,60,56)	-0.151 (± 1.0109)	-1.881 (± 1.0345)	-5.185 (± 1.0394)	-1.749 (± 1.0743)
Android fat mass:Change at Week 6(n= 63,62,64,58)	2.341 (± 1.1918)	0.063 (± 1.2089)	-1.153 (± 1.2046)	-1.756 (± 1.2535)
Android fat mass:Change at Week 10(n= 61,62,62,55)	0.557 (± 1.1988)	0.7 (± 1.2064)	-3.288 (± 1.2122)	-2.118 (± 1.2695)
Android fat mass:Change at Week 12(n= 63,62,62,56)	2.501 (± 1.1177)	-0.496 (± 1.1339)	-3.164 (± 1.1422)	-2.209 (± 1.1897)
Android fat mass:Change at Week 20(n= 63,60,60,56)	1.442 (± 1.4723)	-2.617 (± 1.5083)	-8.245 (± 1.5163)	-2.429 (± 1.5684)
Gynoid fat mass:Change at Week 6(n= 63,62,64,58)	0.875 (± 0.7541)	-0.482 (± 0.7634)	-1.035 (± 0.7625)	-1.116 (± 0.7916)
Gynoid fat mass:Change at Week 10(n= 61,62,62,55)	0.218 (± 0.8226)	-0.012 (± 0.8288)	-2.51 (± 0.8321)	-2.282 (± 0.8693)
Gynoid fat mass:Change at Week 12(n= 63,62,62,56)	0.156 (± 0.7976)	0.022 (± 0.8079)	-2.594 (± 0.813)	-2.185 (± 0.8469)
Gynoid fat mass:Change at Week 20(n= 63,60,60,56)	0.386 (± 1.1487)	-0.741 (± 1.1753)	-4.78 (± 1.1809)	-1.791 (± 1.2217)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Maximal Leg Press Strength (1-RM) from Baseline to Week 6, 10, 12 and 20

End point title	Percent Change in Maximal Leg Press Strength (1-RM) from Baseline to Week 6, 10, 12 and 20

End point description:

For leg press assessments, subjects performed a series of repetitions of the exercises using equipment fitted with progressively heavier weight loads until repetition failure was achieved. Repetition failure was defined as the inability to move against the resistance to the required range of motion, or not using proper technique, or the subject not feeling safe in trying a heavier resistance. Muscle strength in the leg press was expressed in units of 1-RM, defined as the greatest resistance (weight) that could be overcome through a defined range of motion using proper techniques. Analysis was performed on FAS population. Here 'n' signifies number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	63	65	60
Units: Percent Change				
least squares mean (standard error)				
Change at Week 6 (n= 59,56,57,54)	6.7 (± 3.67)	11.3 (± 3.71)	10.7 (± 3.67)	6.4 (± 3.79)
Change at Week 10 (n= 55,58,57,53)	12.3 (± 4.46)	18.6 (± 4.47)	13.6 (± 4.43)	8.2 (± 4.56)
Change at Week 12 (n= 56,58,54,51)	14.7 (± 5.65)	27.1 (± 5.67)	16.5 (± 5.63)	15.3 (± 5.78)
Change at Week 20 (n= 54,57,53,53)	13.1 (± 7.05)	29.5 (± 7.06)	14.6 (± 7.01)	12.9 (± 7.12)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Maximal Chest Press Strength (1-RM) from Baseline to Week 6, 10, 12 and 20

End point title	Percent Change in Maximal Chest Press Strength (1-RM) from Baseline to Week 6, 10, 12 and 20

End point description:

For chest press assessments, subjects performed a series of repetitions of the exercises using equipment fitted with progressively heavier weight loads until repetition failure was achieved. Repetition failure was defined as the inability to move against the resistance to the required range of motion, or not using proper technique, or the subject not feeling safe in trying a heavier resistance. Muscle strength in the chest press was expressed in units of 1-RM, defined as the greatest resistance (weight) that could be overcome through a defined range of motion using proper techniques. Analysis was performed on FAS population. Here "Number of subjects analyzed" = Number of subjects evaluated for this outcome measure and "n" signifies number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	62	64	59
Units: Percent Change				
least squares mean (standard error)				
Change at Week 6 (n= 61,55,57,51)	13.5 (± 10.8)	31.8 (± 11.02)	15.1 (± 10.94)	25 (± 11.51)
Change at Week 10 (n= 56,58,58,50)	17.3 (± 9.76)	37.9 (± 9.8)	24.9 (± 9.78)	19.3 (± 10.33)
Change at Week 12 (n= 57,60,55,51)	19.6 (± 10.16)	44.7 (± 10.21)	24.5 (± 10.25)	21 (± 10.74)
Change at Week 20 (n= 56,57,54,50)	15.8 (± 9.48)	38 (± 9.53)	22.5 (± 9.57)	12.8 (± 10.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Hand Grip Strength (Dominant and Non-Dominant Hands) from Baseline to Week 6, 10, 12 and 20

End point title	Percent Change in Hand Grip Strength (Dominant and Non-Dominant Hands) from Baseline to Week 6, 10, 12 and 20

End point description:

Hand Grip Strength Test measures maximum isometric strength of hand and forearm muscles. Subject was required to squeeze dynamometer with maximum isometric effort while sitting with shoulder adducted and neutrally rotated, elbow flexed at 90 degrees and forearm in neutral position and wrist between 0 to 30 degrees dorsiflexion and a 0 to 15 degrees ulnar deviation. subject performed this task 3 times with each hand, starting with non-paretic hand. If difference between scores for 3 trials were within 3 kg, test was considered complete and if difference in score between any 2 measurement trials was more than 3 kg, procedure was repeated after a resting period. The performance measure for this task was average score measured in pounds of pressure exerted. Analysis was performed on FAS population. Here "Number of subjects analyzed" = Number of subjects evaluated for this outcome measure and "n" signifies number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	62	64	59
Units: Percent Change				
least squares mean (standard error)				
Dominant: Change at Week 6 (n= 64,60,62,57)	6.9 (± 2.62)	11 (± 2.72)	5.9 (± 2.68)	3.4 (± 2.8)
Dominant: Change at Week 10 (n= 61,61,60,55)	7.4 (± 4.36)	16.8 (± 4.46)	8.1 (± 4.43)	4.8 (± 4.6)
Dominant: Change at Week 12 (n= 62,61,60,56)	8.2 (± 4.28)	18.8 (± 4.39)	10.4 (± 4.36)	5.7 (± 4.52)
Dominant: Change at Week 20 (n= 62,59,61,56)	7.8 (± 4.07)	12.5 (± 4.18)	6.2 (± 4.11)	4 (± 4.3)
Non-Dominant: Change at Week 6 (n= 64,61,62,57)	6.3 (± 3.55)	13 (± 3.64)	9.8 (± 3.61)	7.4 (± 3.78)
Non-Dominant: Change at Week 10 (n= 61,62,61,55)	6.1 (± 3.66)	14.9 (± 3.7)	7.4 (± 3.7)	8.3 (± 3.88)
Non-Dominant: Change at Week 12 (n= 62,62,61,56)	10.7 (± 3.57)	17.5 (± 3.62)	17.2 (± 3.62)	9.8 (± 3.79)
Non-Dominant: Change at Week 20 (n= 62,60,61,56)	7.6 (± 4.17)	12.9 (± 4.25)	9.6 (± 4.22)	6.2 (± 4.41)

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Short Physical Performance Battery (SPPB): Total Score from Baseline to Week 6, 10, 12 and 20

End point title	Changes in Short Physical Performance Battery (SPPB): Total Score from Baseline to Week 6, 10, 12 and 20

End point description:

SPPB is a performance measure consisting of 3 components: a 4-meter (4M) gait speed test, a timed repeated chair stand test, and 3 increasingly difficult balance tests. Each component of the SPPB was assigned a categorical score ranging from 0 (inability to complete the test) to 4 (best performing). Total score, which rated the performance of subjects from 0 (worst) to 12 (best), was calculated by summing the 3 component scores. Analysis was performed on FAS population. Here "Number of subjects analyzed" = Number of subjects evaluated for this outcome measure and "n" signifies number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	62	64	59
Units: units on a scale				
least squares mean (standard error)				
Change at Week 6 (n= 64, 61, 63, 58)	0.2 (± 0.06)	0.1 (± 0.06)	0 (± 0.06)	0.1 (± 0.06)
Change at Week 10 (n=62, 62, 62, 55)	0.2 (± 0.06)	0.1 (± 0.06)	0.1 (± 0.06)	0.1 (± 0.07)
Change at Week 12 (n=62, 62, 62, 56)	0.3 (± 0.06)	0.2 (± 0.06)	0.2 (± 0.06)	0.1 (± 0.06)
Change at Week 20 (n=61, 60, 61, 56)	0.3 (± 0.06)	0.2 (± 0.06)	0.3 (± 0.06)	0.2 (± 0.06)

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in SPPB Subscore: Repeated Chair Stand Test from Baseline to Week 6, 10, 12 and 20

End point title	Changes in SPPB Subscore: Repeated Chair Stand Test from Baseline to Week 6, 10, 12 and 20

End point description:

SPPB is performance measure consisting of 3 components: 4M gait speed test, repeated chair stand test & balance tests. In repeated chair stand test, subjects were seated on straight-backed armless chair placed next to a wall with their arms folded across chest and asked to stand up straight while keeping their arms folded across their chest, for 5 times without stopping in between. Length of time required for subjects to stand up 5 times was measured with stop-watch,beginning from when subjects were told to start standing test to when they stood up straight for 5th time.Subjects were given scores: 0(unable to complete 5 stands in >60 seconds),1(completed 5 stands in ≥16.70 seconds),2(completed 5 stands in 13.70 to 16.69 second), 3(completed 5 stands in 11.20 to 13.69 seconds) or 4 (completed 5 chair stands in ≤11.19 seconds). FAS population. Here "Number of subjects analyzed" were subjects evaluated for this outcome measure and "n" signifies number of subjects with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	62	64	59
Units: units on a scale				
least squares mean (standard error)				
Change at Week 6 (n= 59,57,62,54)	0.2 (± 0.1)	0.4 (± 0.1)	0.3 (± 0.1)	0.4 (± 0.11)
Change at Week 10 (n=58,58,60,53)	0.4 (± 0.11)	0.5 (± 0.11)	0.4 (± 0.11)	0.6 (± 0.11)
Change at Week 12 (n=57,59,62,54)	0.5 (± 0.11)	0.5 (± 0.11)	0.5 (± 0.11)	0.7 (± 0.12)
Change at Week 20 (n= 56,57,59,54)	0.5 (± 0.1)	0.5 (± 0.1)	0.5 (± 0.1)	0.7 (± 0.11)

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in SPPB Subscore: Balance Testing from Baseline to Week 6, 10, 12 and 20

End point title	Changes in SPPB Subscore: Balance Testing from Baseline to Week 6, 10, 12 and 20

End point description:

SPPB is a performance measure consisting of 3 components: 4-meter (4M) gait speed test, repeated chair stand test and balance tests. Balance testing component of SPPB consists of side-by-side stand test (subjects were asked to stand with feet together for 10 seconds); a semi-tandem stand test (standing with side of heel of one foot touching other foot for 10 seconds); and tandem stand test (stand with heel of one foot in front of and touching toes of other foot for 10 seconds). Total score for balance testing component range from 0 (inability to complete the test) to 4 (best performing). Analysis was performed on FAS population. Here "Number of subjects analyzed" = Number of subjects evaluated for this outcome measure and "n" signifies number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	62	64	59
Units: units on a scale				
least squares mean (standard error)				
Change at Week 6 (n=64,61,53,58)	0.1 (± 0.08)	0.1 (± 0.08)	0.1 (± 0.08)	0.1 (± 0.08)
Change at Week 10 (n=62,62,62,55)	0.1 (± 0.09)	0 (± 0.09)	0.1 (± 0.09)	0 (± 0.1)
Change at Week 12 (n=62,62,62,56)	0.2 (± 0.09)	0 (± 0.09)	0.2 (± 0.09)	0.1 (± 0.09)
Change at Week 20 (n=61,60,61,56)	0.2 (± 0.08)	0.1 (± 0.09)	0.2 (± 0.09)	0.1 (± 0.09)

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in SPPB Subscore: 4-Meter Walk from Baseline to Week 6, 10, 12 and 20

End point title	Changes in SPPB Subscore: 4-Meter Walk from Baseline to Week 6, 10, 12 and 20

End point description:

The 4-Minute Walk Test (4-MWT), which measures the maximum distance a person can walk in 4 minutes, is a test of exercise endurance in elderly subjects with cardiovascular or pulmonary disease. Analysis was performed on FAS population. Here "Number of subjects analyzed" = Number of subjects evaluated for this outcome measure and "n" signifies number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	62	64	59
Units: units on a scale				
least squares mean (standard error)				
Change at Week 6 (n= 64,61,63,58)	0.2 (± 0.06)	0.1 (± 0.06)	0 (± 0.06)	0.1 (± 0.06)
Change at Week 10 (n= 62,62,62,55)	0.2 (± 0.06)	0.1 (± 0.06)	0.1 (± 0.06)	0.1 (± 0.07)
Change at Week 12 (n= 62,62,62,56)	0.3 (± 0.06)	0.2 (± 0.06)	0.2 (± 0.06)	0.1 (± 0.06)
Change at Week 20 (n= 61,60,61,56)	0.3 (± 0.06)	0.2 (± 0.06)	0.3 (± 0.06)	0.2 (± 0.06)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in 4-Meter Gait Speed from Baseline to Week 6, 10, 12 and 20

End point title	Percent Change in 4-Meter Gait Speed from Baseline to Week 6, 10, 12 and 20

End point description:

SPPB is a performance measure consisting of 3 components: 4-meter (4M) gait speed test, repeated chair stand test and balance tests. 4-meter (4M) gait speed component of the SPPB test was determined on a flat indoor surface marked at the start and at 4 meters from the start. Subjects were instructed to walk from a standing start past the 4-meter mark at their usual pace without hesitation. Completion time was recorded to the nearest 0.01 second using photoelectric cells and timers. Subjects completed 3 trials of the test, and the fastest time of 3 trials was used to calculate the walking speed. Total score for 4M gait speed component range from 0 (inability to complete the test) to 4 (best performing). Analysis was performed on FAS population. Here "Number of subjects analyzed" = Number of subjects evaluated for this outcome measure and "n" signifies number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	62	64	59
Units: Percent Change				
least squares mean (standard error)				
Percent change at Week 6 (n= 64,61,63,58)	7.25 (± 1.988)	3.31 (± 2.033)	5.47 (± 2.004)	10.78 (± 2.096)
Percent change at Week 10 (n= 62,62,62,55)	7.7 (± 2.122)	8.88 (± 2.136)	10.25 (± 2.125)	12.47 (± 2.25)
Percent change at Week 12 (n= 62,62,62,56)	11.65 (± 2.131)	11.89 (± 2.144)	13.06 (± 2.135)	15.17 (± 2.249)
Percent change at Week 20 (n= 61,60,61,56)	10.42 (± 2.23)	11.02 (± 2.251)	14.21 (± 2.235)	12.51 (± 2.345)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Distance Walked in the 6-Minute Walk Test (6MWT) from Baseline to Week 6, 10, 12 and 20

End point title	Percent Change in Distance Walked in the 6-Minute Walk Test (6MWT) from Baseline to Week 6, 10, 12 and 20

End point description:

The 6-Minute Walk Test (6-MWT), which measures the maximum distance a person can walk in 6 minutes, is a test of exercise in elderly subjects with cardiovascular or pulmonary disease. Analysis was performed on FAS population. Here "Number of subjects analyzed" = Number of subjects evaluated for this outcome measure and "n" signifies number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	62	64	59
Units: Percent Change				
least squares mean (standard error)				
Percent change at Week 6 (n=64,61,63,58)	5.2 (± 2.01)	7 (± 2.06)	4.8 (± 2.03)	2.6 (± 2.13)
Percent change at Week 10 (n=60,62,62,55)	7.1 (± 2.29)	7.5 (± 2.28)	6 (± 2.27)	7.9 (± 2.41)
Percent change at Week 12 (n=61,61,61,55)	7 (± 2.52)	9.9 (± 2.53)	9.8 (± 2.52)	7.6 (± 2.65)
Percent change at Week 20 (n=60,59,60,56)	6.3 (± 2.55)	5.4 (± 2.57)	7.8 (± 2.56)	3.3 (± 2.68)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Loaded and Unloaded Stair Climb Power from Baseline to Week 6, 10, 12 and 20

End point title	Percent Change in Loaded and Unloaded Stair Climb Power from Baseline to Week 6, 10, 12 and 20

End point description:

The stair climb test comprising of 8 steps unloaded and 8 steps loaded (performed with an extra weight of approximately 20% of the subject's body weight) involves using step switch pads placed on the bottom and the top steps to record the time required to climb the stairs. Subjects were instructed to climb 1 step at a time without assistance, only using the handrail if they lost their balance. Stair height, subject's weight (including clothing worn during test), and time interval between each step pad, were recorded. The power exerted was calculated as: Power (watts) = Weight (kg) x rise in stairs over the interval (meters) divided by 9.804 m/^2 divided by time over the interval (seconds). Analysis was performed on FAS population. Here "Number of subjects analyzed" = Number of subjects evaluated for this outcome measure and "n" signifies number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 10, 12 and 20

End point values	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w	REGN1033 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	62	64	59
Units: Percent Change				
least squares mean (standard error)				
Loaded; Change at Week 6 (n= 42,43,44,43)	16.5 (± 4.39)	8.9 (± 4.37)	15.7 (± 4.31)	4.4 (± 4.41)
Loaded; Change at Week 10 (n= 36,41,41,36)	10.8 (± 7.69)	14.1 (± 7.29)	29.4 (± 7.26)	9 (± 7.75)
Loaded; Change at Week 12 (n= 45,47,48,41)	28.6 (± 7.02)	24 (± 6.89)	29.8 (± 6.83)	19 (± 7.33)
Loaded; Change at Week 20 (n= 43,46,46,40)	22.5 (± 6.4)	15.8 (± 6.25)	20.9 (± 6.19)	13.5 (± 6.66)
Unloaded; Change at Week 6 (n= 52,53,57,56)	7.2 (± 2.83)	11.7 (± 2.81)	7.6 (± 2.71)	8.1 (± 2.78)
Unloaded; Change at Week 10 (n= 46,51,55,47)	10.5 (± 3.35)	18.2 (± 3.26)	12.1 (± 3.16)	13.5 (± 3.35)
Unloaded; Change at Week 12 (n= 55,57,59,54)	11.5 (± 3.99)	21 (± 3.93)	20 (± 3.85)	16 (± 4.02)
Unloaded; Change at Week 20 (n= 54, 56,57,53)	9.7 (± 3.68)	18.2 (± 3.63)	15.3 (± 3.57)	14.6 (± 3.73)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (Week 20) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment emergent that developed/worsened and deaths that occurred during 'treatment emergent period' (from the first dose of study drug up to the end of study visit [8 weeks after last study dose]). Analysis was performed on safety population that included all randomized subjects who received any study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	Placebo

Reporting group description:

Single subcutaneous (SC) injection of Placebo q2w for 12 weeks.

Reporting group title	REGN1033 100 mg q4w

Reporting group description:

Single SC injection of REGN1033 100 mg q4w alternating with placebo q4w for 12 weeks.

Reporting group title	REGN1033 300 mg q4w

Reporting group description:

Single SC injection of REGN1033 300 mg q4w alternating with placebo q4w for 12 weeks.

Reporting group title	REGN1033 300 mg q2w

Reporting group description:

Single SC injection of REGN1033 300 mg q2w for 12 weeks.

Serious adverse events	Placebo	REGN1033 100 mg q4w	REGN1033 300 mg q4w
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 65 (7.69%)	5 / 63 (7.94%)	5 / 65 (7.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 63 (0.00%)	0 / 65 (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
Squamous cell carcinoma of lung			

subjects affected / exposed	0 / 65 (0.00%)	0 / 63 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 65 (1.54%)	0 / 63 (0.00%)	0 / 65 (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
Hip fracture			
subjects affected / exposed	1 / 65 (1.54%)	1 / 63 (1.59%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	0 / 65 (0.00%)	1 / 63 (1.59%)	0 / 65 (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
Wound dehiscence			
subjects affected / exposed	0 / 65 (0.00%)	1 / 63 (1.59%)	0 / 65 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 65 (0.00%)	0 / 63 (0.00%)	0 / 65 (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
Cardiac disorders			
Atrial tachycardia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 63 (0.00%)	0 / 65 (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
Sinus bradycardia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 63 (0.00%)	0 / 65 (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

Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 65 (0.00%)	1 / 63 (1.59%)	0 / 65 (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
Gastrointestinal disorders			
Haematochezia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 63 (0.00%)	0 / 65 (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
Pancreatic cyst			
subjects affected / exposed	0 / 65 (0.00%)	0 / 63 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	0 / 63 (0.00%)	1 / 65 (1.54%)
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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 65 (1.54%)	1 / 63 (1.59%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 65 (0.00%)	0 / 63 (0.00%)	0 / 65 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 63 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Gastroenteritis viral			
subjects affected / exposed	0 / 65 (0.00%)	0 / 63 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilus sepsis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 63 (1.59%)	0 / 65 (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
Pharyngitis streptococcal			
subjects affected / exposed	0 / 65 (0.00%)	1 / 63 (1.59%)	0 / 65 (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
Pneumonia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 63 (1.59%)	0 / 65 (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
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 63 (0.00%)	1 / 65 (1.54%)
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	REGN1033 300 mg q2w		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 60 (6.67%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic squamous cell carcinoma			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of lung			

subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Periprosthetic fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial tachycardia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Haematochezia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatic cyst			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Gastroenteritis viral			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemophilus sepsis			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pharyngitis streptococcal			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 60 (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	REGN1033 100 mg q4w	REGN1033 300 mg q4w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 65 (49.23%)	27 / 63 (42.86%)	30 / 65 (46.15%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 65 (1.54%)	1 / 63 (1.59%)	2 / 65 (3.08%)
occurrences (all)	1	1	2
Excoriation			
subjects affected / exposed	4 / 65 (6.15%)	0 / 63 (0.00%)	0 / 65 (0.00%)
occurrences (all)	4	0	0

Fall			
subjects affected / exposed	8 / 65 (12.31%)	7 / 63 (11.11%)	5 / 65 (7.69%)
occurrences (all)	11	9	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 65 (3.08%)	1 / 63 (1.59%)	6 / 65 (9.23%)
occurrences (all)	2	1	7
Headache			
subjects affected / exposed	5 / 65 (7.69%)	3 / 63 (4.76%)	4 / 65 (6.15%)
occurrences (all)	5	3	6
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 65 (1.54%)	2 / 63 (3.17%)	0 / 65 (0.00%)
occurrences (all)	1	2	0
Fatigue			
subjects affected / exposed	1 / 65 (1.54%)	1 / 63 (1.59%)	6 / 65 (9.23%)
occurrences (all)	1	1	6
Injection site erythema			
subjects affected / exposed	5 / 65 (7.69%)	4 / 63 (6.35%)	4 / 65 (6.15%)
occurrences (all)	6	6	4
Injection site oedema			
subjects affected / exposed	4 / 65 (6.15%)	1 / 63 (1.59%)	0 / 65 (0.00%)
occurrences (all)	4	1	0
Injection site pruritus			
subjects affected / exposed	0 / 65 (0.00%)	1 / 63 (1.59%)	1 / 65 (1.54%)
occurrences (all)	0	2	1
Injection site reaction			
subjects affected / exposed	1 / 65 (1.54%)	0 / 63 (0.00%)	4 / 65 (6.15%)
occurrences (all)	1	0	6
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 65 (3.08%)	1 / 63 (1.59%)	2 / 65 (3.08%)
occurrences (all)	2	2	2
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	0 / 65 (0.00%)	1 / 63 (1.59%)	6 / 65 (9.23%)
occurrences (all)	0	1	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 65 (7.69%)	4 / 63 (6.35%)	5 / 65 (7.69%)
occurrences (all)	6	4	5
Back pain			
subjects affected / exposed	4 / 65 (6.15%)	0 / 63 (0.00%)	3 / 65 (4.62%)
occurrences (all)	4	0	3
Muscle spasms			
subjects affected / exposed	4 / 65 (6.15%)	4 / 63 (6.35%)	0 / 65 (0.00%)
occurrences (all)	4	4	0
Myalgia			
subjects affected / exposed	3 / 65 (4.62%)	1 / 63 (1.59%)	4 / 65 (6.15%)
occurrences (all)	3	1	4
Pain in extremity			
subjects affected / exposed	0 / 65 (0.00%)	4 / 63 (6.35%)	4 / 65 (6.15%)
occurrences (all)	0	5	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 65 (3.08%)	1 / 63 (1.59%)	0 / 65 (0.00%)
occurrences (all)	2	1	0
Sinusitis			
subjects affected / exposed	1 / 65 (1.54%)	1 / 63 (1.59%)	2 / 65 (3.08%)
occurrences (all)	1	1	2
Urinary tract infection			
subjects affected / exposed	4 / 65 (6.15%)	4 / 63 (6.35%)	0 / 65 (0.00%)
occurrences (all)	4	4	0

Non-serious adverse events	REGN1033 300 mg q2w		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 60 (58.33%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		

Excoriation subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all)	 1 / 60 (1.67%) 1 6 / 60 (10.00%) 7		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 3 / 60 (5.00%) 3 1 / 60 (1.67%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Injection site erythema subjects affected / exposed occurrences (all) Injection site oedema subjects affected / exposed occurrences (all) Injection site pruritus subjects affected / exposed occurrences (all) Injection site reaction subjects affected / exposed occurrences (all)	 4 / 60 (6.67%) 4 3 / 60 (5.00%) 3 10 / 60 (16.67%) 19 2 / 60 (3.33%) 2 3 / 60 (5.00%) 3 6 / 60 (10.00%) 13		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 3 / 60 (5.00%) 3		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2014	Following changes were done: •Added description of the independent Data Monitoring Committee (IDMC). •Clarifications to Inclusion/Exclusion criteria based on requests by health authorities. •Added detail about the severity of injection reactions and adverse events (AEs) that resulted in study drug dosing being permanently stopped. •Added detail about the severity of AEs that resulted in study drug dosing being temporarily stopped. •Clarified the prohibited medications section to specify 'new prescription' medications, to remove the prohibition for over-the-counter medications, and not require discussion in advance. •Clarified the description of the stair climb and 4-meter gait speed function measures. •Added a secondary endpoint. •Clarified the subject confidentiality statement. •Clarified the reasons for premature termination of the study.
10 March 2014	•Increased the number of study sites from 40 sites to 50 sites. •Added The European Quality of Life-5 Dimensions 3 Level System (EQ-5D-3L) Questionnaire. •Updated study procedures and endpoints. •Added the definition of adverse reactions and serious adverse reactions. •Added the definition of and reporting requirements for suspected unexpected serious adverse reactions.
23 July 2014	•Changes in the exclusion criteria, including decreases in the exclusion thresholds for sitting blood pressure and for HbA1C. •Added a 2% variance in the calculated appendicular lean mass to account for test-retest variability in whole-body DXA. •Added language for a first analysis of efficacy and safety assessments after subjects completed week 12 assessments. •Revised language stating that all subjects should attempt, or be asked to attempt, the stair climb test, but allowing subjects to choose not to perform the test, while still remaining eligible to participate in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported