



## Clinical trial results:

### A Phase 2 Randomized, Double-Blind, Placebo-controlled, Multiple Ascending Dose Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of PF-06252616 in Ambulatory Boys With Duchenne Muscular Dystrophy

#### Summary

EudraCT number	2014-002072-92
Trial protocol	GB IT PL BG
Global end of trial date	23 November 2018

#### Results information

Result version number	v2 (current)
This version publication date	16 December 2020
First version publication date	07 June 2019
Version creation reason	• Correction of full data set correction to data

#### Trial information

##### Trial identification

Sponsor protocol code	B5161002
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02310763
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001763-PIP01-15
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	10 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2018
Global end of trial reached?	Yes
Global end of trial date	23 November 2018
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of this study were to determine the safety and tolerability of multiple ascending repeat intravenous doses of domagrozumab (PF-06252616) in ambulatory boys with Duchenne Muscular dystrophy (DMD) and to demonstrate the efficacy of treatment with intravenous doses of domagrozumab based on an observed mean change from baseline on function (4 Stair Climb) as compared to placebo following 49 weeks of treatment.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of subjects.

Background therapy:

Subjects were required to be on a stable dose of glucocorticosteroids.

Evidence for comparator: -

Actual start date of recruitment	24 November 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 67
Worldwide total number of subjects	120
EEA total number of subjects	24

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)	105
Adolescents (12-17 years)	15
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 162 subjects were screened, 121 subjects were enrolled in the study and assigned to 1 of 3 sequences. Only 120 subjects received the study treatment and 1 subject withdrew prior to dosing.

### Period 1

Period 1 title	Period 1 (Weeks 1 to 48)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Sequence 1

Arm description:

Subjects in this sequence received domagrozumab in a dose escalating fashion (5, 20 and 40 mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). From Week 49 (Period 2), subjects continued to receive domagrozumab at the maximum tolerated dose (40 mg/kg) every 4 weeks for additional 48 weeks or until early termination of the study.

Arm type	Experimental
Investigational medicinal product name	Domagrozumab
Investigational medicinal product code	
Other name	PF-06252616
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Domagrozumab was administered over 2 hours (minus 15 or plus 30 minutes) by intravenous infusion. Subjects were observed for 1 hour following completion of domagrozumab administration.

<b>Arm title</b>	Sequence 2
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Arm description:

Subjects in this sequence received domagrozumab in a dose escalating fashion (5, 20 and 40mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). From Week 49 (Period 2), subjects received placebo for additional 48 weeks or until early termination of the study.

Arm type	Experimental
Investigational medicinal product name	Domagrozumab
Investigational medicinal product code	
Other name	PF-06252616
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Domagrozumab was administered over 2 hours (minus 15 or plus 30 minutes) by intravenous infusion. Subjects were observed for 1 hour following completion of domagrozumab administration.

<b>Arm title</b>	Sequence 3
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Arm description:

Subjects in this sequence received placebo for 48 weeks (Period 1). From Week 49 (Period 2), subjects received domagrozumab in a dose escalating fashion (5, 20 and 40 mg/kg) for additional 48 weeks or until early termination of the study. At each dose level, dosing was administered over 2 hours by

intravenous infusion every 4 weeks for a total of 16 weeks (4 doses).

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

Dosage and administration details:

Placebo was administered over 2 hours (minus 15 or plus 30 minutes) by intravenous infusion. Subjects were observed for 1 hour following completion of administration.

Number of subjects in period 1	Sequence 1	Sequence 2	Sequence 3
Started	41	39	40
Completed	38	37	38
Not completed	3	2	2
Consent withdrawn by subject	1	1	1
Adverse event, non-fatal	1	-	-
Unable to comply with study procedures	-	1	1
Lost to follow-up	1	-	-

## Period 2

Period 2 title	Period 2 (Weeks 49 to 96)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

## Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1

Arm description:

Subjects in this sequence received domagrozumab in a dose escalating fashion (5, 20 and 40 mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). From Week 49 (Period 2), subjects continued to receive domagrozumab at the maximum tolerated dose (40 mg/kg) every 4 weeks for additional 48 weeks or until early termination of the study.

Arm type	Experimental
Investigational medicinal product name	Domagrozumab
Investigational medicinal product code	
Other name	PF-06252616
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Domagrozumab was administered over 2 hours (minus 15 or plus 30 minutes) by intravenous infusion.

Subjects were observed for 1 hour following completion of domagrozumab administration.

<b>Arm title</b>	Sequence 2
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Arm description:

Subjects in this sequence received domagrozumab in a dose escalating fashion (5, 20 and 40mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). From Week 49 (Period 2), subjects received placebo for additional 48 weeks or until early termination of the study.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Placebo was administered over 2 hours (minus 15 or plus 30 minutes) by intravenous infusion. Subjects were observed for 1 hour following completion of administration.

<b>Arm title</b>	Sequence 3
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Arm description:

Subjects in this sequence received placebo for 48 weeks (Period 1). From Week 49 (Period 2), subjects received domagrozumab in a dose escalating fashion (5, 20 and 40 mg/kg) for additional 48 weeks or until early termination of the study. At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses).

Arm type	Experimental
Investigational medicinal product name	Domagrozumab
Investigational medicinal product code	
Other name	PF-06252616
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Domagrozumab was administered over 2 hours (minus 15 or plus 30 minutes) by intravenous infusion. Subjects were observed for 1 hour following completion of domagrozumab administration.

<b>Number of subjects in period 2</b>	Sequence 1	Sequence 2	Sequence 3
Started	38	37	38
Completed	22	21	22
Not completed	16	16	16
Study terminated by sponsor	16	16	16

## Baseline characteristics

### Reporting groups

Reporting group title	Sequence 1
Reporting group description:	
Subjects in this sequence received domagrozumab in a dose escalating fashion (5, 20 and 40 mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). From Week 49 (Period 2), subjects continued to receive domagrozumab at the maximum tolerated dose (40 mg/kg) every 4 weeks for additional 48 weeks or until early termination of the study.	
Reporting group title	Sequence 2
Reporting group description:	
Subjects in this sequence received domagrozumab in a dose escalating fashion (5, 20 and 40mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). From Week 49 (Period 2), subjects received placebo for additional 48 weeks or until early termination of the study.	
Reporting group title	Sequence 3
Reporting group description:	
Subjects in this sequence received placebo for 48 weeks (Period 1). From Week 49 (Period 2), subjects received domagrozumab in a dose escalating fashion (5, 20 and 40 mg/kg) for additional 48 weeks or until early termination of the study. At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses).	

Reporting group values	Sequence 1	Sequence 2	Sequence 3
Number of subjects	41	39	40
Age Categorical			
Units: Subjects			
<=18 years	41	39	40
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	8.3	8.5	9.3
standard deviation	± 1.9	± 1.5	± 2.3
Sex: Female, Male			
Units: Subjects			
Female	0	0	0
Male	41	39	40
Race/Ethnicity, Customized			
Units: Subjects			
White	33	33	35
Black	1	0	1
Asian	6	5	4
Other	1	1	0

Reporting group values	Total		
Number of subjects	120		
Age Categorical			
Units: Subjects			
<=18 years	120		
Between 18 and 65 years	0		
>=65 years	0		

Age Continuous Units: Years arithmetic mean standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	0		
Male	120		
Race/Ethnicity, Customized Units: Subjects			
White	101		
Black	2		
Asian	15		
Other	2		



## End points

### End points reporting groups

Reporting group title	Sequence 1
Reporting group description: Subjects in this sequence received domagrozumab in a dose escalating fashion (5, 20 and 40 mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). From Week 49 (Period 2), subjects continued to receive domagrozumab at the maximum tolerated dose (40 mg/kg) every 4 weeks for additional 48 weeks or until early termination of the study.	
Reporting group title	Sequence 2
Reporting group description: Subjects in this sequence received domagrozumab in a dose escalating fashion (5, 20 and 40mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). From Week 49 (Period 2), subjects received placebo for additional 48 weeks or until early termination of the study.	
Reporting group title	Sequence 3
Reporting group description: Subjects in this sequence received placebo for 48 weeks (Period 1). From Week 49 (Period 2), subjects received domagrozumab in a dose escalating fashion (5, 20 and 40 mg/kg) for additional 48 weeks or until early termination of the study. At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses).	
Reporting group title	Sequence 1
Reporting group description: Subjects in this sequence received domagrozumab in a dose escalating fashion (5, 20 and 40 mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). From Week 49 (Period 2), subjects continued to receive domagrozumab at the maximum tolerated dose (40 mg/kg) every 4 weeks for additional 48 weeks or until early termination of the study.	
Reporting group title	Sequence 2
Reporting group description: Subjects in this sequence received domagrozumab in a dose escalating fashion (5, 20 and 40mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). From Week 49 (Period 2), subjects received placebo for additional 48 weeks or until early termination of the study.	
Reporting group title	Sequence 3
Reporting group description: Subjects in this sequence received placebo for 48 weeks (Period 1). From Week 49 (Period 2), subjects received domagrozumab in a dose escalating fashion (5, 20 and 40 mg/kg) for additional 48 weeks or until early termination of the study. At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses).	
Subject analysis set title	Placebo (Period 1)
Subject analysis set type	Intention-to-treat
Subject analysis set description: This analysis set included subjects who received placebo from Week 1 to Week 48.	
Subject analysis set title	Domagrozumab 5 mg/kg (Period 1)
Subject analysis set type	Intention-to-treat
Subject analysis set description: This analysis set included subjects who received domagrozumab at a dose of 5 mg/kg by intravenous infusion over 2 hours every 4 weeks from Week 1 to Week 16 (4 doses).	
Subject analysis set title	Domagrozumab 20 mg/kg (Period 1)
Subject analysis set type	Intention-to-treat
Subject analysis set description: This analysis set included subjects who received domagrozumab at a dose of 20 mg/kg by intravenous infusion over 2 hours every 4 weeks from Week 17 to Week 32 (4 doses).	
Subject analysis set title	Domagrozumab 40 mg/kg (Period 1)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This analysis set included subjects who received domagrozumab at a dose of 40 mg/kg by intravenous infusion over 2 hours every 4 weeks from Week 33 to Week 48 (4 doses).

Subject analysis set title	Domagrozumab (Period 1)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This analysis set included subjects who received domagrozumab in a dose escalating fashion (5, 20 and 40mg/kg) from Week 1 to Week 48. At each dose level, dosing was administered by intravenous infusion over 2 hours every 4 weeks for a total of 16 weeks (4 doses).

Subject analysis set title	NH Control Group (4SC, Week 49)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The natural history (NH) control group was established by filtering the CINRG (Cooperative International Neuromuscular Research Group) natural history database. Subjects who met the following requirements at baseline and had evaluable 4 stair climb (4SC) data on Week 49 were included in this analysis set: 1) age: 6 to <16 years; 2) treatment of glucocorticoid steroids  $\geq$  6 months prior to baseline and continuous use until the latest visit week; 3) 4SC time: 2-15.9 seconds; 4) subjects who were ambulatory at baseline; 5) left ventricular ejection fraction (LVEF):  $\geq$  55% or missing.

Subject analysis set title	NH Control Group (4SC, Week 97)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The NH control group was established by filtering the CINRG (Cooperative International Neuromuscular Research Group) natural history database. Subjects who met the following requirements at baseline and had evaluable 4SC data on Week 97 were included in this analysis set: 1) age: 6 to <16 years; 2) treatment of glucocorticoid steroids  $\geq$  6 months prior to baseline and continuous use until the latest visit week; 3) 4SC time: 2-15.9 seconds; 4) subjects who were ambulatory at baseline; 5) LVEF:  $\geq$  55% or missing.

Subject analysis set title	NH Control Group (FVC, Week 49)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The NH control group was established by filtering the CINRG (Cooperative International Neuromuscular Research Group) natural history database. Subjects who met the following requirements at baseline and had evaluable forced vital capacity (FVC) data on Week 49 were included in this analysis set: 1) age: 6 to <16 years; 2) treatment of glucocorticoid steroids  $\geq$  6 months prior to baseline and continuous use until the latest visit week; 3) 4SC: 2-15.9 seconds; 4) subjects who were ambulatory at baseline; 5) LVEF:  $\geq$  55% or missing.

Subject analysis set title	NH Control Group (FVC, Week 97)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The NH control group was established by filtering the CINRG (Cooperative International Neuromuscular Research Group) natural history database. Subjects who met the following requirements at baseline and had evaluable FVC data on Week 97 were included in this analysis set: 1) age: 6 to <16 years; 2) treatment of glucocorticoid steroids  $\geq$  6 months prior to baseline and continuous use until the latest visit week; 3) 4SC time: 2-15.9 seconds; 4) subjects who were ambulatory at baseline; 5) LVEF:  $\geq$  55% or missing.

Subject analysis set title	NH Control Group (NSAA, Week 49)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The NH control group was established by filtering the CINRG (Cooperative International Neuromuscular Research Group) natural history database. Subjects who met the following requirements at baseline and had evaluable northstar ambulatory assessment (NSAA) data on Week 49 were included in this analysis set: 1) age: 6 to <16 years; 2) treatment of glucocorticoid steroids  $\geq$  6 months prior to baseline and continuous use until the latest visit week; 3) 4SC time: 2-15.9 seconds; 4) subjects who were ambulatory at baseline; 5) LVEF:  $\geq$  55% or missing.

Subject analysis set title	NH Control Group (NSAA, Week 97)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The NH control group was established by filtering the CINRG (Cooperative International Neuromuscular Research Group) natural history database. Subjects who met the following requirements at baseline and had evaluable NSAA data on Week 97 were included in this analysis set: 1) age: 6 to <16 years; 2)

treatment of glucocorticoid steroids  $\geq 6$  months prior to baseline and continuous use until the latest visit week; 3) 4SC time: 2-15.9 seconds; 4) subjects who were ambulatory at baseline; 5) LVEF:  $\geq 55\%$  or missing.

Subject analysis set title	NH Control Group (6MWD, Week 49)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The NH history control group was established by filtering the CINRG (Cooperative International Neuromuscular Research Group) natural history database. Subjects who met the following requirements at baseline and had evaluable 6 minute walk distance (6MWD) data on Week 49 were included in this analysis set: 1) age: 6 to <16 years; 2) treatment of glucocorticoid steroids $\geq 6$ months prior to baseline and continuous use until the latest visit week; 3) 4SC time: 2-15.9 seconds; 4) subjects who were ambulatory at baseline; 5) LVEF: $\geq 55\%$ or missing.	
Subject analysis set title	NH Control Group (6MWD, Week 97)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The NH control group was established by filtering the CINRG (Cooperative International Neuromuscular Research Group) natural history database. Subjects who met the following requirements at baseline and had evaluable 6MWD data on Week 97 were included in this analysis set: 1) age: 6 to <16 years; 2) treatment of glucocorticoid steroids $\geq 6$ months prior to baseline and continuous use until the latest visit week; 3) 4SC time: 2-15.9 seconds; 4) subjects who were ambulatory at baseline; 5) LVEF: $\geq 55\%$ or missing.	
Subject analysis set title	Placebo (4SC < 3.5 seconds, Period 1)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set included subjects who received placebo from Week 1 to Week 48 and had baseline 4SC time <3.5 seconds.	
Subject analysis set title	Domagrozumab (4SC < 3.5 seconds, Period 1)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set included subjects who received domagrozumab in a dose escalating fashion (5, 20 and 40mg/kg) from Week 1 to Week 48 and had baseline 4SC time <3.5 seconds. At each dose level, dosing was administered by intravenous infusion over 2 hours every 4 weeks for a total of 16 weeks (4 doses).	
Subject analysis set title	Placebo (4SC $\geq 3.5$ and $\leq 8$ seconds, Period 1)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set included subjects who received placebo from Week 1 to Week 48 and had baseline 4SC time $\geq 3.5$ seconds and $\leq 8$ seconds.	
Subject analysis set title	Domagrozumab (4SC $\geq 3.5$ and $\leq 8$ seconds, Period 1)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set included subjects who received domagrozumab in a dose escalating fashion (5, 20 and 40mg/kg) from Week 1 to Week 48 and had baseline 4SC time $\geq 3.5$ seconds and $\leq 8$ seconds. At each dose level, dosing was administered by intravenous infusion over 2 hours every 4 weeks for a total of 16 weeks (4 doses).	
Subject analysis set title	Placebo (4SC > 8 seconds, Period 1)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set included subjects who received placebo from Week 1 to Week 48 and had baseline 4SC > 8 seconds.	
Subject analysis set title	Domagrozumab (4SC > 8 seconds, Period 1)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set included subjects who received domagrozumab in a dose escalating fashion (5, 20 and 40mg/kg) from Week 1 to Week 48 and had baseline 4SC time > 8 seconds. At each dose level, dosing was administered by intravenous infusion over 2 hours every 4 weeks for a total of 16 weeks (4 doses).	
Subject analysis set title	Domagrozumab 5 mg/kg (Sequence 3)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This analysis set included subjects in Sequence 3 who received domagrozumab at a dose of 5 mg/kg by intravenous infusion over 2 hours every 4 weeks from Week 49 to Week 64 (4 doses).

Subject analysis set title	Domagrozumab 20 mg/kg (Sequence 3)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This analysis set included subjects in Sequence 3 who received domagrozumab at a dose of 20 mg/kg by intravenous infusion over 2 hours every 4 weeks from Week 65 to Week 80 (4 doses).

Subject analysis set title	Domagrozumab 40 mg/kg (Sequence 3)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This analysis set included subjects in Sequence 3 who received domagrozumab at a dose of 40 mg/kg by intravenous infusion over 2 hours every 4 weeks from Week 81 to Week 96 (4 doses).

### Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) by Week 49

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) by Week 49 <sup>[1]</sup>
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End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical investigation subject administered a product; the event did not need to have a causal relationship with the treatment. A serious adverse event (SAE) was any untoward medical occurrence at any dose that resulted in death; was life threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in congenital anomaly/birth defect. AEs included both SAEs and AEs. TEAEs were AEs occurred following the start of treatment or AEs increasing in severity during treatment. Severe TEAEs were TEAEs that interfered significantly with subjects' usual function. Treatment-related TEAEs were determined by the investigator. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Study Day 1 to Week 49 visit

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	80	78	76
Units: Subjects				
All-causalities TEAE	38	66	57	59
Treatment-related TEAE	14	18	14	16
All-causalities serious TEAE	0	1	1	1
Treatment-related serious TEAE	0	0	0	1
All-causalities severe TEAE	2	2	3	2
Treatment-related severe TEAE	0	0	0	1

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects Who Discontinued From the Study Due to TEAEs by

**Week 49**

End point title	Number of Subjects Who Discontinued From the Study Due to TEAEs by Week 49 <sup>[2]</sup>
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End point description:

An AE was any untoward medical occurrence in a clinical investigation subject administered a product; the event did not need to have a causal relationship with the treatment. TEAEs were AEs occurred following the start of treatment or AEs increasing in severity during treatment. Treatment-related TEAEs were determined by the investigator. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Study Day 1 to Week 49 visit

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	80	78	76
Units: Subjects				
All-causalities TEAE	0	0	0	1
Treatment-related TEAE	0	0	0	1

**Statistical analyses**

No statistical analyses for this end point

**Primary: Number of Subjects With Dose Reduced or Temporary Discontinuation Due to TEAEs by Week 49**

End point title	Number of Subjects With Dose Reduced or Temporary Discontinuation Due to TEAEs by Week 49 <sup>[3]</sup>
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End point description:

An AE was any untoward medical occurrence in a clinical investigation subject administered a product; the event did not need to have a causal relationship with the treatment. TEAEs were AEs occurred following the start of treatment or AEs increasing in severity during treatment. Treatment-related TEAEs were determined by the investigator. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Study Day 1 to Week 49 visit

Notes:

[3] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	80	78	76
Units: Subjects				
All-causalities TEAE	8	4	4	0
Treatment-related TEAE	3	0	1	0

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Hematology

End point title	Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Hematology <sup>[4]</sup>
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End point description:

Hematology evaluation included: hemoglobin, hematocrit, red blood cell (RBC) count, platelets, RBC morphology, white blood cell (WBC) count, absolute lymphocytes, absolute atypical lymphocytes, absolute total neutrophils, absolute total neutrophils count, absolute band cells, absolute basophils, absolute eosinophils, absolute monocytes and absolute myelocytes. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint. "99999" represents "not applicable" because data were not collected for specified rows of categories.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	80	78	76
Units: Subjects				
Hemoglobin <0.8*lower limit of normal (LLN)	0	0	0	0
Hematocrit <0.8*LLN	0	0	0	0
RBC count <0.8*LLN	0	0	0	0
Platelets <0.5*LLN	1	1	1	1
Platelets >1.75*upper limit of normal (ULN)	0	0	0	0
RBC Morphology >0	0	0	1	1
WBC count <0.6*LLN	0	0	0	0
WBC count >1.5*ULN	0	1	1	0
Absolute Lymphocytes <0.8*LLN	0	2	2	0
Absolute lymphocytes >1.2*ULN	1	1	0	0
Absolute atypical lymphocytes >0 (10 <sup>3</sup> /uL)	99999	1	99999	1
Absolute total neutrophils <0.8*LLN	1	0	0	0

Absolute total neutrophils >1.2*ULN	13	8	5	5
Absolute total neutrophils count <1.35 (10*3/uL)	2	0	2	1
Absolute total neutrophils count >8.15 (10*3/uL)	20	13	12	9
Absolute band cells >0.27 (10*3/uL)	0	0	0	0
Absolute basophils >1.2*ULN	2	1	1	2
Absolute eosinophils >1.2*ULN	6	2	6	6
Absolute monocytes >1.2*ULN	1	1	2	2
Absolute myelocytes >0 (10*3/uL)	99999	99999	99999	1

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Coagulation

End point title	Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Coagulation <sup>[5]</sup>
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End point description:

Coagulation evaluation included activated partial thromboplastin time (aPTT) and prothrombin time (PT). All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

Notes:

[5] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	80	78	76
Units: Subjects				
aPTT >1.1*ULN	1	1	1	2
PT >1.1*ULN	13	6	3	7

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Liver Function

End point title	Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Liver Function <sup>[6]</sup>
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**End point description:**

Liver function evaluation included: total/direct/indirect bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, total protein, albumin and glutamate dehydrogenase. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint. "99999" represents "not applicable" because data were not collected for specified rows of categories.

End point type	Primary
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**End point timeframe:**

Baseline to Week 49 visit

**Notes:**

[6] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	80	78	76
Units: Subjects				
Total bilirubin >1.5*ULN	0	0	0	0
Direct bilirubin >1.5*ULN	0	99999	99999	0
Indirect bilirubin >1.5*ULN	0	99999	99999	0
AST >3*ULN	39	80	76	74
ALT >3*ULN	40	80	78	75
GGT >3*ULN	0	0	0	0
Alkaline phosphatase >3*ULN	0	0	0	0
Total protein <0.8*LLN	0	0	0	0
Total protein >1.2*ULN	0	0	0	0
Albumin <0.8*LLN	0	0	0	0
Albumin >1.2*ULN	0	0	0	0
Glutamate dehydrogenase >1.0*ULN	8	8	6	5

**Statistical analyses**

No statistical analyses for this end point

**Primary: Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Renal Function**

End point title	Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Renal Function <sup>[7]</sup>
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**End point description:**

Renal function evaluation included: blood urea nitrogen (BUN), creatinine and uric acid. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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**End point timeframe:**

Baseline to Week 49 visit

**Notes:**

[7] - 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: No statistical analysis was planned for this endpoint



End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	80	78	76
Units: Subjects				
BUN >1.3*ULN	0	0	0	0
Creatinine >1.3*ULN	0	0	0	0
Uric acid >1.2*ULN	0	1	3	3

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Electrolytes

End point title	Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Electrolytes <sup>[8]</sup>
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End point description:

Electrolytes evaluation included: sodium, potassium, chloride, calcium, phosphate, bicarbonate, ferritin, transferrin saturation, iron, iron binding capacity and unsaturated iron binding capacity. Number of subjects with iron abnormalities was reported in different age groups. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

Notes:

[8] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	80	78	76
Units: Subjects				
Sodium <0.95*LLN	0	0	0	0
Sodium >1.05*ULN	0	0	0	0
Potassium <0.9*LLN	0	0	0	0
Potassium >1.1*ULN	0	0	0	0
Chloride <0.9*LLN	0	0	0	0
Chloride >1.1*ULN	0	0	0	0
Calcium <0.9*LLN	0	0	0	0
Calcium >1.1*ULN	0	0	0	0
Phosphate <0.8*LLN	0	0	0	0
Phosphate >1.2*ULN	0	0	0	0
Bicarbonate <0.9*LLN	8	2	3	4
Bicarbonate >1.1*ULN	1	0	0	0
Iron (1 Year<=Age<11 Years) <50 (ug/dL)	19	23	14	11

Iron (1 Year<=Age<11 Years) >120 (ug/dL)	12	29	33	39
Iron (11 Years<=Age<18 Years) <50 (ug/dL)	2	4	2	2
Iron (11 Years<=Age<18 Years) >170 (ug/dL)	0	1	1	0
Ferritin <15 (ug/L)	20	32	38	42
Ferritin >140 (ug/L)	1	1	0	0
Iron binding capacity <37.6 (ug/dL)	0	0	0	0
Unsaturated iron binding capacity<130 (ug/dL)	3	7	6	10
Unsaturated iron binding capacity >375 (ug/dL)	1	0	0	0
Transferrin saturation <20%	26	34	26	20
Transferrin saturation >50%	4	9	19	18

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Hormones

End point title	Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Hormones <sup>[9]</sup>
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End point description:

Hormone evaluations included free thyroxine (T4), thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and androstenedione. Numbers of subjects with abnormalities of LH, FSH and androstenedione were reported in different age groups. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint. "99999" represents "not applicable" because data were not collected for specified rows of categories.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

Notes:

[9] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	80	78	76
Units: Subjects				
Free T4 <0.8*LLN	0	0	0	0
Free T4 >1.2*ULN	0	0	0	0
TSH <0.8*LLN	0	2	0	1
TSH >1.2*ULN	0	0	0	0
LH (15 Days<=Age<7 Years) <0.3 (mIU/mL)	1	2	0	99999
LH (15 Days<=Age<7 Years) >2.8 (mIU/mL)	0	0	0	99999
LH (7 Years<=Age<9 Years) <0.3 (mIU/mL)	6	23	21	14

LH (7 Years<=Age<9 Years) >2.8 (mIU/mL)	0	0	0	0
LH (9 Years<=Age<11 Years) <0.3 (mIU/mL)	17	17	23	27
LH (9 Years<=Age<11 Years) >2.8 (mIU/mL)	0	0	0	0
LH (11 Years<=Age<12 Years) <0.3 (mIU/mL)	2	2	3	1
LH (11 Years<=Age<12 Years) >1.8 (mIU/mL)	1	1	0	0
LH (12 Years<=Age<13 Years) <0.3 (mIU/mL)	1	1	2	2
LH (12 Years<=Age<13 Years) >4.0 (mIU/mL)	0	0	0	0
LH (13 Years<=Age<14 Years) <0.3 (mIU/mL)	3	1	0	1
LH (13 Years<=Age<14 Years) >6.0 (mIU/mL)	0	1	1	1
FSH (4 Years<=Age<7 Years) >6.70 (mIU/mL)	0	0	0	99999
FSH (7 Years<=Age<9 Years) >4.10 (mIU/mL)	0	0	0	0
FSH (9 Years<=Age<11 Years) >4.50 (mIU/mL)	0	0	0	0
FSH (11 Years<=Age<12 Years) <0.40 (mIU/mL)	0	0	0	0
FSH (11 Years<=Age<12 Years) >8.90 (mIU/mL)	0	0	0	0
FSH (12 Years<=Age<13 Years) <0.50 (mIU/mL)	0	0	0	0
FSH (12 Years<=Age<13 Years) >10.50 (mIU/mL)	0	0	0	0
FSH (13 Years<=Age<14 Years) <0.70 (mIU/mL)	0	1	0	2
FSH (13 Years<=Age<14 Years) >10.80 (mIU/mL)	0	0	0	0
Androstenedione (1 Year<=Age<7 Years) <8 (ng/dL)	1	2	1	99999
Androstenedione (1 Year<=Age<7Years) >50(ng/dL)	0	0	0	99999
Androstenedione (7 Years<=Age<10Years)<3(ng/dL)	5	11	10	7
Androstenedione(7Years<=Age<10Years) >31(ng/dL)	1	0	4	4
Androstenedione(10Years<=Age<12Years) <7(ng/dL)	13	8	8	10
Androstenedione (10Years<=Age<12Years)>41 (ng/dL)	3	0	0	0
Androstenedione (12Years<=Age<14Years)<11 (ng/dL)	3	4	2	2
Androstenedione(12 Years<=Age<14Years)>64 (ng/dL)	0	0	0	0

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects With Laboratory Test Abnormalities (Without Regard

**to Baseline Abnormality) by Week 49 - Clinical Chemistry**

End point title	Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Clinical Chemistry <sup>[10]</sup>
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End point description:

Clinical chemistry evaluation included glucose, creatine kinase (CK), troponin I, and amylase. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

Notes:

[10] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	80	78	76
Units: Subjects				
Glucose <0.6*LLN	0	0	0	0
Glucose >1.5*ULN	0	1	0	2
CK >2.0*ULN	40	80	78	76
Troponin I >3.0*ULN	11	12	10	13
Amylase >1.5*ULN	0	0	0	1

**Statistical analyses**

No statistical analyses for this end point

**Primary: Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Urinalysis**

End point title	Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Urinalysis <sup>[11]</sup>
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End point description:

Urinalysis included: urine pH, qualitative urine glucose, qualitative urine ketones, qualitative urine protein, qualitative blood/hemoglobin, urine nitrite, urine leukocytes, urine RBC, urine WBC, urine granular casts, urine hyaline casts, urine urate (uric acid) acidic crystal, urine calcium oxalate crystals, urine amorphous crystals, urine bacteria, urine microscopic exam. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint. "99999" represents "not applicable" because data were not collected for specified rows of categories.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

Notes:

[11] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	80	78	76
Units: Subjects				
Qualitative urine glucose (dipstick) $\geq 1$	1	0	0	0
Qualitative urine ketones (dipstick) $\geq 1$	3	3	5	6
Qualitative urine protein (dipstick) $\geq 1$	0	1	0	0
Qualitative urine blood/hemoglobin dipstick $\geq 1$	0	2	1	0
Urine nitrite (dipstick) $\geq 1$	0	0	0	0
Urine leukocytes (dipstick): +1	0	0	1	1
Urine RBC $\geq 20$ (/high power field [HPF])	0	0	0	0
Urine WBC $\geq 20$ (/HPF)	0	0	0	0
Urine granular casts $> 1$ (/low power field [LPF])	1	99999	99999	99999
Urine hyaline casts $> 1$ (/LPF)	2	99999	99999	99999
Urine urate (uric acid) acidic crystal: Present	4	2	2	2
Urine calcium oxalate crystals: Present	19	24	23	24
Urine amorphous crystals: Present	7	7	6	11
Urine bacteria $> 20$ (/HPF)	0	0	0	0
Urine microscopic exam: Positive	31	50	49	45
Urine pH (dipstick) $< 4.5$	0	0	0	0
Urine pH (dipstick) $> 8$	0	1	1	1

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Fecal

End point title	Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) by Week 49 - Fecal <sup>[12]</sup>
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End point description:

Number of subjects with blood detected in fecal samples is presented. All subjects who received at least 1 dose of investigational drug and had at least 1 fecal evaluation were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

Notes:

[12] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	79	78	74
Units: Subjects	2	8	2	3

## Statistical analyses

No statistical analyses for this end point

## Primary: Categorical Summary of Liver Iron Accumulation by Week 49

End point title	Categorical Summary of Liver Iron Accumulation by Week 49 <sup>[13]</sup>
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End point description:

Magnetic resonance imaging (MRI) of Liver was obtained to quantify liver iron accumulation for safety monitoring. MRIs were sent to an independent central radiology imaging facility for calculation of the average transverse relaxation rate (R2\*) value which was used to monitor for iron accumulation in the liver. Number of subjects meeting the following criteria is presented as follows: 1) normal: R2\* ≤ 75Hz at 1.5T or ≤ 139 Hz at 3.0T; 2) above normal: R2\* > 75Hz and ≤ 190Hz at 1.5T or R2\* > 139Hz and ≤ 369Hz at 3.0T; 3) mild overload: R2\* > 190Hz at 1.5T or R2\* > 360Hz at 3.0T. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Screening, Weeks 13, 29 and 45

Notes:

[13] - 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: No statistical analysis was planned for this endpoint

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	40	
Units: Subjects				
Normal, Screening	41	39	40	
Above normal, Screening	0	0	0	
Mild overload, Screening	0	0	0	
Normal, Week 13	27	24	26	
Above normal, Week 13	0	0	0	
Mild overload, Week 13	0	0	0	
Normal, Week 29	23	21	21	
Above normal, Week 29	0	0	0	
Mild overload, Week 29	0	0	0	
Normal, Week 45	37	37	38	
Above normal, Week 45	0	0	0	
Mild overload, Week 45	0	0	0	

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Physical Examination Findings Reported as SAEs by Week 49

End point title	Number of Subjects With Physical Examination Findings Reported as SAEs by Week 49 <sup>[14]</sup>
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End point description:

Physical examination included head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. A targeted nose and throat mucosal exam were also performed to monitor for any signs of mucosal telangiectasias. An SAE was any untoward medical occurrence at any dose that resulted in death; was life threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in congenital anomaly/birth defect. Investigators determined which physical examination findings were reported as SAEs. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

Notes:

[14] - 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: No statistical analysis was planned for this endpoint

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	40	
Units: Subjects	0	0	0	

### Statistical analyses

No statistical analyses for this end point

### Primary: Summary of Tanner Stage Rating by Week 49

End point title	Summary of Tanner Stage Rating by Week 49 <sup>[15]</sup>
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End point description:

Tanner staging was performed before the first dose of each dose escalation to monitor for signs of accelerated sexual development. The physical changes in pubertal development (pubic hair, penis and testes) were assessed using the system described by Marshall and Tanner. More details about the system can be referred to Tanner JM. Growth at Adolescence. Blackwell Scientific Publications 1962; 2nd edition. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline, Weeks 17, 33 and 49

Notes:

[15] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Subjects				
Pubic hair, Stage 1, Baseline	35	70		
Pubic hair, Stage 2, Baseline	4	7		
Pubic hair, Stage 3, Baseline	0	1		
Pubic hair, Stage 4, Baseline	1	0		
Pubic hair, Stage 5, Baseline	0	0		
Pubic hair, Stage 1, Week 17	30	64		
Pubic hair, Stage 2, Week 17	9	11		
Pubic hair, Stage 3, Week 17	0	2		
Pubic hair, Stage 4, Week 17	1	0		
Pubic hair, Stage 5, Week 17	0	0		
Pubic hair, Stage 1, Week 33	23	60		
Pubic hair, Stage 2, Week 33	11	13		
Pubic hair, Stage 3, Week 33	1	1		
Pubic hair, Stage 4, Week 33	1	1		
Pubic hair, Stage 5, Week 33	0	0		
Pubic hair, Stage 1, Week 49	21	52		
Pubic hair, Stage 2, Week 49	11	15		
Pubic hair, Stage 3, Week 49	3	4		
Pubic hair, Stage 4, Week 49	1	1		
Pubic hair, Stage 5, Week 49	1	0		
Penis, Stage 1, Baseline	30	70		
Penis, Stage 2, Baseline	9	7		
Penis, Stage 3, Baseline	0	1		
Penis, Stage 4, Baseline	1	0		
Penis, Stage 5, Baseline	0	0		
Penis, Stage 1, Week 17	29	68		
Penis, Stage 2, Week 17	10	8		
Penis, Stage 3, Week 17	0	1		
Penis, Stage 4, Week 17	1	0		
Penis, Stage 5, Week 17	0	0		
Penis, Stage 1, Week 33	22	58		
Penis, Stage 2, Week 33	11	16		
Penis, Stage 3, Week 33	3	1		
Penis, Stage 4, Week 33	0	0		
Penis, Stage 5, Week 33	0	0		
Penis, Stage 1, Week 49	21	57		
Penis, Stage 2, Week 49	9	14		
Penis, Stage 3, Week 49	5	1		
Penis, Stage 4, Week 49	2	0		
Penis, Stage 5, Week 49	0	0		
Testes, Stage 1, Baseline	34	67		
Testes, Stage 2, Baseline	4	10		
Testes, Stage 3, Baseline	1	1		
Testes, Stage 4, Baseline	1	0		
Testes, Stage 5, Baseline	0	0		
Testes, Stage 1, Week 17	29	66		
Testes, Stage 2, Week 17	10	10		



Testes, Stage 3, Week 17	0	1		
Testes, Stage 4, Week 17	1	0		
Testes, Stage 5, Week 17	0	0		
Testes, Stage 1, Week 33	24	59		
Testes, Stage 2, Week 33	9	15		
Testes, Stage 3, Week 33	1	1		
Testes, Stage 4, Week 33	2	0		
Testes, Stage 5, Week 33	0	0		
Testes, Stage 1, Week 49	19	53		
Testes, Stage 2, Week 49	11	15		
Testes, Stage 3, Week 49	4	3		
Testes, Stage 4, Week 49	3	0		
Testes, Stage 5, Week 49	0	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Vital Signs Findings Reported as SAEs by Week 49

End point title	Number of Subjects With Vital Signs Findings Reported as SAEs by Week 49 <sup>[16]</sup>
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End point description:

Vital signs evaluation included supine systolic and diastolic blood pressure (BP), pulse rate, and respiratory rate. An SAE was any untoward medical occurrence at any dose that resulted in death; was life threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in congenital anomaly/birth defect. Investigators determined which vital signs findings were reported as SAEs. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

Notes:

[16] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Subjects	0	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Electrocardiogram (ECG) Data Meeting Pre-specified Criteria by Week 49

End point title	Number of Subjects With Electrocardiogram (ECG) Data Meeting Pre-specified Criteria by Week 49 <sup>[17]</sup>
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End point description:

Number of subjects with ECG data meeting the following criteria are presented: 1) corrected QT interval using Fridericia's formula (QTcF interval) <450msec; 2) QTcF interval ≥450 and <480msec; 3) QTcF interval ≥480 and <500msec; 4) QTcF interval ≥500msec; 5) QTcF interval increase from baseline <30msec; 6) QTcF interval increase from baseline ≥30 and <60msec; 7) QTcF interval increase from baseline ≥60msec. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

Notes:

[17] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	70	67	69
Units: Subjects				
QTcF interval <450msec	40	70	67	68
QTcF interval ≥450 and <480msec	0	0	0	1
QTcF interval ≥480 and <500msec	0	0	0	0
QTcF interval ≥500msec	0	0	0	0
QTcF interval increase <30msec	40	66	65	63
QTcF interval increase ≥30 and <60msec	0	4	2	6
QTcF interval increase ≥60msec	0	0	0	0

## Statistical analyses

No statistical analyses for this end point

## Primary: Change From Baseline in Left Ventricular Ejection Fraction (LVEF) as Compared to Placebo by Week 49

End point title	Change From Baseline in Left Ventricular Ejection Fraction (LVEF) as Compared to Placebo by Week 49
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End point description:

The LVEF was the ratio of blood ejected during systole to blood in the ventricle at the end of diastole. LVEF was measured by cardiac magnetic resonance image (MRI) or echocardiogram. The same method of cardiac imaging was used consistently within a single subject. Cardiac MRIs were read by a central imaging vendor and echocardiograms were read locally at each site. The LVEF values measured by cardiac MRI and echocardiogram are combined in the following presentation. The analysis of covariance (ANCOVA) model was used to analyze the change from baseline for domagrozumab compared to placebo on LVEF. The baseline result, age, use of angiotensin receptor blocker (ARB)/beta blocker/angiotensin converting enzyme (ACE) inhibitor and treatment were included as fixed effects in the model. All subjects who received at least 1 dose of investigational drug and had evaluable LVEF data at Week 49 were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	72		
Units: Ratio of blood				
least squares mean (standard error)	-0.063 ( $\pm$ 0.8464)	-1.356 ( $\pm$ 0.5620)		

## Statistical analyses

Statistical analysis title	Statistical Comparison in LVEF by Week 49
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority <sup>[18]</sup>
P-value	= 0.2088 <sup>[19]</sup>
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.293
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7343
upper limit	3.32
Variability estimate	Standard error of the mean
Dispersion value	1.022

Notes:

[18] - Least square mean difference was calculated by placebo minus domagrozumab.

[19] - The significance level is 0.05.

## Primary: Height-adjusted Z-score of Lumbar Spine Bone Mineral Density Over Time by Week 49

End point title	Height-adjusted Z-score of Lumbar Spine Bone Mineral Density Over Time by Week 49 <sup>[20]</sup>
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End point description:

Bone mineral density (BMD) was evaluated by Dual energy X-ray Absorptiometry (DXA). The height adjusted Z-score presented below is the number of standard deviations which compares the BMD of the subject to the average BMD matched for their age, sex and ethnicity. If the Z-score was -2 standard deviations or lower, the result was "below the expected range for age". If the Z-score was above -2 standard deviations, the result was "within the expected range for age". All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Screening and Week 49

Notes:

[20] - 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: No statistical analysis was planned for this endpoint

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	40	
Units: Standard deviations				
arithmetic mean (standard deviation)				
Screening	-0.545151 (± 1.2845570)	-0.622784 (± 1.0778788)	-0.572650 (± 1.0283031)	
Week 49	-0.683750 (± 1.0673420)	-0.401631 (± 1.0758951)	-0.489513 (± 1.0057285)	

## Statistical analyses

No statistical analyses for this end point

### Primary: Bone Age to Chronological Age Ratio by Week 49

End point title	Bone Age to Chronological Age Ratio by Week 49 <sup>[21]</sup>
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End point description:

Bone age assessment was evaluated by the ratio of the bone age to the chronological age using the X rays of the hand and wrist. Ratio of bone age to chronological age was calculated by bone age/chronological age at scan date. Chronological age at scan date was calculated by (scan date-date of birth+1)/365.25. All subjects who received at least 1 dose of investigational drug were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Screening, Weeks 17, 33 and 49

Notes:

[21] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Ratio				
arithmetic mean (standard deviation)				
Screening	0.809 (± 0.1656)	0.762 (± 0.1650)		
Week 17	0.805 (± 0.1567)	0.749 (± 0.1654)		
Week 33	0.790 (± 0.1614)	0.750 (± 0.1589)		
Week 49	0.770 (± 0.1604)	0.761 (± 0.1778)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Suicidal Ideation and Suicidal Behavior Reported

## as AEs by Week 49

End point title	Number of Subjects With Suicidal Ideation and Suicidal Behavior Reported as AEs by Week 49 <sup>[22]</sup>
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End point description:

An AE was any untoward medical occurrence in a clinical investigation subject administered a product; the event did not need to have a causal relationship with the treatment. The Columbia Suicide Severity Rating Scale (C-SSRS) was performed to identify the risk of suicide ideation or behavior. AEs of suicide ideation or behavior were determined by the investigator.

End point type	Primary
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End point timeframe:

Baseline to Week 49 visit

Notes:

[22] - 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: No statistical analysis was planned for this endpoint

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Subjects				
Suicidal ideation	0	0		
Suicidal behavior	0	0		

## Statistical analyses

No statistical analyses for this end point

## Primary: Change From Baseline on the 4 Stair Climb (4SC) as Compared to Placebo at Weeks 17, 33 and 49

End point title	Change From Baseline on the 4 Stair Climb (4SC) as Compared to Placebo at Weeks 17, 33 and 49
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End point description:

The 4SC quantified the time required for a subject to ascend 4 standard steps. Mixed effect model for repeated measures (MMRM) was used to analyze the change from baseline on 4SC for domagrozumab compared to placebo. The baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline, Weeks 17, 33 and 49

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Seconds				
least squares mean (standard error)				

Week 17	1.6896 ( $\pm$ 0.6776)	1.6051 ( $\pm$ 0.4814)		
Week 33	3.6407 ( $\pm$ 1.5837)	4.2244 ( $\pm$ 1.1209)		
Week 49	8.0122 ( $\pm$ 3.03)	8.2835 ( $\pm$ 2.1507)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Comparison on 4SC at Week 17
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[23]</sup>
P-value	= 0.9191 <sup>[24]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.0845
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7354
upper limit	1.5663

Notes:

[23] - Mean difference was calculated by domagrozumab minus placebo.

[24] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 4SC at Week 33
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[25]</sup>
P-value	= 0.7642 <sup>[26]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.5837
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2978
upper limit	4.4652

Notes:

[25] - Mean difference was calculated by domagrozumab minus placebo.

[26] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 4SC at Week 49
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[27]</sup>
P-value	= 0.9423 <sup>[28]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.2712
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3799
upper limit	7.9223

Notes:

[27] - Mean difference was calculated by domagrozumab minus placebo.

[28] - The significance level is 0.05.

### **Secondary: Change From Baseline as Compared to Placebo on Forced Vital Capacity (FVC) at Weeks 17, 33 and 49**

End point title	Change From Baseline as Compared to Placebo on Forced Vital Capacity (FVC) at Weeks 17, 33 and 49
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End point description:

FVC was measured by spirometry to evaluate respiratory muscle function. MMRM was used to analyze the change from baseline on FVC for domagrozumab compared to placebo. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33 and 49

<b>End point values</b>	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Liters				
least squares mean (standard error)				
Week 17	0.0578 (± 0.0327)	0.0578 (± 0.0250)		
Week 33	0.1008 (± 0.0385)	0.0749 (± 0.0286)		
Week 49	0.1513 (± 0.0367)	0.1092 (± 0.0278)		

### **Statistical analyses**

<b>Statistical analysis title</b>	Statistical Comparison on FVC at Week 17
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[29]</sup>
P-value	= 0.9993 <sup>[30]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0693
upper limit	0.0693

Notes:

[29] - Mean difference was calculated by domagrozumab minus placebo.

[30] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on FVC at Week 33
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[31]</sup>
P-value	= 0.5464 <sup>[32]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.0259
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1107
upper limit	0.0589

Notes:

[31] - Mean difference was calculated by domagrozumab minus placebo.

[32] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on FVC at Week 49
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[33]</sup>
P-value	= 0.3041 <sup>[34]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1227
upper limit	0.0386

Notes:

[33] - Mean difference was calculated by domagrozumab minus placebo.

[34] - The significance level is 0.05.



## Secondary: Change From Baseline as Compared to Placebo on the Northstar Ambulatory Assessment (NSAA) at Weeks 17, 33 and 49

End point title	Change From Baseline as Compared to Placebo on the Northstar Ambulatory Assessment (NSAA) at Weeks 17, 33 and 49
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### End point description:

The NSAA was a 17-item test that measured gross motor function. Each individual item received a score of 0-unable to perform independently, 1-able to perform with assistance, or 2-able to perform without assistance. A total score was achieved by summing all the individual items. The total score could range from 0 to 34 (fully-independent function). MMRM was used to analyze the change from baseline for domagrozumab compared to placebo. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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### End point timeframe:

Baseline, Weeks 17, 33 and 49

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Units on a scale				
least squares mean (standard error)				
Week 17	-1.9 (± 0.8)	-1.1 (± 0.6)		
Week 33	-4.5 (± 0.8)	-2.0 (± 0.6)		
Week 49	-5.2 (± 0.9)	-3.6 (± 0.7)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on NSAA at Week 17
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[35]</sup>
P-value	= 0.3522 <sup>[36]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	2.5

### Notes:

[35] - Mean difference was calculated by domagrozumab minus placebo.

[36] - The significance level is 0.05.

	Statistical Comparison on NSAA at Week 33
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Statistical analysis title	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[37]</sup>
P-value	= 0.0061 <sup>[38]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	4.2

Notes:

[37] - Mean difference was calculated by domagrozumab minus placebo.

[38] - The significance level is 0.05.

Statistical analysis title	
Statistical Comparison on NSAA at Week 49	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[39]</sup>
P-value	= 0.1268 <sup>[40]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	3.8

Notes:

[39] - Mean difference was calculated by domagrozumab minus placebo.

[40] - The significance level is 0.05.

## Secondary: Change From Baseline as Compared to Placebo on the Ankle Range of Motion (ROM) at Weeks 17, 33 and 49

End point title	Change From Baseline as Compared to Placebo on the Ankle Range of Motion (ROM) at Weeks 17, 33 and 49
End point description:	
ROM was evaluated by using goniometry to evaluate the loss of motion in the ankles. MMRM was used to analyze the change from baseline on ROM for domagrozumab compared to placebo. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 17, 33 and 49	

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Degrees of passive dorsiflexion				
least squares mean (standard error)				
Left ankle, Week 17	-1.0 ( $\pm$ 1.2)	-1.4 ( $\pm$ 0.9)		
Left ankle, Week 33	-1.9 ( $\pm$ 1.2)	-1.7 ( $\pm$ 0.9)		
Left ankle, Week 49	-2.3 ( $\pm$ 1.3)	-3.7 ( $\pm$ 1.0)		
Right ankle, Week 17	-2.1 ( $\pm$ 1.3)	-1.3 ( $\pm$ 1.0)		
Right ankle, Week 33	-4.1 ( $\pm$ 1.3)	-1.3 ( $\pm$ 0.9)		
Right ankle, Week 49	-3.6 ( $\pm$ 1.4)	-3.6 ( $\pm$ 1.1)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on ROM(Left ankle, Week 17)
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[41]</sup>
P-value	= 0.7337 <sup>[42]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	2.1

Notes:

[41] - Mean difference was calculated by domagrozumab minus placebo.

[42] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on ROM(Left ankle, Week 33)
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[43]</sup>
P-value	= 0.8893 <sup>[44]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	2.7

Notes:

[43] - Mean difference was calculated by domagrozumab minus placebo.

[44] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on ROM(Left ankle, Week 49)
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[45]</sup>
P-value	= 0.2939 <sup>[46]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	1.3

Notes:

[45] - Mean difference was calculated by domagrozumab minus placebo.

[46] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on ROM(Right ankle,Week 17)
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[47]</sup>
P-value	= 0.5995 <sup>[48]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	3.6

Notes:

[47] - Mean difference was calculated by domagrozumab minus placebo.

[48] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on ROM(Right ankle,Week 33)
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[49]</sup>
P-value	= 0.0385 <sup>[50]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	5.6

Notes:

[49] - Mean difference was calculated by domagrozumab minus placebo.

[50] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on ROM(Right ankle,Week 49)
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[51]</sup>
P-value	= 0.9927 <sup>[52]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	3.2

Notes:

[51] - Mean difference was calculated by domagrozumab minus placebo.

[52] - The significance level is 0.05.

### **Secondary: Change From Baseline as Compared to Placebo on the Performance of Upper Limb (PUL) Overall Score at Weeks 17, 33 and 49**

End point title	Change From Baseline as Compared to Placebo on the Performance of Upper Limb (PUL) Overall Score at Weeks 17, 33 and 49
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End point description:

The PUL was used to assess motor performance of the upper limb. The PUL scale includes 22 items; an entry item defining the starting functional level, and 21 items subdivided into three levels: shoulder(4 items), middle(9 items) and distal(8 items).Scoring options per item may not be uniform and may vary from 0–1 and 0–6, according to the performance, with higher values corresponding to better performance. A total maximum score of 74 is achieved by adding the individual level scores. MMRM was used to analyze the change from baseline for domagrozumab compared to placebo.The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model.Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33 and 49

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Units on a scale				
least squares mean (standard error)				
Week 17	-0.7 (± 0.6)	-1.0 (± 0.4)		
Week 33	-2.7 (± 1.1)	-0.9 (± 0.8)		
Week 49	-1.3 (± 0.5)	-1.4 (± 0.4)		

## Statistical analyses

Statistical analysis title	Statistical Comparison in PUL at Week 17
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[53]</sup>
P-value	= 0.6049 <sup>[54]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	1

Notes:

[53] - Mean difference was calculated by domagrozumab minus placebo.

[54] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison in PUL at Week 33
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[55]</sup>
P-value	= 0.2065 <sup>[56]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	4.4

Notes:

[55] - Mean difference was calculated by domagrozumab minus placebo.

[56] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison in PUL at Week 49
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[57]</sup>
P-value	= 0.9391 <sup>[58]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1.2

Notes:

[57] - Mean difference was calculated by domagrozumab minus placebo.

[58] - The significance level is 0.05.

### **Secondary: Change From Baseline as Compared to Placebo on the Six Minute Walk Distance (6MWD) score at Weeks 17, 33 and 49**

End point title	Change From Baseline as Compared to Placebo on the Six Minute Walk Distance (6MWD) score at Weeks 17, 33 and 49
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End point description:

6MWD evaluated ambulation ability by measuring the distance walked in 6 minutes. MMRM was used to analyze the change from baseline on 6MWD for domagrozumab compared to placebo. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33 and 49

<b>End point values</b>	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Meters				
least squares mean (standard error)				
Week 17	-32.0 (± 9.1)	-30.2 (± 6.9)		
Week 33	-52.3 (± 9.9)	-43.4 (± 7.4)		
Week 49	-56.5 (± 12.7)	-58.0 (± 9.3)		

### **Statistical analyses**

<b>Statistical analysis title</b>	Statistical Comparison on 6MWD at Week 17
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[59]</sup>
P-value	= 0.8499 <sup>[60]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.7
upper limit	20.3

Notes:

[59] - Mean difference was calculated by domagrozumab minus placebo.

[60] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 6MWD at Week 33
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[61]</sup>
P-value	= 0.4008 <sup>[62]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	29.8

Notes:

[61] - Mean difference was calculated by domagrozumab minus placebo.

[62] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 6MWD at Week 49
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[63]</sup>
P-value	= 0.916 <sup>[64]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30
upper limit	27

Notes:

[63] - Mean difference was calculated by domagrozumab minus placebo.

[64] - The significance level is 0.05.



**Secondary: Change From Baseline as Compared to Placebo on Muscle Strength of Elbow Extension at Weeks 17, 33 and 49**

End point title	Change From Baseline as Compared to Placebo on Muscle Strength of Elbow Extension at Weeks 17, 33 and 49
End point description: Muscle strength was quantified by means of a handheld dynamometer. The following muscle groups were evaluated: knee extension, elbow flexion, hip abduction, elbow extension and shoulder abduction. MMRM was used to analyze the change from baseline on muscle strength for domagrozumab compared to placebo. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.	
End point type	Secondary
End point timeframe: Baseline, Weeks 17, 33 and 49	

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Kilograms				
least squares mean (standard error)				
Left elbow extension, Week 17	-0.182 (± 0.183)	-0.067 (± 0.141)		
Left elbow extension, Week 33	-0.213 (± 0.187)	-0.376 (± 0.141)		
Left elbow extension, Week 49	-0.353 (± 0.200)	-0.479 (± 0.150)		
Right elbow extension, Week 17	-0.064 (± 0.209)	-0.086 (± 0.158)		
Right elbow extension, Week 33	-0.052 (± 0.197)	-0.491 (± 0.148)		
Right elbow extension, Week 49	-0.396 (± 0.192)	-0.562 (± 0.145)		

**Statistical analyses**

Statistical analysis title	Statistical Comparison on Muscle Strength
Statistical analysis description: Left elbow extension at Week 17 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[65]</sup>
P-value	= 0.5726 <sup>[66]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.115

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.287
upper limit	0.517

Notes:

[65] - Mean difference was calculated by domagrozumab minus placebo.

[66] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on Muscle Strength
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Statistical analysis description:

Left elbow extension at Week 33 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[67]</sup>
P-value	= 0.4334 <sup>[68]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.163

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.574
upper limit	0.248

Notes:

[67] - Mean difference was calculated by domagrozumab minus placebo.

[68] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on Muscle Strength
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Statistical analysis description:

Left elbow extension at Week 49 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[69]</sup>
P-value	= 0.5767 <sup>[70]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.126

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.573
upper limit	0.321

Notes:

[69] - Mean difference was calculated by domagrozumab minus placebo.

[70] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on Muscle Strength
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Statistical analysis description:

Right elbow extension at Week 17 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[71]</sup>
P-value	= 0.9274 <sup>[72]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.489
upper limit	0.446

Notes:

[71] - Mean difference was calculated by domagrozumab minus placebo.

[72] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on Muscle Strength
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Statistical analysis description:

Right elbow extension at Week 33 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[73]</sup>
P-value	= 0.0469 <sup>[74]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.439
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.872
upper limit	-0.006

Notes:

[73] - Mean difference was calculated by domagrozumab minus placebo.

[74] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on Muscle Strength
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Statistical analysis description:

Right elbow extension at Week 49 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[75]</sup>
P-value	= 0.4362 <sup>[76]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.166

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.587
upper limit	0.255

Notes:

[75] - Mean difference was calculated by domagrozumab minus placebo.

[76] - The significance level is 0.05.

## Secondary: Change From Baseline as Compared to Placebo on Muscle Strength of Elbow Flexion at Weeks 17, 33 and 49

End point title	Change From Baseline as Compared to Placebo on Muscle Strength of Elbow Flexion at Weeks 17, 33 and 49
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End point description:

Muscle strength was quantified by means of a handheld dynamometer. The following muscle groups were evaluated: knee extension, elbow flexion, hip abduction, elbow extension and shoulder abduction. MMRM was used to analyze the change from baseline on muscle strength for domagrozumab compared to placebo. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33 and 49

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Kilograms				
least squares mean (standard error)				
Left elbow flexion, Week 17	-0.096 (± 0.237)	-0.252 (± 0.181)		
Left elbow flexion, Week 33	-0.194 (± 0.244)	-0.497 (± 0.183)		
Left elbow flexion, Week 49	-0.573 (± 0.205)	-0.734 (± 0.159)		
Right elbow flexion, Week 17	-0.035 (± 0.220)	-0.118 (± 0.168)		
Right elbow flexion, Week 33	-0.057 (± 0.234)	-0.418 (± 0.175)		
Right elbow flexion, Week 49	-0.495 (± 0.199)	-0.684 (± 0.152)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on Muscle Strength
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Statistical analysis description:

Left elbow flexion at Week 17 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
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Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[77]</sup>
P-value	= 0.5557 <sup>[78]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.679
upper limit	0.367

Notes:

[77] - Mean difference was calculated by domagrozumab minus placebo.

[78] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on Muscle Strength
Statistical analysis description:	
Left elbow flexion at Week 33 was measured.	
Comparison groups	Domagrozumab (Period 1) v Placebo (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[79]</sup>
P-value	= 0.2669 <sup>[80]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.303
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.841
upper limit	0.235

Notes:

[79] - Mean difference was calculated by domagrozumab minus placebo.

[80] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on Muscle Strength
Statistical analysis description:	
Left elbow flexion at Week 49 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[81]</sup>
P-value	= 0.4665 <sup>[82]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.161
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.598
upper limit	0.276

Notes:

[81] - Mean difference was calculated by domagrozumab minus placebo.

[82] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on Muscle Strength
Statistical analysis description: Right elbow flexion at Week 17 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[83]</sup>
P-value	= 0.7335 <sup>[84]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.564
upper limit	0.399

Notes:

[83] - Mean difference was calculated by domagrozumab minus placebo.

[84] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on Muscle Strength
Statistical analysis description: Right elbow flexion, Week 33	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[85]</sup>
P-value	= 0.1695 <sup>[86]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.361
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.877
upper limit	0.156

Notes:

[85] - Mean difference was calculated by domagrozumab minus placebo.

[86] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on Muscle Strength
Statistical analysis description: Right elbow flexion at Week 49 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[87]</sup>
P-value	= 0.3783 <sup>[88]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.189
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.612
upper limit	0.234

Notes:

[87] - Mean difference was calculated by domagrozumab minus placebo.

[88] - The significance level is 0.05.

### Secondary: Change From Baseline as Compared to Placebo on Muscle Strength of Hip Abduction at Weeks 17, 33 and 49

End point title	Change From Baseline as Compared to Placebo on Muscle Strength of Hip Abduction at Weeks 17, 33 and 49
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End point description:

Muscle strength was quantified by means of a handheld dynamometer. The following muscle groups were evaluated: knee extension, elbow flexion, hip abduction, elbow extension and shoulder abduction. MMRM was used to analyze the change from baseline on muscle strength for domagrozumab compared to placebo. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33 and 49

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Kilograms				
least squares mean (standard error)				
Left hip abduction, Week 17	0.430 (± 0.321)	-0.156 (± 0.245)		
Left hip abduction, Week 33	-0.217 (± 0.318)	-0.171 (± 0.236)		
Left hip abduction, Week 49	-0.097 (± 0.334)	-0.475 (± 0.251)		
Right hip abduction, Week 17	0.535 (± 0.320)	-0.154 (± 0.247)		
Right hip abduction, Week 33	0.087 (± 0.340)	-0.249 (± 0.255)		
Right hip abduction, Week 49	0.056 (± 0.343)	-0.266 (± 0.260)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on Muscle Strength
Statistical analysis description: Left hip abduction at Week 17 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[89]</sup>
P-value	= 0.1078 <sup>[90]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.586
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.303
upper limit	0.13
Notes:	
[89] - Mean difference was calculated by domagrozumab minus placebo.	
[90] - The significance level is 0.05.	

Statistical analysis title	Statistical Comparison on Muscle Strength
Statistical analysis description: Left hip abduction at Week 33 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[91]</sup>
P-value	= 0.8967 <sup>[92]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.654
upper limit	0.746
Notes:	
[91] - Mean difference was calculated by domagrozumab minus placebo.	
[92] - The significance level is 0.05.	

Statistical analysis title	Statistical Comparison on Muscle Strength
Statistical analysis description: Left hip abduction at Week 49 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)



Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[93]</sup>
P-value	= 0.3196 <sup>[94]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.378
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.128
upper limit	0.371

Notes:

[93] - Mean difference was calculated by domagrozumab minus placebo.

[94] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on Muscle Strength
Statistical analysis description:	
Right hip abduction at Week 17 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[95]</sup>
P-value	= 0.0526 <sup>[96]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.689
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.386
upper limit	0.008

Notes:

[95] - Mean difference was calculated by domagrozumab minus placebo.

[96] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on Muscle Strength
Statistical analysis description:	
Right hip abduction at Week 33 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[97]</sup>
P-value	= 0.3739 <sup>[98]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.336
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.082
upper limit	0.41

Notes:

[97] - Mean difference was calculated by domagrozumab minus placebo.

[98] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on Muscle Strength
Statistical analysis description: Right hip abduction at Week 49 was measured	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[99]</sup>
P-value	= 0.4019 <sup>[100]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.322
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.079
upper limit	0.436

Notes:

[99] - Mean difference was calculated by domagrozumab minus placebo.

[100] - The significance level is 0.05.

### Secondary: Change From Baseline as Compared to Placebo on Muscle Strength of Knee Extension at Weeks 17, 33 and 49

End point title	Change From Baseline as Compared to Placebo on Muscle Strength of Knee Extension at Weeks 17, 33 and 49
End point description: Muscle strength was quantified by means of a handheld dynamometer. The following muscle groups were evaluated: knee extension, elbow flexion, hip abduction, elbow extension and shoulder abduction. MMRM was used to analyze the change from baseline on muscle strength for domagrozumab compared to placebo. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.	
End point type	Secondary
End point timeframe: Baseline, Weeks 17, 33 and 49	

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Kilograms				
least squares mean (standard error)				
Left knee extension, Week 17	-0.326 (± 0.336)	-0.434 (± 0.261)		
Left knee extension, Week 33	-0.713 (± 0.359)	-1.036 (± 0.272)		
Left knee extension, Week 49	-1.223 (± 0.369)	-1.110 (± 0.279)		

Right knee extension, Week 17	-0.213 ( $\pm$ 0.328)	-0.450 ( $\pm$ 0.253)		
Right knee extension, Week 33	-0.413 ( $\pm$ 0.380)	-0.880 ( $\pm$ 0.283)		
Right knee extension, Week 49	-0.976 ( $\pm$ 0.391)	-1.125 ( $\pm$ 0.292)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on Muscle Strength
Statistical analysis description: Left knee extension at Week 17 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[101]</sup>
P-value	= 0.7676 <sup>[102]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.107
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.825
upper limit	0.61

Notes:

[101] - Mean difference was calculated by domagrozumab minus placebo.

[102] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on Muscle Strength
Statistical analysis description: Left knee extension at Week 33 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[103]</sup>
P-value	= 0.4127 <sup>[104]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.322
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.098
upper limit	0.454

Notes:

[103] - Mean difference was calculated by domagrozumab minus placebo.

[104] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on Muscle Strength
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Statistical analysis description:

Left knee extension at Week 49 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[105]</sup>
P-value	= 0.7815 <sup>[106]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.693
upper limit	0.919

Notes:

[105] - Mean difference was calculated by domagrozumab minus placebo.

[106] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparion on Muscle Strength
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Statistical analysis description:

Right knee extension at Week 17 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[107]</sup>
P-value	= 0.4975 <sup>[108]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.236
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.924
upper limit	0.451

Notes:

[107] - Mean difference was calculated by domagrozumab minus placebo.

[108] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparion on Muscle Strength
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Statistical analysis description:

Right knee extension at Week 33 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[109]</sup>
P-value	= 0.2646 <sup>[110]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.467

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.294
upper limit	0.359

Notes:

[109] - Mean difference was calculated by domagrozumab minus placebo.

[110] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparion on Muscle Strength
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Statistical analysis description:

Right knee extension at Week 49 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[111]</sup>
P-value	= 0.732 <sup>[112]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.149

Confidence interval

level	95 %
sides	2-sided
lower limit	-1.008
upper limit	0.71

Notes:

[111] - Mean difference was calculated by domagrozumab minus placebo.

[112] - The significance level is 0.05.

### **Secondary: Change From Baseline as Compared to Placebo on Muscle Strength of Shoulder Abduction at Weeks 17, 33 and 49**

End point title	Change From Baseline as Compared to Placebo on Muscle Strength of Shoulder Abduction at Weeks 17, 33 and 49
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End point description:

Muscle strength was quantified by means of a handheld dynamometer. The following muscle groups were evaluated: knee extension, elbow flexion, hip abduction, elbow extension and shoulder abduction. MMRM was used to analyze the change from baseline on muscle strength for domagrozumab compared to placebo. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33 and 49

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Kilograms				
least squares mean (standard error)				
Left shoulder abduction, Week 17	-0.099 ( $\pm$ 0.213)	-0.143 ( $\pm$ 0.163)		
Left shoulder abduction, Week 33	-0.123 ( $\pm$ 0.226)	-0.278 ( $\pm$ 0.166)		
Left shoulder abduction, Week 49	-0.296 ( $\pm$ 0.238)	-0.319 ( $\pm$ 0.177)		
Right shoulder abduction, Week 17	0.079 ( $\pm$ 0.217)	-0.157 ( $\pm$ 0.165)		
Right shoulder abduction, Week 33	0.421 ( $\pm$ 0.251)	-0.336 ( $\pm$ 0.185)		
Right shoulder abduction, Week 49	0.140 ( $\pm$ 0.313)	-0.300 ( $\pm$ 0.229)		

## Statistical analyses

Statistical analysis title	Statistical Comparion on Muscle Strength
Statistical analysis description: Left shoulder abduction at Week 17 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[113]</sup>
P-value	= 0.8569 <sup>[114]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.525
upper limit	0.437

Notes:

[113] - Mean difference was calculated by domagrozumab minus placebo.

[114] - The significance level is 0.05.

Statistical analysis title	Statistical Comparion on Muscle Strength
Statistical analysis description: Left shoulder abduction at Week 33 was measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[115]</sup>
P-value	= 0.5495 <sup>[116]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.154

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.663
upper limit	0.355

Notes:

[115] - Mean difference was calculated by domagrozumab minus placebo.

[116] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparion on Muscle Strength
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Statistical analysis description:

Left shoulder abduction at Week 49 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[117]</sup>
P-value	= 0.934 <sup>[118]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.023

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.566
upper limit	0.521

Notes:

[117] - Mean difference was calculated by domagrozumab minus placebo.

[118] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparion on Muscle Strength
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Statistical analysis description:

Right shoulder abduction at Week 17 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[119]</sup>
P-value	= 0.3279 <sup>[120]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.236

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.711
upper limit	0.239

Notes:

[119] - Mean difference was calculated by domagrozumab minus placebo.

[120] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparion on Muscle Strength
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Statistical analysis description:

Right shoulder abduction at Week 33 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[121]</sup>
P-value	= 0.0086 <sup>[122]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.757
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.318
upper limit	-0.196

Notes:

[121] - Mean difference was calculated by domagrozumab minus placebo.

[122] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparion on Muscle Strength abduction
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Statistical analysis description:

Right shoulder abduction at Week 49 was measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[123]</sup>
P-value	= 0.2328 <sup>[124]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.439
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.165
upper limit	0.286

Notes:

[123] - Mean difference was calculated by domagrozumab minus placebo.

[124] - The significance level is 0.05.

### **Secondary: Change From Baseline to Weeks 49 on 4SC for Subjects in Sequence 3 Compared to the Natural History Control Group**

End point title	Change From Baseline to Weeks 49 on 4SC for Subjects in Sequence 3 Compared to the Natural History Control Group <sup>[125]</sup>
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End point description:

The 4SC quantified the time required for a subject to ascend 4 standard steps. MMRM was used to analyze the change from baseline on 4SC for the natural history control group compared to placebo group (Sequence 3). The baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. This MMRM was established to assess the appropriateness on using the natural history control group as a comparator. This analysis population included all subjects randomized in Sequence 3 and received at least 1 dose of randomized treatment, and the natural history control group who had evaluable 4SC data at Week 49.

End point type	Secondary
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End point timeframe:

Baseline, Week 49



Notes:

[125] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Sequence 3	NH Control Group (4SC, Week 49)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	32	58		
Units: Seconds				
least squares mean (standard error)	3.464 ( $\pm$ 1.232)	3.253 ( $\pm$ 0.91)		

## Statistical analyses

Statistical analysis title	Comparison on 4SC Between Sequence 3 and NH group
Comparison groups	Sequence 3 v NH Control Group (4SC, Week 49)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[126]</sup>
P-value	= 0.8908 <sup>[127]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8353
upper limit	3.2573

Notes:

[126] - Mean difference was calculated by Sequence 3 minus NH control group.

[127] - The significance level is 0.05.

## Secondary: Change From Baseline to Weeks 97 on 4SC for Subjects in Sequence 1 Compared to the Natural History Control Group

End point title	Change From Baseline to Weeks 97 on 4SC for Subjects in Sequence 1 Compared to the Natural History Control Group <sup>[128]</sup>
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End point description:

The 4SC quantified the time required for a subject to ascend 4 standard steps. MMRM was used to analyze the change from baseline on 4SC for domagrozumab compared to the natural history control group. The baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. This analysis population included all subjects randomized in Sequence 1 and received at least 1 dose of randomized treatment, and the natural history control group who had evaluable 4SC data at Week 97.

End point type	Secondary
End point timeframe:	
Baseline, Week 97	

Notes:

[128] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Sequence 1	NH Control Group (4SC, Week 97)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18	77		
Units: Seconds				
least squares mean (standard error)	4.205 ( $\pm$ 1.011)	3.386 ( $\pm$ 0.531)		

## Statistical analyses

Statistical analysis title	Comparison on 4SC Between Sequence 1 and NH group
Comparison groups	Sequence 1 v NH Control Group (4SC, Week 97)
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority <sup>[129]</sup>
P-value	= 0.4748 <sup>[130]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.819
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4514
upper limit	3.0895

Notes:

[129] - Mean difference was calculated by Sequence 1 minus NH control group.

[130] - The significance level is 0.05.

## Secondary: Change From Baseline to Week 49 on FVC for Subjects in Sequence 3 Compared to the Natural History Control Group

End point title	Change From Baseline to Week 49 on FVC for Subjects in Sequence 3 Compared to the Natural History Control Group <sup>[131]</sup>
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End point description:

FVC was measured by spirometry to evaluate respiratory muscle function. MMRM was used to analyze the change from baseline on FVC for the natural history control group compared to placebo group (Sequence 3). The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. This MMRM was established to match the natural history control group with the placebo group. This MMRM was established to assess the appropriateness on using the natural history control group as a comparator. This analysis population included all subjects randomized in Sequence 3 and received at least 1 dose of randomized treatment, and the natural history control group who had evaluable FVC data at Week 49.

End point type	Secondary
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End point timeframe:

Baseline, Week 49

Notes:

[131] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Sequence 3	NH Control Group (FVC, Week 49)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38	49		
Units: Liters				
least squares mean (standard error)	0.1358 ( $\pm$ 0.0328)	0.1261 ( $\pm$ 0.0294)		

## Statistical analyses

Statistical analysis title	Comparison on FVC Between Sequence 3 and NH group
Comparison groups	Sequence 3 v NH Control Group (FVC, Week 49)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[132]</sup>
P-value	= 0.807 <sup>[133]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.0097
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0692
upper limit	0.0887

Notes:

[132] - Mean difference was calculated by Sequence 3 minus NH control group.

[133] - The significance level is 0.05.

## Secondary: Change From Baseline to Week 97 on FVC for Subjects in Sequence 1 Compared to the Natural History Control Group

End point title	Change From Baseline to Week 97 on FVC for Subjects in Sequence 1 Compared to the Natural History Control Group <sup>[134]</sup>
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End point description:

FVC was measured by spirometry to evaluate respiratory muscle function. MMRM was used to analyze the change from baseline on FVC for domagrozumab compared to the natural history control group. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. This analysis population included all subjects randomized in Sequence 1 and received at least 1 dose of randomized treatment, and the natural history control group who had evaluable FVC data at Week 97.

End point type	Secondary
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End point timeframe:

Baseline, Week 97

Notes:

[134] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Sequence 1	NH Control Group (FVC, Week 97)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	22	86		
Units: Liters				
least squares mean (standard error)	0.2528 ( $\pm$ 0.0508)	0.2022 ( $\pm$ 0.0292)		

## Statistical analyses

Statistical analysis title	Comparison on FVC Between Sequence 1 and NH Group
Comparison groups	Sequence 1 v NH Control Group (FVC, Week 97)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority <sup>[135]</sup>
P-value	= 0.3643 <sup>[136]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.0506
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0594
upper limit	0.1607

Notes:

[135] - Mean difference was calculated by Sequence 1 minus NH control group.

[136] - The significance level is 0.05.

## Secondary: Change From Baseline to Week 49 on NSAA for Subjects in Sequence 3 Compared to the Natural History Control Group

End point title	Change From Baseline to Week 49 on NSAA for Subjects in Sequence 3 Compared to the Natural History Control Group <sup>[137]</sup>
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End point description:

The NSAA is a 17-item test that measured gross motor function. Each individual item received a score of 0-unable to perform independently, 1-able to perform with assistance, or 2-able to perform without assistance. The total score could range from 0 to 34 (fully-independent function). MMRM was used to analyze the change from baseline for natural history control group compared to placebo group (Sequence 3). The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. This MMRM was established to assess the appropriateness on using natural history control group as a comparator. This analysis population included all subjects randomized in Sequence 3 and received at least 1 dose of randomized treatment, and the natural history control group who had evaluable NSAA data at Week 49.

End point type	Secondary
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End point timeframe:

Baseline, Week 49

Notes:

[137] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Sequence 3	NH Control Group (NSAA, Week 49)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	37	18		
Units: Units on a scale				
least squares mean (standard error)	-4.8 (± 1.2)	-2.0 (± 1.4)		

## Statistical analyses

Statistical analysis title	Comparison on NSAA Between Sequence 3 and NH Group
Comparison groups	Sequence 3 v NH Control Group (NSAA, Week 49)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[138]</sup>
P-value	= 0.0483 <sup>[139]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	0

Notes:

[138] - Mean difference was calculated by Sequence 3 minus NH control group.

[139] - The significance level is 0.05.

## Secondary: Change From Baseline to Week 97 on NSAA for Subjects in Sequence 1 Compared to the Natural History Control Group

End point title	Change From Baseline to Week 97 on NSAA for Subjects in Sequence 1 Compared to the Natural History Control Group <sup>[140]</sup>
End point description:	The NSAA is a 17-item test that measured gross motor function. Each individual item received a score of 0-unable to perform independently, 1-able to perform with assistance, or 2-able to perform without assistance. The total score ranged from 0 to 34 (fully-independent function). MMRM was used to analyze the change from baseline for domagrozumab compared to natural history control group. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. This analysis population included all subjects randomized in Sequence 1 and received at least 1 dose of randomized treatment, and the natural history control group who had evaluable NSAA data at Week 97.
End point type	Secondary
End point timeframe:	
Baseline, Week 97	

Notes:

[140] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Sequence 1	NH Control Group (NSAA, Week 97)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	15		
Units: Units on a scale				
least squares mean (standard error)	-4.5 (± 1.2)	-0.6 (± 1.3)		

## Statistical analyses

Statistical analysis title	Comparison on NSAA Between Sequence 1 and NH Group
Comparison groups	Sequence 1 v NH Control Group (NSAA, Week 97)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority <sup>[141]</sup>
P-value	= 0.0146 <sup>[142]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	-0.8

Notes:

[141] - Mean difference was calculated by Sequence 1 minus NH control group.

[142] - The significance level is 0.05.

## Secondary: Change From Baseline to Week 49 on 6MWD for Subjects in Sequence 3 Compared to Natural History Control Group

End point title	Change From Baseline to Week 49 on 6MWD for Subjects in Sequence 3 Compared to Natural History Control Group <sup>[143]</sup>
End point description:	6MWD evaluated ambulation ability by measuring the distance walked in 6 minutes. MMRM was used to analyze the change from baseline on 6MWD for the natural history control group compared to placebo group (Sequence 3). The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. This MMRM was established to assess the appropriateness on using the natural history control group as a comparator. This analysis population included all subjects randomized in Sequence 3 and received at least 1 dose of randomized treatment, and the natural history control group who had evaluable 6MWD data at Week 49.
End point type	Secondary
End point timeframe:	
Baseline, Week 49	

Notes:

[143] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Sequence 3	NH Control Group (6MWD, Week 49)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	17		
Units: Meters				
least squares mean (standard error)	-80.8 (± 19.3)	-49.2 (± 22.2)		

## Statistical analyses

Statistical analysis title	Comparison on 6MWD Between Sequence 3 and NH Group
Comparison groups	Sequence 3 v NH Control Group (6MWD, Week 49)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[144]</sup>
P-value	= 0.1669 <sup>[145]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-31.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-76.9
upper limit	13.6

Notes:

[144] - Mean difference was calculated by Sequence 3 minus NH control group.

[145] - The significance level is 0.05.

## Secondary: Change From Baseline to Week 97 on 6MWD for Subjects in Sequence 1 Compared to the Natural History Control Group

End point title	Change From Baseline to Week 97 on 6MWD for Subjects in Sequence 1 Compared to the Natural History Control Group <sup>[146]</sup>
End point description:	6MWD evaluated ambulation ability by measuring the distance walked in 6 minutes. MMRM was used to analyze the change from baseline on 6MWD for domagrozumab compared to the natural history control group. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. This analysis population included all subjects randomized in Sequence 1 and received at least 1 dose of randomized treatment, and the natural history control group who had evaluable 6MWD data at Week 97.
End point type	Secondary
End point timeframe:	
Baseline, Week 97	

Notes:

[146] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Sequence 1	NH Control Group (6MWD, Week 97)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	17	12		
Units: Meters				
least squares mean (standard error)	-97.6 (± 20.7)	-31.3 (± 24.8)		

## Statistical analyses

Statistical analysis title	Comparison on 6MWD Between Sequence 1 and NH Group
Comparison groups	Sequence 1 v NH Control Group (6MWD, Week 97)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority <sup>[147]</sup>
P-value	= 0.0267 <sup>[148]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-66.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-124.5
upper limit	-8.1

Notes:

[147] - Mean difference was calculated by Sequence 1 minus NH control group.

[148] - The significance level is 0.05.

## Secondary: Change From Baseline as Compared to Placebo on 4SC at Week 17 in Pre-specified Subsets

End point title	Change From Baseline as Compared to Placebo on 4SC at Week 17 in Pre-specified Subsets
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End point description:

The 4SC quantified the time required for a subject to ascend 4 standard steps. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1) <3.5 seconds, 2) ≥3.5 seconds and ≤8 seconds, 3) >8 seconds. MMRM was used to analyze the change from baseline for domagrozumab compared to placebo in subsets. The baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
End point timeframe:	
Baseline, Week 17	



End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	74		
Units: Seconds				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	0.2329 ( $\pm$ 0.1513)	0.1637 ( $\pm$ 0.092)		
Baseline 4SC $\geq$ 3.5 and $\leq$ 8 seconds	0.7644 ( $\pm$ 0.4108)	0.9758 ( $\pm$ 0.3283)		
Baseline 4SC>8 seconds	7.7149 ( $\pm$ 4.8455)	5.071 ( $\pm$ 3.0969)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on 4SC in Subsets
Statistical analysis description: Subjects with baseline 4SC<3.5 seconds were measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[149]</sup>
P-value	= 0.7033 <sup>[150]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.0692
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4345
upper limit	0.2961

Notes:

[149] - Mean difference was calculated by domagrozumab minus placebo.

[150] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on 4SC in Subsets
Statistical analysis description: Subjects with baseline 4SC $\geq$ 3.5 and $\leq$ 8 seconds were measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[151]</sup>
P-value	= 0.6893 <sup>[152]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.2114
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8472
upper limit	1.27

Notes:

[151] - Mean difference was calculated by domagrozumab minus placebo.

[152] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 4SC in Subsets
Statistical analysis description:	
Subjects with baseline 4SC>8 seconds were measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[153]</sup>
P-value	= 0.6469 <sup>[154]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.6439
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.4292
upper limit	9.1414

Notes:

[153] - Mean difference was calculated by domagrozumab minus placebo.

[154] - The significance level is 0.05.

### Secondary: Change From Baseline as Compared to Placebo on 4SC at Week 33 in Pre-specified Subsets

End point title	Change From Baseline as Compared to Placebo on 4SC at Week 33 in Pre-specified Subsets
End point description:	
The 4SC quantified the time required for a subject to ascend 4 standard steps. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1) <3.5 seconds, 2)>=3.5 seconds and <=8 seconds, 3) >8 seconds. Mixed effect model for repeated measures (MMRM) was used to analyze the change from baseline for domagrozumab compared to placebo in subsets. The baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline, Week 33	

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	70		
Units: Seconds				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	0.435 (± 0.1852)	0.1062 (± 0.1061)		
Baseline 4SC>=3.5 and <=8 seconds	2.2085 (± 0.8933)	2.5542 (± 0.7234)		
Baseline 4SC>8 seconds	3.7436 (± 8.1156)	12.0329 (± 3.6174)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Comparison on 4SC in Subsets
Statistical analysis description: Subjects with baseline 4SC<3.5 seconds were measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority <sup>[155]</sup>
P-value	= 0.1353 <sup>[156]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.3289
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7649
upper limit	0.1072

Notes:

[155] - Mean difference was calculated by domagrozumab minus placebo.

[156] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 4SC in Subsets
Statistical analysis description: Subjects with baseline 4SC>=3.5 and <=8 seconds	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority <sup>[157]</sup>
P-value	= 0.7648 <sup>[158]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.3457
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9614
upper limit	2.6528

Notes:

[157] - Mean difference was calculated by domagrozumab minus placebo.

[158] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 4SC in Subsets
Statistical analysis description: Subjects with baseline 4SC>8 seconds were measured.	

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority <sup>[159]</sup>
P-value	= 0.3562 <sup>[160]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	8.2893
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.6409
upper limit	26.2194

Notes:

[159] - Mean difference was calculated by domagrozumab minus placebo.

[160] - The significance level is 0.05.

### Secondary: Change From Baseline as Compared to Placebo on 4SC at Week 49 in Pre-specified Subsets

End point title	Change From Baseline as Compared to Placebo on 4SC at Week 49 in Pre-specified Subsets
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End point description:

The 4SC quantified the time required for a subject to ascend 4 standard steps. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1) <3.5 seconds, 2) ≥3.5 seconds and ≤8 seconds, 3) >8 seconds. Mixed effect model for repeated measures (MMRM) was used to analyze the change from baseline for domagrozumab compared to placebo in subsets. The baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 49

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	63		
Units: Seconds				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	1.0056 (± 0.294)	0.4474 (± 0.1816)		
Baseline 4SC≥3.5 and ≤8 seconds	3.526 (± 1.1574)	3.6204 (± 0.9391)		
Baseline 4SC>8 seconds	30.3411 (± 9.7373)	19.053 (± 4.1965)		

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Comparison on 4SC in Subsets
Statistical analysis description: Subjects with baseline 4SC<3.5 seconds were measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority <sup>[161]</sup>
P-value	= 0.1163 <sup>[162]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.5582
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2615
upper limit	0.1451

Notes:

[161] - Mean difference was calculated by domagrozumab minus placebo.

[162] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 4SC in Subsets
Statistical analysis description: Subjects with baseline 4SC>8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority <sup>[163]</sup>
P-value	= 0.2947 <sup>[164]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-11.2881
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.8328
upper limit	10.2566

Notes:

[163] - Mean difference was calculated by domagrozumab minus placebo.

[164] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 4SC in Subsets
Statistical analysis description: Subjects with baseline 4SC>=3.5 and <=8 seconds were measured.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority <sup>[165]</sup>
P-value	= 0.9503 <sup>[166]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.0944

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.0798
upper limit	3.2686

Notes:

[165] - Mean difference was calculated by domagrozumab minus placebo.

[166] - The significance level is 0.05.

## Secondary: Change From Baseline as Compared to Placebo on FVC at Week 17 in Pre-specified Subsets

End point title	Change From Baseline as Compared to Placebo on FVC at Week 17 in Pre-specified Subsets
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End point description:

FVC was measured by spirometry to evaluate respiratory muscle function. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1) <3.5 seconds, 2) ≥3.5 seconds and ≤8 seconds, 3) >8 seconds. MMRM was used to analyze the change from baseline on FVC for domagrozumab compared to placebo in subsets. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 17

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	78		
Units: Liters				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	0.0562 (± 0.0603)	0.0722 (± 0.0368)		
Baseline 4SC≥3.5 and ≤8 seconds	0.0543 (± 0.0352)	0.0411 (± 0.0276)		
Baseline 4SC>8 seconds	-0.0168 (± 0.0800)	0.0721 (± 0.0534)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on FVC in Subset
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Statistical analysis description:

Subjects with baseline 4SC<3.5 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
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Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority <sup>[167]</sup>
P-value	= 0.8229 <sup>[168]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.0159
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.127
upper limit	0.1588

Notes:

[167] - Mean difference was calculated by domagrozumab minus placebo.

[168] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on FVC in Subset
Statistical analysis description:	
Subjects with baseline 4SC>=3.5 and <=8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority <sup>[169]</sup>
P-value	= 0.7709 <sup>[170]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.0132
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1036
upper limit	0.0772

Notes:

[169] - Mean difference was calculated by domagrozumab minus placebo.

[170] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on FVC in Subset
Statistical analysis description:	
Subjects with baseline 4SC>8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority <sup>[171]</sup>
P-value	= 0.3746 <sup>[172]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.0889
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1219
upper limit	0.2996

Notes:

[171] - Mean difference was calculated by domagrozumab minus placebo.

[172] - The significance level is 0.05.

## Secondary: Change From Baseline as Compared to Placebo on FVC at Week 33 in Pre-specified Subsets

End point title	Change From Baseline as Compared to Placebo on FVC at Week 33 in Pre-specified Subsets
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End point description:

FVC was measured by spirometry to evaluate respiratory muscle function. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1) <3.5 seconds, 2) ≥3.5 seconds and ≤8 seconds, 3) >8 seconds. MMRM was used to analyze the change from baseline on FVC for domagrozumab compared to placebo in subsets. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 33

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	76		
Units: Liters				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	0.1971 (± 0.0659)	0.1036 (± 0.0389)		
Baseline 4SC≥3.5 and ≤8 seconds	0.0585 (± 0.0476)	0.0468 (± 0.0376)		
Baseline 4SC>8 seconds	0.0332 (± 0.1053)	0.0895 (± 0.0703)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on FVC in Subset
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Statistical analysis description:

Subjects with baseline 4SC<3.5 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[173]</sup>
P-value	= 0.2294 <sup>[174]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.0934



Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2481
upper limit	0.0613

Notes:

[173] - Mean difference was calculated by domagrozumab minus placebo.

[174] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on FVC in Subset
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Statistical analysis description:

Subjects with baseline 4SC>=3.5 and <= 8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[175]</sup>
P-value	= 0.8485 <sup>[176]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.0117

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.1339
upper limit	0.1105

Notes:

[175] - Mean difference was calculated by domagrozumab minus placebo.

[176] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on FVC in Subset
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Statistical analysis description:

Subjects with baseline 4SC>8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[177]</sup>
P-value	= 0.6645 <sup>[178]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.0562

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.2187
upper limit	0.3312

Notes:

[177] - Mean difference was calculated by domagrozumab minus placebo.

[178] - The significance level is 0.05.

## Secondary: Change From Baseline as Compared to Placebo on FVC at Week 49 in Pre-specified Subsets

End point title	Change From Baseline as Compared to Placebo on FVC at Week
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## End point description:

FVC was measured by spirometry to evaluate respiratory muscle function. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1) <3.5 seconds, 2) ≥3.5 seconds and ≤8 seconds, 3) >8 seconds. MMRM was used to analyze the change from baseline on FVC for domagrozumab compared to placebo in subsets. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 49

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	74		
Units: Liters				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	0.2199 (± 0.0675)	0.1186 (± 0.0418)		
Baseline 4SC≥3.5 and ≤8 seconds	0.1364 (± 0.0376)	0.1006 (± 0.0297)		
Baseline 4SC>8 seconds	0.0052 (± 0.0936)	0.1091 (± 0.0634)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on FVC in Subset
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Statistical analysis description:

Subjects with baseline 4SC&lt;3.5 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority <sup>[179]</sup>
P-value	= 0.2101 <sup>[180]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.1013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2622
upper limit	0.0597

Notes:

[179] - Mean difference was calculated by domagrozumab minus placebo.

[180] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on FVC in Subset
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Statistical analysis description:

Subjects with baseline 4SC $\geq$ 3.5 and  $\leq$  8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority <sup>[181]</sup>
P-value	= 0.4603 <sup>[182]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.0359
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1326
upper limit	0.0608

Notes:

[181] - Mean difference was calculated by domagrozumab minus placebo.

[182] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on FVC in Subset
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Statistical analysis description:

Subjects with baseline 4SC $>$ 8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority <sup>[183]</sup>
P-value	= 0.3739 <sup>[184]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.1039
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1386
upper limit	0.3463

Notes:

[183] - Mean difference was calculated by domagrozumab minus placebo.

[184] - The significance level is 0.05.

## **Secondary: Change From Baseline as Compared to Placebo on NSAA at Week 17 in Pre-specified Subsets**

End point title	Change From Baseline as Compared to Placebo on NSAA at Week 17 in Pre-specified Subsets
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End point description:

The NSAA is a 17-item test measuring gross motor function. Each individual item received a score of 0-unable to perform independently, 1-able to perform with assistance, or 2-able to perform without assistance. A total score was achieved by summing all the individual items. The total score could range from 0 to 34 (fully-independent function). A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1)  $<$ 3.5 sec, 2)  $\geq$ 3.5 sec and  $\leq$ 8 sec, 3)  $>$ 8 sec. MMRM was used to analyze the change from baseline for domagrozumab compared to placebo in subsets. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 17

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	77		
Units: Units on a scale				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	-0.4 (± 1.8)	-0.7 (± 1.1)		
Baseline 4SC>=3.5 and <=8 seconds	-1.3 (± 0.8)	-0.1 (± 0.6)		
Baseline 4SC>8 seconds	-3.2 (± 0.9)	-1.9 (± 0.6)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on NSAA in Subset
Statistical analysis description: Subjects with baseline 4SC<3.5 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority <sup>[185]</sup>
P-value	= 0.8925 <sup>[186]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	3.9

Notes:

[185] - Mean difference was calculated by domagrozumab minus placebo.

[186] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on NSAA in Subset
Statistical analysis description: Subjects with baseline 4SC>=3.5 and <=8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority <sup>[187]</sup>
P-value	= 0.2107 <sup>[188]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	3.2

Notes:

[187] - Mean difference was calculated by domagrozumab minus placebo.

[188] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on NSAA in Subset
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Statistical analysis description:

Subjects with baseline 4SC>8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority <sup>[189]</sup>
P-value	= 0.2298 <sup>[190]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.3

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.9
upper limit	3.5

Notes:

[189] - Mean difference was calculated by domagrozumab minus placebo.

[190] - The significance level is 0.05.

### **Secondary: Change From Baseline as Compared to Placebo on NSAA at Week 33 in Pre-specified Subsets**

End point title	Change From Baseline as Compared to Placebo on NSAA at Week 33 in Pre-specified Subsets
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End point description:

The NSAA is a 17-item test measuring gross motor function. Each individual item received a score of 0- unable to perform independently, 1-able to perform with assistance, or 2-able to perform without assistance. A total score was achieved by summing all the individual items. The total score could range from 0 to 34 (fully-independent function). A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1) <3.5 sec, 2)>=3.5 sec and <=8 sec, 3) >8 sec. MMRM was used to analyze the change from baseline for domagrozumab compared to placebo in subsets. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 33

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	75		
Units: Units on a scale				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	-3.9 (± 1.5)	-0.4 (± 0.9)		
Baseline 4SC≥3.5 and ≤8 seconds	-3.5 (± 1.0)	-2.0 (± 0.8)		
Baseline 4SC>8 seconds	-5.6 (± 1.3)	-2.7 (± 0.9)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on NSAA in Subset
Statistical analysis description: Subjects with baseline 4SC<3.5 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[191]</sup>
P-value	= 0.0554 <sup>[192]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	7.1

Notes:

[191] - Mean difference was calculated by domagrozumab minus placebo.

[192] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on NSAA in Subset
Statistical analysis description: Subjects with baseline 4SC≥3.5 and ≤ 8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[193]</sup>
P-value	= 0.2027 <sup>[194]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	4

Notes:

[193] - Mean difference was calculated by domagrozumab minus placebo.

[194] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on NSAA in Subset
Statistical analysis description:	
Subjects with baseline 4SC>8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[195]</sup>
P-value	= 0.0926 <sup>[196]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	6.3

Notes:

[195] - Mean difference was calculated by domagrozumab minus placebo.

[196] - The significance level is 0.05.

### **Secondary: Change From Baseline as Compared to Placebo on NSAA at Week 49 in Pre-specified Subsets**

End point title	Change From Baseline as Compared to Placebo on NSAA at Week 49 in Pre-specified Subsets
End point description:	
The NSAA is a 17-item test measuring gross motor function. Each individual item received a score of 0- unable to perform independently, 1-able to perform with assistance, or 2-able to perform without assistance. A total score was achieved by summing all the individual items. The total score could range from 0 to 34 (fully-independent function). A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1) <3.5 sec, 2)>=3.5 sec and <=8 sec, 3) >8 sec. MMRM was used to analyze the change from baseline for domagrozumab compared to placebo in subsets. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline, Week 49	

<b>End point values</b>	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	73		
Units: Units on a scale				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	-3.8 (± 1.8)	-1.8 (± 1.1)		
Baseline 4SC>=3.5 and <= 8 seconds	-4.2 (± 1.1)	-3.7 (± 0.9)		
Baseline 4SC>8 seconds	-8.4 (± 1.4)	-4.4 (± 0.9)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Comparison on NSAA in Subset
Statistical analysis description: Subjects with baseline 4SC<3.5 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority <sup>[197]</sup>
P-value	= 0.3597 <sup>[198]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	6.3

Notes:

[197] - Mean difference was calculated by domagrozumab minus placebo.

[198] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on NSAA in Subset
Statistical analysis description: Subjects with baseline 4SC>=3.5 and <=8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority <sup>[199]</sup>
P-value	= 0.7345 <sup>[200]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	3.3

Notes:

[199] - Mean difference was calculated by domagrozumab minus placebo.

[200] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on NSAA in Subset
Statistical analysis description: Subjects with baseline 4SC>8 seconds were analyzed.	



Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority <sup>[201]</sup>
P-value	= 0.032 <sup>[202]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	7.7

Notes:

[201] - Mean difference was calculated by domagrozumab minus placebo.

[202] - The significance level is 0.05.

### Secondary: Change From Baseline as Compared to Placebo on PUL Overall Scores at Week 17 in Pre-specified Subsets

End point title	Change From Baseline as Compared to Placebo on PUL Overall Scores at Week 17 in Pre-specified Subsets
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End point description:

The PUL was used to assess motor performance of the upper limb. The PUL scale includes 22 items; an entry item defining the starting functional level, and 21 items subdivided into three levels: shoulder (4 items), middle (9 items) and distal (8 items). Scoring options per item may not be uniform and may vary from 0–1 and 0–6, according to the performance, with higher values corresponding to better performance. A total maximum score of 74 is achieved by adding the individual level scores. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time. MMRM was used to analyze the change from baseline. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures.

End point type	Secondary
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End point timeframe:

Baseline, Week 17

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	78		
Units: Units on a scale				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	-1.1 (± 1.1)	0.2 (± 0.7)		
Baseline 4SC>=3.5 and <=8 seconds	0.2 (± 0.7)	-1.0 (± 0.5)		
Baseline 4SC>8 seconds	0.4 (± 1.7)	-0.5 (± 1.2)		

### Statistical analyses

Statistical analysis title	Statistical Comparison on PUL in Subset
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Statistical analysis description:

Subjects with baseline 4SC<3.5 seconds were measured.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority <sup>[203]</sup>
P-value	= 0.3345 <sup>[204]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	3.8

Notes:

[203] - Mean difference was calculated by domagrozumab minus placebo.

[204] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on PUL in Subset
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Statistical analysis description:

Subjects with baseline 4SC>=3.5 and <= 8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority <sup>[205]</sup>
P-value	= 0.14 <sup>[206]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	0.4

Notes:

[205] - Mean difference was calculated by domagrozumab minus placebo.

[206] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on PUL in Subset
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Statistical analysis description:

Subjects with baseline 4SC>8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority <sup>[207]</sup>
P-value	= 0.6764 <sup>[208]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	3.6

Notes:

[207] - Mean difference was calculated by domagrozumab minus placebo.

[208] - The significance level is 0.05.

## Secondary: Change From Baseline as Compared to Placebo on PUL Overall Score at Week 33 in Pre-specified Subsets

End point title	Change From Baseline as Compared to Placebo on PUL Overall Score at Week 33 in Pre-specified Subsets
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End point description:

The PUL was used to assess motor performance of the upper limb. The PUL scale includes 22 items; an entry item defining the starting functional level, and 21 items subdivided into three levels: shoulder (4 items), middle (9 items) and distal (8 items). Scoring options per item may not be uniform and may vary from 0–1 and 0–6, according to the performance, with higher values corresponding to better performance. A total maximum score of 74 is achieved by adding the individual level scores. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time. MMRM was used to analyze the change from baseline. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures.

End point type	Secondary
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End point timeframe:

Baseline, Week 33

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	76		
Units: Units on a scale				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	-6.4 (± 3.3)	0.1 (± 2.0)		
Baseline 4SC>=3.5 and <= 8 seconds	0 (± 0.6)	-0.3 (± 0.5)		
Baseline 4SC>8 seconds	-1.0 (± 1.9)	-2.0 (± 1.2)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on PUL in Subset
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Statistical analysis description:

Subjects with baseline 4SC<3.5 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
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Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[209]</sup>
P-value	= 0.097 <sup>[210]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	14.2

Notes:

[209] - Mean difference was calculated by domagrozumab minus placebo.

[210] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on PUL in Subset
Statistical analysis description:	
Subjects with baseline 4SC>=3.5 and <=8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[211]</sup>
P-value	= 0.6919 <sup>[212]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	1.3

Notes:

[211] - Mean difference was calculated by domagrozumab minus placebo.

[212] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on PUL in Subset
Statistical analysis description:	
Subjects with baseline 4SC>8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[213]</sup>
P-value	= 0.6736 <sup>[214]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	3.9

Notes:

[213] - Mean difference was calculated by domagrozumab minus placebo.

[214] - The significance level is 0.05.

## Secondary: Change From Baseline as Compared to Placebo on PUL Overall Score at Week 49 in Pre-specified Subsets

End point title	Change From Baseline as Compared to Placebo on PUL Overall Score at Week 49 in Pre-specified Subsets
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End point description:

The PUL was used to assess motor performance of the upper limb. The PUL scale includes 22 items; an entry item defining the starting functional level, and 21 items subdivided into three levels: shoulder(4 items), middle(9 items) and distal(8 items). Scoring options per item may not be uniform and may vary from 0–1 and 0–6, according to the performance, with higher values corresponding to better performance. A total maximum score of 74 is achieved by adding the individual level scores. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time. MMRM was used to analyze the change from baseline. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures.

End point type	Secondary
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End point timeframe:

Baseline, Week 49

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	75		
Units: Units on a scale				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	0.3 (± 0.6)	0.3 (± 0.4)		
Baseline 4SC>=3.5 and <=8 seconds	-0.9 (± 0.7)	-1.0 (± 0.5)		
Baseline 4SC>8 seconds	-2.6 (± 1.7)	-3.5 (± 1.1)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on PUL in Subset
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Statistical analysis description:

Subjects with baseline 4SC<3.5 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[215]</sup>
P-value	= 0.9582 <sup>[216]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.5

Notes:

[215] - Mean difference was calculated by domagrozumab minus placebo.

[216] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on PUL in Subset
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Statistical analysis description:

Subjects with baseline 4SC>=3.5 and <= 8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[217]</sup>
P-value	= 0.8629 <sup>[218]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.1

Confidence interval

level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.5

Notes:

[217] - Mean difference was calculated by domagrozumab minus placebo.

[218] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on PUL in Subset
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Statistical analysis description:

Subjects with baseline 4SC>8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority <sup>[219]</sup>
P-value	= 0.6746 <sup>[220]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.9

Confidence interval

level	95 %
sides	2-sided
lower limit	-5.5
upper limit	3.7

Notes:

[219] - Mean difference was calculated by domagrozumab minus placebo.

[220] - The significance level is 0.05.

## **Secondary: Change From Baseline as Compared to Placebo on 6MWD at Week 17 in Pre-specified Subsets**

End point title	Change From Baseline as Compared to Placebo on 6MWD at
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## End point description:

6MWD evaluated ambulation ability by measuring the distance walked in 6 minutes. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1) <3.5 seconds, 2) ≥3.5 seconds and ≤8 seconds, 3) >8 seconds. MMRM was used to analyze the change from baseline on 6MWD for domagrozumab compared to placebo in subsets. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 17

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	74		
Units: Meters				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	-6.9 (± 15.4)	-12.7 (± 9.3)		
Baseline 4SC≥3.5 and ≤8 seconds	-21.0 (± 8.8)	-22.4 (± 7.0)		
Baseline 4SC>8 seconds	-34.0 (± 28.3)	-20.9 (± 16.3)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on 6MWD in Subset
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Statistical analysis description:

Subjects with baseline 4SC&lt;3.5 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority <sup>[221]</sup>
P-value	= 0.7483 <sup>[222]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.4
upper limit	30.7

Notes:

[221] - Mean difference was calculated by domagrozumab minus placebo.

[222] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on 6MWD in Subset
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Statistical analysis description:

Subjects with baseline 4SC≥3.5 and ≤8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority <sup>[223]</sup>
P-value	= 0.9053 <sup>[224]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.9
upper limit	21.2

Notes:

[223] - Mean difference was calculated by domagrozumab minus placebo.

[224] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 6MWD in Subset
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Statistical analysis description:

Subjects with baseline 4SC>8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority <sup>[225]</sup>
P-value	= 0.6896 <sup>[226]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	13.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.4
upper limit	79.7

Notes:

[225] - Mean difference was calculated by domagrozumab minus placebo.

[226] - The significance level is 0.05.

### **Secondary: Change From Baseline as Compared to Placebo on 6MWD at Week 33 in Pre-specified Subsets**

End point title	Change From Baseline as Compared to Placebo on 6MWD at Week 33 in Pre-specified Subsets
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End point description:

6MWD evaluated ambulation ability by measuring the distance walked in 6 minutes. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1) <3.5 seconds, 2) >=3.5 seconds and <=8 seconds, 3) >8 seconds. MMRM was used to analyze the change from baseline on 6MWD for domagrozumab compared to placebo in subsets. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 33



End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	70		
Units: Meters				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	-12.0 (± 13.2)	-15.7 (± 7.8)		
Baseline 4SC>=3.5 and <=8 seconds	-45.7 (± 10.9)	-38.4 (± 8.6)		
Baseline 4SC>8 seconds	-71.9 (± 40.6)	-55.6 (± 17.5)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on 6MWD in Subset
Statistical analysis description: Subjects with baseline 4SC<3.5 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority <sup>[227]</sup>
P-value	= 0.8117 <sup>[228]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.8
upper limit	27.5

Notes:

[227] - Mean difference was calculated by domagrozumab minus placebo.

[228] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on 6MWD in Subset
Statistical analysis description: Subjects with baseline 4SC>=3.5 and <=8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority <sup>[229]</sup>
P-value	= 0.6018 <sup>[230]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	7.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.6
upper limit	35.2

Notes:

[229] - Mean difference was calculated by domagrozumab minus placebo.

[230] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 6MWD in Subset
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Statistical analysis description:

Subjects with baseline 4SC>8 seconds were analyzed.

Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority <sup>[231]</sup>
P-value	= 0.7152 <sup>[232]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	16.3

Confidence interval

level	95 %
sides	2-sided
lower limit	-73.4
upper limit	106

Notes:

[231] - Mean difference was calculated by domagrozumab minus placebo.

[232] - The significance level is 0.05.

## **Secondary: Change From Baseline as Compared to Placebo on 6MWD at Week 49 in Pre-specified Subsets**

End point title	Change From Baseline as Compared to Placebo on 6MWD at Week 49 in Pre-specified Subsets
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End point description:

6MWD evaluated ambulation ability by measuring the distance walked in 6 minutes. A subset analysis was performed by categorizing subjects into 3 subsets according to the baseline 4SC time: 1) <3.5 seconds, 2) ≥3.5 seconds and ≤8 seconds, 3) >8 seconds. MMRM was used to analyze the change from baseline on 6MWD for domagrozumab compared to placebo in subsets. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 49

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	61		
Units: Meters				
least squares mean (standard error)				
Baseline 4SC<3.5 seconds	-33.5 (± 16.4)	-26.5 (± 10.1)		
Baseline 4SC>=3.5 and <=8 seconds	-42.0 (± 16.7)	-57.8 (± 13.4)		
Baseline 4SC>8 seconds	-75.1 (± 47.6)	-71.2 (± 18.9)		

## Statistical analyses

Statistical analysis title	Statistical Comparison on 6MWD in Subset
Statistical analysis description: Subjects with baseline 4SC<3.5 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority <sup>[233]</sup>
P-value	= 0.719 <sup>[234]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.1
upper limit	46.1

Notes:

[233] - Mean difference was calculated by domagrozumab minus placebo.

[234] - The significance level is 0.05.

Statistical analysis title	Statistical Comparison on 6MWD in Subset
Statistical analysis description: Subjects with baseline 4SC>=3.5 and <=8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority <sup>[235]</sup>
P-value	= 0.4634 <sup>[236]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-15.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.9
upper limit	27.3

Notes:

[235] - Mean difference was calculated by domagrozumab minus placebo.

[236] - The significance level is 0.05.

<b>Statistical analysis title</b>	Statistical Comparison on 6MWD in Subset
Statistical analysis description:	
Subjects with baseline 4SC>8 seconds were analyzed.	
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority <sup>[237]</sup>
P-value	= 0.94 <sup>[238]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-100.7
upper limit	108.5

Notes:

[237] - Mean difference was calculated by domagrozumab minus placebo.

[238] - The significance level is 0.05.

### Secondary: Change From Baseline on Muscle Strength at Weeks 17, 33 and 49 in Pre-specified Subset (Baseline 4SC <3.5 Seconds)

End point title	Change From Baseline on Muscle Strength at Weeks 17, 33 and 49 in Pre-specified Subset (Baseline 4SC <3.5 Seconds)
End point description:	
Muscle strength was quantified by means of a handheld dynamometer. The following muscle groups were evaluated: knee extension, elbow flexion, hip abduction, elbow extension and shoulder abduction. Change from baseline on muscle strength in all randomized subjects who had received at least 1 dose of randomized treatment and had baseline 4SC <3.5 seconds are presented below.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 17, 33 and 49	

End point values	Placebo (4SC< 3.5 seconds, Period 1)	Domagrozumab (4SC< 3.5 seconds, Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	30		
Units: Kilograms				
arithmetic mean (confidence interval 95%)				
Left elbow extension, Week 17	-0.08 (-0.811 to 0.647)	-0.33 (-0.960 to 0.301)		
Left elbow extension, Week 33	-0.30 (-1.217 to 0.617)	-0.61 (-1.263 to 0.042)		
Left elbow extension, Week 49	-1.13 (-2.130 to -0.130)	-0.60 (-1.304 to 0.097)		

Right elbow extension, Week 17	0.35 (-0.260 to 0.969)	-0.50 (-1.305 to 0.297)		
Right elbow extension, Week 33	0.46 (-0.681 to 1.606)	-0.88 (-1.591 to -0.168)		
Right elbow extension, Week 49	-0.74 (-1.727 to 0.247)	-0.78 (-1.601 to 0.037)		
Left elbow flexion, Week 17	0.65 (-0.290 to 1.600)	-0.61 (-1.602 to 0.387)		
Left elbow flexion, Week 33	0.95 (-0.700 to 2.600)	-0.77 (-1.628 to 0.083)		
Left elbow flexion, Week 49	-0.88 (-1.664 to -0.096)	-0.96 (-1.857 to -0.057)		
Right elbow flexion, Week 17	1.29 (0.401 to 2.181)	-0.21 (-0.938 to 0.517)		
Right elbow flexion, Week 33	1.38 (-0.806 to 3.556)	-0.35 (-0.913 to 0.217)		
Right elbow flexion, Week 49	-0.33 (-1.082 to 0.422)	-0.69 (-1.310 to -0.061)		
Left hip abduction, Week 17	0.62 (-0.774 to 2.011)	-0.18 (-1.206 to 0.849)		
Left hip abduction, Week 33	-0.51 (-2.235 to 1.210)	-0.02 (-0.835 to 0.786)		
Left hip abduction, Week 49	-1.18 (-2.358 to -0.002)	-0.30 (-1.001 to 0.394)		
Right hip abduction, Week 17	1.47 (0.185 to 2.760)	-0.26 (-1.295 to 0.781)		
Right hip abduction, Week 33	0.40 (-0.739 to 1.539)	-0.34 (-1.172 to 0.496)		
Right hip abduction, Week 49	-0.75 (-1.785 to 0.285)	-0.14 (-1.121 to 0.831)		
Left knee extension, Week 17	0.99 (-0.192 to 2.174)	-1.12 (-2.186 to -0.050)		
Left knee extension, Week 33	0.11 (-2.096 to 2.321)	-1.31 (-2.367 to -0.261)		
Left knee extension, Week 49	-1.54 (-3.308 to 0.228)	-1.33 (-2.516 to -0.140)		
Right knee extension, Week 17	1.01 (-0.395 to 2.413)	-0.97 (-2.035 to 0.092)		
Right knee extension, Week 33	0.26 (-1.037 to 1.562)	-1.31 (-2.494 to -0.120)		
Right knee extension, Week 49	-1.79 (-4.347 to 0.767)	-1.47 (-2.646 to -0.299)		
Left shoulder abduction, Week 17	0.66 (-0.218 to 1.545)	-0.33 (-0.866 to 0.206)		
Left shoulder abduction, Week 33	0.48 (-0.574 to 1.524)	-0.32 (-0.747 to 0.112)		
Left shoulder abduction, Week 49	-0.32 (-1.357 to 0.717)	-0.16 (-0.627 to 0.306)		
Right shoulder abduction, Week 17	1.16 (0.421 to 1.899)	-0.40 (-1.058 to 0.258)		
Right shoulder abduction, Week 33	1.06 (-0.222 to 2.347)	-0.50 (-1.020 to 0.027)		
Right shoulder abduction, Week 49	0.17 (-0.749 to 1.089)	-0.20 (-0.852 to 0.445)		

## Statistical analyses

**Secondary: Change From Baseline on Muscle Strength at Weeks 17, 33 and 49 in Pre-specified Subset (Baseline 4SC  $\geq 3.5$  Seconds and  $\leq 8$  Seconds)**

End point title	Change From Baseline on Muscle Strength at Weeks 17, 33 and 49 in Pre-specified Subset (Baseline 4SC $\geq 3.5$ Seconds and $\leq 8$ Seconds)
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## End point description:

Muscle strength was quantified by means of a handheld dynamometer. The following muscle groups were evaluated: knee extension, elbow flexion, hip abduction, elbow extension and shoulder abduction. Change from baseline on muscle strength in all randomized subjects who had received at least 1 dose of randomized treatment and had baseline 4SC  $\geq 3.5$  seconds and  $\leq 8$  seconds are presented below.

End point type	Secondary
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## End point timeframe:

Baseline, Weeks 17, 33 and 49

End point values	Placebo(4SC $\geq 3.5$ and $\leq 8$ seconds, Period 1)	Domagrozumab (4SC $\geq 3.5$ and $\leq 8$ seconds, Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	38		
Units: Kilograms				
arithmetic mean (confidence interval 95%)				
Left elbow extension, Week 17	-0.05 (-0.353 to 0.244)	0.31 (-0.073 to 0.689)		
Left elbow extension, Week 33	-0.02 (-0.441 to 0.396)	-0.09 (-0.480 to 0.302)		
Left elbow extension, Week 49	0.15 (-0.223 to 0.532)	-0.26 (-0.803 to 0.289)		
Right elbow extension, Week 17	0 (-0.297 to 0.297)	0.31 (-0.070 to 0.686)		
Right elbow extension, Week 33	0.02 (-0.367 to 0.412)	-0.17 (-0.558 to 0.209)		
Right elbow extension, Week 49	-0.02 (-0.294 to 0.257)	-0.29 (-0.735 to 0.146)		
Left elbow flexion, Week 17	-0.10 (-0.523 to 0.331)	0.31 (-0.052 to 0.668)		
Left elbow flexion, Week 33	-0.26 (-0.598 to 0.071)	-0.13 (-0.515 to 0.254)		
Left elbow flexion, Week 49	-0.22 (-0.719 to 0.273)	-0.31 (-0.766 to 0.149)		
Right elbow flexion, Week 17	-0.20 (-0.471 to 0.063)	0.19 (-0.200 to 0.589)		
Right elbow flexion, Week 33	-0.15 (-0.529 to 0.239)	-0.23 (-0.682 to 0.225)		
Right elbow flexion, Week 49	-0.21 (-0.600 to 0.182)	-0.43 (-0.920 to 0.068)		
Left hip abduction, Week 17	0.65 (-0.019 to 1.319)	0.34 (-0.134 to 0.823)		
Left hip abduction, Week 33	-0.04 (-0.823 to 0.750)	-0.02 (-0.562 to 0.518)		
Left hip abduction, Week 49	0.48 (-0.336 to 1.290)	-0.09 (-1.042 to 0.865)		

Right hip abduction, Week 17	0.30 (-0.444 to 1.052)	0.29 (-0.189 to 0.779)		
Right hip abduction, Week 33	0 (-1.062 to 1.071)	-0.05 (-0.655 to 0.555)		
Right hip abduction, Week 49	0.32 (-0.555 to 1.200)	0.20 (-0.681 to 1.087)		
Left knee extension, Week 17	-0.51 (-1.266 to 0.249)	0.50 (-0.025 to 1.025)		
Left knee extension, Week 33	-0.59 (-1.576 to 0.404)	-0.67 (-1.339 to 0)		
Left knee extension, Week 49	-0.80 (-1.856 to 0.256)	-0.59 (-1.373 to 0.201)		
Right knee extension, Week 17	-0.41 (-1.092 to 0.267)	0.14 (-0.360 to 0.633)		
Right knee extension, Week 33	-0.35 (-1.227 to 0.536)	-0.53 (-1.237 to 0.170)		
Right knee extension, Week 49	-0.33 (-1.144 to 0.489)	-0.69 (-1.547 to 0.158)		
Left shoulder abduction, Week 17	-0.24 (-0.757 to 0.274)	0.49 (0.072 to 0.902)		
Left shoulder abduction, Week 33	-0.19 (-0.552 to 0.170)	0.03 (-0.442 to 0.503)		
Left shoulder abduction, Week 49	-0.20 (-0.679 to 0.288)	-0.01 (-0.749 to 0.727)		
Right shoulder abduction, Week 17	-0.18 (-0.493 to 0.134)	0.14 (-0.296 to 0.581)		
Right shoulder abduction, Week 33	0.38 (-0.260 to 1.014)	-0.18 (-0.683 to 0.319)		
Right shoulder abduction, Week 49	0.31 (-0.167 to 0.785)	-0.19 (-1.168 to 0.780)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline on Muscle Strength at Weeks 17, 33 and 49 in Pre-specified Subset (Baseline 4SC >8 seconds)

End point title	Change From Baseline on Muscle Strength at Weeks 17, 33 and 49 in Pre-specified Subset (Baseline 4SC >8 seconds)
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End point description:

Muscle strength was quantified by means of a handheld dynamometer. The following muscle groups were evaluated: knee extension, elbow flexion, hip abduction, elbow extension and shoulder abduction. Change from baseline on muscle strength in all randomized subjects who had received at least 1 dose of randomized treatment and had baseline 4SC >8 seconds are presented below.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33 and 49

End point values	Placebo (4SC>8 seconds, Period 1)	Domagrozumab (4SC>8 seconds, Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	12		
Units: Kilograms				
arithmetic mean (confidence interval 95%)				
Left elbow extension, Week 17	0.10 (-0.665 to 0.865)	0.14 (-0.226 to 0.498)		
Left elbow extension, Week 33	0.14 (-0.672 to 0.952)	0.06 (-0.485 to 0.612)		
Left elbow extension, Week 49	0.08 (-0.380 to 0.540)	-0.15 (-0.456 to 0.146)		
Right elbow extension, Week 17	0.32 (-0.231 to 0.871)	0.41 (0.099 to 0.719)		
Right elbow extension, Week 33	0.10 (-0.434 to 0.634)	0.23 (-0.380 to 0.834)		
Right elbow extension, Week 49	0.06 (-0.275 to 0.395)	-0.13 (-0.467 to 0.213)		
Left elbow flexion, Week 17	-0.12 (-0.657 to 0.417)	0.10 (-0.199 to 0.399)		
Left elbow flexion, Week 33	-0.36 (-1.108 to 0.388)	0.33 (-0.684 to 1.339)		
Left elbow flexion, Week 49	-0.34 (-0.810 to 0.130)	-0.27 (-0.691 to 0.146)		
Right elbow flexion, Week 17	-0.30 (-0.933 to 0.333)	0.20 (-0.168 to 0.568)		
Right elbow flexion, Week 33	-0.02 (-0.488 to 0.448)	0.12 (-0.671 to 0.908)		
Right elbow flexion, Week 49	-0.14 (-0.567 to 0.287)	-0.34 (-0.646 to -0.027)		
Left hip abduction, Week 17	0.12 (-1.321 to 1.561)	-0.18 (-1.104 to 0.741)		
Left hip abduction, Week 33	0.36 (-1.232 to 1.952)	0.65 (-1.112 to 2.403)		
Left hip abduction, Week 49	0.16 (-1.785 to 2.105)	-0.68 (-1.714 to 0.351)		
Right hip abduction, Week 17	0.22 (-0.698 to 1.138)	0.09 (-0.546 to 0.728)		
Right hip abduction, Week 33	0.32 (-1.826 to 2.466)	0.80 (-1.501 to 3.101)		
Right hip abduction, Week 49	0.68 (-1.743 to 3.103)	-0.55 (-1.569 to 0.460)		
Left knee extension, Week 17	0.04 (-0.505 to 0.585)	0.22 (-0.052 to 0.488)		
Left knee extension, Week 33	-0.24 (-1.188 to 0.708)	0.32 (-0.749 to 1.386)		
Left knee extension, Week 49	-0.02 (-0.971 to 0.931)	-0.33 (-0.734 to 0.079)		
Right knee extension, Week 17	0.32 (-0.442 to 1.082)	0.17 (-0.204 to 0.549)		
Right knee extension, Week 33	-0.02 (-0.462 to 0.422)	0.35 (-0.926 to 1.617)		
Right knee extension, Week 49	0.06 (-0.410 to 0.530)	-0.20 (-0.564 to 0.164)		
Left shoulder abduction, Week 17	0.02 (-0.722 to 0.762)	-0.39 (-1.137 to 0.356)		
Left shoulder abduction, Week 33	-0.12 (-0.692 to 0.452)	0.29 (-1.461 to 2.042)		



Left shoulder abduction, Week 49	0.06 (-0.718 to 0.838)	-0.39 (-1.346 to 0.564)		
Right shoulder abduction, Week 17	0.14 (-0.820 to 1.100)	0 (-0.568 to 0.568)		
Right shoulder abduction, Week 33	0.36 (-0.226 to 0.946)	0.28 (-1.244 to 1.807)		
Right shoulder abduction, Week 49	0.32 (-0.357 to 0.997)	-0.17 (-1.132 to 0.787)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Whole Thigh Muscle Volume as Compared to Placebo by Weeks 17, 33 and 49

End point title	Percent Change From Baseline in Whole Thigh Muscle Volume as Compared to Placebo by Weeks 17, 33 and 49
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End point description:

The whole thigh muscle volume was measured by the proton density weighted sequence with magnetic resonance imaging (MRI) which was used to segment the entire thigh region into 3 primary regions for volumetric measure including 1) muscle; 2) inter/intra-muscular fat, 3) subcutaneous fat. MMRM was used to analyze the percent change from baseline for domagrozumab compared to placebo. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in the analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33 and 49

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Percent change of thigh muscle volume				
least squares mean (standard error)				
Week 17	1.202 (± 1.360)	3.391 (± 1.110)		
Week 33	1.390 (± 1.538)	3.500 (± 1.202)		
Week 49	0.065 (± 1.962)	2.928 (± 1.473)		

## Statistical analyses

Statistical analysis title	Comparison on Thigh Muscle Volume at Week 17
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[239]</sup>
P-value	= 0.1323 <sup>[240]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.189
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6721
upper limit	5.0506

Notes:

[239] - Mean difference was calculated by domagrozumab minus placebo.

[240] - The significance level is 0.05.

<b>Statistical analysis title</b>	Comparison on Thigh Muscle Volume at Week 49
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[241]</sup>
P-value	= 0.2035 <sup>[242]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.864
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5718
upper limit	7.2994

Notes:

[241] - Mean difference was calculated by domagrozumab minus placebo.

[242] - The significance level is 0.05.

<b>Statistical analysis title</b>	Comparison on Thigh Muscle Volume at Week 33
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[243]</sup>
P-value	= 0.2102 <sup>[244]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2078
upper limit	5.4279

Notes:

[243] - Mean difference was calculated by domagrozumab minus placebo.

[244] - The significance level is 0.05.

## Secondary: Percent Change From Baseline as Compared to Placebo in Whole Thigh Muscle Volume Index by Weeks 17, 33 and 49

End point title	Percent Change From Baseline as Compared to Placebo in Whole Thigh Muscle Volume Index by Weeks 17, 33 and 49
End point description:	
The thigh muscle volume index was derived from the thigh muscle volume measurements as a fraction of the total thigh tissue that was the lean muscle. MMRM was used to analyze the percent change from baseline for domagrozumab compared to placebo. The stratification factor, baseline result, treatment, time and treatment by time interaction were included as fixed effects in the model. Subjects were included as a random effect and the model was fit with an unstructured covariance for the repeated measures. All subjects randomized and who had received at least 1 dose of randomized treatment were included in this endpoint's analysis set.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 17, 33 and 49	

End point values	Placebo (Period 1)	Domagrozumab (Period 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	80		
Units: Percent change of muscle volume index				
least squares mean (standard error)				
Week 17	-4.837 (± 1.070)	-4.076 (± 0.839)		
Week 33	-8.802 (± 1.229)	-7.046 (± 0.931)		
Week 49	-12.013 (± 1.497)	-10.033 (± 1.101)		

## Statistical analyses

Statistical analysis title	Comparison on Muscle Volume Index at Week 17
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[245]</sup>
P-value	= 0.4921 <sup>[246]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.761
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4272
upper limit	2.9491

Notes:

[245] - Mean difference was calculated by domagrozumab minus placebo.

[246] - The significance level is 0.05.

<b>Statistical analysis title</b>	Comparison on Muscle Volume Index at Week 33
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[247]</sup>
P-value	= 0.1866 <sup>[248]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.755
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8621
upper limit	4.3729

Notes:

[247] - Mean difference was calculated by domagrozumab minus placebo.

[248] - The significance level is 0.05.

<b>Statistical analysis title</b>	Comparison on Muscle Volume Index at Week 49
Comparison groups	Placebo (Period 1) v Domagrozumab (Period 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority <sup>[249]</sup>
P-value	= 0.2414 <sup>[250]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3513
upper limit	5.3112

Notes:

[249] - Mean difference was calculated by domagrozumab minus placebo.

[250] - The significance level is 0.05

## Secondary: Change From Baseline in Whole Thigh Muscle Volume Through Week 97

End point title	Change From Baseline in Whole Thigh Muscle Volume Through Week 97
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End point description:

The whole thigh muscle volume was measured by the proton density weighted sequence with magnetic resonance imaging (MRI) which was used to segment the entire thigh region into 3 primary regions for volumetric measure including 1) muscle; 2) inter/intra-muscular fat, 3) subcutaneous fat. All subjects randomized and who had received at least 1 dose of randomized treatment were included in this endpoint's analysis set.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49 and 97

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	40	
Units: Cubic centimeters				
arithmetic mean (confidence interval 95%)				
Muscle volume, Week 17	35162.785 (9765.665 to 60559.904)	40069.778 (9755.393 to 70384.162)	14486.191 (-6398.245 to 35370.626)	
Muscle volume, Week 33	39361.864 (9578.842 to 69144.886)	42442.344 (6099.748 to 78784.939)	21526.141 (-4965.968 to 48018.249)	
Muscle volume, Week 49	42380.843 (5398.079 to 79363.607)	31792.214 (-10741.381 to 74325.809)	1331.221 (-37506.169 to 40168.611)	
Muscle volume, Week 97	45574.235 (-17573.955 to 108722.425)	-41695.894 (-129739.929 to 46348.141)	2126.471 (-75729.101 to 79982.043)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Whole Thigh Muscle Volume Index Through Week 97

End point title	Change From Baseline in Whole Thigh Muscle Volume Index Through Week 97
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End point description:

The thigh muscle volume index was derived from the thigh muscle volume measurements as the fraction of total thigh tissue that was the lean muscle. All subjects randomized and who had received at least 1 dose of randomized treatment were included in this endpoint's analysis set.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49 and 97

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	40	
Units: Percentage of whole thigh volume				
arithmetic mean (confidence interval 95%)				
Week 17	-1.736 (-2.685 to -0.787)	-1.782 (-2.976 to -0.587)	-2.616 (-3.794 to -1.439)	
Week 33	-3.911 (-5.322 to -2.500)	-3.510 (-5.163 to -1.856)	-5.076 (-6.439 to -3.713)	
Week 49	-5.298 (-7.076 to -3.519)	-6.283 (-8.406 to -4.160)	-6.908 (-8.590 to -5.225)	
Week 97	-11.598 (-15.219 to -7.977)	-14.803 (-19.417 to -10.189)	-13.481 (-17.682 to -9.279)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Concentration of Growth Differentiation Factor 8 (GDF-8) at Time 0 (pre-dose),(C0(GDF-8) )

End point title	Concentration of Growth Differentiation Factor 8 (GDF-8) at Time 0 (pre-dose),(C0(GDF-8) )
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End point description:

GDF-8, also called myostatin, is the target of domagrozumab. C0(GDF-8) was observed directly from data. All enrolled subjects in whom at least 1 GDF-8 concentration value was reported were included in this endpoint's analysis set. Subjects without contributing to the summary statistics are excluded below.

End point type	Secondary
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End point timeframe:

Predose on Day 1 of Week 1

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	39	39	
Units: Nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	0.3187 ( $\pm$ 38773)	0.4557 ( $\pm$ 6787)	0.5052 ( $\pm$ 7405)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Trough Serum Concentration of GDF-8 (Ctough,(GDF-8)) for Subjects Receiving Domagrozumab in Period 1

End point title	Trough Serum Concentration of GDF-8 (Ctough,(GDF-8)) for Subjects Receiving Domagrozumab in Period 1
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End point description:

GDF-8, also called myostatin, is the target of domagrozumab. Ctough,(GDF-8) was observed directly from data. This endpoint's analysis set included all enrolled subjects of Sequence 1 and 2 and in whom at least 1 GDF-8 concentration value was reported. Subjects without contributing to the summary statistics are excluded below.

End point type	Secondary
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End point timeframe:

Every 4 weeks on dosing day (at predose, end of 2-hour infusion and 6 hours since start of infusion) from Week 1 to Week 48

End point values	Domagrozumab 5 mg/kg (Period 1)	Domagrozumab 20 mg/kg (Period 1)	Domagrozumab 40 mg/kg (Period 1)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	78	76	75	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	4.540 ( $\pm$ 43)	6.257 ( $\pm$ 42)	7.449 ( $\pm$ 40)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Ctrough,(GDF-8) for Subjects of Sequence 3 in Period 2

End point title	Ctrough,(GDF-8) for Subjects of Sequence 3 in Period 2
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End point description:

GDF-8, also called myostatin, is the target of domagrozumab. Ctrough,(GDF-8) was observed directly from data. This endpoint's analysis set included all enrolled subjects of Sequence 3 and in whom at least 1 GDF-8 concentration value was reported. Subjects without contributing to the summary statistics are excluded below.

End point type	Secondary
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End point timeframe:

Every 4 weeks on dosing day (predose, end of 2-hour infusion and 6 hours since start of infusion) from Week 49 to Week 96

End point values	Domagrozumab 5 mg/kg (Sequence 3)	Domagrozumab 20 mg/kg (Sequence 3)	Domagrozumab 40 mg/kg (Sequence 3)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	37	30	21	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	5.572 ( $\pm$ 36)	7.776 ( $\pm$ 45)	8.383 ( $\pm$ 53)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Trough (pre-dose) Serum Concentration (Ctrough) of Domagrozumab

End point title	Trough (pre-dose) Serum Concentration (Ctrough) of Domagrozumab
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End point description:

Ctrough was observed directly from data. This endpoint's analysis set included all subjects who received at least 1 dose of domagrozumab and in whom at least 1 concentration value was reported. Subjects

without contributing to the summary statistics are excluded below. "99999" represents "not applicable" because data were not collected for specified rows of time points. The geometric coefficient of variation for Sequence 2 at Week 1 is 99999 because only 1 subject was analyzed for Ctrough at Week 1 and thus the geometric mean is an individual data.

End point type	Secondary
End point timeframe:	
Every 4 weeks on dosing day (predose, end of 2-hour infusion and 6 hours since start of infusion) from Week 1 to Week 96 for Sequence 1; from Week 1 to Week 48 for Sequence 2; from Week 49 to Week 96 for Sequence 3	

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	38	
Units: Microgram per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Week 1	99999 (± 99999)	75.3 (± 99999)	99999 (± 99999)	
Week 5	18.66 (± 28)	19.26 (± 48)	99999 (± 99999)	
Week 9	25.11 (± 32)	27.95 (± 28)	99999 (± 99999)	
Week 13	30.36 (± 28)	31.98 (± 39)	99999 (± 99999)	
Week 17	31.36 (± 30)	35.08 (± 33)	99999 (± 99999)	
Week 21	89.57 (± 43)	97.5 (± 32)	99999 (± 99999)	
Week 25	122.2 (± 25)	129.4 (± 28)	99999 (± 99999)	
Week 29	131.4 (± 26)	140.4 (± 31)	99999 (± 99999)	
Week 33	130.9 (± 36)	148.2 (± 32)	99999 (± 99999)	
Week 37	227.5 (± 33)	250.7 (± 44)	99999 (± 99999)	
Week 41	260.9 (± 31)	284.5 (± 29)	99999 (± 99999)	
Week 45	295.7 (± 32)	323.4 (± 22)	99999 (± 99999)	
Week 49	289.1 (± 31)	99999 (± 99999)	99999 (± 99999)	
Week 53	307.3 (± 29)	99999 (± 99999)	25.72 (± 36)	
Week 57	331.3 (± 29)	99999 (± 99999)	39.9 (± 31)	
Week 61	327.6 (± 34)	99999 (± 99999)	42.62 (± 46)	
Week 65	315.4 (± 39)	99999 (± 99999)	48.39 (± 39)	
Week 69	315.7 (± 28)	99999 (± 99999)	139.5 (± 47)	
Week 73	333.8 (± 34)	99999 (± 99999)	168.1 (± 30)	
Week 77	309.6 (± 51)	99999 (± 99999)	185.9 (± 27)	



Week 81	340.5 ( $\pm$ 26)	99999 ( $\pm$ 99999)	201.2 ( $\pm$ 30)	
Week 85	367 ( $\pm$ 27)	99999 ( $\pm$ 99999)	314.6 ( $\pm$ 32)	
Week 89	352.9 ( $\pm$ 26)	99999 ( $\pm$ 99999)	367.4 ( $\pm$ 33)	
Week 93	380.2 ( $\pm$ 17)	99999 ( $\pm$ 99999)	418.4 ( $\pm$ 33)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Serum Concentration (Cmax) of Domagrozumab

End point title	Maximum Serum Concentration (Cmax) of Domagrozumab
End point description: Cmax was observed directly from data.	
End point type	Secondary
End point timeframe: Every 4 weeks on dosing day (predose, end of 2-hour infusion and 6 hours since start of infusion) from Week 1 to Week 96 for Sequence 1; from Week 1 to Week 48 for Sequence 2; from Week 49 to Week 96 for Sequence 3	

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 <sup>[251]</sup>	0 <sup>[252]</sup>	0 <sup>[253]</sup>	
Units: ug/mL				
geometric mean (geometric coefficient of variation)	()	()	()	

Notes:

[251] - Data were not collected and analyzed due to study early termination.

[252] - Data were not collected and analyzed due to study early termination.

[253] - Data were not collected and analyzed due to study early termination.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time for Cmax (Tmax) of Domagrozumab

End point title	Time for Cmax (Tmax) of Domagrozumab
End point description: Tmax was observed directly from the data.	
End point type	Secondary
End point timeframe: Every 4 weeks on dosing day (predose, end of 2-hour infusion and 6 hours since start of infusion) from Week 1 to Week 96 for Sequence 1; from Week 1 to Week 48 for Sequence 2; from Week 49 to Week 96 for Sequence 3	

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 <sup>[254]</sup>	0 <sup>[255]</sup>	0 <sup>[256]</sup>	
Units: Hours				
median (full range (min-max))	( to )	( to )	( to )	

Notes:

[254] - Data were not collected and analyzed due to study early termination.

[255] - Data were not collected and analyzed due to study early termination.

[256] - Data were not collected and analyzed due to study early termination.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Terminal Half-life (t<sub>1/2</sub>) for Subjects in Sequence 2 After the Last Dose of Domagrozumab

End point title	Terminal Half-life (t <sub>1/2</sub> ) for Subjects in Sequence 2 After the Last Dose of Domagrozumab <sup>[257]</sup>
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End point description:

t<sub>1/2</sub> was calculated by Loge(2)/kel, where kel was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Subjects in Sequence 2 received the last dose of domagrozumab at Week 45.

End point type	Secondary
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End point timeframe:

At predose, end of 2-hour infusion and 6 hours since start of infusion at Week 45

Notes:

[257] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Sequence 2			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[258]</sup>			
Units: Hours				
arithmetic mean (standard deviation)	( )			

Notes:

[258] - Data were not collected and analyzed due to study early termination.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Serum Concentration-time Curve Over the Dosing Interval tau (AUCtau) of Domagrozumab

End point title	Area Under the Serum Concentration-time Curve Over the Dosing Interval tau (AUCtau) of Domagrozumab
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End point description:

The dosing interval tau was 672 hours (4 weeks). AUCtau was obtained by linear/log trapezoidal

method. The AUCtau was assessed to fully characterize PK data and it was only assessed on the first 12 subjects enrolled in the study who were required to complete additional PK visits. This endpoint's analysis set included subjects who were among the first 12 subjects enrolled in the study, had received at least 1 dose of domagrozumab and in whom at least 1 of the PK parameters of interest was calculated. Subjects without contributing to the summary statistics are excluded below. "99999" represents "not applicable" because data were not collected for specified rows of time points.

End point type	Secondary
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End point timeframe:

At predose, end of 2-hour infusion, 6 hours and 168 hours since start of infusion on Weeks 1, 13, 17, 29, 33 and 45

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	5	0 <sup>[259]</sup>	
Units: Microgram*hour per milliliter (ug*hr/mL)				
median (full range (min-max))				
Week 1	26500 (21700 to 31300)	26300 (14700 to 31000)	( to )	
Week 13	34650 (29500 to 39800)	40500 (32300 to 50900)	( to )	
Week 17	120500 (102000 to 139000)	117000 (109000 to 128000)	( to )	
Week 29	152000 (129000 to 175000)	195500 (149000 to 197000)	( to )	
Week 33	244500 (216000 to 273000)	291000 (238000 to 372000)	( to )	
Week 45	333500 (285000 to 382000)	99999 (99999 to 99999)	( to )	

Notes:

[259] - Subjects received placebo in Period 1.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Average Serum Concentration Over the Dosing Interval (Cav) of Domagrozumab

End point title	Average Serum Concentration Over the Dosing Interval (Cav) of Domagrozumab
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End point description:

Cav was calculated by AUCtau/tau. The Cav was assessed to fully characterize PK data and it was only assessed on the first 12 subjects enrolled in the study who were required to complete additional PK visits. This endpoint's analysis set included subjects who were among the first 12 subjects enrolled in the study, had received at least 1 dose of domagrozumab and in whom at least 1 of the PK parameters of interest was calculated. Subjects without contributing to the summary statistics are excluded below. "99999" represents "not applicable" because data were not collected for specified rows of time points.

End point type	Secondary
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End point timeframe:

At predose, end of 2-hour infusion, 6 hours and 168 hours since start of infusion on Weeks 1, 13, 17, 29, 33 and 45

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	5	0 <sup>[260]</sup>	
Units: ug/mL				
median (full range (min-max))				
Week 1	39.45 (32.3 to 46.6)	39.2 (21.9 to 46.1)	( to )	
Week 13	51.55 (43.9 to 59.2)	60.3 (48 to 75.7)	( to )	
Week 17	179 (151 to 207)	174 (162 to 191)	( to )	
Week 29	226.5 (192 to 261)	291 (221 to 293)	( to )	
Week 33	364 (322 to 406)	433.5 (354 to 553)	( to )	
Week 45	496 (424 to 568)	99999 (99999 to 99999)	( to )	

Notes:

[260] - Subjects received placebo in Period 1.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clearance (CL) of Domagrozumab

End point title	Clearance (CL) of Domagrozumab
End point description:	
CL was calculated by Dose/AUCtau. The CL was assessed to fully characterize PK data and it was only assessed on the first 12 subjects enrolled in the study who were required to complete additional PK visits. This endpoint's analysis set included subjects who were among the first 12 subjects enrolled in the study, had received at least 1 dose of domagrozumab and in whom at least 1 of the PK parameters of interest was calculated. Subjects without contributing to the summary statistics are excluded below. "99999" represents "not applicable" because data were not collected for specified rows of time points.	
End point type	Secondary
End point timeframe:	
At predose, end of 2-hour infusion, 6 hours and 168 hours since start of infusion on Weeks 13, 29 and 45	

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	5	0 <sup>[261]</sup>	
Units: Milliliter/hr/kilogram(mL/hr/kg)				
median (full range (min-max))				
Week 13	0.148 (0.126 to 0.17)	0.123 (0.0983 to 0.155)	( to )	
Week 29	0.1345 (0.114 to 0.155)	0.102 (0.102 to 0.134)	( to )	

Week 45	0.1225 (0.105 to 0.14)	99999 (99999 to 99999)	( to )	
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Notes:

[261] - Subjects received placebo in Period 1.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Volume of distribution at steady state (Vss) of Domagrozumab for Subjects in Sequence 2 Required for Additional PK Assessment

End point title	Volume of distribution at steady state (Vss) of Domagrozumab for Subjects in Sequence 2 Required for Additional PK Assessment <sup>[262]</sup>
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End point description:

Vss was calculated by CL\*MRT, where MRT was the mean residence time. Vss was assessed to fully characterize PK data.

End point type	Secondary
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End point timeframe:

At predose, end of 2-hour infusion, 6 hours and 168 hours since start of infusion on Week 45

Notes:

[262] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Sequence 2			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[263]</sup>			
Units: milliliter per kilogram (mL/kg)				
geometric mean (geometric coefficient of variation)	( )			

Notes:

[263] - Data were not collected and analyzed due to study early termination.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Anti-drug Antibodies (ADA) Development by Week 97

End point title	Number of Subjects With Anti-drug Antibodies (ADA) Development by Week 97
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End point description:

The criterion for positive result of ADA samples was ADA titer  $\geq 1.88$ . All subjects who received at least 1 dose of investigational drug were included in this endpoint's analysis set. "99999" represents "not applicable" because data were not collected for specified rows of time points.

End point type	Secondary
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End point timeframe:

Baseline, every 4 weeks from Week 5 to Week 97 visit or early termination

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	40	
Units: Subjects				
Baseline	0	0	99999	
Week 5	0	0	99999	
Week 9	0	0	99999	
Week 13	0	0	99999	
Week 17	0	0	99999	
Week 21	0	0	99999	
Week 25	0	0	99999	
Week 29	0	0	99999	
Week 33	0	0	99999	
Week 37	0	0	99999	
Week 41	0	0	99999	
Week 45	0	0	99999	
Week 49	0	0	0	
Week 53	0	99999	0	
Week 57	0	99999	0	
Week 61	0	99999	0	
Week 65	0	99999	1	
Week 69	0	99999	0	
Week 73	0	99999	0	
Week 77	0	99999	0	
Week 81	0	99999	0	
Week 85	0	99999	0	
Week 89	0	99999	0	
Week 93	0	99999	0	
Week 97	0	0	0	
Early termination	0	0	0	

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Area Under the Curve From Time Zero to Last Quantifiable Serum Concentration (AUClast) of Domagrozumab

End point title	Area Under the Curve From Time Zero to Last Quantifiable Serum Concentration (AUClast) of Domagrozumab
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End point description:

AUClast was calculated by linear/log trapezoidal method. AUCtau was obtained by linear/log trapezoidal method. AUClast was assessed to fully characterize PK data and it was only assessed on the first 12 subjects enrolled in the study who were required to complete additional PK visits.

End point type	Other pre-specified
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End point timeframe:

At predose, end of 2-hour infusion, 6 hours and 168 hours since start of infusion on Weeks 1, 13, 17,

End point values	Sequence 1	Sequence 2	Sequence 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 <sup>[264]</sup>	0 <sup>[265]</sup>	0 <sup>[266]</sup>	
Units: ug*hr/mL				
geometric mean (geometric coefficient of variation)	()	()	()	

Notes:

[264] - Data were not collected and analyzed due to study early termination.

[265] - Data were not collected and analyzed due to study early termination.

[266] - Data were not collected and analyzed due to study early termination.

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

105 weeks

Adverse event reporting additional description:

The same event may appear as both an AE and an SAE. An event may be categorized as serious in one subject and as non-serious in another subject, or one subject may have experienced both a serious and non-serious event during the study. Total number at risk below refers to the number of subjects evaluable for SAEs or AEs.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	Sequence 1, Period 1
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Reporting group description:

Subjects received domagrozumab in a dose escalating fashion (5, 20 and 40mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). Subjects in this sequence continued to receive domagrozumab at the maximum tolerated dose (40 mg/kg) in the next period.

Reporting group title	Sequence 1, Period 2
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Reporting group description:

From Week 49 (Period 2), subjects received domagrozumab intravenously at the maximum tolerated dose (40 mg/kg) every 4 weeks for additional 48 weeks or until early termination of the study.

Reporting group title	Sequence 2, Period 1
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Reporting group description:

Subjects received domagrozumab in a dose escalating fashion (5, 20 and 40mg/kg) for 48 weeks (Period 1). At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses). Subjects in this sequence received placebo in the next period.

Reporting group title	Sequence 2, Period 2
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Reporting group description:

From Week 49 (Period 2), subjects received placebo for additional 48 weeks or until early termination of the study.

Reporting group title	Sequence 3, Period 1
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Reporting group description:

Subjects received placebo for 48 weeks (Period 1). Subjects in this sequence received active treatment in a dose escalating fashion in the next period.

Reporting group title	Sequence 3, Period 2
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Reporting group description:

From Week 49 (Period 2), subjects received domagrozumab in a dose escalating fashion (5, 20 and 40 mg/kg) for additional 48 weeks or until early termination of the study. At each dose level, dosing was administered over 2 hours by intravenous infusion every 4 weeks for a total of 16 weeks (4 doses).

Serious adverse events	Sequence 1, Period 1	Sequence 1, Period 2	Sequence 2, Period 1
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 41 (2.44%)	1 / 38 (2.63%)	1 / 39 (2.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			



Investigations			
Troponin increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 41 (0.00%)	0 / 38 (0.00%)	0 / 39 (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
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 41 (0.00%)	1 / 38 (2.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 38 (0.00%)	0 / 39 (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			
Superior sagittal sinus thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 38 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 41 (2.44%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 38 (0.00%)	0 / 39 (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
<b>Serious adverse events</b>	Sequence 2, Period 2	Sequence 3, Period 1	Sequence 3, Period 2
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	2 / 38 (5.26%)
number of deaths (all causes)	0	0	0
number of deaths resulting from			

adverse events			
Investigations			
Troponin increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	0 / 38 (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
Femur fracture			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Superior sagittal sinus thrombosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	0 / 38 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	0 / 38 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	0 / 38 (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

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

<b>Non-serious adverse events</b>	Sequence 1, Period 1	Sequence 1, Period 2	Sequence 2, Period 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 41 (92.68%)	32 / 38 (84.21%)	36 / 39 (92.31%)
Investigations			
Blood iron increased			
subjects affected / exposed	3 / 41 (7.32%)	2 / 38 (5.26%)	1 / 39 (2.56%)
occurrences (all)	5	2	1
Ejection fraction decreased			
subjects affected / exposed	0 / 41 (0.00%)	2 / 38 (5.26%)	0 / 39 (0.00%)
occurrences (all)	0	2	0
Occult blood positive			
subjects affected / exposed	0 / 41 (0.00%)	2 / 38 (5.26%)	1 / 39 (2.56%)
occurrences (all)	0	2	1
Troponin increased			
subjects affected / exposed	2 / 41 (4.88%)	1 / 38 (2.63%)	0 / 39 (0.00%)
occurrences (all)	2	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 41 (2.44%)	1 / 38 (2.63%)	2 / 39 (5.13%)
occurrences (all)	1	1	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 41 (9.76%)	3 / 38 (7.89%)	4 / 39 (10.26%)
occurrences (all)	5	4	4
Fall			
subjects affected / exposed	16 / 41 (39.02%)	13 / 38 (34.21%)	16 / 39 (41.03%)
occurrences (all)	37	20	30
Head injury			
subjects affected / exposed	0 / 41 (0.00%)	2 / 38 (5.26%)	2 / 39 (5.13%)
occurrences (all)	0	2	3
Hip fracture			
subjects affected / exposed	1 / 41 (2.44%)	0 / 38 (0.00%)	2 / 39 (5.13%)
occurrences (all)	1	0	2
Joint injury			
subjects affected / exposed	3 / 41 (7.32%)	0 / 38 (0.00%)	1 / 39 (2.56%)
occurrences (all)	3	0	1

Ligment sprain subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	4 / 38 (10.53%) 4	2 / 39 (5.13%) 2
Skin abrasion subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4	1 / 38 (2.63%) 1	2 / 39 (5.13%) 3
Spinal compression fracture subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	1 / 38 (2.63%) 1	1 / 39 (2.56%) 1
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2
Headache subjects affected / exposed occurrences (all)	9 / 41 (21.95%) 16	4 / 38 (10.53%) 10	6 / 39 (15.38%) 21
General disorders and administration site conditions			
Chest pain subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2	1 / 38 (2.63%) 1	1 / 39 (2.56%) 1
Fatigue subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 7	1 / 38 (2.63%) 1	2 / 39 (5.13%) 2
Gait inability subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3	2 / 38 (5.26%) 2	2 / 39 (5.13%) 2
Infusion site bruising subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1
Infusion site pain subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2
Infusion site swelling subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	3 / 38 (7.89%) 3	1 / 39 (2.56%) 1
Pain			

subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2
Pyrexia subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 9	5 / 38 (13.16%) 7	10 / 39 (25.64%) 11
Vessel puncture site bruise subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1
Ear and labyrinth disorders Ear disorder subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2
Abdominal pain subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 10	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 8	3 / 38 (7.89%) 6	3 / 39 (7.69%) 6
Constipation subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3	3 / 38 (7.89%) 3	1 / 39 (2.56%) 1
Diarrhoea subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 5	6 / 38 (15.79%) 8	3 / 39 (7.69%) 3
Nausea subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	8 / 41 (19.51%) 10	3 / 38 (7.89%) 3	12 / 39 (30.77%) 13
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 6	7 / 38 (18.42%) 9	5 / 39 (12.82%) 5
Epistaxis subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 20	3 / 38 (7.89%) 14	5 / 39 (12.82%) 17
Nasal congestion subjects affected / exposed occurrences (all)	8 / 41 (19.51%) 8	6 / 38 (15.79%) 7	4 / 39 (10.26%) 6
Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2	4 / 38 (10.53%) 5	4 / 39 (10.26%) 4
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3	5 / 38 (13.16%) 7	3 / 39 (7.69%) 5
Sleep apnoea syndrome subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 38 (0.00%) 0	0 / 39 (0.00%) 0
Skin and subcutaneous tissue disorders			
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 38 (0.00%) 0	0 / 39 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	1 / 38 (2.63%) 1	2 / 39 (5.13%) 2
Pruritus subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1
Rash subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3	2 / 38 (5.26%) 2	1 / 39 (2.56%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2
Obsessive-compulsive disorder			

subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 41 (17.07%)	1 / 38 (2.63%)	2 / 39 (5.13%)
occurrences (all)	7	1	4
Back pain			
subjects affected / exposed	5 / 41 (12.20%)	1 / 38 (2.63%)	4 / 39 (10.26%)
occurrences (all)	7	1	4
Mobility decreased			
subjects affected / exposed	0 / 41 (0.00%)	2 / 38 (5.26%)	0 / 39 (0.00%)
occurrences (all)	0	2	0
Muscular weakness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 38 (2.63%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	2 / 41 (4.88%)	1 / 38 (2.63%)	0 / 39 (0.00%)
occurrences (all)	2	1	0
Pain in extremity			
subjects affected / exposed	5 / 41 (12.20%)	4 / 38 (10.53%)	4 / 39 (10.26%)
occurrences (all)	7	5	5
Scoliosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 38 (0.00%)	1 / 39 (2.56%)
occurrences (all)	0	0	1
Tendon disorder			
subjects affected / exposed	0 / 41 (0.00%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 41 (2.44%)	2 / 38 (5.26%)	0 / 39 (0.00%)
occurrences (all)	1	2	0
Ear infection			
subjects affected / exposed	5 / 41 (12.20%)	3 / 38 (7.89%)	0 / 39 (0.00%)
occurrences (all)	5	3	0
Gastroenteritis			

subjects affected / exposed	4 / 41 (9.76%)	3 / 38 (7.89%)	1 / 39 (2.56%)
occurrences (all)	4	4	1
Gastroenteritis viral			
subjects affected / exposed	3 / 41 (7.32%)	0 / 38 (0.00%)	1 / 39 (2.56%)
occurrences (all)	3	0	1
Hordeolum			
subjects affected / exposed	0 / 41 (0.00%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	2 / 41 (4.88%)	6 / 38 (15.79%)	1 / 39 (2.56%)
occurrences (all)	2	6	1
Localised infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 38 (2.63%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	13 / 41 (31.71%)	6 / 38 (15.79%)	14 / 39 (35.90%)
occurrences (all)	21	8	21
Otitis media			
subjects affected / exposed	0 / 41 (0.00%)	1 / 38 (2.63%)	2 / 39 (5.13%)
occurrences (all)	0	1	2
Pharyngitis streptococcal			
subjects affected / exposed	1 / 41 (2.44%)	2 / 38 (5.26%)	1 / 39 (2.56%)
occurrences (all)	1	3	1
Rhinitis			
subjects affected / exposed	4 / 41 (9.76%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	6	0	0
Sinusitis			
subjects affected / exposed	1 / 41 (2.44%)	2 / 38 (5.26%)	0 / 39 (0.00%)
occurrences (all)	1	2	0
Upper respiratory tract infection			
subjects affected / exposed	8 / 41 (19.51%)	7 / 38 (18.42%)	9 / 39 (23.08%)
occurrences (all)	9	9	11
Pharyngitis			



subjects affected / exposed	1 / 41 (2.44%)	2 / 38 (5.26%)	0 / 39 (0.00%)
occurrences (all)	1	2	0

<b>Non-serious adverse events</b>	Sequence 2, Period 2	Sequence 3, Period 1	Sequence 3, Period 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 37 (81.08%)	38 / 40 (95.00%)	35 / 38 (92.11%)
Investigations			
Blood iron increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Occult blood positive			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Troponin increased			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	2 / 38 (5.26%)
occurrences (all)	1	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	2 / 38 (5.26%)
occurrences (all)	0	1	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 37 (8.11%)	3 / 40 (7.50%)	1 / 38 (2.63%)
occurrences (all)	3	4	1
Fall			
subjects affected / exposed	7 / 37 (18.92%)	20 / 40 (50.00%)	15 / 38 (39.47%)
occurrences (all)	13	43	38
Head injury			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	1 / 38 (2.63%)
occurrences (all)	1	2	1
Hip fracture			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0

Joint injury subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	2 / 40 (5.00%) 2	0 / 38 (0.00%) 0
Ligment sprain subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 4	3 / 40 (7.50%) 3	1 / 38 (2.63%) 1
Skin abrasion subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	1 / 40 (2.50%) 1	1 / 38 (2.63%) 1
Spinal compression fracture subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	4 / 40 (10.00%) 4	3 / 38 (7.89%) 3
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 40 (0.00%) 0	1 / 38 (2.63%) 3
Headache subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 5	14 / 40 (35.00%) 24	11 / 38 (28.95%) 22
General disorders and administration site conditions			
Chest pain subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	3 / 40 (7.50%) 3	1 / 38 (2.63%) 2
Fatigue subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	3 / 40 (7.50%) 5	2 / 38 (5.26%) 2
Gait inability subjects affected / exposed occurrences (all)	6 / 37 (16.22%) 6	5 / 40 (12.50%) 5	4 / 38 (10.53%) 4
Infusion site bruising subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	1 / 40 (2.50%) 1	2 / 38 (5.26%) 2
Infusion site pain subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	1 / 40 (2.50%) 1	1 / 38 (2.63%) 1
Infusion site swelling			

subjects affected / exposed	2 / 37 (5.41%)	1 / 40 (2.50%)	0 / 38 (0.00%)
occurrences (all)	2	2	0
Pain			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	2 / 38 (5.26%)
occurrences (all)	0	3	2
Pyrexia			
subjects affected / exposed	2 / 37 (5.41%)	9 / 40 (22.50%)	4 / 38 (10.53%)
occurrences (all)	2	15	4
Vessel puncture site bruise			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	2 / 38 (5.26%)
occurrences (all)	0	2	2
Ear and labyrinth disorders			
Ear disorder			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	0 / 38 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	0 / 37 (0.00%)	3 / 40 (7.50%)	1 / 38 (2.63%)
occurrences (all)	0	3	1
Abdominal pain upper			
subjects affected / exposed	1 / 37 (2.70%)	4 / 40 (10.00%)	4 / 38 (10.53%)
occurrences (all)	1	5	4
Constipation			
subjects affected / exposed	1 / 37 (2.70%)	4 / 40 (10.00%)	0 / 38 (0.00%)
occurrences (all)	1	5	0
Diarrhoea			
subjects affected / exposed	5 / 37 (13.51%)	7 / 40 (17.50%)	4 / 38 (10.53%)
occurrences (all)	6	10	5
Nausea			
subjects affected / exposed	1 / 37 (2.70%)	5 / 40 (12.50%)	1 / 38 (2.63%)
occurrences (all)	1	5	1
Vomiting			

subjects affected / exposed occurrences (all)	8 / 37 (21.62%) 13	9 / 40 (22.50%) 13	5 / 38 (13.16%) 5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 37 (10.81%)	3 / 40 (7.50%)	10 / 38 (26.32%)
occurrences (all)	5	3	11
Epistaxis			
subjects affected / exposed	3 / 37 (8.11%)	4 / 40 (10.00%)	2 / 38 (5.26%)
occurrences (all)	13	5	3
Nasal congestion			
subjects affected / exposed	1 / 37 (2.70%)	6 / 40 (15.00%)	3 / 38 (7.89%)
occurrences (all)	1	8	4
Oropharyngeal pain			
subjects affected / exposed	3 / 37 (8.11%)	5 / 40 (12.50%)	3 / 38 (7.89%)
occurrences (all)	4	6	3
Rhinorrhoea			
subjects affected / exposed	3 / 37 (8.11%)	6 / 40 (15.00%)	3 / 38 (7.89%)
occurrences (all)	3	6	3
Sleep apnoea syndrome			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	1 / 38 (2.63%)
occurrences (all)	2	0	1
Erythema			
subjects affected / exposed	2 / 37 (5.41%)	1 / 40 (2.50%)	0 / 38 (0.00%)
occurrences (all)	3	1	0
Pruritus			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	1	0	3
Rash			
subjects affected / exposed	0 / 37 (0.00%)	6 / 40 (15.00%)	3 / 38 (7.89%)
occurrences (all)	0	6	6
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 37 (2.70%)	1 / 40 (2.50%)	1 / 38 (2.63%)
occurrences (all)	1	1	1
Obsessive-compulsive disorder			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 37 (2.70%)	6 / 40 (15.00%)	5 / 38 (13.16%)
occurrences (all)	1	10	7
Back pain			
subjects affected / exposed	1 / 37 (2.70%)	6 / 40 (15.00%)	5 / 38 (13.16%)
occurrences (all)	1	7	6
Mobility decreased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 37 (0.00%)	3 / 40 (7.50%)	1 / 38 (2.63%)
occurrences (all)	0	3	1
Musculoskeletal pain			
subjects affected / exposed	0 / 37 (0.00%)	3 / 40 (7.50%)	0 / 38 (0.00%)
occurrences (all)	0	3	0
Pain in extremity			
subjects affected / exposed	3 / 37 (8.11%)	7 / 40 (17.50%)	8 / 38 (21.05%)
occurrences (all)	3	9	8
Scoliosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Tendon disorder			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	0 / 38 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Ear infection			

subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	2 / 38 (5.26%)
occurrences (all)	1	2	2
Gastroenteritis			
subjects affected / exposed	0 / 37 (0.00%)	3 / 40 (7.50%)	1 / 38 (2.63%)
occurrences (all)	0	3	1
Gastroenteritis viral			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	1 / 38 (2.63%)
occurrences (all)	0	1	1
Hordeolum			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	3 / 38 (7.89%)
occurrences (all)	0	1	5
Influenza			
subjects affected / exposed	3 / 37 (8.11%)	2 / 40 (5.00%)	0 / 38 (0.00%)
occurrences (all)	3	2	0
Localised infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	3
Lower respiratory tract infection			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	0 / 38 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	9 / 37 (24.32%)	11 / 40 (27.50%)	9 / 38 (23.68%)
occurrences (all)	12	21	14
Otitis media			
subjects affected / exposed	1 / 37 (2.70%)	1 / 40 (2.50%)	0 / 38 (0.00%)
occurrences (all)	1	1	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	1 / 38 (2.63%)
occurrences (all)	1	0	1
Sinusitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 40 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Upper respiratory tract infection			

subjects affected / exposed	7 / 37 (18.92%)	6 / 40 (15.00%)	8 / 38 (21.05%)
occurrences (all)	7	13	8
Pharyngitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	0 / 38 (0.00%)
occurrences (all)	0	2	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

This study was terminated because the primary efficacy objective (the efficacy of treatment with domagrozumab based on a mean change from baseline on 4 Stair Climb as compared to placebo following 48 weeks of treatment) was not met.
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Notes: