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Sponsor: Pfizer Inc.

Investigational Product: Domagrozumab

Clinical Study Report Synopsis: Protocol B5161002

Protocol Title: 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

Investigators: See Principal Investigator List in Section 16.1.4.1

Study Centers: The study was conducted at 35 centers in 8 countries (Australia, Bulgaria, Canada, Italy, Japan, Poland, United Kingdom, and United States).

Publications Based on the Study: None

Study Initiation and Completion Dates: First Participant First Visit (FPFV): 24 November 2014, Primary Completion Date: 30 April 2018, Last Participant Last Visit (LPLV): 23 November 2018

Report Date: 10 May 2019

Previous Report Date(s): Not Applicable.

Phase of Development: Phase 2

Study Objectives:

The primary safety and efficacy objectives of this study were:

- To determine the safety and tolerability of multiple ascending repeat intravenous (IV) doses of domagrozumab in ambulatory boys with Duchenne muscular dystrophy (DMD).

- To demonstrate the efficacy of treatment with IV doses of domagrozumab based on an observed mean change from baseline on function (4 stair climb [4SC]) as compared to placebo following 49 weeks of treatment.

The secondary objectives of this study were:

- To characterize the effects of domagrozumab on muscle strength and other functional assessments compared to placebo.

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- To evaluate the pharmacodynamic (PD) activity of domagrozumab based on the percent change of muscle volume from baseline as compared to placebo.

- To evaluate the PD profile of domagrozumab based on growth differentiation factor 8 (GDF-8, myostatin) modulation in blood.

- To characterize the pharmacokinetic (PK) profile of domagrozumab.

- To evaluate the immunogenicity of domagrozumab.

- To characterize the long-term effects following approximately 2 years of treatment with domagrozumab on functional assessments compared to historical control.

- To characterize the effects of domagrozumab on muscle strength and functional assessments compared to placebo in subset of participants who may demonstrate a rapid disease decline and with relatively low variability over a 1-year period.

The exploratory objectives of this study were:

- To evaluate biomarkers that may be informative in demonstrating the pharmacologic effect of domagrozumab. Specifically, to evaluate the effect of domagrozumab on muscle quality and fat fraction as evaluated by time constant describing the exponential decay of signal, due to spin-spin interactions (T2)-mapping and fat fraction imaging (Dixon magnetic resonance imaging [MRI]).

- To evaluate biomarkers that may be informative for monitoring hepatic liver injury in the setting of dystrophic muscle.

- To evaluate the Functional Health Status via the Pediatric Outcomes Data Collection Instrument (PODCI).

- To evaluate long-term safety of domagrozumab in participants treated for >1 year.

- To evaluate duration of treatment response following withdrawal and/or continuation of treatment for >1 year.

- To evaluate response in a delayed treatment group (Sequence Group 3, Period 2).

Exploratory results are not presented in this clinical study report synopsis.

METHODS

Study Design: This was a Phase 2, randomized, 2-period, blinded, placebo-controlled study to evaluate the safety, efficacy, PK and PD of domagrozumab administered to ambulatory boys diagnosed with DMD. At the time of primary completion, a limited number of Sponsor personnel were unblinded in order to complete the primary analysis, while the sites and

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participants remained blinded until the study terminated early, the last study visits were completed and the database was locked for final analysis.

The study was designed to randomize approximately 105 eligible participants to 1 of 3 sequence groups so that the participants received investigational product and/or placebo for approximately 96 weeks (2 treatment periods of approximately 48 weeks each). The primary completion was reached when all enrolled participants completed through Week 49.

Sequence 1 (n=35):
Period 1: Active treatment (domagrozumab) within participant dose escalation (5, 20 and 40 mg/kg)
Period 2: Active treatment (domagrozumab) at the maximum tolerated dose (MTD) in Period 1, which was 40 mg/kg for all participants.

Sequence 2 (n=35):
Period 1: Active treatment (domagrozumab) within participant dose escalation (5, 20 and 40 mg/kg)
Period 2: Placebo

Sequence 3 (n=35):
Period 1: Placebo
Period 2: Active treatment (domagrozumab) within participant dose escalation (5, 20 and 40 mg/kg)

Diagnosis and Main Criteria for Inclusion: The study population consisted of ambulatory male participants, ages 6 to <16 years, diagnosed with DMD.

Study Treatment: Study drug information is summarized in Table S1. Each dose level was explored in a dose escalating fashion within participants, starting with the lowest dose. At each dose level, domagrozumab was administered every 4 weeks for a total of 16 weeks (4 doses). Dose escalation within a participant occurred following review of all available safety data through the planned fourth dose within each dose level.

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Table S1. Investigational Product Description

Investigational Product Description	Vendor Lot Numbers	Pfizer Lot Numbers	Strength/ Potency	Dosage Form
Placebo for domagrozumab for injection	CMPLI003-14	14-003280	0 mg/vl	Liquid solution
Domagrozumab powder for injection, 100 mg/vial	PLI031-15	15-006041	100 mg/vl	Lyophile
Domagrozumab powder for solution for infusion, 260 mg/vial	S32397	17-001610	260 mg/vl	Lyophile
Domagrozumab powder for injection, 100 mg/vial	PLI030-14	14-003281	100 mg/vl	Lyophile
Domagrozumab powder for solution for infusion, 260 mg/vial	N19897	16-001457	260 mg/vl	Lyophile
Placebo for domagrozumab for injection	CMPLI023-16	16-005013	0 mg/vl	Liquid solution
Placebo for domagrozumab for injection	PLI051-11	12-000205	0 mg/vl	Liquid solution
Domagrozumab powder for injection, 100 mg/vial	PLI054-11	12-000910	100 mg/vl	Lyophile

Efficacy Evaluations:

Primary Efficacy Endpoint: Mean change from baseline on the 4SC as compared to placebo by Week 49.

Secondary Efficacy Endpoints:

- Mean change from baseline as compared to placebo on function tests including, forced vital capacity (FVC), Northstar Ambulatory Assessment (NSAA), range of motion (ROM), performance of upper limb (PUL), 6 minute walk distance (6MWD) at Weeks 17, 33 and 49. Mean change from baseline as compared to placebo on the 4SC at Weeks 17 and 33.

- Mean change from baseline as compared to placebo on muscle strength by myometry at Weeks 17, 33 and 49.

- In participants randomized to Sequence 1, mean change from baseline as compared to historical control on functional tests including, 4SC, 6MWD, FVC, NSAA at Week 97.

- In a pre-specified subset of participants who may demonstrate a rapid disease decline and with relatively low variability, the mean change from baseline as compared to placebo on function tests including, 4SC, FVC, NSAA, PUL, 6MWD at Weeks 17, 33 and 49. The 3 pre-specified subsets of participants were defined as participants with baseline 4SC <3.5 sec, ≥3.5 sec to ≤8 sec, and >8 sec.

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- In a pre-specified subset of participants who may demonstrate a rapid disease decline, the mean change from baseline as compared to placebo on muscle strength at Weeks 17, 33 and 49.

Pharmacokinetic, Pharmacodynamic and Immunogenicity Evaluations: Blood samples (2 mL) to provide serum for PK analysis were collected into the appropriately labeled tubes (containing no anticoagulant or gel separator). PK samples were assayed for domagrozumab using a validated, sensitive and specific enzyme-linked immunosorbent assay (ELISA) method.

Images of the same thigh by MRI were obtained to measure the percent change in muscle volume as compared to placebo at Weeks 17, 33, and 49. Thigh MRIs were obtained at approximately the same time of day (morning) to provide optimal testing conditions and consistency in endpoint measurements. In addition, whole thigh muscle volume index was also analyzed. Total GDF-8 levels in human serum samples were assayed using a validated, sensitive and specific immunoprecipitation high-performance liquid chromatography tandem mass spectrometric method (HPLC-MS/MS).

Whole blood samples were collected at the designated times to provide serum for evaluation of domagrozumab immunogenicity. Immunogenicity blood samples were assayed for anti-domagrozumab antibodies using a validated, sensitive and specific electrochemiluminescent (ECL) assay.

Safety Evaluations: Safety assessments consisted of the collection of adverse events (AEs), serious adverse events (SAEs), vital signs, physical examination/nose and throat mucosal examinations, dual energy X-ray absorptiometry (DXA) of the spine for bone mineral density, X-ray of the hand and wrist for bone age, Tanner stage and testicular volume, 12-lead electrocardiogram (ECG), cardiac MRI/echocardiogram, liver MRI, gamma-glutamyl transferase (GLDH, biomarker of liver injury) data, laboratory assessment, and assessment of suicidal ideation and behavior as per the Columbia Suicide Severity Rating Scale (C-SSRS).

Statistical Methods: The primary endpoint, change from baseline in 4SC, was analyzed based on the Full Analysis Set (FAS) using the mixed effects model. For the primary efficacy analysis, Per-Protocol Analysis Set (PPAS) was used to assess the sensitivity of the analysis results. Model assumptions were tested using appropriate statistical or graphical techniques. Missing data were handled using mixed effect model for repeated measures (MMRM). This analysis was unbiased under the assumption of missing at random when the model assumptions held. Participants who lost the ability to complete a functional assessment and/or ambulate were assumed to be missing not at random. Additional methods to assess the impact of the missing-not-at-random data were also performed. The methods included transforming time to complete a functional assessment to velocity, so that participants with a missing time were assumed to have a velocity of 0, and performing a completer analysis (only participants who completed through Week 49 were analyzed). An analysis using the natural log transformation of the 4SC data was conducted to address the

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skewness in the results and a Wilcoxon Rank-Sum test was also performed to address the non-normality of the data.

These analyses were performed based on the data for all participants through 49 weeks. The primary efficacy analysis was tested at α=0.025 (one-sided). The same type I error rate was used for testing the secondary analyses. This test was performed based on the data in Period 1 from all participants. Participants assigned to Sequence 1 and Sequence 2 were analyzed together in an active treatment group compared to participants in Sequence 3 (placebo during Period 1). Secondary endpoints were analyzed using the same longitudinal mixed model as described for the primary analysis.

PK parameters for domagrozumab were determined from the serum concentration-time profiles. Actual PK sampling times were used in the derivation of PK parameters. Serum concentrations for domagrozumab were listed and summarized descriptively by nominal PK sampling time and dose.

To assess the PD profile of domagrozumab, total GDF-8 concentrations were listed, summarized and plotted for participants in the PD analysis set. Total GDF-8 parameters were derived from concentration data.

Safety data were summarized according to Sponsor data standards.

RESULTS

Subject Disposition and Demography: A summary of participant disposition by treatment sequence is presented in Table S2. A summary of participant disposition by combined active treatment and placebo in Period 1 is presented in Table S3.

All 120 participants treated were male. The majority (80%) were 6 to 10 years of age, with a mean (standard deviation [SD]) age of 8.7 (2.0) years. Most (84.2%) participants were White. The mean (SD) body mass index (BMI) was 19.9 (4.6) kg/m^2 (range from 11.7 to 39.7 kg/m^2). The mean weight (SD) of Sequence 3 (35.3 [14.4] kg) was slightly higher than that of Sequence 1 (29.9 [8.5] kg) and Sequence 2 (30.3 [8.8] kg), which was driven by 2 participants with weights of 86.4 kg and 81.8 kg. Other demographic characteristics were comparable among 3 sequences. Demographic characteristics were comparable between Sequence 1 and historical control, and between combined domagrozumab and placebo treatment groups.

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Table S2. Participant Evaluation Groups (ITT Population) by Treatment Sequence

Number (%) of Participants	Sequence 1	Sequence 2	Sequence 3	Total
Screened				162
Assigned to Study Treatment				121
Treated	41	39	40	120
Completed	22 (53.7)	21 (53.8)	22 (55.0)	65 (54.2)
Discontinued - Period 1	3 (7.3)	2 (5.1)	2 (5.0)	7 (5.8)
No longer willing to participate in study	1 (2.4)	1 (2.6)	1 (2.5)	3 (2.5)
Other	0	1 (2.6)	1 (2.5)	2 (1.7)
Lost to follow-up	1 (2.4)	0	0	1 (0.8)
AE	1 (2.4)	0	0	1 (0.8)
Discontinued - Period 2	16 (39.0)	16 (41.0)	16 (40.0)	48 (40.0)
Study terminated by Sponsor	16 (39.0)	16 (41.0)	16 (40.0)	48 (40.0)
Analyzed for PK:				
PK concentration	41 (100.0)	39 (100.0)	38 (95.0)	118 (98.3)
PK parameter	41 (100.0)	39 (100.0)	38 (95.0)	118 (98.3)
Analyzed for PD:				
Whole body DXA	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
Thigh MRI	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
GDF-8 concentration	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
GDF-8 parameter	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
Analyzed for efficacy:				
4SC	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
NSAA	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
FVC	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
Muscle strength	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
PUL	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
6MWD	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
ROM	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
Analyzed for safety:				
AEs	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)
Laboratory data	41 (100.0)	39 (100.0)	40 (100.0)	120 (100.0)

Laboratory data (Analyzed): number of participants who dosed in this sequence with at least 1 evaluable laboratory result.

Efficacy data (Analyzed): participants who dosed and had conducted at least 1 efficacy assessment in this sequence were included.

PK data (Analyzed): participants who dosed and had conducted at least 1 PK assessment in this sequence were included.

PD data (Analyzed): participants who dosed and had conducted at least 1 PD assessment in this sequence were included. A total of 121 participants were enrolled and 41 participants were screening failure among all screened participants.

Sequence 1: Period 1-Active treatment within participant dose escalation (5, 20, 40 mg/kg); Period 2-Active treatment at the highest tolerated dose in Period 1.

Sequence 2: Period 1-Active treatment within participant dose escalation (5, 20, 40 mg/kg); Period 2-Placebo.

Sequence 3: Period 1-Placebo; Period 2-Active treatment within participant dose escalation (5, 20, 40 mg/kg).

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Table S3. Participant Evaluation Groups (ITT Population) by Combined Active Treatment and Placebo - Period 1

Number (%) of Participants		Domagrozumab	Placebo
Screened	162		
Assigned to Study Treatment	121		
Treated		80	40
Completed		75 (93.8)	38 (95.0)
Discontinued		5 (6.3)	2 (5.0)
No longer willing to participate in study		2 (2.5)	1 (2.5)
Other		1 (1.3)	1 (2.5)
Lost to follow-up		1 (1.3)	0
AE		1 (1.3)	0
Analyzed for PK:			
PK concentration		80 (100.0)	1 (2.5)
PK parameter		80 (100.0)	0
Analyzed for PD:			
Whole body DXA		80 (100.0)	40 (100.0)
Thigh MRI		80 (100.0)	40 (100.0)
GDF-8 concentration		80 (100.0)	40 (100.0)
GDF-8 parameter		80 (100.0)	40 (100.0)
Analyzed for efficacy:			
4SC		80 (100.0)	40 (100.0)
NSAA		80 (100.0)	40 (100.0)
FVC		80 (100.0)	40 (100.0)
Muscle strength		80 (100.0)	40 (100.0)
PUL		80 (100.0)	40 (100.0)
6MWD		80 (100.0)	40 (100.0)
ROM		80 (100.0)	40 (100.0)
Analyzed for safety:			
AEs		80 (100.0)	40 (100.0)
Laboratory data		80 (100.0)	40 (100.0)

AEs (Analyzed): number of participants who dosed in this treatment with AE evaluation.

Laboratory data (Analyzed): number of participants who dosed in this treatment with at least 1 evaluable laboratory result.

Efficacy data (Analyzed): participants who dosed and had conducted at least 1 efficacy assessment in this treatment were included in this analysis.

PK data (Analyzed): participants who dosed and had conducted at least 1 PK assessment in this treatment were included in this analysis.

PD data (Analyzed): participants who dosed and had conducted at least 1 PD assessment in this treatment were included in this analysis.

A total of 121 participants were enrolled and 41 participants were screening failure among all screened participants.

Efficacy Results:

Primary Endpoint: The primary efficacy endpoint was the mean change from baseline on the 4SC as compared to placebo at Week 49. Primary analysis and sensitivity analyses showed that there were no statistically significant differences in the mean change from baseline on 4SC between the domagrozumab and placebo groups at Week 49 (Table S4).

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Table S4. Primary and Sensitivity Analyses of Mean Change from Baseline on the 4 Stair Climb for Domagrozumab Compared to Placebo at Week 49

MMRM Analysis	N		Adjusted Mean (SE)		Difference	Two-sided	P-Value
	Active	Control	Active	Control	(Active-Control)	95% CI	
4SC, FAS	63	32	8.2835 (2.1507)	8.0122 (3.03)	0.2712	(-7.3799, 7.9223)	0.9423
4SC, PPAS	61	31	7.0257 (2.0214)	7.7726 (2.7867)	-0.7469	(-7.981, 6.4871)	0.8303
Velocity of 4SC, FAS	75	38	-0.0467 (0.0093)	-0.0635 (0.013)	0.0168	(-0.0149, 0.0485)	0.297
Log transformed 4SC, FAS	63	32	0.3045 (0.0535)	0.4033 (0.0754)	-0.0989	(-0.2834, 0.0856)	0.2884
4SC Completer, FAS	63	32	1.8801 (0.7438)	2.7539 (1.0437)	-0.8738	(-3.4196, 1.6719)	0.4971

Wilcoxon Rank-Sum Test	N		Mean Score		Normal Approximation P-value (2 sided)		t Approximation P-value (2 sided)
	Active	Control	Active	Control			
4SC, FAS	63	32	45.532	52.859	0.2222		0.2252
Velocity of 4SC, FAS	75	38	59.233	52.592	0.3101		0.3123

N=number of participants with data available at this time point.

All 4SC data through Week 49 were included for MMRM analysis and Wilcoxon Rank-Sum Test.

Completer was defined as participant with 4SC data at week 49. Participants with missing 4SC values at Week 49 have been excluded.

Baseline was defined as the last pre-dose assessment which was collected at the baseline visit.

Velocity was defined as the reciprocal of the time to climb 4 stairs. For those 4SC missing values when a participant had the test but didn't have a value, for whatever reason (lost of ambulation/could not complete or others), its velocity was to have a 0 value. For those who didn't have the test, missing was to stay missing.

MMRM with baseline result, treatment, time, and treatment by time interaction as fixed effects, participants as random effect.

Change from baseline for each visit was attributed to the last dose received at the previous visit.

Unscheduled and early termination 4SC assessments have been excluded from the presentation.

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Secondary Endpoints: There were no statistically significant differences in the 4SC at Week 17 or Week 33 between participants on domagrozumab and participants on placebo.

The MMRM analysis for mean change from baseline on NSAA total score using FAS dataset showed that there were no statistically significant differences between the domagrozumab and placebo groups at Week 49, with the mean (95% confidence interval [CI]) difference of 1.6 (-0.5, 3.8; p-value=0.1268). However, there was a statistically significant difference between the domagrozumab and placebo groups at Week 33, with the mean (95% CI) differences of 2.5 (0.7, 4.2; p-value=0.0061).

The MMRM analysis showed that there were no statistically significant differences between the domagrozumab and placebo groups at Week 17, Week 33 and Week 49 in the mean changes from baseline on FVC, PUL overall score and 6 minute walk test (6MWT). There were statistically significant differences in the mean change from baseline on myometry-based muscle strength (right elbow extension and right shoulder abduction) between the domagrozumab and placebo groups at Week 33; however, the differences favored placebo.

Subgroup analysis showed that there were no statistically significant differences in the mean change from baseline on the 4SC, FVC, PUL, and 6MWT between the domagrozumab and placebo groups in all the 3 pre-specified subgroups at Weeks 17, 33 and 49. There were statistically significant differences in myometry-based muscle strength at Weeks 17 and 33 in participants with a baseline 4SC<3.5 sec, however, the differences favored placebo. There was a statistically significant difference in the mean change from baseline on the NSAA total score between the domagrozumab and placebo groups at Week 49 in participant with baseline 4SC>8 sec and the difference favored domagrozumab.

The historical control group was selected using age, 4SC baseline function, glucocorticosteroid use, ambulatory status and baseline left ventricular ejection fraction (LVEF) function. While there were no statistically significant differences observed when comparing the historical control group with the placebo (Sequence 3) group at Week 49 for 4SC, there were some differences in the mean change from baseline on the NSAA total score and 6MWD suggesting that they may not have been optimally matched for the functional tests being analyzed.

Pharmacokinetic, Pharmacodynamic and Immunogenicity Results:

PK Results:

Median serum concentrations increased with increasing dose for participants within each dose level (Period 1 and Period 2) following IV administration at 5, 20 and 40 mg/kg. Following repeated IV administration at 40 mg/kg, the MTD observed in Period 1, Sequence 1, median serum concentrations remained generally constant for those participants in Period 2, Sequence 1. Pre-dose concentration (C_{trough}) values generally increased from the

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first dose through the last dose within each dose escalation and appeared to be at steady state by the last dose across all Period 1 and Period 2 sequence treatments with the exception of the repeated MTD in Period 2 Sequence 1 as concentrations were at steady state prior to entry into Period 2.

The elimination of the 6-hour PK time point in Protocol Amendment 2 impacted the estimation of maximum serum concentration (C_{max}) and time for C_{max} (T_{max}), therefore in place of C_{max} and T_{max}, the concentration at planned 2 hours (C_2), the end of infusion, was determined for all participants irrespective of those participants with a 6-hour PK sample collected. Following a total of 4 IV doses within each dose level, C_2 levels were similar between the first through the last dose administered. Following the last dose of each dose level, C_{trough} and C_2 values were similar for both Process 1 (original manufacturing process) and Process 2 (commercial ready process) material.

Additional summarized PK parameters showed that C_{max} were generally observed in samples collected immediately at the end of infusion (about 2 hours). Serum domagrozumab exposure (C_{max} and area under the curve over the dosing interval [AUC_τ]) increased with increasing dose from 5 mg/kg to 40 mg/kg. Overall, exposures were slightly higher at each dose level after the last dose relative to the first dose reflecting accumulation of domagrozumab. Following the last dose, systemic clearance (CL) was similar across treatment sequences.

PD Results:

The MMRM analysis showed that there were no statistically significant differences between the domagrozumab and placebo groups in the mean percent change from baseline on thigh tissue volume measures at Weeks 17, 33 and 49. Although there were no statistically significant differences in the mean percent change from baseline for both muscle volume and muscle volume index, there were directionally favorable differences between the domagrozumab and placebo groups.

Linear regression analyses were conducted on combined treatment groups to understand the relationship between MRI imaging measures and functional measures (log transformed 4SC and NSAA). MRI endpoints presented in this synopsis include percent change from baseline in both thigh muscle volume and thigh muscle volume index. When comparing Week 49 log transformed 4SC versus Week 49 thigh volume, there was no significant relationship. When comparing Week 97 log transformed 4SC versus Week 49 thigh volume, both muscle volume and muscle volume index were significantly associated with longer term functional changes suggesting that imaging changes precede functional changes.

Similar results were obtained when comparing imaging measures with NSAA changes at Week 49 or Week 97. When comparing Week 49 muscle volume imaging changes to NSAA measures, muscle volume index was correlated with NSAA changes after 49 weeks. Comparing Week 49 muscle volume imaging measures to Week 97 NSAA changes, muscle

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volume and muscle volume index were significantly correlated with functional changes at a later time point.

As anticipated total serum GDF-8 was modulated at all dose levels given domagrozumab was anticipated to bind to GDF-8. After domagrozumab treatment was completed in Period 1, Sequence 2, total serum GDF-8 gradually declined towards the baseline level in Period 2, Sequence 2 corresponding to the expected decline in drug concentrations. Total serum GDF-8 C_{trough} levels were slightly higher for all dose levels compared to placebo while C_{trough} values at the 5 mg/kg dose were similar to placebo at Week 61. There were no apparent dose specific trends observed for total GDF-8 C_{trough} levels. Following the last dose of each dose level, total serum GDF-8 C_{trough} values were similar for both Process 1 (original manufacturing process) and Process 2 (commercial ready process) material.

Immunogenicity Results:

Among the participants tested for anti-drug antibody (ADA), only 1 (2.7%) participant in the domagrozumab 20 mg/kg treatment group in Sequence 3 had a positive ADA (titer≥1.88) at Week 65 (Study Day 451) and the subsequent sample timepoint was ADA negative. Neutralizing antibody (NAb) analysis was not performed on the ADA positive sample. There were no AEs of hypersensitivity reported for this participant.

Safety Results: The majority of participants experienced at least 1 treatment-emergent adverse event (TEAE). The incidence of TEAEs was comparable between the placebo and domagrozumab groups, and among the 3 dose levels of domagrozumab. The majority of the TEAEs were not treatment related. There were no clinically meaningful differences in the incidence of Tier-1 and Tier-2 TEAEs between the domagrozumab and placebo groups. The incidence of the TEAE of gait inability, which was due to disease progression, was comparable between the domagrozumab and placebo groups. The number of combined vertebral and non-vertebral fractures was comparable between the domagrozumab and placebo groups. For participants in the domagrozumab treatment group, 2 participants reported all-causality SAEs in Period 1 and 3 participants reported all-causality SAEs in Period 2. Three participants had treatment-related SAEs (1 femoral neck fracture, 1 anxiety and 1 troponin increased). One participant in the domagrozumab 40 mg/kg permanently discontinued from study due to the SAE of anxiety.

There were no clinically meaningful differences in laboratory abnormalities between the domagrozumab and placebo groups. No participants with elevated liver enzymes and/or bilirubin met Hy's law criteria.

There were no clinically meaningful differences in vital signs, 12-lead ECGs, sexual development, bone age, bone mineral density, LVEF, and C-SSRS between the domagrozumab and placebo groups.

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The AE of troponin increased was reported for 2 participants each in the placebo group and domagrozumab group in Period 1. The AE of troponin increased was reported for 1 participant in the placebo treatment group and 3 participants in the domagrozumab group in Period 2. All of the AEs of troponin increased were mild in severity. The AE of ejection fraction decreased was reported for 1 participant in placebo group and 2 participants in the domagrozumab group in Period 2. All of the AEs were mild or moderate in severity and were caused by disease under study. Only 1 participant in Sequence 1 had both the AEs of troponin increased and ejection fraction decreased. Both AEs were not related to study drug.

Overall, there were no safety signals identified. However, a letter of special safety concern was issued on 14 November 2018 due to the preliminary data of potential greater LVEF decline with domagrozumab exposure for 24 months than with 12 months. The External Data Monitoring Committee (E-DMC), whose members included a pediatric cardiologist with expertise in DMD, reviewed the data. Both Sponsor and the E-DMC agreed that no urgent intervention was required. The final data did not remove this potential risk observed in Sequence 1. The quantitative difference in LVEF was neither statistically different nor clinically meaningful. However, it should remain an important potential risk in a population at-risk for progressive cardiac dysfunction.

Conclusions:

Efficacy

- The study did not achieve the primary endpoint at Week 49: the difference (95% CI) in the mean change from baseline of 4SC for the domagrozumab group compared to placebo using FAS was 0.2712 sec (95% CI: -7.3799, 7.9223; p-value=0.9423), which favored placebo, and was not statistically significant. The sensitivity analyses showed small changes that favored domagrozumab; however, they were not statistically significant.

- The MMRM analysis based on FAS for the secondary functional endpoints including: NSAA, FVC, myometry-based muscle strength, PUL and 6MWT at Week 49 did not demonstrate statistically significant changes between the domagrozumab and placebo groups.

- Results observed on the primary endpoint and other secondary functional endpoints using the MMRM analysis methodology are difficult to interpret due to skewness in the observed data and missing data due to loss of ambulation (LOA) or physical inability. Sensitivity analyses have been presented to address these limitations of the MMRM method and did not contradict the findings of the primary analysis.

- The historical control group performed similar to the placebo group (Sequence 3) at Week 49 for the 4SC and therefore it was an appropriate comparator for participants who received domagrozumab through both Periods 1 and 2. There was no statistically

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significant difference in the mean change from baseline on the 4SC at Week 97 between the Sequence 1 participants and the historical control group.

PK, Immunogenicity and PD

- Following a total of 4 IV doses at 5, 20 and 40 mg/kg within a participant dose escalating fashion, serum domagrozumab C_2 and C_{trough} levels were similar between the first through the last dose in both Periods 1 and 2. Trough values generally increased from the first dose through the last dose within each dose escalation and appeared to be at steady state following the last dose across all Period 1 and Period 2 sequence treatments.

- Following the last dose of each dose level, serum domagrozumab C_{trough} and C_2 values were similar for both Process 1 (original manufacturing process) and Process 2 (commercial ready process) material.

- Following the first and last dose administration at each dose level for participants with additional PK sampling timepoints, serum domagrozumab exposure (C_{max} and AUC_τ) increased with increasing dose from 5 mg/kg to 40 mg/kg. Overall, exposure was slightly higher for the last dose relative to first dose due to accumulation across all Period 1, Sequences 1 and 2 treatments.

- Domagrozumab demonstrated low immunogenicity potential, with only 1 participant in Sequence 3 developing positive ADA (titer≥1.88). No AEs of hypersensitivity were reported for the participant.

- The mean T2 relaxation time in both thigh muscle bundle and thigh muscle demonstrated a statistically significant difference between domagrozumab and placebo treated participants at Week 49.

- Muscle volume and fat fraction analysis both trended in favor of domagrozumab treatment at Week 49. However, statistical significance was not observed as compared to placebo.

- Regression analyses of MRI changes at Week 49 vs 4SC and NSAA changes at Week 97 indicated statistically significant regression coefficients for thigh muscle, thigh T2 mapping and thigh fat fraction.

- Compared to placebo, there were statistically significant increases in lean tissue mass in both the appendicular skeleton and arms by whole body DXA in the domagrozumab group at Week 49.

- Increases of total serum GDF-8 post domagrozumab treatment from baseline were observed for all the treatment sequences.

CLINICAL STUDY REPORT SYNOPSIS

- Total serum GDF-8 C_{trough} levels were slightly higher for all dose levels compared to placebo while C_{trough} values at the 5 mg/kg dose were similar to placebo in Week 61. There were no apparent dose specific trends observed for total GDF-8 C_{trough} levels. Following the last dose of each dose level, total serum GDF-8 C_{trough} values were similar for both Process 1 (original manufacturing process) and Process 2 (commercial ready process) material.

Safety

- Multiple ascending repeat IV doses of domagrozumab at 5, 20 and 40 mg/kg were generally safe and well tolerated.

- The majority of participants experienced at least 1 TEAE. The incidence of TEAEs was comparable between the placebo and domagrozumab groups, and among the 3 dose levels of domagrozumab. The majority of the TEAEs were not treatment related.

- There were no clinically meaningful differences in the incidence of Tier-1 and Tier-2 TEAEs between the domagrozumab and placebo groups.

- The incidence of the TEAE of gait inability, which was due to disease progression, was comparable between the domagrozumab and placebo groups.

- The number of combined vertebral and non-vertebral fractures was comparable between the domagrozumab and placebo groups.

- There were no clinically meaningful differences in laboratory abnormalities between the domagrozumab and placebo groups. No participant with elevated liver enzymes and/or bilirubin met Hy's law criteria.

- There were no clinically meaningful differences in vital signs, 12-lead ECGs, sexual development, bone age, bone mineral density, LVEF, and C-SSRS between the domagrozumab and placebo groups. LVEF was noted as an important potential risk in a population at-risk for progressive cardiac dysfunction.