CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc

Investigational Product: PF-06252616 (Domagrozumab)

Clinical Study Report Synopsis: Protocol B5161004

Protocol Title: A Multicenter, Open-Label Extension Study to Evaluate the Long Term Safety of PF-06252616 in Boys With Duchenne Muscular Dystrophy

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Centers: The study was conducted at 22 sites, including 4 sites in Canada, 2 sites in Italy, 2 sites in Japan, 2 sites in the United Kingdom and 12 sites in the United States.

Publications Based on the Study: None

Study Initiation Date: 13 October 2016

Study Completion Date: 22 November 2018

Report Date: 15 May 2019

Previous Report Date(s): Not applicable

Phase of Development: Phase 2

Primary and Secondary Study Objectives and Endpoints: The primary and secondary study objectives and endpoints are listed in Table S1.

Study B5161004 was designed as a 4-year study, however this study was prematurely terminated by the sponsor as no significant treatment effect was observed in Parent Study B5161002. Therefore, there are less long-term data available in Study B5161004. As planned, both the changes from overall baseline (B5161002 baseline) in Parent Study B5161002 and B5161004 baseline in this open-label extension (OLE) study were evaluated whenever possible. Changes from overall baseline provide a long-term analysis on the safety and efficacy of domagrozumab, which may have not been possible by only evaluating the changes from B5161004 baseline. See Statistical Methods section for the definition of the overall baseline and B5161004 baseline for the efficacy endpoints.

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Table S1. Study Objectives and Endpoints

Type	Objective	Endpoint
Primary		
Safety	To evaluate the long-term safety of IV dosing of domagrozumab in boys with DMD	• Incidence and/or rate of intolerability or dose limiting treatment related AEs following up to an additional 4 years of treatment • Incidence and/or rate, severity and causal relationship of TEAEs and withdrawals due to TEAEs following up to an additional 4 years of treatment • Incidence and magnitude of abnormal laboratory findings (clinical laboratory tests: hematology, chemistry, GGT, GLDH, PT, aPTT, creatine kinase, amylase, serum ferritin, serum iron, total iron binding capacity, % transferrin saturation; hormones: luteinizing hormone, follicle stimulating hormone, thyroxine, thyroid stimulating hormone; fecal occult blood; cardiac Troponin I and urinalysis) following up to an additional 4 years of treatment • Abnormal and clinically relevant changes in liver MRI, physical examination (including a targeted nose and throat mucosal examination), Tanner staging and testicular volume, weight, vitals, ECG, LVEF measured by echocardiogram (or cardiac MRI), bone mineral density by DXA, x-ray (hand and wrist for bone age evaluation) and C-SSRS
Secondary		
Efficacy	To evaluate the long-term efficacy of domagrozumab using functional assessments and strength	• Mean change from baseline following up to an additional 4 years of treatment in the following functional assessment tests: PFTs (including FVC, FEV_1 and PEFR), 4SC, NSAA, PUL, ROM and 6MWD • Mean change from baseline in muscle strength measured by myometry following up to an additional 4 years of treatment
PK and immunogenicity	To assess the PK and immunogenicity of domagrozumab	• Trough serum domagrozumab concentrations for all participants receiving active drug • Incidence of ADA and NAb

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METHODS

Study Design: This was a Phase 2 OLE study to Protocol B5161002 and provided an assessment of the long-term safety, efficacy, pharmacokinetics (PK), immunogenicity and pharmacodynamics (PD) of intravenous (IV) dosing of domagrozumab in boys with Duchenne muscular dystrophy (DMD).

The individual dose level selected for each participant was based on the maximum tolerated dose (MTD) from the parent study B5161002. In the parent study B5161002, eligible participants were randomized to one of 3 sequence groups:

- Sequence 1: Period 1 - active treatment (domagrozumab) within participant dose escalation (5, 20, 40 mg/kg); Period 2 - active treatment (domagrozumab) at the MTD in Period 1.
- Sequence 2: Period 1 - active treatment (domagrozumab) within participant dose escalation (5, 20, 40 mg/kg); Period 2 - placebo.
- Sequence 3: Period 1 - placebo; Period 2 - active treatment (domagrozumab) within participant dose escalation (5, 20, 40 mg/kg).

All participants who continued into Study B5161004 from the parent study B5161002 tolerated the 40 mg/kg dose, and therefore all participants received 40 mg/kg of domagrozumab monthly via an infusion in this OLE study.

Diagnosis and Main Criteria for Inclusion: Eligible participants were boys with DMD who enrolled and completed through Week 97 of Study B5161002 and who had adequate hepatic function, glutamate dehydrogenase (GLDH) ≤20 units/liter (2 × upper limit of normal [ULN]), iron content estimate on the liver magnetic resonance imaging (MRI) within the normal range as determined by R2* value.

Study Treatment: The investigational product (domagrozumab) was infused over a 2-hour period (-15 or +30 minutes) which included the flush time. Participants received 40 mg/kg domagrozumab monthly up to Week 93 in Study B5161004. Investigational product description is provided in Table S2.

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Table S2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
PF-06252616 Powder for Solution for Infusion, 260mg/vial	N58801	16-002923	260 mg/vl	Lyophile
PF-06252616 Powder for Solution for Infusion, 260mg/vial	N99971	16-003498	260 mg/vl	Lyophile
PF-06252616 Powder for Solution for Infusion, 260mg/vial	N19897	16-001457	260 mg/vl	Lyophile

Efficacy Evaluations:

Refer to Table S1 for the efficacy endpoints evaluated in the study.

All functional assessments were completed in the following order, pulmonary function tests (PFTs), 4 stair climb (4SC), Northstar Ambulatory Assessment (NSAA), range of motion (ROM), muscle strength, performance of upper limb (PUL), 6-minute walk distance (6MWD). If loss of ambulation occurred, the 4SC, NSAA and 6MWD assessments were not completed. Loss of ambulation was defined as the inability to walk unassisted and without braces for at least 10 m, as assessed and reported by the investigator at each study visit, and confirmed by the inability to walk/run 10 m (as 1 component of the NSAA) evaluated at the next visit at which timed function tests were performed.

Pharmacokinetic and Immunogenicity Evaluations:

Pharmacokinetics

Trough serum domagrozumab concentrations for all participants receiving domagrozumab was the only parameter analyzed for PK in this study. Trough serum domagrozumab concentrations were observed directly from data.

Blood samples (2 mL) providing serum for PK analysis were collected at pre-specified times. PK samples were assayed for domagrozumab using a validated, sensitive and specific enzyme-linked immunosorbent assay (ELISA) method.

Immunogenicity

Blood samples (2 mL) providing serum for analysis of anti- domagrozumab were collected at pre-specified times. Human serum anti-drug antibody (ADA) samples were analyzed for the presence or absence of anti-domagrozumab antibodies using a validated, sensitive and specific electrochemiluminescent (ECL) assay. A tiered approach using screening,

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confirmation and titer assays was used for sample analysis. Samples that were determined to be positive for ADA were to be further tested for the presence of neutralizing antibody (NAb).

Safety Evaluations: Refer to Table S1 for the safety endpoints evaluated in the study.

Statistical Methods:

Efficacy

Overall baseline was defined as the last pre-dose assessment prior to the first day of dosing in Study B5161002. B5161004 baseline was defined as the last assessment prior to dosing on Day 1 in Study B5161004. The B5161004 baseline value was the screening visit which may in some cases, be the same data as the Week 97 visit for Study B5161002.

The efficacy analysis was performed based on the Full Analysis Set (FAS), which included all participants who received as least 1 dose of domagrozumab in Study B5161004.

The long-term effect on 4SC following treatment with domagrozumab was characterized compared to a natural history control group; a sensitivity analysis of 4SC and NSAA were performed based on the velocity (defined as the reciprocal of time); and a time-to-event analysis was performed for loss of ambulation.

Pharmacokinetics

The PK concentration analysis set included all participants who received at least 1 dose of domagrozumab in Study B5161004 and had at least 1 domagrozumab concentration measured.

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) was set to 0. Summary statistics were provided for trough serum concentrations by sequence and timepoint.

Immunogenicity

Immunogenicity analysis was performed based on the Safety Analysis Set (SAS), which included all participants who received at least 1 dose of domagrozumab in Study B5161004.

Categorical endpoints (ie, positive, negative not tested and missing) were reported for the ADA assays overall and by sequence and timepoint.

Safety

Safety analysis was performed based on the SAS. No formal statistical analysis of safety was undertaken. Descriptive summaries were generated.

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RESULTS

Participant Disposition and Demography:

Table S3 summarizes the participant disposition in the study. Of 61 participants who were screened, 2 participants failed at screening due to not meeting entrance criteria and study termination by the sponsor, and 59 participants were assigned to study treatment and were treated with domagrozumab. No participants completed the study. The most commonly reported reason for discontinuation was study termination by the sponsor (55/59 [93.2%] participants).

All 59 participants were males. Most participants were white (53 participants, 89.8%). Overall, the mean age was 9.9 years (range: 7.0 to 11.0 years), the mean weight was 37.2 kg (range: 18.9 to 92.9 kg), and the mean body mass index (BMI) was 21.4 kg/m^2 (range: 14.3 to 39.4 kg/m^2). Weight was slightly greater in Sequence 2 and Sequence 3 compared to Sequence 1, which was driven by a single participant in each sequence, whose weight was 79.1 kg (Sequence 2) and 92.9 kg (Sequence 3). Overall, comparability was observed on all demographic characteristics across each sequence.

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Table S3. Participant Evaluation Groups by Sequence - SAS

Number (%) of Participants	Sequence 1	Sequence 2	Sequence 3	Total
Screened: 61				
Assigned to Study Treatment: 59				
Treated	19 (100.0)	20 (100.0)	20 (100.0)	59 (100.0)
Completed	0	0	0	0
Discontinued	19 (100.0)	20 (100.0)	20 (100.0)	59 (100.0)
Participant died	0	0	1 (5.0)	1 (1.7)
Other	0	1 (5.0)	0	1 (1.7)
Did not meet entrance criteria	0	0	0	0
No longer willing to participate in study	1 (5.3)	1 (5.0)	0	2 (3.4)
Study terminated by sponsor	18 (94.7)	18 (90.0)	19 (95.0)	55 (93.2)
Analyzed for PD				
Whole body DXA	19 (100.0)	20 (100.0)	20 (100.0)	59 (100.0)
Analyzed for Efficacy				
4SC	17 (89.5)	13 (65.0)	13 (65.0)	43 (72.9)
NSAA	16 (84.2)	13 (65.0)	12 (60.0)	41 (69.5)
FVC	19 (100.0)	20 (100.0)	20 (100.0)	59 (100.0)
Muscle strength	19 (100.0)	20 (100.0)	19 (95.0)	58 (98.3)
PUL	19 (100.0)	20 (100.0)	19 (95.0)	58 (98.3)
6MWD	19 (100.0)	20 (100.0)	18 (90.0)	57 (96.6)
ROM	19 (100.0)	20 (100.0)	19 (95.0)	58 (98.3)
Analyzed for Safety				
Adverse events	19 (100.0)	20 (100.0)	20 (100.0)	59 (100.0)
Laboratory data	19 (100.0)	20 (100.0)	20 (100.0)	59 (100.0)

Adverse event analysis included participants with adverse events evaluation in the database. Laboratory data analysis included participants with at least 1 evaluable lab result.
Efficacy data analysis included participants who were dosed and had at least 1 efficacy assessment in this sequence.
PD data analysis included participants who were dosed and had at least 1 PD assessment in this sequence.

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Efficacy Results:

All the efficacy endpoints evaluated in Study B5161004 were secondary endpoints (Table S1).

All efficacy assessments measured meaningful disease progression while participants were enrolled in the study. Not all efficacy endpoints were measured in both Studies B5161002 and B5161004. When endpoints were measured in both Studies B5161002 and B5161004, the changes from baseline in Study B5161004 are listed as Weeks 13, 25, 49 and 73, reflecting the changes from pre-dose Day 1 of Study B5161004. However, when these same visits in Study B5161004 were evaluated as the changes from the overall (B5161002) baseline, they were listed as Weeks 110, 122, 146 and 170, reflecting timepoints starting from the pre-dose Day 1 of Study B5161002 (Table S4). As a result of participants enrolling at various timepoints, the follow-up duration for each participant in Study B5161004 was limited. Less than 10 participants reached Week 73 for the B5161004 baseline (Week 170 for the overall baseline), and therefore data from these visits are not included in the description of efficacy results.

Table S4. Timepoint Equivalence of B5161004 Baseline and Overall Baseline

Week Number From Baseline in Study B5161004	Week Number From Overall Baseline in Study B5161004
13	110
25	122
49	146
73	170

B5161004 baseline was defined as the last assessment prior to dosing on Day 1 in Study B5161004.
Overall baseline was defined as the last pre-dose assessment prior to the first day of dosing in Study B5161002.

Four Stair Climb (4SC)

There was a mean increase from overall baseline of 6.784 seconds with a 95% confidence interval (CI) of 0.749 to 12.819 seconds observed in the 4SC time among 15/59 evaluable participants at Week 146. There was no statistically significant difference in change from overall baseline for the 4SC time between Sequence 1 and the natural history control group over the course of Studies B5161002 and B5161004, which was confirmed by a velocity-based sensitivity analysis.

Northstar Ambulatory Assessment (NSAA)

The NSAA total score decreased over the course of Studies B5161002 and B5161004. At Week 146, the mean decrease from overall baseline in the NSAA total score was -8.6 with a 95% CI of -11.9 to -5.3 among 19/59 evaluable participants in the study.

Increases from overall baseline were observed in the time to complete 10 m run/walk over the course of Studies B5161002 and B5161004, which was confirmed by a velocity-based

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sensitivity analysis. At Week 146, the mean increase from overall baseline in the time to complete 10 m run/walk was 1.785 seconds with a 95% CI of 0.840 to 2.731 seconds among 13/59 evaluable participants in the study.

Increases from overall baseline in the time to stand from supine were observed over the course of Studies B5161002 and B5161004, which was confirmed by a velocity-based sensitivity analysis. At Week 122, the mean increase from overall baseline in the time to stand from supine was 2.573 seconds with a 95% CI of 0.903 to 4.243 seconds among 18/59 evaluable participants in the study.

Pulmonary Function Tests (PFTs)

Forced vital capacity (FVC) increased over the course of Studies B5161002 and B5161004. At Week 146, mean increase from overall baseline was 0.3960 L with a 95% CI of 0.2797 to 0.5123 L among 20/59 evaluable participants in the study.

Percent predicted FVC remained stable over the course of Studies B5161002 and B5161004. At Week 146, the mean change from overall baseline in percent predicted FVC was 1.2100% with a 95% CI of -4.8019% to 7.2219% among 20/59 evaluable participants in the study.

Forced expiratory volume in 1 second (FEV_1) increased over the course of OLE Study B5161004. At Week 49, the mean increase from B5161004 baseline for FEV_1 was 0.2100 L with a 95% CI of 0.0874 to 0.3326 L among 19/59 evaluable participants in the study. For percent predicted FEV_1, there was a mean increase from B5161004 baseline of 6.3889 L with a 95% CI of -2.4989 to 15.2767 L observed among 18/59 evaluable participants at Week 49. This increase of percent predicted FEV_1 was primarily driven by Sequence 1.

For peak expiratory flow rate (PEFR), the mean increase from B5161004 baseline was 8.305 L/min with a 95% CI of -24.489 to 41.099 L/min among 19/59 evaluable participants at Week 49.

There was no summary data for the mean change from overall baseline for the FEV_1 (including FEV_1 and percent predicted FEV_1) and PEFR as they were not collected in Parent Study B5161002.

Muscle Strength

Knee extension strength decreased over the course of Studies B5161002 and B5161004. The loss of knee extension strength was similar between Sequences 1 and 2 with less loss of knee extension strength in Sequence 3 over time.

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Performance of Upper Limb (PUL)

The total PUL score combines all 3 dimension level scores (shoulder, middle and distal). Decreases from overall baseline in the total PUL score were observed over the course of Studies B5161002 and B5161004. Changes over time were similar across the 3 sequences.

At Week 146, the mean decrease from overall baseline in shoulder level score was -2.7 with a 95% CI of -5.0 to -0.5 among 21/59 evaluable participants; the mean decrease from overall baseline in the middle level score was -1.0 with a 95% CI of -2.3 to 0.4 among 21/59 evaluable participants; the mean decrease from overall baseline in the distal level score was -0.1 with a 95% CI of -0.9 to 0.6 among 21/59 evaluable participants.

Six-Minute Walk Test (6MWT)

The 6MWD decreased over the course of Studies B5161002 and B5161004. At Week 146, the mean decrease from overall baseline in the 6MWD was -138.1 m with a 95% CI of -213.2 to -62.9 m among 19/59 evaluable participants in the study.

Ankle Range of Motion (ROM)

Passive flexion ankle ROM decreased in both the left and right ankles over the course of Studies B5161002 and B5161004. At Week 146, the mean decrease of degrees of passive flexion for the left and right ankles from overall baseline were -10.6 (95% CI = -15.7 to -5.4) and -11.4 (95% CI = -16.8 to -6.0) among 20/59 evaluable participants, respectively.

Pharmacokinetic and Immunogenicity Results:

Pharmacokinetics

For all sequences, trough concentrations increased from the first dose on Day 1, Week 1 and appeared to be at steady state at Week 25 based on similar median serum trough levels by Weeks 25, 49 and 73.

Immunogenicity

No participants tested positive (titer ≥1.88) for ADA.

Safety Results:

There were 195 all causalities treatment emergent adverse events (TEAEs) reported by 49 (83.1%) participants. Of these, 6 TEAEs were determined by the investigator as treatment related, and were reported by 6 (10.2%) participants. The majority of all causalities TEAEs were mild in severity (173/195 events at preferred term level). All 6 treatment related TEAEs were mild in severity.

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The most commonly reported TEAEs, regardless of causality, were in the SOCs of infections and infestations (28/59 participants, 47.5%), and injury, poisoning and procedural complications (23/59 participants, 39.0%). The most frequently reported TEAEs, regardless of causality, were fall (13/59 participants, 22.0%), headache (11/59 participants, 18.6%), and nasopharyngitis (11/59 participants, 18.6%). Treatment related TEAEs are summarized in Table S5.

Table S5. Treatment-Emergent Adverse Events by MedDRA Preferred Term (Treatment Related) by Sequence in Descending Order of Frequency - SAS

MedDRA (version 21.1) Preferred Term	Sequence 1 (N=19)	Sequence 2 (N=20)	Sequence 3 (N=20)	Total (N=59)
Epistaxis	1 (5.3)	1 (5.0)	0	2 (3.4)
Blood uric acid increased	0	1 (5.0)	0	1 (1.7)
Hair growth abnormal	0	1 (5.0)	0	1 (1.7)
Headache	0	0	1 (5.0)	1 (1.7)
Nausea	0	0	1 (5.0)	1 (1.7)

Treatment-Emergent adverse events were reported under the last treatment received prior to the onset of the adverse event.
Included all data collected since the first dose of study drug.
MedDRA version 21.1 coding dictionary applied.

There were 5 (8.5%) participants who experienced serious adverse events (SAEs), none of which were determined by the investigator as treatment related. There was 1 (1.7%) participant who discontinued from study due to an SAE of fat embolism syndrome that resulted in death. This SAE was due to a left tibial fracture, which was caused by a fall from wheelchair.

There were 4 (6.8%) participants who experienced severe AEs, none of which were determined by the investigator as treatment related. No participants experienced dose reduction or temporary discontinuation due to AEs. There was no intolerability or dose limiting treatment related AEs reported over the course of Study B5161004.

No participants met the potential Hy's Law criteria. One (1) participant from Sequence 3 had a transient abnormal elevation in GLDH (>2 × ULN) during the study; there were no other signs of hepatic injury observed.

Three (3) participants from Sequence 1 had reported TEAEs of increased cardiac troponin I, one of which was determined as an SAE. All TEAEs of increased cardiac troponin I were determined as not treatment related but due to disease under study.

There were no clinically significant findings observed in relation to vital signs or electrocardiogram (ECG). The majority of physical examination abnormalities were due to disease under study. A mild treatment related TEAE of abnormal pubertal hair growth was experienced by 1 participant from Sequence 2. Precocious puberty was not observed. No advanced bone age was identified as assessed by hand and wrist x-rays.

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There was no apparent change observed in bone mineral density (BMD) (including z-score and height adjusted z-score) in anteroposterior (AP) spine total L1 to L4 or body without head over time.

There was 1 participant from Sequence 1, whose left ventricular ejection fracture (LVEF) was ≥50% at both overall and B5161004 baseline, had an LVEF of <50% at early termination visit. Overall baseline for LVEF was defined as the last pre-dose assessment prior to the first day of dosing in Study B5161002; B5161004 baseline was defined as the last assessment prior to dosing on Day 1 in Study B5161004.

There was no iron accumulation observed above normal or mild overload in the study.

One (1) participant from Sequence 2 had suicidal ideation at Week 13 but did not have any suicidal behavior.

Conclusions:

- A 40 mg/kg dose of domagrozumab administered every 4 weeks by IV infusion over 97 weeks (B5161004) was generally safe and well tolerated in boys with DMD in this study.
- There were no long-term safety issues associated with dosing DMD boys with domagrozumab in Parent Study B5161002 for 96 weeks following an additional 97-week treatment of domagrozumab in OLE Study B5161004.
- In general, the mean changes from baseline for 4SC, NSAA, PFTs, muscle strength, PUL, 6MWT and ROM appeared to be consistent with the CINRG natural history dataset. No apparent treatment effect was observed in Study B5161004.
- Following domagrozumab IV administration every 4 weeks at 40 mg/kg, trough values steadily increased relative to the first dose.
- Trough values appeared to be at steady state at approximately Week 25 for all sequences.
- No participants tested positive for ADA in the study.