

CLINICAL STUDY REPORT SYNOPSIS

SYNOPSIS

Study Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of PF-06939926 for the Treatment of Duchenne Muscular Dystrophy

Study Number: C3391003

Study Phase: 3

Regulatory Agency or Public Disclosure Identifier Number:

US IND Number: 017598

EudraCT Number: 2019-002921-31

ClinicalTrials.gov ID: NCT04281485

Pediatric Investigational Plan Number: EMEA-002741-PIP01-M02

Compound: fordadistrogene movaparvovec (PF-06939926)

Trade Name: Not Available

Study Sponsor: Pfizer Inc.

Study Initiation Date (FPFV): 05 November 2020

Primary Completion Date (PCD): 15 May 2024

Presentation of data in this CSR synopsis is based on the PCD.

Early Termination Status: This study was not terminated early and will be completed as per protocol.

CSR Version and Report Date:

Document Version	Report Date
Interim CSR Version 1.0	11 September 2024

Number of Study Center(s) and Investigator(s): A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications: None

GOOD CLINICAL PRACTICE STATEMENT

This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

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Brief Description of the Trial Design and Methodology:

The purpose of the study is to demonstrate the safety and efficacy of fordadistrogene movaparvovec (PF-06939926) in participants with Duchenne Muscular Dystrophy (DMD).

Study C3391003 is a Phase 3, global, multi-center, randomized, double-blind, placebo-controlled study in ambulatory male participants, ages ≥ 4 to < 8 years, with a genetic diagnosis of DMD who were on a stable daily regimen of glucocorticoids.

Eligible participants were to be randomized into Cohort 1 or Cohort 2 in a 2:1 fashion and stratified by their age at Screening (< 6 or ≥ 6 years old). Study enrollment was managed to ensure that no more than approximately 55% of dosed participants were in either of the Screening age strata.

Treatment was planned to consist of two single intravenous (IV) infusions, one of fordadistrogene movaparvovec and one of placebo. Participants were to be followed for 5 years after the administration of the single dose of fordadistrogene movaparvovec, with the timing and sequence as described below:

- Cohort 1 (approximately 66 participants) were planned to receive a single dose of fordadistrogene movaparvovec on Day 1 (Visit 3) and a single dose of placebo at Year 2 Day 1 (Visit 20). Total time on study will have been approximately 5 years.
- Cohort 2 (approximately 33 participants) were planned to receive a single dose of placebo on Day 1 (Visit 3) and a single dose of fordadistrogene movaparvovec at Year 2 Day 1 (Visit 20), if they had remained eligible. Total time on study will have been approximately 6 years.

Number of Participants (planned and analyzed):

Table S1. Number of Participants (Planned and Analyzed)

Population	N	Definition
Enrolled	226	All participants who sign the informed consent document (ICD).
All Randomized	122	All participants, including siblings and those meeting exclusion criterion 15, who were randomly assigned to Cohort 1 (initially fordadistrogene movaparvovec) or Cohort 2 (initially placebo).
Full Analysis Set (FAS) – Week 52 ^a	92	All participants, excluding siblings and those meeting exclusion criterion 15, who were randomly assigned and received a single dose of study intervention on Day 1 (Year 1 Day 1). Participants were analyzed according to the cohort to which they were randomized.
Efficacy Analysis Set – LTFU (Long-Term Efficacy Analysis)	92	All participants, including siblings, but excluding those meeting protocol exclusion criterion 15, who received a single dose of fordadistrogene movaparvovec (either at Year 1 or Year 2). Participants were analyzed according to the investigational product (IP) they actually received.
Safety Analysis Set (SAS) – Week 52	114	All participants, including siblings and those meeting exclusion criterion 15, who were randomly assigned and received a single dose of study intervention on Day 1 (Year 1 Day 1). Participants were analyzed according to the IP they actually received.

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Table S1. Number of Participants (Planned and Analyzed)

SAS - EPC (Extended Placebo- Controlled Safety Analysis)	114	All participants, including siblings and those meeting exclusion criterion 15, who were randomly assigned and received a single dose of study intervention on Year 1 Day 1. Participants were analyzed according to the IP they actually received.
SAS – LTFU (Combined Safety Analysis)	97	All participants, including siblings and those meeting protocol exclusion criterion 15, who received a single dose of fordadistrogene movaparvovec (either at Year 1 or Year 2). Participants were analyzed according to the IP they actually received.
Viral Vector Shedding	38	Approximately the first 45 treated participants (approximately 30 treated with fordadistrogene movaparvovec and approximately 15 treated with placebo). For each matrix, all participants, including siblings and those meeting exclusion criterion 15, who were randomly assigned, received a single dose of fordadistrogene movaparvovec on Day 1 (Year 1 Day 1), and who had at least 2 post-baseline measurements within the first 7 days after fordadistrogene movaparvovec administration.

a. Of note, per the PCD definition in Protocol Amendment 15, the primary analysis will occur after at least 90 FAS participants complete Day 360 (Visit 19) or discontinue from the study prior to Week 52 if they had received Year 1 IP at least one year prior to the data cutoff.

Diagnosis and Main Criteria for Inclusion and Exclusion:

This study included male participants with DMD who were ≥ 4 to < 8 years of age at Screening (Visit 1). All participants were ambulatory, defined as being able to walk 10 meters unassisted, at Screening (Visit 1).

Additional key eligibility criteria included confirmed diagnosis of DMD by prior genetic testing, receipt of a stable daily dose of glucocorticoids (≥ 0.5 mg/kg/day prednisone, prednisolone, or ≥ 0.75 mg/kg/day deflazacort) for at least 3 months prior to Screening, North Star Ambulatory Assessment (NSAA) total score > 16 and < 30 at Screening, and no positive test for neutralizing antibody (NAb) to AAV9, based on the threshold determined by the Central Laboratory, from a sample taken at Screening.

Study Intervention:

Study intervention consisted of 2 single IV infusions, one of fordadistrogene movaparvovec (2E14 vg/kg of body weight) and one of placebo.

The manufacturing lot numbers for fordadistrogene movaparvovec, placebo and eculizumab dispensed in this study are provided in Table S2.

Table S2. Study Interventions Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
PF-06939926 Solution for Infusion [5 mL/vial]	EJ2855	20-005635	9.86E13 vg/mL	Solution
	FD7994	21-DP-00673	9.54E13 vg/mL	Solution
	DM3954	20-002630	1.02E14 vg/mL	Solution
	FG1211	22-DP-01071	1E14 vg/mL	Solution
	EN5043	21-000521	1E14 vg/mL	Solution
	CN9850	20-002451	9.63E13 vg/mL	Solution
	DM3965	20-003501	0 vg/mL	Solution
	EP9081	21-DP-00551	0 vg/mL	Solution

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Table S2. Study Interventions Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
Placebo for PF-06939926	FF6493	21-DP-00819	0 vg/mL	Solution
Solution for Infusion [5 mL/vial]	EC4569	20-005482	0 vg/mL	Solution
	DG6963	20-002448	0 vg/mL	Solution
Eculizumab 300 mg/30 mL Solution for Injection [single-dose vial]	P0013701	22-AE-00462	10 mg/mL	Solution
	1002478	23-AE-00881	10 mg/mL	Solution
	P20030802	20-004079	10 mg/mL	Solution
	1001576	21-AE-00337	10 mg/mL	Solution
	1002284	22-AE-00752	10 mg/mL	Solution
	1003023	23-AE-01044	10 mg/mL	Solution

Global Substantial Modifications

Table S3. Global Substantial Modifications

Date of Protocol Amendment	Amendment
28-Dec-2023	To specify that PCD may occur when at least 90 randomized participants have received Year 1 IP; this will provide > 95% power to address the primary objective of the study. To clarify that if a participant/caregiver declines Year 2 IP administration, the participant will remain in the study for follow-up with a modified visit schedule.
07-Jun-2023	To include the clarification of procedures for follow-up of participants with events of elevated troponin or myocarditis and to clarify the steps that the Sponsor will take if post-IP administration serious adverse events (SAEs) of elevated troponin or myocarditis are reported, as requested by the external Data Monitoring Committee (E-DMC).
06-Apr-2023	To update IP dosing instructions starting at Year 2 IP administration so that the nominal drug concentration is used for dose calculations instead of lot specific concentrations starting when instructed by the Sponsor. An additional update was the addition of anti-mini-dystrophin anti-drug antibodies (ADA) testing at Visit 12 (Day 21) and Visit 12.2 (Day 28) in Year 1 and at Visit 29 (Day 410) and Visit 29.2 (Day 417) in Year 2.
30-Sep-2022	To address the newly identified risk of myositis by updating exclusion criterion 15, to update the objective of interim analyses, and to make relevant clarifications regarding tests and procedures.
13-May-2022	To incorporate country-specific changes by adding new visits as requested by the German Federal Institute for Vaccines and Biomedicines.
04-Mar-2022	To incorporate country-specific changes for Germany; incorporate updates previously captured in global, Belgium-specific, and Japan-specific Protocol Administrative Changes and Clarifications letters; and incorporate Medicines and Healthcare products Regulatory Agency (MHRA) requirements previously relayed to United Kingdom sites via a Dear Investigator Letter.
01-Sep-2021	To clarify study size was approximately 99 participants in the FAS to ensure that the study had adequate power for the primary endpoint analysis. To optimize safety monitoring for mini-dystrophin, myocardial injury, cardiac injury, and muscle injury.
14-Apr-2021	To modify exclusion criteria and other applicable protocol sections to prevent enrollment of participants at risk of hypersensitivity reactions, to increase flexibility in administration of vaccines and specific medications, and to account for elevated cystatin C values as a result of treatment with steroids that did not reflect renal impairment. To allow early identification of participants with potential kidney injury, to provide guidance when participants have hypersensitivity reactions during IP infusion, and to modify the glucocorticoid regimen to ensure participants receive adequate treatment. To incorporate updates previously captured in global and Japan-specific Protocol Administrative Changes and Clarifications letters, and to incorporate country-specific changes requested by regulatory authorities and initially implemented in country-specific protocol amendments. To update protocol throughout to align with sponsor's new protocol template requirements.

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Global Interruptions and Re-starts

On 03 August 2021, a temporary screening, randomization, and dosing pause was implemented as a precautionary measure while an SAE of rhabdomyolysis and 2 SAEs of myocarditis considered related to an anti-transgene immune response in Study C3391003 were evaluated. Screening, randomization, and dosing were restarted with implementation of Protocol Amendment 6 (dated 01 September 2021).

On 21 December 2021, following a fatal SAE of cardiogenic shock in a non-ambulatory participant in ongoing Phase 1b Study C3391001, all activities related to screening, randomization, and dosing were paused in Study C3391003 while an evaluation of the SAE was completed. Screening, randomization, and dosing were restarted with implementation of Protocol Amendment 8 (dated 04 March 2022).

On 01 June 2023, a temporary pause in dosing was implemented following 2 events of myocarditis (considered related to an immune response to the viral capsid) in Study C3391003. The pause was implemented due to protocol language mandating a temporary halt for any case of myocarditis. Dosing was restarted with implementation of Protocol Amendment 14 (dated 07 June 2023).

Following a fatal SAE reported as cardiac arrest in a participant in Study C3391008, a temporary pause in dosing in Study C3391003 was implemented on 03 May 2024 and remained in place at the time of data cutoff. Decisions on the study pauses were made in collaboration with the E-DMC. Safety data for participants whose Year 2 Day 1 dosing was delayed due to dosing pause(s) were reported as part of the SAS-EPC.

Endpoints and Statistical Methods:

Type	Objectives	Endpoints
Primary		
Efficacy	To demonstrate superior efficacy of treatment with fordadistrogene movaparvovec as compared to placebo based on change from Baseline in the NSAA.	Change from Baseline at Week 52 in the NSAA total score.
Secondary		
Pharmacodynamics	To quantify the mini-dystrophin expression level in the muscle of participants treated with fordadistrogene movaparvovec.	Change from Baseline in percent normal mini-dystrophin expression level in biceps brachii muscle biopsies at Day 360 using a liquid chromatography mass spectrometry (LC-MS) assay.
Pharmacodynamics	To characterize the distribution of mini-dystrophin expression in the muscle of participants treated with fordadistrogene movaparvovec.	Change from Baseline in percent of muscle fibers expressing mini-dystrophin in biceps brachii muscle biopsies at Day 360 as assessed by immunofluorescence.
Efficacy	To characterize the change in serum creatine kinase (CK) concentration in participants treated with fordadistrogene movaparvovec as compared to placebo.	Change from Baseline at Week 52 in serum CK concentration.

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Type	Objectives	Endpoints
Efficacy	To characterize the skills gained, based on the individual items of the NSAA, in participants treated with fordadistrogene movaparovec as compared to placebo.	Number of skills gained at Week 52 based on the individual items of the NSAA.
Efficacy	To characterize the skills either improved or maintained, based on the individual items of the NSAA, in participants treated with fordadistrogene movaparovec as compared to placebo.	Number of skills either improved or maintained at Week 52 based on the individual items of the NSAA.
Efficacy	To characterize the 10-meter run/walk velocity in participants treated with fordadistrogene movaparovec as compared to placebo.	Change from Baseline at Week 52 in the 10-meter run/walk velocity.
Efficacy	To characterize the rise from floor velocity in participants treated with fordadistrogene movaparovec as compared to placebo.	Change from Baseline at Week 52 in the rise from floor velocity.
Efficacy	To characterize the functional health status in participants treated with fordadistrogene movaparovec as compared to placebo.	Change from Baseline at Week 52 in the Modified Pediatric Data Outcomes Collection Instrument (PODCI): Transfer and Basic Mobility Core Scale (Pediatric Parent).
Efficacy		Change from Baseline at Week 52 in the Modified PODCI: Sports and Physical Functioning Core Scale (Pediatric Parent).
Safety		
Safety	To characterize the safety of treatment with fordadistrogene movaparovec as compared to placebo.	<p>Incidence, severity and causal relationship of treatment-emergent adverse events (TEAEs) (AEs and SAEs) through Week 52.</p> <p>Incidence of abnormal laboratory findings and magnitude of change through Week 52.</p> <p>Abnormal and clinically relevant changes through Week 52 in Physical exam, Neurologic exam, Weight, Vital signs, ECG, Echocardiogram, Cardiac MRI, and CBCL</p>
Safety	To characterize the safety of treatment with fordadistrogene movaparovec in participants in Cohort 2.	<p>Incidence, severity and causal relationship of TEAEs (AEs and SAEs) after fordadistrogene movaparovec administration through Year 2 Week 52.</p> <p>Incidence of abnormal laboratory findings and magnitude of change from pre-fordadistrogene movaparovec Baseline through Year 2 Week 52.</p> <p>Abnormal and clinically relevant changes from pre-fordadistrogene movaparovec Baseline through Year 2 Week 52 in Physical exam, Neurologic exam, Weight, Vital signs, ECG, Echocardiogram, Cardiac MRI, and CBCL</p>
Safety	To characterize the long-term safety of treatment with fordadistrogene movaparovec.	<p>Incidence, severity and causal relationship of TEAEs (AEs and SAEs) through 5 years post fordadistrogene movaparovec administration.</p> <p>Incidence of abnormal laboratory findings and magnitude of change through 5 years post fordadistrogene movaparovec administration.</p>

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Type	Objectives	Endpoints
		Abnormal and clinically relevant changes through 5 years post fordadistrogene movaparvovec administration in Physical exam, Neurologic exam, Weight, Vital signs, ECG, Echocardiogram, Cardiac MRI, and CBCL

Statistical Hypothesis

For the primary endpoint, the null hypothesis is that there is no difference between fordadistrogene movaparvovec and placebo with respect to mean change from Baseline at Week 52 in the NSAA total score. The alternative hypothesis is that fordadistrogene movaparvovec is different from placebo with respect to mean change from Baseline at Week 52 in the NSAA total score.

The experiment-wise Type I error ($\alpha=0.05$ [two-sided]) was controlled using gatekeeping and fixed-sequence procedures for the primary and select secondary endpoints listed below. The hypotheses for the secondary endpoints are similar to those for the primary endpoint.

1. Change from Baseline at Week 52 in the 10-meter run/walk velocity.
2. Change from Baseline at Week 52 in the rise from floor velocity.
3. Number of skills either improved or maintained at Week 52 based on the individual items of the NSAA.
4. Number of skills gained at Week 52 based on the individual items of the NSAA.

If the null hypothesis for the primary endpoint is rejected, statistical testing proceeds to the hypotheses for the secondary endpoints; otherwise, formal statistical testing in the sense of controlling the experiment-wise Type I error stops and nominal p-values for secondary endpoints will be reported and interpreted accordingly.

The secondary endpoints will be tested in the order specified above. To maintain the study-wise Type 1 error rate, the secondary endpoints were tested using the same p-value boundary as the primary endpoint as detailed in the interim analysis (IA) statistical analysis plan (SAP). If the null hypothesis for the first endpoint in the sequence is rejected, statistical testing moves to the next endpoint in the sequence. Statistical testing proceeds to subsequent endpoints in the sequence only if the null hypothesis for the previous endpoint is rejected. If a null hypothesis in the sequence is not rejected, formal statistical testing in the sense of controlling the experiment-wise Type I error is stopped for all endpoints later in the sequence and nominal p-values will be reported and interpreted accordingly.

Safety Analyses

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Descriptive summaries are provided by treatment group for participants in the Safety Analysis Set up to the data cutoff date. Adverse events of interest were determined and categorized based on review of known pharmacology, toxicology findings, possible class effects of viral vector-based gene therapies, published literature, and signals arising from safety data assessments.

Summary of Results:

Participant Disposition:

Enrollment was completed in May 2023 across 45 sites in 15 countries. As of the data cutoff date (15 May 2024), 226 participants (including 1 sibling) had been enrolled and 122 participants (including 1 sibling) had been randomized. Day 1 refers to Year 1 Day 1, unless noted otherwise throughout this report.

8 participants were randomized but withdrawn from the study prior to Year 1 Day 1 infusion (4 participants were found to meet exclusion criterion 15, 1 participant did not meet inclusion criterion 4, 1 participant met exclusion criterion 8, 1 participant had myocarditis and met exclusion criterion 16, and 1 participant was withdrawn by parent/guardian).

Demographic and Other Baseline Characteristics:

Among all participants in the FAS, demographic and baseline characteristics were balanced between Cohort 1 and Cohort 2. Per study design, all participants were male. The mean (standard deviation [SD]) age at Screening was 5.9 (1.2) years in fordadistrogene movaparvovec group and 6.0 (1.3) years in the placebo group. In the fordadistrogene movaparvovec group, 40 (62.5%) participants were White, 19 (29.7%) were Asian, 4 (6.3%) reported Unknown for race, and 1 (1.6%) was not reported. In the placebo group, 21 (75%) participants were White, 6 (21.4%) were Asian and for 1 (3.6%) race was not reported [[source: Table 14.1.2.1.2]] Exposure:

As of the data cut off date, in the combined SAS, the mean (SD) actual administered dose of fordadistrogene movaparvovec for all fordadistrogene movaparvovec dosed participants was 2.00×10^{14} (0.031×10^{14}) vg/kg.

Summary of Efficacy Results:

Primary Endpoint: At Week 52, there was no statistically significant improvement in change from baseline in the NSAA total score between fordadistrogene movaparvovec and placebo.

Secondary Endpoints:

- At Week 52, there was no statistically significant improvement from baseline in 10-meter run/walk velocity, rise from floor velocity, number of skills either improved or maintained, and number of skills gained in the fordadistrogene movaparvovec group compared to the placebo group.

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- At Week 52, serum CK concentrations were lower in the fordadistrogene movaparovec group compared to the placebo group.
- At Week 52, no statistically significant treatment differences were observed in the fordadistrogene movaparovec group compared to the placebo group in the ability to complete activities of daily living based on caregiver assessment in the PODCI Transfer and Basic Mobility Core Scale and Sports and Physical Functioning Core Scale.

Summary of Safety Results:

Unless otherwise specified, the term “AE” refers to “TEAE” in this synopsis.

During the first year post-infusion, the safety profile of fordadistrogene movaparovec was considered manageable, with mostly mild or moderate AEs and treatment-related SAEs generally responding to clinical management. No new safety signals were identified during long-term follow-up.

- The percentage of participants with all-causality AEs was higher in the fordadistrogene movaparovec group (98.7%) than in the placebo group (77.1%).
 - At 52 weeks, the most commonly reported all-causality AEs (occurring in $\geq 10\%$ of the fordadistrogene movaparovec-treated group) in participants in the fordadistrogene movaparovec group compared to participants in the placebo group were Vomiting (75.9% vs 14.3%), Pyrexia (62.0% vs 8.6%), Decreased appetite (32.9% vs 2.9%), Nausea (29.1% vs 8.6%), Nasopharyngitis (24.1% vs 17.1%), Glutamate dehydrogenase increased (24.1% vs 0%), Abdominal pain (21.5% vs 8.6%), Thrombocytopenia (19% vs 0%), Headache (17.7% vs 11.4%), Diarrhoea (12.7% vs 11.4%), Platelet count decreased (12.7% vs 0%), SARS-CoV-2 test positive (11.4% vs 5.7%), and Hypertension (10.1% vs 0%).
- The percentage of participants with treatment-related AEs was higher in the fordadistrogene movaparovec group (92.4%) than in the placebo group (28.6%).
 - At 52 weeks, the most commonly reported treatment-related AEs in the fordadistrogene movaparovec group were Vomiting, Pyrexia, and Decreased appetite.
- The percentage of participants with all-causality SAEs was higher in the fordadistrogene movaparovec group (31.6%) than in the placebo group (14.3%).
 - At Week 52, all-causality SAEs reported by more than 1 participant in the fordadistrogene movaparovec group were Myocarditis, Vomiting, Thrombocytopenia, Thrombotic microangiopathy, COVID-19, Hepatitis, Hypophagia, Muscular weakness, and Rhabdomyolysis. There were no all-causality SAEs reported by more than 1 participant in the placebo group.
- At the time of data cut off, no deaths were reported among participants in the study.

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- Through Week 52, the incidences of abnormal platelets, monocytes, haptoglobin, GLDH, and C-reactive protein, and ketones in urine were higher (>15% difference) in the fordadistrogene movaparvovec group than in the placebo group.
- There were no additional safety signals identified from the review of physical exams, neurological exams, weight, vital signs, ECG, echocardiogram, cardiac MRI and CBCL.
- The AE profile was similar in the Combined Safety Analyses and Week 52 Analyses and no new safety signals were identified in the Combined Safety Analyses.

Summary of Pharmacodynamics Results:

Mini-dystrophin expression and distribution in muscles showed successful and widespread transduction in ambulatory DMD male participants who received fordadistrogene movaparvovec up to 12 months.

Conclusions:

The study did not meet its primary endpoint of a statistically significant improvement in the change from baseline in NSAA total score for the fordadistrogene movaparvovec group compared to the placebo and the key secondary endpoints were also not supportive of a functional benefit. The safety profile of fordadistrogene movaparvovec was considered manageable.

Limitations and Caveats: This report includes data from an ongoing study (with an open database) and was prepared using summary data as of 15 May 2024. The data presented represent the latest data as of the time of report preparation. A report will be written after completion of the whole study.