Title Page

A LOW-INTERVENTIONAL STUDY OF AAV9 NEUTRALIZING ANTIBODY SEROCONVERSION IN HOUSEHOLD CONTACTS OF PARTICIPANTS WITHIN FORDADISTROGENE MOVAPARVOVEC CLINICAL TRIALS

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Short Title: A Low-Interventional Study to Assess Development of Neutralizing Antibodies (NAbs) to AAV9 in Household Contacts of Duchenne Muscular Dystrophy Patients Treated with Fordadistrogene Movaparvovec

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	05 April 2022	• Added inclusion of household contacts of patients dosed in interventional studies C3391001, C3391002, and C3391008 (Multiple Sections). • Study drug name updated from PF-06939926 to fordadistrogene movaparvovec (Multiple Sections). • Clarified that informed consent may be conducted remotely (Sections 1.3 and 8). • Updated Clinical Overview of fordadistrogene movaparvovec studies with latest information (Section 2.2.2). • Moved content to current LIS1 protocol template version (dated Dec 2020) and updated text and formatting accordingly (Multiple Sections). • Added Scientific Rationale for study design per new protocol template requirement (Section 4.2). • Added definition for End of Study per new protocol template requirement (Section 4.4). • Modified definition of Screen Failure for clarity (Section 5.4). • Removed requirement for topical analgesic prior to blood draws in

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		order to decrease operational complexity (Sections 8 and 8.9.1). • Updated table of 95% CIs for the estimate of the proportion of participants who are negative for NAb to AAV9 at Baseline and develop NAb to AAV9 post-Baseline for various numbers of enrolled participants (Section 9.2). • Administrative changes were made to enhance readability.
Original protocol	19 March 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs, and any protocol administrative clarification letters.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title

A Low-Interventional Study to Assess Development of Neutralizing Antibodies (NAbs) to AAV9 in Household Contacts of Duchenne Muscular Dystrophy Patients Treated with Fordadistrogene Movaparvovec

Rationale

At present, there is uncertainty regarding the risk of developing NAbs to AAV9 for a household contact of a patient who has received an AAV9 based gene therapy and may be shedding vial vector. The result is that families must consider this unknown risk when considering this therapy for others that may also be treated in the future, such as siblings, or when considering participation in activities for DMD patients who may want to receive AAV gene therapy in the future, or when considering attendance at camps or conferences.

The results of this study will help quantify the risk of developing NAbs to AAV9 in household contacts of patients treated with fordadistrogene movaparvovec. This will be valuable information to future patients, families, and perhaps even casual contacts of DMD patients because of the theoretical possibility of losing access to an AAV9-based gene therapy by developing NAbs to AAV9 after contact with other treated patients.

Banked biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of fordadistrogene movaparvovec research questions and objectives.

Objectives and Endpoints

Primary Objective:	**Primary Endpoint:**
To quantify the proportion of participants (previously seronegative for NAb to AAV9) who develop NAb to AAV9 (ie, seroconversion).	Development of NAb to AAV9 (ie, NAb seroconversion) as defined by an increase of ≥6-fold above Baseline titer in participants with a detectable, but negative test (ie, titer ≥1 and <4) for NAb to AAV9 at Baseline. If there is an undetectable titer at Baseline (ie, titer <1), then development of NAb to AAV9 as defined by a NAb to AAV9 titer ≥6.
Secondary Objective:	**Secondary Endpoint:**
To quantify the proportion of participants (previously seronegative for ADA to AAV9) who develop ADA to AAV9.	Development of ADA to AAV9 (ie, ADA seroconversion) defined by a titer ≥300 in

	participants with a negative test (ie, titer <50) for ADA to AAV9 at Baseline.
Exploratory Objectives:	**Exploratory Endpoints:**
To quantify the proportion of participants (previously seropositive for NAb to AAV9) who have an increase in the NAb to AAV9 titer.	NAb to AAV9 titer ≥6-fold higher than Baseline titer in participants who are seropositive (ie, titer ≥4) for NAb to AAV9 at Baseline.
To quantify the proportion of participants (previously seropositive for ADA to AAV9) who have an increase in the ADA to AAV9 titer.	ADA to AAV9 titer ≥6-fold higher than Baseline titer in participants who are seropositive (ie, titer ≥50) for ADA to AAV9 at Baseline.
To quantify the proportion of participants who seroconvert and have detectable fordadistrogene movaparvovec vector DNA in blood.	Detectable fordadistrogene movaparvovec vector DNA in participants who seroconvert via either ADAs or NAbs.

Overall Design

This single center, low-interventional study to include approximately 50 to 250 participants is designed to estimate the likelihood of developing NAbs to AAV9 because of exposure to shed viral vector material released by a DMD patient treated with fordadistrogene movaparvovec in clinical studies. This study will include participants who live or work in the same household as a participant in one of the fordadistrogene movaparvovec interventional studies, which may include Study C3391003, C3391002, C3391008, or C3391001. Up to 5 participants from the same household may be enrolled. Eligible participants will undergo phlebotomy provided by a Home Health Care Vendor at three home visits as specified in the Schedule of Activities. As a control, seroconversion or rise of antibody titer against other AAVs may also be quantified.

Number of Participants

Approximately 50 to 250 participants will be enrolled. Table 1 shows the expected precision, defined as the upper and lower 95% confidence limits, of the estimate of the proportion of participants who are negative for NAb to AAV9 at Baseline and who develop NAb to AAV9 post-Baseline for various numbers of enrolled participants. These calculations assume that 75% of the participants will be seronegative for NAb to AAV9 at Baseline.

Study Cohorts and Duration of Study Participation

The total duration of participation in the study is approximately 4 months, including up to 48 days for the screening/baseline period and 56 ± 10 days of follow-up after the interventional study patient is dosed with investigational product. The screening/baseline period may be extended if there are delays in the interventional studies.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

For the primary, secondary, and each of the exploratory endpoints listed in Section 3, the proportion (and 95% CI) of C3391007 participants will be estimated for 2 groups of participants:

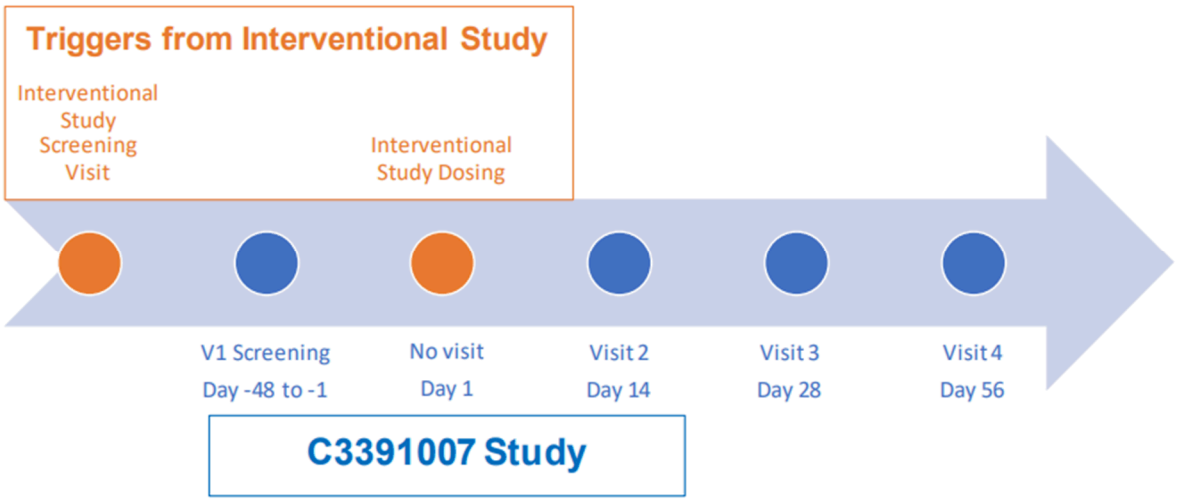
- fordadistrogene movaparvovec: household contacts of patients in interventional studies C3391002, C3391003, C3391001, and C3391008
- placebo: household contacts of patients in interventional studies C3391002 and C3391003

using generalized estimating equations methods with study as covariate to account for correlated responses within the same household. A binomial distribution with a log link and an exchangeable correlation matrix within each household (ie, between any two members of a household the correlation is the same) will be used. Proportions and 95% confidence intervals will be provided separately for each visit (except for Detectable fordadistrogene movaparvovec vector DNA in participants who seroconvert via either ADAs or NAbs) and overall at any time during the study.

Incidence of AEs will be summarized/listed.

Pharmacogenomic or biomarker data from banked biospecimens will be collected pursuant to local regulations/IRB during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

1.2. Schema



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier Abbreviations used in this table may be found in Section 10.4.	**Visit 1 (Screening and Baseline visit)** [a]	**N/A**	**Visit 2**[c]	**Visit 3**	**Visit 4**
Visit Day (±days visit window) [b]	**-48 to -1**	**Day 1**	**Day 14 (+2 days)**	**Day 28 (±8 days)**	**Day 56 (±10 days)**
Informed consent/assent[c]	X				
Review of inclusion/exclusion criteria	X	X			
Medical history	X				
Demographic information	X				
Extent of contact with the patient of the interventional study	X		X		
Weight measurement	X				
Concomitant treatments	X			X	X
Serious and non-serious adverse event monitoring	X		X	X	X
Blood Samples for NAb and ADA to AAV9[d]	X			X	X
fordadistrogene movaparvovec vector DNA	X			X	X
Banked biospecimens[e]	X				
Enrollment		X			
Home visit[f]	X			X	X

a. Screening/baseline period of this study may be extended if there are delays in the interventional study.
b. Day relative to first dose of IP administration (Day 1) of the interventional study patient who is in the same household as the main study participant.
c. May be conducted via a phone call or other remote communication.
d. Unscheduled/additional blood draws for NAb and ADA to AAV9 may be required if the quality of the scheduled collected sample is deemed unacceptable for analysis.
e. Biobank specimens will only be drawn in participants who weigh >20 kg.
f. Study procedures will be conducted by the home health care vendor at the participant's home, and/or by the Investigator via remote communication.

2. INTRODUCTION

Duchenne muscular dystrophy (DMD) is a severe, X-linked, progressive neuromuscular disease affecting approximately 1 in 3600 to 9300 live male births.[1] It is caused by mutations in the dystrophin gene that eliminate or severely reduce the expression of functional dystrophin protein.[2] The near lack of the dystrophin protein in skeletal muscles, including those required for respiration and in the heart, leads to muscle degeneration which results in loss of ambulation and premature death.[3]

Fordadistrogene movaparvovec is a candidate disease modifying gene therapy treatment for DMD that has the potential to slow the disease progression, improve motor function, and/or normalize motor development milestones. Fordadistrogene movaparvovec is a rAAV serotype 9 (AAV9) vector expressing a codon-optimized, miniaturized version of the dystrophin gene ("mini-dystrophin"). Due to the existence of AAV9 in nature, about 15-35% of adults have pre-existing neutralizing antibodies to the AAV9 capsid.[4,5,6]

2.1. Study Rationale

At present, there is uncertainty regarding the risk of developing NAbs to AAV9 for a household contact of a patient who has received an AAV9 based gene therapy and may be shedding viral vector. The result is that families must consider this unknown risk when considering this therapy for others that may also be treated in the future, such as siblings, or when considering participation in activities for DMD patients who may want to receive AAV gene therapy in the future, or when considering attendance at camps or conferences.

The results of this study will help quantify the risk of developing NAbs to AAV9 in household contacts of patients treated with fordadistrogene movaparvovec. This will be valuable information to future patients, families, and perhaps even casual contacts of DMD patients because of the theoretical possibility of losing access to an AAV9-based gene therapy by developing NAbs to AAV9 after contact with other treated patients.

2.2. Background

Viral vectors are metabolized by the same general processes as naturally occurring adenoviruses. Although naturally occurring viruses utilize the cellular machinery to reproduce viral particles using the viral DNA, rAAVs have eliminated this DNA, and therefore, new viral particles are not produced.

Viral vector shedding has been investigated in the clinical studies of other gene therapies utilizing AAV. LUXTURNA® is an approved AAV2-based gene therapy product for treatment of an inherited retinal disease and is injected intraocularly.[7] Shedding data were reported only for tears. In 29 subjects receiving LUXTURNA, peak levels of vector DNA were detected in tear samples on Day 1 post-injection, after which no vector DNA was detected in a majority of the subjects (8 of 13). Three (3 [10%]) subjects had vector DNA in tear samples until Day 3 post-injection, and 2 (7%) subjects had vector DNA in tear samples for approximately 2 weeks post-injection. In 2 (7%) subjects, vector DNA was detected in

tear samples from the uninjected (or previously injected) eye until Day 3 post-injection. Vector DNA was detected in serum in 3/29 (10%) subjects, and 2 of these had vector DNA detected in tear samples up to Day 3. ZOLGENSMA® is an approved AAV9-based gene therapy product for the treatment of a neuromuscular disease and is administered intravenously.[8] Shedding data from 5 subjects is described in the prescribing information, demonstrating that the vector DNA was shed in saliva, urine, and stool after infusion of ZOLGENSMA. The vector DNA concentration in saliva was low on Day 1 after infusion and declined to undetectable levels within 3 weeks. In urine, the vector DNA concentration was very low on Day 1 after infusion and declined to undetectable levels within 1 to 2 weeks. In stool, the vector DNA concentration was much higher than in saliva or urine for 1 to 2 weeks after infusion and declined to undetectable levels by 1 to 2 months after infusion.

The available non-clinical and clinical data describing viral vector shedding kinetics suggests that DNA is detectable in multiple bodily fluids including plasma, tears, saliva, urine, and stool following IV infusion of rAAV and that it is usually cleared from these matrices within approximately 40 days.[9] Since the kinetics are likely dependent upon the specific rAAV serotype as well as on the dose administered, the viral vector shedding profile of fordadistrogene movaparvovec will be determined within ongoing and planned clinical studies.

2.2.1. NonClinical Overview

Fluid samples (serum, urine, and saliva) were collected from 7 GRMD dogs treated with fordadistrogene movaparvovec to determine the level and duration of viral vector shedding. None of these dogs reached sexual maturity during the study, so semen samples were not collected. In samples collected before treatment, no vector genomes were detected. At 3 days post infusion (p.i.), the first timepoint assessed, the number of vector genomes detected in serum ranged from 0.01 to 0.32% of the total injected dose. This value decreased to ≤0.001% of the total injected dose by 7 days p.i. in saliva and by 28 days in serum and urine. With the exception of a single dog urine sample collected at 6 months p.i., all of the other dogs (6 out of 7) had negative urine samples after day 21.

2.2.2. Clinical Overview

As of December 2021, there are 4 ongoing or planned interventional studies evaluating fordadistrogene movaparvovec for the treatment of DMD patients:

- C3391001 is a Phase 1b, first-in-human, open-label, single ascending dose study in ambulatory and non-ambulatory patients with DMD.
- C3391003 is a Phase 3, global, multi-center, randomized, double blind, placebo-controlled study in ambulatory DMD patients.
- C3391002 is a Phase 3, global, multicenter, randomized, double blind, placebo-controlled study in non-ambulatory DMD patients.

- C3391008 is a Phase 2, global, multicenter, open label, study in patients with early stage DMD.

Viral vector shedding will be evaluated for fordadistrogene movaparvovec in C3391001 and C3391003. Whole blood, saliva, and urine samples will be collected in patients from interventional studies C3391001 and C3391003. This evaluation is designed to provide information about 2 factors that contribute to the risk of exposure to viral vectors for untreated individuals: the magnitude of viral vector shedding, and the duration of the period in which the vector is present in bodily secretions. Individuals living or working in the same household of a DMD patient who has recently received fordadistrogene movaparvovec may be exposed to shed viral material. Whilst this does not pose a risk of infection, those individuals, who had not previously been environmentally exposed to AAV9, in consequence may develop neutralizing antibodies (NAbs) or other binding antibodies (anti-drug antibodies; ADAs) against the viral vector (seroconversion). NAb seroconversion to AAV9 would likely result in exclusion from AAV9-based gene therapies in the future. In particular, an untreated DMD patient who seroconverted would likely be excluded from receiving fordadistrogene movaparvovec, therefore profoundly impacting that patient's potential treatment option.

2.3. Benefit/Risk Assessment

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with the blood draws (the study interventions) are justified by the anticipated benefits that may be afforded to household contacts of patients with DMD treated with a gene therapy.

Exposure to shed viral material is not anticipated to pose a safety risk due to the following reasons: (1) Only a small portion of fordadistrogene movaparvovec is expected to be shed from participants in C3391003 in comparison to the IV dose received;[10] (2) The amount of functional, intact fordadistrogene movaparvovec taken up through exposure to shed viral material by C3391007 participants is expected to be negligible; (3) fordadistrogene movaparvovec is replication incompetent. Thus, there is no anticipated risk for a viral infection as would be expected from exposure to a wildtype AAV. The only risk for participants in C3391007 is to develop antibodies or increase their antibody titer in response to exposure to minute amounts of shed viral material from an interventional study patient. The minimal immune response is not expected to manifest with any symptoms.

3. RESEARCH QUESTIONS, OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
To quantify the proportion of participants (previously seronegative for NAb to AAV9) who develop NAb to AAV9 (ie, seroconversion).	Development of NAb to AAV9 (ie, NAb seroconversion) as defined by an increase of ≥6-fold above Baseline titer in participants with a detectable, but negative

Objectives	Endpoints
	test (ie, titer ≥1 and <4) for NAb to AAV9 at Baseline. If there is an undetectable titer at Baseline (ie, titer <1), then development of NAb to AAV9 as defined by a NAb to AAV9 titer ≥6.
Secondary:	**Secondary:**
To quantify the proportion of participants (previously seronegative for ADA to AAV9) who develop ADA to AAV9.	Development of ADA to AAV9 (ie, ADA seroconversion) defined by a titer ≥300 in participants with a negative test (ie, titer <50) for ADA to AAV9 at Baseline.
Exploratory:	**Exploratory:**
To quantify the proportion of participants (previously seropositive for NAb to AAV9) who have an increase in the NAb to AAV9 titer.	NAb to AAV9 titer ≥6-fold higher than Baseline titer in participants who are seropositive (ie, titer ≥4) for NAb to AAV9 at Baseline.
To quantify the proportion of participants (previously seropositive for ADA to AAV9) who have an increase in the ADA to AAV9 titer.	ADA to AAV9 titer ≥6-fold higher than Baseline titer in participants who are seropositive (ie, titer ≥50) for ADA to AAV9 at Baseline.
To quantify the proportion of participants who seroconvert and have detectable fordadistrogene movaparvovec vector DNA in blood.	Detectable fordadistrogene movaparvovec vector DNA in participants who seroconvert via either ADAs or NAbs.

3.1. Variables

Variable	Role	Data source(s)	Operational definition
Demographic information	Participant baseline characteristic	CRF	N/A
Age of interventional study patient and C3391007 participant	Participant baseline characteristic	CRF	N/A
Extent of contact with the patient in the interventional study	Participant characteristic	CRF	N/A
Weight	Participant baseline characteristic	CRF	N/A

Variable	Role	Data source(s)	Operational definition
Concomitant treatments	Participant baseline characteristic	CRF	N/A
Medical history	Participant baseline characteristic	CRF	N/A
Adverse events (AEs)	Safety assessment	CRF	N/A
Blood samples for NAb to AAV9, ADA to AAV9 and fordadistrogene movaparvovec vector DNA	Outcome to assess primary, secondary, and exploratory objectives	Central laboratory and CRO data transfer files	N/A

4. STUDY DESIGN

4.1. Overall Design

This single center, low-interventional study to include approximately 50 to 250 participants is designed to estimate the likelihood of developing NAbs to AAV9 because of exposure to shed viral vector material released by a DMD patient treated with fordadistrogene movaparvovec in clinical studies. This study will include participants who live or work in the same household as a patient in one of the fordadistrogene movaparvovec interventional studies which may include Study C3391003, C3391002, C3391008, or C3391001. Given the timing and logistics of the interventional studies, some may have no household contacts participating in C3391007. Up to 5 participants from the same household may be enrolled.

Eligible participants will undergo phlebotomy provided by a Home Health Care Vendor at three home visits as specified in the Schedule of Activities. As a control, seroconversion or rise of antibody titer against other AAVs may also be quantified.

The total duration of participation in the study is approximately 4 months, including up to 48 days for the screening/baseline period and 56 $\pm$ 10 days of follow-up after the interventional study patient is dosed with investigational product. The screening/baseline period may be extended if there are delays in the interventional studies.

The single center conducting this study is located in the United States.

4.2. Scientific Rationale for Study Design

People working or living in the same household of patients who are enrolled in an interventional study of fordadistrogene movaparvovec were chosen as the participant

population for this study as they are expected to have the most contact with those patients and therefore most likely to be exposed to shed viral vector material.

Blood was chosen in this study as the bodily fluid with which to investigate seroconversion in household contacts of patients who have been dosed with fordadistrogene movaparvovec because it is the most sensitive to detect NAbs.

Banked biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of fordadistrogene movaparvovec research questions and objectives.

4.2.1. Limitations of the Study Design and Methods

Not applicable.

4.3. Justification for Dose

Not applicable.

4.4. End of Study Definition

A participant is considered to have completed the study if they have completed all visits and procedures in the SoA.

The end of the study is defined as the date of study completion for the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Males or females who weigh at least 9 kg.

2. Anticipated to be living or working in the same household (≥10 hours per week and expected to have direct contact) with a patient in one of the fordadistrogene movaparvovec interventional studies (C3391003, C3391002, C3391008, or C3391001) for at least 4 months from the time of the screening visit of this study.

3. The interventional study patient is dosed with IP after the Baseline Visit.

4. Evidence of a signed and dated ICD or assent indicating that the participant (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

5. Willing and able to comply with scheduled visits, laboratory tests, and other study procedures.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Prior treatment with gene therapy utilizing AAV vectors of any serotype.

2. Living or working in a household where 5 other participants are already participating in this study (C3391007).

3. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the Investigator, and their respective family members.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in this study but are not subsequently enrolled in the study.

Screen failure data are collected and remain as source and are not reported to the clinical database.

6. STUDY INTERVENTIONS

In this study, there are no therapeutic study interventions, however the study does involve protocol-required diagnostic or monitoring procedures (study interventions) that are considered to be low risk or burden to the study participant, specifically blood draws.

6.1. Study Intervention(s)

6.1.1. Performance or Administration of Diagnostic or Monitoring Study Interventions

Not applicable.

6.2. Methods to Minimize Bias

To maintain the blinded nature of interventional studies C3391003 and C3391002, all C3391007 study participants and investigators as well as the sponsor will remain blinded to the Cohort assignment of the C3391002 or C3391003 study participant in the same household until C3391003 and C3391002 becomes unblinded. Additionally, the detailed individual results of NAb and ADA to AAV and fordadistrogene movaparvovec vector DNA

will be considered sensitive clinical data and will not be shared with the participants, investigators, or the sponsor until any blinded interventional study that contributes to this study becomes unblinded. Data results from this study of household contacts of DMD patients from the open-label interventional studies C3391008 and C3391001 will not be blinded.

7. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

7.1. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent for disclosure of future information (see Section 7.1.1), no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.1.1. Withdrawal of Consent

Participants should notify the investigator in writing of the decision to withdraw consent for future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal was from study procedures and/or study follow-up, and this information should be entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only in a manner that is in accordance with local law.

7.2. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for/attend a protocol-required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and ascertain whether or not the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD and assent, as appropriate (Section 10.1.3), before performing any protocol-required procedure, in accordance with the site's remote consenting process and guidelines.

Study procedures will be conducted by the home health care vendor at the participant's home, and/or by the investigator via remote communication. Results of any assessments performed by the home health care vendor will be documented by the home health care vendor personnel, (electronically) transferred to the central site, reviewed by the PI or his/her designee, and transcribed to a CRF by study site personnel.

Protocol-required study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Safety issues related to protocol-required procedures should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue from the study.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures (study interventions) are completed as described. However, it is anticipated that there may be circumstances outside the control of the investigator that may make it infeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the

investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

The total blood sampling volume for individual participants in this study is approximately 18 mL. For participants who weigh <20 kg, the expected blood volume is approximately 8 mL.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points and description for all safety assessments (AE collection) are provided in the SoA. Unscheduled clinical laboratory measurements or other safety assessments may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Weight Measurement

Weight will be measured with a standardized, digital scale placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets. Participants should be instructed to step gently onto the scale, place both feet together in the center of the scale and stand straight with eyes directed ahead. Participants should be instructed to stand still and not sway. Measurement will be recorded after the weight has stabilized. Body weight should be reported with precision to one decimal place (eg, 0.1 kg).

8.2.2. Protocol-Required Clinical Safety Laboratory Assessments

Protocol-required clinical safety laboratory assessments will not be performed in this study.

8.2.3. Baseline Characteristics

Demographic information such as year of birth (for the patients of the interventional studies and C3391007 participants), race, ethnicity, gender, and relationship to the interventional study patient will be collected in compliance with local regulations.

At Screening, the average number of hours per week that the participant is in the same room as the interventional study patient will be collected. At Visit 2, the best estimate of number of days of contact (in same room) as the interventional study patient during the first two weeks after administration of IP will be collected.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE, SAE, and Research Related Injury (RRI) can be found in Appendix 2. The investigator is required to assess whether any AE may be related to participation in the study. All AEs (ie, serious and non-serious, including those attributed to a protocol-required procedure identified as RRI) are collected in the clinical study database.

AEs may arise from symptoms or other complaints reported to the Investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) or they may arise from clinical findings of the Investigator or other HCPs (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 6.1).

During the active collection period for safety events (see Section 8.3.1), each participant or parent/legal guardian/legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins at the time that the blood collection is performed at Visits 1, 3, and 4, and ends 2 hours after that procedure/intervention has completed.

The investigator is required to perform appropriate follow-up of each adverse event throughout and after the active collection period and until the AE/SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the NIS AE Report form.

Since there is no product under study, there is no post-study active reporting period for the SAEs to be communicated to Pfizer Safety.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period (see Section 8.3.1) are reported to Pfizer Safety on the NIS AE Report form immediately upon awareness, as indicated in Appendix 2; under no circumstance should the time between awareness and reporting of the SAE exceed 24 hours. The investigator will also submit any updated SAE data to the sponsor within 24 hours of it being available.

Reportable SAEs include events related to an approved, Pfizer product taken by the participant under routine care, during the time they are participating in the study, should such events come to the attention of the Investigator (including an overdose or a medication error that led to the SAE). Refer to Appendix 2 for the definition of an overdose or medication error.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All applicable SAEs and nonserious AEs, as described in Appendix 2, that are directly observed and/or spontaneously reported by the participant during the active collection period (described in Section 8.3.1) will be recorded on the AE page of the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Environmental Exposure

The requirements for reporting pregnancy or breastfeeding and environmental exposure apply throughout the entire active collection period and are outlined below; when such reports are required per protocol, the report must be transmitted to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while taking any Pfizer product under routine care, at any time during the study period (eg, a concomitant medication that is not required by the study protocol); or,
- A male participant uses any Pfizer product under routine care during the study period (ie, a concomitant medication that is not required by the study protocol) and his partner subsequently becomes pregnant; or,
- A female participant is found to be pregnant and is a household contact of a person who received a Pfizer gene therapy (such as fordadistrogene movaparvovec) within 2 months prior to or during pregnancy.

The investigator must report the EDP to Pfizer Safety within 24 hours of the investigator's awareness, whether or not an SAE has occurred.

- The initial information submitted should include the anticipated delivery date of the baby (see below for information related to termination of pregnancy).
- An EDP report is not required if the Pfizer product taken under routine care is specifically approved for use in pregnant women (eg, vitamins) and is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE must be reported along with the EDP.
- The Investigator must report the EDP to Pfizer Safety on the NIS AE Report Form and the EDP Supplemental Form. Relevant details of the exposure and the pregnancy

will be collected from the time informed consent was provided until final study follow-up. If there is an SAE associated with the EDP, then the SAE is reported to Pfizer Safety using the NIS AE Report Form.

Follow-up must be conducted to obtain general information on the pregnancy and its outcome for all EDP reports. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. For a live birth, information regarding the structural integrity of the neonate at the time of birth should be provided. In the event of a termination, the reason(s) for termination should be provided and information regarding the structural integrity of the terminated fetus should be included in the report (if available; not required if pre-procedure test findings were conclusive for a congenital anomaly and those findings are provided in the report).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), then the investigator should follow the procedures for reporting SAEs.

Additional pregnancy outcomes that must be reported to Pfizer Safety as SAEs include:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death may be related to exposure to the Pfizer product used under routine care during the study.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants may be requested to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form.

8.3.5.2. Exposure During Breastfeeding

- An EDB occurs if female participant is found to be breastfeeding while taking any Pfizer product under routine care, at any time during the study period (eg, a concomitant medication that is not required by the study protocol).
- A female participant is found to be breastfeeding while being a household contact of a person who received a Pfizer gene therapy (such as fordadistrogene movaparvovec).

- An EDB report is not required when a Pfizer product specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE must be reported along with the EDB.

The investigator must report an EDB to Pfizer Safety within 24 hours of the investigator's awareness, whether or not an SAE has occurred.

- The investigator must report EDB to Pfizer Safety using the NIS AE Report form.
- If the EDB is associated with a SAE, then the SAE must be reported using the same NIS AE Report form.

8.3.5.3. Environmental Exposure

Not applicable. Environmental or occupational exposure is not reportable in this study since there is no Pfizer product under study.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

In this study, lack of efficacy is reportable to Pfizer Safety for an approved Pfizer product used by the participant under routine care, if the Investigator is made aware.

Lack of efficacy is the failure of expected pharmacologic action or therapeutic benefit. Lack of efficacy should be reported as an SAE to Pfizer Safety if the lack of efficacy involves a vaccine, a contraceptive or a product that is used in the treatment of life-threatening diseases or conditions (eg, anti-infectives) (excluding HIV and cancer).

For Pfizer products that are not covered in paragraph above, lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.4. Treatment of Overdose

Not applicable.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Not applicable.

8.8. Biomarkers

8.8.1. Banked Biospecimens

Biobank specimens will only be drawn in participants who weigh >20 kg.

Banked Biospecimens in this study are:

- 10 mL whole blood Prep B2 sample(s) optimized for serum.

- Banked Biospecimens will be collected as local regulations and IRB/ECs allow.
  - Banked Biospecimens may be used for research related to fordadistrogene movaparvovec and DMD.

- The samples may be analyzed as part of a multistudy assessment of analytes or biomarkers involved in immunity and/or immune response to fordadistrogene movaparvovec or other gene therapies.

- The sponsor will store the Banked Biospecimens in a secure storage space with adequate measures to protect confidentiality. Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying *information* (eg, name, address) will be held at the study site and will not be provided to the sample bank.

- Samples for banking will be stored indefinitely or for another period as per local requirements.

- Details on processes for collection and shipment of these samples can be found in the central laboratory manual.

8.9. Immunogenicity Assessments

8.9.1. Blood Samples for Immunogenicity and Vector DNA Measurement

Blood samples will be collected for analysis of NAb to AAV9 and ADA to AAV9 titers.

Blood samples will also be collected for qPCR analysis of fordadistrogene movaparvovec vector DNA.

Detailed collection, processing, storage, and shipment instructions will be provided in the central laboratory manual.

Samples will be analyzed using validated analytical methods in compliance with Pfizer SOPs.

Lab results will be electronically transferred from the central lab to the Sponsor's database.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There are no hypotheses to be tested.

9.2. Sample Size Determination

Approximately 50 to 250 participants will be enrolled. Table 1 below shows the expected precision, defined as the upper and lower 95% confidence limits, of the estimate of the proportion of participants who are negative for NAb to AAV9 at Baseline and who develop NAb to AAV9 post-Baseline for various numbers of enrolled participants. These calculations assume that 75% of the participants will be seronegative for NAb to AAV9 at Baseline.

Table 1. 95% CI of the Estimate of the Proportion of Participants who are NAb Seronegative to AAV9 at Baseline and who Seroconvert to AAV9 Post-Baseline

	Interventional study patient who received fordadistrogene movaparvovec				Interventional study patient who received placebo			
Total Enrolled in C3391007	N[a]	Number NAb seronegative to AAV9 at Baseline[b]	Percent who seroconvert to AAV9	95%, CI[c]	N[a]	Number NAb seronegative to AAV9 at Baseline[b]	Percent who seroconvert to AAV9	95%, CI[c]
50	33	25	1%	(0, 4.9)	17	13	1%	(0, 6.4)
			5%	(0, 13.5)				
			10%	(0, 21.8)				
			25%	(8.0, 42.0)				
			50%	(30.4, 69.6)				
100	66	50	1%	(0, 3.8)	34	26	1%	(0, 4.8)
			5%	(0, 11.0)				
			10%	(1.7, 18.3)				
			25%	(13.0, 37.0)				
			50%	(36.1, 63.9)				
150	100	75	1%	(0, 3.3)	50	38	1%	(0, 4.2)
			5%	(0.1, 9.9)				
			10%	(3.2, 16.8)				
			25%	(15.2, 34.8)				
			50%	(38.7, 61.3)				
200	133	100	1%	(0, 3.0)	67	50	1%	(0, 3.8)
			5%	(0.7, 9.3)				
			10%	(4.1, 15.9)				
			25%	(16.5, 33.5)				
			50%	(40.2, 59.8)				
250	167	125	1%	(0, 2.7)	83	62	1%	(0, 3.5)
			5%	(1.2, 8.8)				
			10%	(4.7, 15.3)				
			25%	(17.4, 32.6)				
			50%	(41.2, 58.8)				

a. Assumes, on average two thirds of patients are treated with fordadistrogene movaparvovec and one third are treated with placebo across the interventional studies.
b. Assumes 75%, are NAb seronegative at Baseline.
c. Assumes all participants within households and between households are independent.

9.3. Data Management

A Pfizer database will be used, and Pfizer will be responsible for the data management of this study, including quality checking of the data. Details are included in the Data Management Plan.

9.4. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included participant. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents will be collected by both the Home Health Care provider and the Investigator site; data collected on the CRFs must match the source documents.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

9.5. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

For the primary, secondary, and each of the exploratory endpoints listed in Section 3, the proportion (and 95% CI) of C3391007 participants will be estimated for 2 groups of participants:

- fordadistrogene movaparvovec: household contacts of patients in interventional studies C3391002, C3391003, C3391001, and C3391008
- placebo: household contacts of patients in interventional studies C3391002 and C3391003

using generalized estimating equations methods with study as covariate to account for correlated responses within the same household. A binomial distribution with a log link and an exchangeable correlation matrix within each household (ie, between any two members of a household the correlation is the same) will be used. Proportions and 95% confidence intervals will be provided separately for each visit (except for Detectable fordadistrogene

movaparvovec vector DNA in participants who seroconvert via either ADAs or NAbs) and overall at any time during the study.

Incidence of AEs will be summarized/listed.

Pharmacogenomic or biomarker data from banked biospecimens will be collected pursuant to local regulations/IRB during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.6. Interim Analyses

To enable potentially informing participants and investigators of the estimated seroconversion rate as soon as possible, an independent, external team of statistician(s) and programmer(s) will be established to estimate the seroconversion rates. Only summary seroconversion rates will be communicated.

Full reporting of C3391007 will occur when C3391003 and C3391002 have completed the primary analysis; however, the sponsor may analyze the data during the course of the study (eg, for the purpose of regulatory submissions, safety reporting). Section 6.2 includes information for protecting the blind of the interventional studies.

The detailed blinding plan and data dissemination plan will be provided in conjunction with the Statistical Analysis Plan

9.7. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a Data Monitoring Committee.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and

of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Responsible Parties

Contact details and the list of all responsible parties (PI names and site contact information) will be stored in the Pfizer Registry System and will be available upon request.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center. The participant may also be required to provide assent in compliance with local regulations and institutional review board (IRB) requirements.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 1 year from the previous ICD signature date.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not

be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, the participant's current medical record must be available.

Definition of what constitutes source data can be found in the Study Monitoring Plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study site start date is the date on which the clinical study will be open for recruitment of participants study site.

The first act of recruitment is the date of the first study participant's first visit and will be the study start date.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the PI of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical

Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study participants, and the CSA will control as to all other issues.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with a study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with a study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
    - Is associated with accompanying symptoms.
    - Requires additional diagnostic testing or medical/surgical intervention.
    - Leads to a change in the study intervention schedule (outside of any protocol-specified adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
    - Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Research Related Injury

Should a participant, in the investigator's opinion, suffer a medically important research related injury caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately by telephone or email.

A medically important research related injury is any untoward medical occurrence that:

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an injury is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as a research related injury.

- An investigator may be requested by the designated Pfizer clinician or medical monitor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant treatments, vaccines, and/or illnesses must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

- **Definition of Medication Error (for an approved Pfizer product used by the participant under routine care if the Investigator is made aware):**
- A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the healthcare professional, patient, or consumer. Such events may be related to:
    - professional practice,
    - procedures,
    - systems, including:
        - Prescribing
        - Order communication
        - Product labeling, packaging, and nomenclature
        - Dispensing
        - Distribution
        - Administration
        - Education
        - Monitoring

- Use

- Medication errors include near-misses involving or not involving a patient directly or confusion regarding invented names (eg, trade name, brand name).

- **Definition of Overdose**

- An overdose is an administration of a quantity of a medicinal product given per administration or cumulatively that is above the maximum recommended dose according to the authorized product information.

10.2.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting During the Active Collection Period

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the NIS AE Report form to Pfizer Safety throughout the active collection period(s). These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to a Pfizer product used under routine care during pregnancy or breastfeeding.

It should be noted that the NIS AE Report form for reporting of SAE information is not the same as the AE page of the CRF. Wherever the same data or information are to be collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and, when referring to a specific event, the same AE term should be used on both the CRF and the NIS AE Report form.

Safety Event	Record on the CRF	Report on the NIS AE Report Form to Pfizer Safety within 24 hours of awareness
SAE	Any SAE that occurs during the active collection period(s). Any SAE that occurs outside the active collection period(s) that the investigator suspects may be related to the protocol-required procedure/intervention.	Any SAE that the investigator suspects may be related to any Pfizer product used by the participant under routine care during and outside any active collection period.
Non-serious AEs	Any non-serious AE that occurs during the active collection period(s). Any AE that occurs outside the active collection period(s) that the investigator suspects may be related to the protocol-required procedure/intervention.	None
Scenarios involving exposure during pregnancy (EDP) and exposure during breast feeding (EDB).	Instances of EDP or EDB are not captured in the CRF.	All instances of EDP (whether or not there is an associated SAE). * All instances of EDB are reported (whether or not there is an associated AE/SAE). **

***EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the NIS AE Report Form and the EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the NIS AE Report Form.

****EDB** is reported to Pfizer Safety using the NIS AE Report Form, which would also include details of any SAE that might be associated with the EDB.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

- The investigator will then record all relevant AE/SAE information in the CRF.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the NIS AE Report form or the Adverse Event CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between any study intervention (or Pfizer product used under routine care) and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- In making his/her assessment, the investigator will also consult the product information for a marketed Pfizer product used under routine care, if the Investigator is made aware.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedure/intervention, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the NIS AE Report form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

- **SAE Reporting to Pfizer Safety via NIS AE Report Form**

  - Facsimile transmission of the NIS AE Report form is the preferred method to transmit this information to Pfizer Safety.

  - In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the NIS AE Report form sent by overnight mail or courier service.

  - Initial notification via telephone does not replace the need for the investigator to complete and sign the NIS AE Report form pages within the designated reporting time frames.

10.3. Appendix 3: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury (for an approved Pfizer product used by the participant under routine care, if the Investigator is made aware)

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms that the investigator suspects may be due to a Pfizer product used under routine care, then, such LFT results should be managed and followed as described below.

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

        - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.4. Appendix 4: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AAV	adeno associated virus
AAV2	adeno associated virus serotype 2
AAV6	adeno associated virus serotype 6
AAV9	adeno associated virus serotype 9
ADA	anti-drug antibody
AE	adverse event
BLA	Biologics license application
CI	confidence interval
CRF	case report form
CRO	contract research organization
CSA	clinical study agreement
CSR	clinical study report
DCTs	data collection tools
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
EC	ethics committee
GCPs	Good Clinical Practices
GPP	Good Pharmacoepidemiology Practices
GRMD	Golden Retriever Muscular Dystrophy
IB	Investigator's Brochure
ICD	Informed consent document
ICH	International Council for Harmonisation
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IV	intravenously
kg	kilogram
mL	milliliter
N/A	not applicable
NAb	neutralizing antibodies
PI	principal investigator
p.i.	Post-infusion
qPCR	quantitative polymerase chain reaction
rAAV	Recombinant adeno associated virus
RRI	research related injury
SAE	serious adverse event
SAP	statistical analysis plan
SOA	schedule of activities

Abbreviation	Term
SOP	standard operating procedure
SRSD	single reference safety document
US	United States

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