

DRUG: WVE-210201 (suvodirsen)

TRIAL NUMBER(S): WVE-DMDX51-003

PROTOCOL(S) TITLE: A Randomized, Double-blind, Placebo-controlled, Efficacy and Safety Study of WVE-210201 with Open-label Extension in Ambulatory Patients with Duchenne Muscular Dystrophy (DYSTANCE 51)

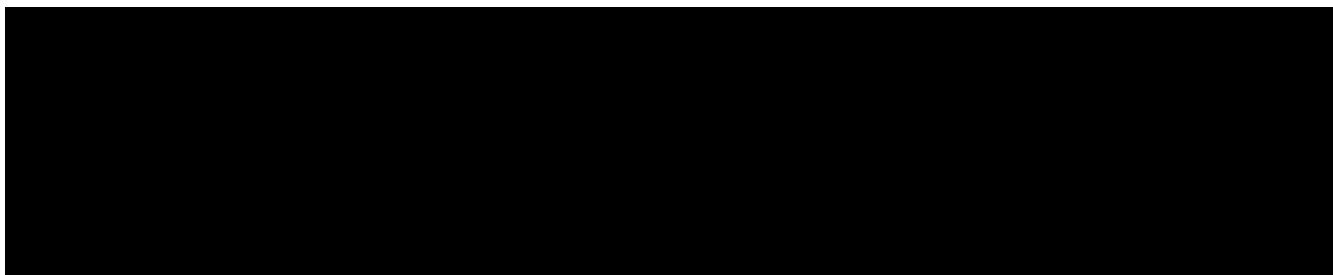
EUDRACT NUMBER, if applicable: #2018-004009-22

SPONSOR: Wave Life Sciences (USA, Inc. and UK Limited, together “Wave Life Sciences”)

ORIGINAL PROTOCOL DATE 15 January 2019

AMENDMENT NUMBER: 2.0

AMENDMENT DATE: 09 July 2019



CLINICAL PROTOCOL APPROVAL FORM

SPONSOR: WAVE LIFE SCIENCES

I have read and understand the contents of this clinical protocol for Study No.

WVE-DMDX51-003 Amendment 2.0 Dated 09 July 2019 and agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.



PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. WVE-DMDX51-003 dated Amendment 2.0 Dated 09 July 2019 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current International Conference on Harmonization guidelines governing Good Clinical Practices, applicable Food and Drug Administration (FDA) regulations, and other local regulatory requirements:

Name of Principal Investigator:

Title:

Institution:

Address:

Phone:

Fax:

Signature

Date

PROTOCOL SYNOPSIS

| | | | |
|---|---|--|---|
| Sponsor: Wave Life Sciences | Investigational Product: WVE-210201 (suvodirsen) | Developmental Phase: Phase 2/3 | EudraCT Number: #2018-004009-22 |
| Title of Study: A Randomized, Double-blind, Placebo-controlled, Efficacy and Safety Study of WVE-210201 with Open-label Extension in Ambulatory Patients with Duchenne Muscular Dystrophy (DYSTANCE 51) | | | |
| Protocol Number: WVE-DMDX51-003 | | | |
| Study Center(s): Up to 50 sites | | | |
| Objectives: Double-blind Treatment Period | | | |
| <p>Primary Objectives</p> <ul style="list-style-type: none"> • To evaluate the efficacy of WVE-210201 by assessing changes in dystrophin levels (United States/Other regions, as applicable) • To evaluate the efficacy of WVE-210201 by assessing changes in motor function by North Star Ambulatory Assessment (NSAA) (European Union [EU]/Japan) | | | |
| <p>Secondary Objectives</p> <ul style="list-style-type: none"> • To evaluate the efficacy of WVE-210201 by assessing changes in upper limb proximal strength • To evaluate the efficacy of WVE-210201 by assessing changes in lower limb motor function • To evaluate the efficacy of WVE-210201 by assessing changes in respiratory function • To evaluate the efficacy of WVE-210201 by assessing changes in stride velocity • To evaluate the safety of WVE-210201 | | | |
| <p>Exploratory Objectives:</p> <ul style="list-style-type: none"> • To evaluate the efficacy of WVE-210201 by assessing changes in quality of life • To assess the pharmacokinetics (PK) of WVE-210201 in plasma • To evaluate the efficacy of WVE-210201 by assessing changes in upper limb function • To evaluate the effect of WVE-210201 on dystrophin protein localization • To evaluate the effect of WVE-210201 on exon-skipping • To evaluate the efficacy of WVE-210201 by assessing changes in cardiac function (by echocardiogram [ECHO]) • To evaluate the efficacy of WVE-210201 by assessing changes in daily activity as measured by a wearable device • To evaluate the efficacy of WVE-210201 by assessing time to milestone events | | | |
| <p>Objective: Open-label Treatment Period</p> <p>To evaluate the long-term efficacy, safety and PK of WVE-210201</p> | | | |

Methodology

This is a Phase 2/3, multicenter, randomized, double-blind, placebo-controlled study with an open-label (OL) extension to evaluate the safety and efficacy of WVE-210201 in ambulatory male pediatric patients with Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping intervention. The study will include a screening period (up to 6 weeks), a double-blind treatment period (48 weeks), an OL treatment period (48 weeks), and a safety follow-up (2 weeks).

Screening evaluations must be completed within 6 weeks of signing the informed consent form (ICF) and these assessments can occur on multiple days, provided they are within the Screening Period. The Investigator will determine whether patients meet eligibility criteria and will collect the demographic and medical data permitting full characterization of the patient. A baseline open muscle biopsy (from deltoid) will be collected at least 2 weeks prior to the Day 1 visit. This will allow full recovery from the surgery prior to obtaining baseline functional assessments (e.g. NSAA). All attempts should be made to complete all screening assessments and confirm patient eligibility for the study prior to muscle biopsy collection to prevent biopsies from being performed on patients not eligible for the study. The time from signing the ICF to Day 1, including screening and open muscle biopsy collection cannot exceed 6 weeks. Patients who screen fail for the first time may be rescreened once.

Double-blind Treatment Period

In the Double-blind Treatment Period, patients will receive weekly intravenous (IV) doses of either placebo or WVE-210201. Patients will be randomized in a 1:1:2:2 ratio to placebo 3 mg/kg, placebo 4.5 mg/kg, WVE-210201 3 mg/kg, and WVE-210201 4.5 mg/kg. Patients must be randomized within 1 day prior to their first dose.

Assessments of safety, efficacy, pharmacokinetics, and immunogenicity will be performed throughout the study.

A second open muscle biopsy (from deltoid) will be collected at 1 of the 3 time points below:

- First 30 patients: Week 12
- Next 40 patients: Week 22
- Remaining patients: Week 46, 2 weeks prior to Week 48 visit.

The biopsy timing facilitates interim analyses of dystrophin; all biopsies will be used in the primary efficacy analysis. The open muscle biopsies will be collected to allow for adequate tissue quantity and quality for analysis of dystrophin related study endpoints via Western blot and other pharmacodynamic assessment methods (e.g. immunohistochemistry, exon skipping via reverse transcription polymerase chain reaction [RT-PCR]).

Functional assessments (performance of upper limb [PUL], NSAA, myometry, timed function tests and pulmonary function tests (peak flow rate [PFR], cough peak flow [CPF], forced vital capacity [FVC])) must be performed pre-dose (on the dosing day or up to 24 hours prior to the respective dosing day). The pediatric quality of life questionnaire will also be completed during this time. The ActiMyo wearable device will be given to patients, and activity data will be collected throughout the study at specified timepoints.

To minimize potential unblinding, functional assessments must be completed by an assessor not involved in administration of study drug or assessment and recording of adverse events (AEs) during the study. The same assessor should perform the functional assessments throughout the study for a given patient to minimize variability of assessments.

After the Week 48 efficacy assessments are completed, all patients will transition to the Open-label (OL) Treatment Period and receive WVE-210201 (further details on OL Treatment Period are described below).

Interim Analyses

The Double-blind Treatment Period includes several planned interim efficacy analyses. Interim analyses of dystrophin will determine if efficacy is demonstrated prior to conclusion of the Double-blind Treatment Period and if adaptations to treatment arm allocation or clinical efficacy analyses are warranted. The first interim dystrophin analysis will compare dystrophin protein levels between WVE-210201 and placebo using the Week 12 open biopsies collected from up to the first 30 patients randomized. The second interim dystrophin analysis will compare dystrophin protein levels between WVE-210201 and placebo from approximately 40 patients using the Week 22 open biopsies. Trial adaptations based on the interim dystrophin results are described in [Section 11.5](#).

The interim dystrophin analyses may serve to provide early evidence of efficacy as established by dystrophin production, which is the expected mechanism of action of WVE-210201. Positive evidence from these interim analyses may support early registration efforts in some regions in consideration of established regulatory policy where increased dystrophin protein levels are accepted as a surrogate endpoint reasonably likely to predict clinical benefit in support of accelerated approval. In the event that either interim dystrophin analysis results in a statistically significant finding in the dystrophin level in favor of WVE-210201, the study will continue and all patients will remain in the Double-blind Treatment Period (up to 48 weeks) to assess clinical outcomes and other endpoints. However, if a futility boundary is crossed at the second interim analysis, the study may be stopped due to lack of efficacy.

Interim analyses of the NSAA endpoint will determine if study enrollment can stop based on the predictive probability of success and will be performed at 4 pre-specified enrollment targets. Historical control datasets will be included in the computation of the predicted probability of success and the NSAA efficacy analysis.

Japanese Pharmacokinetics Cohort:

This is a global study that will include study sites in Japan. The pharmacokinetics of WVE-210201 in Japanese patients will be assessed in patients enrolled at clinical sites in Japan. The first 12 patients enrolled in Japan will be randomized in a 1:1:2:2 ratio to placebo 3 mg/kg, placebo 4.5 mg/kg, WVE-210201 3 mg/kg, and WVE-210201 4.5 mg/kg and undergo intensive PK sampling. Japanese patients in the PK cohort will remain in the clinic for a period of at least 24 hours after the first dose of study drug (WVE-210201 or placebo) or longer, based on the Investigator's judgement.

Enrollment of additional patients at Japanese clinical sites will not occur until 12 patients have completed at least 2 weeks of follow-up, the PK and safety data have been reviewed, and a decision has been made to proceed. The Sponsor will be blinded to the results of these analyses. Patients will be replaced if they drop out before 2 weeks of follow-up.

Except for the intensive PK sampling and additional safety monitoring in the 24-hour period following the first dose of WVE-210201, the schedule of events for the Japanese PK cohort will be the same as for patients not enrolled at Japanese clinical sites, including the biopsy procedures.

Stopping Criteria for Japanese PK Cohort

If any of the stopping criteria, as defined below, are met in the Japanese PK cohort, dosing will be suspended for patients in the Japanese PK cohort and the data will be reviewed by the unblinded Data Monitoring Committee (DMC) to determine whether it is safe to proceed with dosing in the cohort.

- If a single patient experiences a SAE assessed as related to treatment
- If 2 or more patients experience a treatment emergent adverse event (TEAE) graded by the investigator as severe in intensity and assessed as related to treatment.

If a determination is made to resume dosing in the Japanese PK cohort following the review of safety data related to any event(s) that meet the stopping criteria, information will be submitted to the applicable regulatory authorities in Japan in accordance with local regulations prior to restarting treatment. If a decision is made to terminate dosing in the Japanese PK cohort, all Investigators in Japan will be informed immediately.

Open-label Treatment Period

After the Double-blind Treatment Period efficacy assessments are completed pre-dose at Week 48, all patients will transition to the OL Treatment Period and start receiving WVE-210201. Patients randomized to WVE-210201 will continue receiving the dose level administered at the end of the Double-blind Treatment Period. Patients randomized to placebo will be treated at the matching WVE-210201 dose level. Patients will remain blinded to the treatment they received in the Double-blind Treatment Period. Assessments of safety, efficacy, PK, and immunogenicity will be performed during the OL Treatment Period.

At subsequent visits, all functional assessments, PUL, NSAA, myometry, timed function tests, and pulmonary function tests (PFR, CPF, FVC) must be performed pre-dose (on the dosing day or up to 24 hours prior to the respective dosing day). The pediatric quality of life questionnaires will also be completed.

Safety Follow-up

A follow-up call approximately 2 weeks after the last visit will be required to ensure that the patients do not have any AEs/SAEs since their last visit.

Data Monitoring Committee (DMC)

Unblinded safety data will be reviewed periodically and on an ad hoc basis at least until completion of the double-blind treatment period by a DMC. In addition, the DMC will review the results from the planned interim analyses.

Magnetic Resonance Imaging (MRI) Sub-study

A subset of patients at selected sites may be asked to participate in an optional imaging sub-study that will assess cardiac and muscle parameters by MRI. The details will be provided via a separate protocol and patients participating in that study will be consented specifically for the imaging study.

Number of Patients (Planned):

Approximately 150 patients are planned to enroll in this study.

Study Population:

Patients will be randomized to study treatment only if they qualify according to all of the following inclusion and exclusion criteria.

Inclusion Criteria:

1. Patient and/or parent or legal guardian must have the ability and be willing to provide written informed consent prior to any study-related procedures.
2. Diagnosis of DMD based on clinical phenotype with increased serum creatine kinase.
3. Documented mutation in the *Dystrophin* gene associated with DMD that is amenable to exon 51 skipping.
4. Ambulatory male, able to walk independently for at least 10 meters in 10 seconds or less at the time of Screening visit (performed as part of the NSAA)
5. Age of ≥ 5 and ≤ 12 years at time of randomization
6. Willing and able to comply with scheduled visits, drug administration plan, laboratory tests, study restrictions, and all study procedures, including undergoing the biopsy procedures.
7. Stable pulmonary and cardiac function, as measured by:
 - a. Reproducible percent predicted forced vital capacity (FVC) $\geq 50\%$
 - b. Left ventricular ejection fraction (LVEF) $> 55\%$ in patients < 10 years of age and $> 45\%$ in patients ≥ 10 years of age, as measured (and documented) by echocardiogram.
8. Currently on a stable corticosteroid therapy regimen, defined as: initiation of systemic corticosteroid therapy occurred ≥ 6 months prior to Screening, and no changes in dose ≤ 3 months prior to Screening visit.
9. Adequate deltoid muscle at Screening to perform open muscle biopsies
10. Sexually mature males must be willing to use contraception for the duration of the study, if the patient is

sexually active.

11. Patient and caregivers must agree not to post any study-related information on social media.

Exclusion Criteria:

1. Clinically significant medical finding on the physical examination other than DMD that, in the judgment of the Investigator, will make the patient unsuitable for participation in, and/or completion of the study procedures.
2. Other prior or ongoing medical conditions including:
 - a. Acute illness within 4 weeks of the initial Screening visit;
 - b. Abnormal physical findings, other than those associated with musculoskeletal findings attributable to DMD
3. Laboratory abnormality, that, in the Investigator's opinion, could adversely affect the safety of the patient, make it unlikely that the course of treatment or follow-up would be completed, or impair the assessment of study results. These include, but are not limited to:
 - a. Renal insufficiency;
 - b. Impaired hepatic function glutamate dehydrogenase (GLDH) $\geq 2.5 \times$ upper limit of normal (ULN) and bilirubin $\geq 2 \times$ ULN (or International Normalized Ratio [INR] $\geq 1.5 \times$ ULN);
 - c. Activated partial thromboplastin time (aPTT) values above ULN;
 - d. Platelet count $<$ lower limit of normal (LLN).
4. Documented positive hepatitis B surface antigen or hepatitis C antibody test.
5. Known to be positive for human immunodeficiency virus (HIV).
6. Severe mental retardation and/or behavioral problems that, in the opinion of the Investigator, could prohibit participation in this study.
7. Cardiac insufficiency:
 - a. Severe cardiomyopathy that, in the opinion of the Investigator, prohibits participation in this study; however, cardiomyopathy that is managed by ACE inhibitors or beta blockers is acceptable provided the patient meets the LVEF inclusion criterion
 - b. Any other evidence of clinically significant structural or functional heart abnormality
 - c. A cardiac troponin I value >0.2 ng/ml on initial and repeat testing if initial test is elevated at screening.
8. Need for daytime mechanical or non-invasive ventilation OR anticipated need for daytime mechanical or non-invasive ventilation within the next year, in the opinion of the Investigator. Nighttime non-invasive ventilation is permitted.
9. Changes in nutritional or herbal supplements or concomitant medications within 1 month prior to Screening visit or plans to modify (dose or regimen) during the study.
10. Currently on anticoagulants or drugs that are known to significantly increase the risk of bleeding, such as NSAIDs and heparin.
11. Received prior treatment with drisapersen or with an investigational peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO).
12. Received prior treatment with WVE-210201.
13. Received prior treatment with gene therapy for DMD
14. Received treatment with ataluren or eteplirsen within the 14 weeks prior to the planned Baseline biopsy collection.
15. Received any investigational drug within 3 months or 5 half-lives, whichever is longer prior to the planned baseline biopsy collection.
16. Known hypersensitivity to any oligonucleotide, as demonstrated by a systemic allergic reaction such as changes in pulse, blood pressure, breathing function, etc.
17. Parent or legal guardian is directly or indirectly involved in the conduct and administration of this study as an Investigator, sub-investigator, study coordinator, or other study staff member, or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved

directly or indirectly in the study.

Investigational Product, Dose, Route and Regimen:

WVE-210201 will be provided as an isotonic solution for dilution for infusion. WVE-210201 will be administered at 2 dose levels (3 and 4.5 mg/kg). The route of administration will be IV. The infusion should be administered over a minimum of 60 minutes. However, investigators should consider initiating treatment with longer infusion times (i.e., 3 hours) to potentially enhance tolerability.

Reference Therapy, Dose, Route and Regimen:

A matched placebo will be manufactured for use (i.e., solution in an identical single-use vial containing no active ingredient). Placebo will be visually identical in appearance to WVE-210201 and administered as weekly IV in order to maintain the blind. The route of administration will be IV. The infusion should be administered over a minimum of 60 minutes. However, investigators should consider initiating treatment with longer infusion times (i.e., 3 hours) to potentially enhance tolerability.

Study Duration (for an individual patient):

The total study duration per patient is expected to be approximately 104 weeks:

- Screening (Up to 6 weeks)
- Double-blind period (48 weeks)
- OL period (48 weeks)
- Safety follow-up (A follow-up call approximately 2 weeks after the last visit will be required to ensure that the patients do not have any AEs/SAEs since their last visit)

Study Endpoints: The primary and key secondary efficacy endpoints differ by region. All other endpoints are the same across regions.

Double-blind Treatment Period**Primary Efficacy Endpoint**

- Change from baseline in dystrophin level (% normal dystrophin) assessed by Western blot of muscle tissue (United States/Other regions, as applicable)
- Change from baseline in NSAA through 48 weeks (EU/Japan)

Secondary Efficacy Endpoints

- Key secondary endpoint - Change from baseline in NSAA through 48 weeks (United States/Other regions as applicable)
- Key secondary endpoint - Change from baseline dystrophin level (% normal dystrophin) assessed by Western blot of muscle tissue (EU/Japan)
- Change from baseline in upper limb proximal strength assessed by hand held myometry through 48 weeks
- Change from baseline in 4-stair climb (4SC) through 48 weeks
- Change from baseline in the 10-meter walk/run test through 48 weeks
- Change from baseline in FVC (% predicted) through 48 weeks
- Change from baseline in the 95th percentile of stride velocity through 48 weeks

Exploratory Efficacy Endpoints

- Change from baseline in Pediatric Quality of Life Inventory (PedsQLTM)-neuromuscular module at

48 weeks

- Change from baseline in Pediatric Quality of Life Inventory (PedsQLTM)-Generic Core Scale module at 48 weeks
- Change from baseline in individual NSAA items through 48 weeks
- Change from baseline in respiratory function (PFR, CPF) through 48 weeks
- Change from baseline in PUL 2.0 through 48 weeks
- Time to milestone events (loss of ambulation, loss of self-feeding, requirement of daytime ventilation on a regular basis)
- Changes from baseline in daily activity as measured by a wearable device measure

Safety, Pharmacokinetic and Pharmacodynamic Endpoints

- AEs, laboratory values, physical exams and vital signs
- Changes from baseline in cardiac functions by ECHO
- Concentration of WVE-210201 in plasma
- Concentration of WVE-210201 in muscle
- Exon-skipping by RT-PCR in muscle
- Dystrophin localization by immunofluorescence

Open-label Treatment Period

- Long-term efficacy, safety, and PK of WVE-210201

Statistical Methods:

Sample size determination

This study was designed to demonstrate the efficacy of WVE-210201 compared to placebo on a clinical endpoint, NSAA. The sample size determination for the NSAA endpoint was based on the following assumptions:

- Two-sample t-test to test for statistical significance of treatment difference
- 1:1:2:2 placebo 3 mg/kg, placebo 4.5 mg/kg, WVE-210201 3 mg/kg, WVE-210201 4.5 mg/kg randomization ratio
- Standard deviation of change in NSAA from baseline to 48 weeks of 4.5
- Treatment difference of change in NSAA from baseline to 48 weeks of 3.0 between WVE-210201 and placebo
- Dropout rate of 10%
- Two-sided significance level of 5%

With these assumptions, a sample size of 150 patients provides 88% power to detect a difference of 3 in the change in NSAA from baseline to 48 weeks.

The power of the dystrophin endpoint was based on the following assumptions:

- Two-sample t-test to test for statistical significance of treatment difference
- 150 patients randomized 1:1:2:2 placebo 3 mg/kg, placebo 4.5 mg/kg, WVE-210201 3 mg/kg or WVE-210201 4.5 mg/kg
- Standard deviation of change in dystrophin level from baseline to 46 weeks of 3.0%

- Treatment difference of change in dystrophin level from baseline to 46 weeks of 4.0% between WVE-210201 and placebo
- Dropout rate of 10%
- Two-sided significance level of 5%

With these assumptions, the power is greater than 99% to detect a difference of 4% in the change in dystrophin level from baseline to 46 weeks.

Analysis Populations

The primary efficacy analysis population will be the intent-to-treat (ITT) population, which consists of all randomized patients. All patients will be analyzed according to the treatment to which they are randomized.

The safety population will include all randomized patients who have received at least one dose of the study drug. All patients will be analyzed according to the treatment they have actually received.

The pharmacokinetic population will be a subset of the safety population and include subjects with evaluable pharmacokinetics data.

Analysis of Change in Dystrophin Level (% of Normal)

The change in dystrophin level (% of normal) from baseline (primary efficacy endpoint for United States/Other regions; key secondary endpoint for EU/Japan) will be compared between the treatment arms using a Bayesian analysis of covariance model in the ITT population. Treatment comparisons will be performed using random samples generated via Gibbs sampling from the posterior distribution of the treatment effect variables.

Analysis of Change in NSAA

The change in NSAA from baseline through 48 weeks (primary efficacy endpoint for EU/Japan; key secondary endpoint for United States/Other regions) will be compared between the treatment arms using a Bayesian progression model in the ITT population. Treatment comparisons will be performed using random samples generated via Gibbs sampling from the posterior distribution of the treatment effect variables.

Analysis of Other Secondary Efficacy Endpoints

The other secondary endpoints will be analyzed using a Bayesian progression model analogous to that used for the NSAA analysis.

Interim Analyses

The interim analyses will be performed by an independent statistical center and the results will be reviewed by the DMC.

Analysis of Open-label Treatment Period

Extensions to the Bayesian progression model described above will be used to perform efficacy analyses of the extended follow-up in the OL Treatment Period

STUDY CONTACTS

| | |
|----------------------|---|
| Sponsor | Wave Life Sciences USA, Inc (for US) 733 Concord Avenue Cambridge, MA 02138 United States of America Wave Life Sciences UK Limited (for all other Ex-US) Hays Galleria 1 Hays Lane London, SE1 2RD United Kingdom |
| SAE Reporting | <u>North America and rest of the world (unless otherwise mentioned)</u> SAE Hotline: +1 888 483 7729 SAE Fax line: +1 888 529 3580 <u>Europe</u> SAE Hotline: +44 1223 374 240 SAE Fax line: +44 1223 374 102 |

TABLE OF CONTENTS

| | |
|--|-----------|
| Clinical Protocol Approval Form | 2 |
| Principal Investigator's Agreement | 3 |
| Protocol Synopsis | 4 |
| Study Contacts | 12 |
| Table of Contents | 13 |
| List of Tables | 16 |
| List of Abbreviations | 17 |
| 1 Introduction..... | 20 |
| 1.1 Disease Background..... | 20 |
| 1.2 Investigational Product WVE-210201..... | 21 |
| 1.3 Nonclinical Data | 22 |
| 1.4 Clinical Experience | 24 |
| 2 Rationale for the trial | 24 |
| 2.1 Rationale for the Pharmacokinetic Analysis in Japanese Patients | 26 |
| 2.2 Rationale for the Doses and the Dosing Regimen | 26 |
| 2.3 Rationale for the Open-label Treatment Period | 27 |
| 3 Study Objectives | 27 |
| 3.1 Study Objectives-Double-blind Treatment Period | 27 |
| 3.2 Study Objective-Open-label Treatment Period | 28 |
| 4 Study Design..... | 28 |
| 4.1 Study Design Overview..... | 28 |
| 4.1.1 Screening..... | 28 |
| 4.1.2 Double-blind Treatment Period..... | 29 |
| 4.1.3 Open-label Treatment Period | 31 |
| 4.1.4 Discontinuation and Withdrawal | 31 |
| 4.1.5 Safety Follow-up..... | 31 |
| 4.2 Schedule of Assessments..... | 32 |
| 4.3 Study Endpoints | 39 |
| 4.3.1 Double-blind Treatment Period..... | 39 |
| 4.3.2 Open-label Treatment Period | 40 |
| 4.4 Data Monitoring Committee | 40 |
| 5 Patient Selection and Withdrawal Criteria | 40 |
| 5.1 Inclusion Criteria | 41 |
| 5.2 Exclusion Criteria | 41 |
| 5.3 Additional Study Restrictions | 43 |
| 5.3.1 Contraception | 43 |
| 5.3.2 Social Media | 43 |
| 5.4 Withdrawal and Study Treatment Discontinuation | 43 |
| 5.4.1 Withdrawal of Patients from the Study | 43 |
| 5.4.2 Discontinuation of Study Treatment | 44 |
| 5.4.3 Lost to Follow-up | 44 |
| 5.4.4 Replacements..... | 45 |

| | | |
|--------------|---|-----------|
| 6 | Investigational Drug and Placebo | 45 |
| 6.1 | Method of Assigning Patients to Investigational Drug or Placebo..... | 45 |
| 6.1.1 | Double-blind Treatment Period..... | 45 |
| 6.1.2 | Open-label Treatment Period | 45 |
| 6.2 | Dose and Study Drug Administration of Investigational Drug or Placebo | 45 |
| 6.2.1 | Identity of Investigational Drug | 45 |
| 6.2.2 | Administration of Study Drug | 46 |
| 6.2.3 | Monitoring for Infusion-Associated Reactions | 46 |
| 6.2.4 | Monitoring and Criteria for Withholding Study Drug | 47 |
| 6.3 | Management of Clinical Supplies | 49 |
| 6.3.1 | Study Drug Packaging and Storage | 49 |
| 6.3.2 | Investigational Drug Accountability | 50 |
| 6.3.3 | Other Supplies..... | 50 |
| 7 | Blinding Procedures | 50 |
| 7.1 | Blinding..... | 50 |
| 7.2 | Breaking the Blind | 51 |
| 7.2.1 | Unblinding for Medical Emergency:..... | 51 |
| 7.3 | Recording the Unblinding | 51 |
| 8 | Methods of Assessment and Endpoints..... | 51 |
| 8.1 | Safety Assessments..... | 51 |
| 8.1.1 | Medical History and Demographics..... | 52 |
| 8.1.2 | Prior and Concomitant Medications | 52 |
| 8.1.3 | Physical Examination | 52 |
| 8.1.4 | Vital Signs (Blood Pressure, Heart Rate and Temperature) | 53 |
| 8.1.5 | Height and Weight | 53 |
| 8.1.6 | 12-Lead ECG..... | 53 |
| 8.1.7 | Echocardiogram..... | 53 |
| 8.1.8 | Clinical Laboratory Evaluations | 54 |
| 8.2 | Pharmacokinetic Assessments in Japanese PK Cohort Patients | 54 |
| 8.3 | Pharmacokinetic Assessments (Overall)..... | 55 |
| 8.4 | Immunogenicity..... | 55 |
| 8.5 | Pharmacodynamic Assessments | 55 |
| 8.5.1 | Dystrophin Localization | 55 |
| 8.5.2 | Exon 51-Skipped mRNA in Muscle Tissue..... | 55 |
| 8.6 | Muscle Concentration of WVE-210201 | 56 |
| 8.7 | Efficacy Assessments | 56 |
| 8.7.1 | Dystrophin Quantification by Western Blot..... | 56 |
| 8.7.2 | Functional Assessments | 56 |
| 8.7.3 | Quality of Life | 59 |
| 8.7.4 | Milestone Events | 60 |
| 9 | Adverse Events | 60 |
| 9.1 | Eliciting and Documenting Adverse Events | 60 |
| 9.2 | Definitions of Adverse Event Severity and Relationship to Study Drug | 61 |
| 9.2.1 | Severity..... | 61 |
| 9.2.2 | Relationship to Study Drug..... | 61 |

| | | |
|---------------|--|-----------|
| 9.3 | Serious Adverse Events | 62 |
| 9.3.1 | Serious Adverse Event Criteria | 62 |
| 9.3.2 | Suspected, Unexpected Serious Adverse Reaction..... | 63 |
| 9.3.3 | Serious Adverse Event Follow-up..... | 63 |
| 9.3.4 | Serious Adverse Event Reporting..... | 63 |
| 9.4 | Overdose | 64 |
| 10 | Pregnancies..... | 64 |
| 11 | Statistical Methods..... | 64 |
| 11.1 | Sample Size Determination | 64 |
| 11.2 | Disposition of Patients | 65 |
| 11.2.1 | Analysis Populations..... | 66 |
| 11.3 | Statistical Methods..... | 66 |
| 11.3.1 | Study Drug Exposure and Compliance..... | 66 |
| 11.3.2 | Analyses of Efficacy Endpoints..... | 66 |
| 11.3.3 | Multiplicity considerations..... | 70 |
| 11.3.4 | Analysis of Safety Data..... | 70 |
| 11.4 | Analysis of Pharmacokinetic and Pharmacodynamic Variables | 71 |
| 11.4.1 | Pharmacokinetic Analyses | 71 |
| 11.4.2 | Immunogenicity..... | 72 |
| 11.4.3 | Muscle tissue concentration of WVE-210201 | 72 |
| 11.5 | Interim Analyses | 72 |
| 11.5.1 | Dystrophin Interim Analyses | 72 |
| 11.5.2 | NSAA Interim Analyses | 73 |
| 12 | Regulatory, Ethical, and Legal Obligations | 74 |
| 12.1 | Declaration of Helsinki | 74 |
| 12.2 | Good Clinical Practice..... | 74 |
| 12.3 | Institutional Review Boards/Ethics Committees..... | 74 |
| 12.4 | Informed Consent Forms | 74 |
| 12.5 | Minor Assent | 75 |
| 13 | Investigator's Obligations | 75 |
| 13.1 | Confidentiality..... | 75 |
| 13.2 | Investigator Documentation..... | 75 |
| 13.3 | Study Conduct..... | 76 |
| 13.4 | Adherence to Protocol | 76 |
| 13.5 | Adverse Events and Study Report Requirements | 76 |
| 13.6 | Investigator's Final Report | 76 |
| 13.7 | Records Retention | 76 |
| 13.8 | Publications | 77 |
| 14 | Study Committees | 77 |
| 14.1 | Data Monitoring Committee | 77 |
| 14.2 | Clinical Advisory Committee..... | 77 |
| 15 | Study Management..... | 78 |
| 15.1 | Monitoring | 78 |
| 15.1.1 | Monitoring of the Study | 78 |
| 15.2 | Data Quality Assurance..... | 78 |

| | | |
|--------|--|----|
| 15.2.1 | Electronic Case Report Forms and Data Management..... | 78 |
| 15.2.2 | Inspection of Records | 79 |
| 15.3 | Management of Protocol Amendments and Deviations | 79 |
| 15.3.1 | Modification of the Protocol | 79 |
| 15.3.2 | Protocol Deviations | 79 |
| 15.4 | Study Termination | 80 |
| 15.5 | Final Report..... | 80 |
| 16 | References..... | 81 |

LIST OF TABLES

| | | |
|----------|---|----|
| Table 1 | Schedule of Assessments-Double-blind Treatment Period | 33 |
| Table 2 | Schedule of Assessment-Open-label Treatment Period..... | 36 |
| Table 3 | Schedule of Pharmacokinetic Blood Sample Collection for the Japanese PK Cohort-Double-blind Period..... | 38 |
| Table 4 | Schedule of Sparse PK Blood Sample Collection for All Patients-Double-blind Period | 38 |
| Table 5 | Schedule of Sparse PK Blood Sample Collection for All Patients-Open-label Period | 38 |
| Table 6 | Immunogenicity Sample Collection-Double-blind Period | 38 |
| Table 7 | Immunogenicity Sample Collection-Open-label Period | 39 |
| Table 8 | ActiMyo Device Data Collection- Double-blind Treatment Period | 39 |
| Table 9 | Clinical Laboratory Parameters..... | 54 |
| Table 10 | Definitions of AE Severity Criteria | 61 |
| Table 11 | Guidelines for Determining the Relationship (if any) Between Adverse Event and the Study Drug..... | 62 |
| Table 12 | Pharmacokinetic Parameters..... | 72 |

LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|--------------|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| aPTT | activated partial thromboplastin time |
| ASO | antisense oligonucleotide |
| AST | aspartate aminotransferase |
| AUC | area under the plasma concentration-time curve |
| BMD | Becker muscular dystrophy |
| C_0 | initial concentration at time 0 for bolus iv administration |
| CFR | Code of Federal Regulations |
| C_{\max} | maximum plasma concentration |
| CNS | central nervous system |
| CPF | cough peak flow |
| CRF | case report form |
| CSR | clinical study report |
| DMC | data monitoring committee |
| DMD | Duchenne muscular dystrophy |
| DNA | deoxyribonucleic acid |
| EC | ethics committee |
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| EDC | electronic data capture |
| EF | emotional functioning |
| EOI | end of infusion |
| ET | early termination |
| EU | European Union |
| FVC | forced vital capacity |
| GCP | Good Clinical Practice |
| GLDH | glutamate dehydrogenase |
| HED | human equivalent dose |
| HIV | human immunodeficiency virus |
| hsCRP | high-sensitivity C-reactive protein |

| Abbreviation | Definition |
|--------------|--|
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| INN | International Nonproprietary Name |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| IV | intravenous |
| IXRS | interactive voice/web response system |
| LLN | lower limit of normal |
| LVEF | left ventricular ejection fraction |
| MedDRA | The Medical Dictionary for Regulatory Activities |
| MMRM | mixed model for repeated measures |
| mRNA | messenger ribonucleic acid |
| NCA | noncompartmental PK analysis |
| NOAEL | no observed adverse effect level |
| NSAA | North Star Ambulatory Assessments |
| OL | Open-label |
| PBMC | peripheral blood mononuclear cells |
| PedsQL-GCS | Pediatric Quality of Life Inventory-Generic Core Scale |
| PedsQL-NMM | Pediatric Quality of Life Inventory-Neuromuscular Module |
| PF | physical functioning |
| PFR | peak flow rate |
| PK | pharmacokinetic |
| PMO | phosphorodiamidate morpholino oligomer |
| PS | phosphorothioate |
| PT | Prothrombin time |
| PUL | Performance of Upper Limb |
| RBC | red blood cell |
| RNA | ribonucleic acid |
| RSI | reference safety information |
| RT-PCR | reverse transcription polymerase chain reaction |

| Abbreviation | Definition |
|---------------------|---|
| SAD | single ascending dose |
| SAE | serious adverse event |
| SCF | school functioning |
| SDH | sorbitol dehydrogenase |
| SOC | system organ class |
| SOF | social functioning |
| SOP | Standard Operating Procedure |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TK | toxicokinetics |
| TLC | total lung capacity |
| ULN | upper limit of normal |
| WBC | white blood cell |

1 INTRODUCTION

1.1 Disease Background

Duchenne muscular dystrophy (DMD) is a fatal, progressive, genetic neuromuscular disease that affects approximately one in 5,000 males born worldwide; it is the most common type of childhood muscular dystrophy¹⁻³. Patients with DMD typically present with initial symptoms around 2.5 years of age and are diagnosed at approximately 5 years of age⁴. Progressive muscle degeneration eventually leads to loss of ambulation in most patients by 10 to 12 years of age^{5, 6, 7}. As the disease progresses, DMD patients develop respiratory, orthopedic, and cardiac complications⁶⁻⁸. In the absence of an intervention, patients typically die from respiratory failure or cardiac complications in their mid-20's^{9, 10}. With supportive care, such as corticosteroid use, ventilatory assistance, and scoliosis surgery, life expectancy in DMD patients may be extended to approximately 30 years of age¹¹.

Duchenne muscular dystrophy is an X-linked genetic disorder caused by mutations in the dystrophin-encoding *DMD* gene^{12, 13}. Normal dystrophin protein is part of a protein complex called the dystrophin-glycoprotein complex, which provides structural stability to skeletal muscle and protects the muscle from injury during contraction and relaxation^{14, 15}. In addition, dystrophin is essential for cell survival via a transmembrane signaling function and modulation of vasomotor response to physical activity¹⁵. Mutations in the form of large deletions (one or more exons) account for approximately two-thirds of all *DMD* mutations; the remaining mutations are due to duplications and small deletions, insertions, point mutations, or splicing mutations¹⁶. Deletions, which are typically clustered in a hotspot region between exons 45 and 55, disrupt the open reading frame and prevent translation of dystrophin¹⁷. Mutations in the *DMD* gene that are amenable to exon 51 skipping occur in approximately 13% of patients with DMD¹⁸, the population that might benefit from exon 51 skipping ASOs. These patients might potentially benefit from WVE-210201. Absent or defective dystrophin protein, resulting from *DMD* gene mutations, disrupts the dystrophin glycoprotein complex, leading to increased muscle membrane fragility, chronic muscle damage, inflammation, replacement of muscle fibers with fat and fibrotic tissue, and then loss of muscle function^{6, 7, 19}.

Exon-skipping technology has the potential to induce the cellular machinery to ‘skip over’ a targeted exon and restore the reading frame, resulting in the production of internally truncated, but functional, dystrophin protein^{20, 21}. Using this mechanism, WVE-210201 is being developed as a disease-modifying agent for the treatment of patients with DMD. It is an antisense oligonucleotide (ASO) intended to target human *dystrophin* pre-messenger ribonucleic acid (mRNA) in order to induce exon 51 skipping and dystrophin protein restoration. This therapeutic approach may slow disease progression by converting severe DMD symptoms to the milder symptoms such as those seen in patients with Becker muscular dystrophy (BMD), in which patients are ambulatory longer and have a longer life expectancy^{22, 23}.

Limited therapeutic options are available for patients with DMD. In the EU, there is currently one approved therapy indicated for the treatment of DMD. Ataluren is a small molecule intended to enhance ribosomal read-through of nonsense mutations. It received conditional marketing

approval in the EU for the treatment of DMD resulting from a nonsense mutation (premature stop codon) in the *DMD* gene in ambulatory patients aged 2 years and older. Its efficacy was not established in non-ambulatory patients and additional evidence regarding ataluren's clinical effect is required in order to support its continued approval in the EU. Approximately two-thirds of patients with DMD have a deletion as the underlying mutation in the *DMD* gene²⁴. When considering patients with a mutation amenable to exon 51 skipping, an estimated 0.3% possess what is known as a "small mutation," of which approximately 60% involve a nonsense point mutation that might be amenable to ribosomal read-through technology given the introduction of a translational truncation codon²⁴. It is anticipated that ataluren's use would be limited to a small fraction of the DMD population in consideration of the low prevalence of nonsense mutations and its limited indication for ambulatory patients.

Eteplirsen is an ASO of the phosphorodiamidate morpholino oligomer (PMO) subclass intended to increase dystrophin production via exon 51 skipping¹⁴. Eteplirsen was approved in the US for the treatment of patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping. Approval was based on detection of an average dystrophin protein level of 0.93% of the dystrophin level in normal muscle and a median increase in truncated dystrophin expression of 0.1%, in the only study where an estimate of dystrophin expression in response to eteplirsen treatment was possible²⁵. The clinical benefit of eteplirsen has not yet been established²⁵.

Deflazacort (EMFLAZA) is a corticosteroid shown to improve muscle strength (mean change 0.15 points as measured by the modified Medical Research Council scale) following a 12-week treatment period at a dose of 0.9 mg/kg/day²⁶. Corticosteroids are commonly used in DMD patients to slow the decline in muscle strength, as well as to prolong ambulation and respiratory function^{5,8}. However, the chronic use of corticosteroids has been associated with serious side effects such as immunosuppression and increased risk of infection, changes in endocrine function, hypertension, cataracts, bone demineralization, gastrointestinal perforation, and growth retardation in children^{6,7}. Further, corticosteroids do not correct the underlying genetic defect in DMD.

Given the limitations of available therapies indicated for DMD, patients may benefit from an alternative treatment that can provide an increase in dystrophin protein production, and, therefore, be more likely to provide a long-term clinical benefit.

1.2 Investigational Product WVE-210201

WVE-210201 is an ASO intended to target human *Dystrophin* pre-mRNA in order to induce exon 51 skipping and dystrophin protein restoration.

WVE-210201 is an oligonucleotide. Oligonucleotides are a type of nucleic acid molecule assembled from chemically modified, RNA and/or deoxyribonucleic acid (DNA) mononucleotide building blocks. The potential therapeutic uses of oligonucleotides include modulating the function of target RNAs to affect the production of disease-associated proteins. The phosphorothioate (PS) modification, one of the most common backbone modifications used in oligonucleotides, results from substitution of a sulfur atom for a non-bridging oxygen atom in

a phosphodiester group of the backbone of the molecule^{27,28}. These modifications improve the stability of oligonucleotides against nuclease-mediated degradation and enhance their protein binding interactions to facilitate biodistribution, cellular uptake, and trafficking²⁹⁻³². A consequence of incorporation of PS modifications in an oligonucleotide is the introduction of a chiral center at each phosphorus atom associated with that modification, with either an “Sp” or “Rp” configuration, typically represented in similar proportions as a diastereomeric mixture in the product³³⁻³⁵. Previous work has demonstrated that individual PS oligonucleotide diastereoisomers display different biological properties³⁶. A conventional, fully PS-modified oligonucleotide (20 nucleotides in length, 19 PS modifications) is a mixture of 524,288 diastereoisomers (2^{19}), each having the same nucleotide sequence but differing in the stereochemistry along its backbone, resulting in heterogeneous and uncontrolled pharmacologic properties.

The Sponsor has developed proprietary technology that enables the synthesis of PS modified nucleic acid therapeutics in which stereochemistry at each PS position is precisely controlled, resulting in stereopure ASOs.

1.3 Nonclinical Data

To support clinical development to date, WVE-210201 has been evaluated in GLP single and repeat-dose toxicity studies conducted in CD-1 mice and cynomolgus monkeys, in vitro genotoxicity assays, an in vivo genotoxicity study, and safety pharmacology studies.

Based on the results of the nonclinical studies, WVE-210201 has an acceptable benefit risk profile for further investigation as a disease-modifying agent for the treatment of patients with DMD. In vitro pharmacology studies of WVE-210201 demonstrated efficient exon 51 skipping and dystrophin protein expression in patient-derived myoblasts with mutations amenable to exon 51 skipping ($\Delta 48-50$ and $\Delta 52$). This observed exon skipping was more efficient than what was seen with comparator exon 51 skipping ASOs (WV-942, a 2'-O-methyl modified oligonucleotide with a uniform stereorandom PS backbone), and WV-8806 (PMO). In vivo target engagement was demonstrated with WVE-210201 or a stereopure murine surrogate in nonclinical studies in healthy monkeys and in the *mdx23* model of DMD. Evidence of target engagement was seen in normal, healthy muscle in cynomolgus monkeys with intact cellular architecture. The toxicokinetics (TK) and distribution of WVE-210201 were evaluated in mice and monkeys and in both species, exposure (as measured by area under the plasma concentration-time curve [AUC] and initial concentration at time 0 for bolus intravenous (IV) administration [C_0] or maximum observed concentration [C_{max}]) was generally dose-dependent across the doses evaluated. The distribution of WVE-210201 in an *mdx* mouse model was evaluated to better understand how WVE-210201 is distributed in dystrophin-deficient muscle given the known differences in permeability as compared with normal muscle³⁷. There was no apparent accumulation following repeat-dose administration and no consistent gender differences in mouse or monkey. WVE-210201 is likely eliminated in a biphasic manner.

WVE-210201 was detected in skeletal muscle, heart and diaphragm as well as the liver and kidney postdose in *mdx* mice, CD-1 mice, and cynomolgus monkey after single and repeat dose administration. Concentrations of WVE-210201 decreased in all tissues in animals at the

recovery time point after cessation of dosing, and levels were mostly below the limit of detection.

The primary findings associated with WVE-210201 include renal and liver findings in mice and monkeys. Transient, non-adverse changes in coagulation parameters in both species were observed. Transient, pro-inflammatory effects were noted, and included non-adverse complement and/or cytokine activation in monkeys, and non-adverse inflammatory cell infiltrates in multiple tissues in both species. In addition, reversible minimal to mild inflammation at the injection site was noted microscopically in both species.

Findings in the kidney in both species were noted following repeat doses of WVE-210201. In mice, the adverse finding of glomerulopathy was noted following 14 weekly doses at ≥ 100 mg/kg and was associated with decreased albumin. There was an increased incidence in glomerulopathy after the 13-week recovery period. Glomerulopathy was not observed after single doses in mice, lower doses (≤ 30 mg/kg) in mice over 26 weeks, or in monkeys following biweekly doses of WVE-210201 for 13 weeks in association with complement activation. Microscopic changes in the kidneys of monkeys were minimal to moderate tubular epithelial single cell necrosis, basophilic tubules, and tubular hyperplasia at 30 and 50 mg/kg/week, which were associated with increased creatinine levels. In addition, minimally increased mitotic figures, minimal to mild hemorrhage within tubular lumens, and minimal karyomegaly at 30 and 50 mg/kg/week were noted. Based on the recovery of the microscopic findings and the relatively mild increase in serum creatinine these findings in monkeys were not considered adverse. However, the findings in mice and monkeys taken together indicate that WVE-210201 may have some potential for nephrotoxicity; therefore, kidney function will be monitored in the clinical setting.

Findings in the liver were observed following single or repeat doses and included increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in both species, and sorbitol dehydrogenase (SDH) in mice. In mice only, minimal to mild hepatocellular necrosis was noted after repeated doses at ≥ 100 mg/kg. These liver changes were associated with increases in liver function tests and were fully reversible 13 weeks after dosing concluded. No alterations in serum chemistry liver parameters or histopathological findings were observed in the chronic mouse toxicity study at lower doses (27 weekly doses of 10, 20, and 30 mg/kg), suggesting a dose threshold for liver findings in the mouse (≥ 100 mg/kg) with repeat dosing.

Increases in complement factors C3a and Bb were observed in monkeys in both the single and repeat-dose studies (WIL-469510 and WIL-469511, respectively). In the single-dose study, increases in C3a and Bb were observed at all three doses (mean C3a increases up to 175-fold and mean Bb increases up to 19-fold as compared to control). In addition, one animal at the high dose (75 mg/kg infused over 30 minutes) was euthanized in extremis, likely due to complement-mediated toxicity. Monkeys have been shown to have increased sensitivity to complement activation as compared to other species, including humans³⁸. Non-adverse transient changes in coagulation parameters (activated partial thromboplastin time [aPTT] and prothrombin time [PT]) were also noted in monkeys following single and repeat doses, and minimal increases in

aPTT were observed in mice after repeat doses. Both rodents and monkeys are known to be sensitive to sequence-independent effects of ASOs³⁹.

In addition, minimal to mild inflammation at the injection site was noted microscopically in mice (repeat-dose studies of 13- and 26-weeks) and monkeys (single-dose study only), which was reversible in all animals, and was considered adverse in mice only, following repeat doses of ≥ 100 mg/kg. These injection site findings are common with IV administration of a large molecular weight test article to mice, such as an oligonucleotide, and the incidence and severity did not increase with longer periods of repeat dosing (i.e. the 26-week chronic study in mice) as expected⁴⁰. This finding was not observed in the 13-week repeat-dose study in monkeys. Transient, pro-inflammatory effects were noted, and included non-adverse complement and/or cytokine activation in monkeys, and non-adverse inflammatory cell infiltrates in multiple tissues in both species.

WVE-210201 was not associated with genotoxicity, or adverse cardiovascular, respiratory, or central nervous system (CNS) changes as measured in safety pharmacology studies, or off-target effects via hybridization to the human genome. In vitro, WVE-210201 did not activate toll-like receptor 9 (TLR9) in human reporter cells or increase pro-inflammatory cytokines in human peripheral blood mononuclear cells (PBMCs). WVE-210201 demonstrated minimal potential for thrombocytopenia, which is a recognized toxicity of PS oligonucleotides^{39,41,42}. While decreases in platelets in mice were observed, these were transient and not of the magnitude considered to constitute thrombocytopenia.

In summary, WVE-210201 has the potential to be an effective disease-modifying treatment with a manageable safety profile, to address the significant unmet need experienced by patients with DMD. Primary findings associated with WVE-210201 in the nonclinical studies are monitorable in the clinical setting via frequent laboratory sampling and careful clinical observation of patients during and after infusion. Please refer to the [Investigator's Brochure](#) for further details.

1.4 Clinical Experience

All 36 patients in the first-in-human (FIH) Phase 1 clinical study have completed the study and results have been finalized. Analyses of safety and plasma exposure data along with review of preclinical in vivo target engagement studies have led to the selection of two doses (3 and 4.5 mg/kg), to be evaluated further in repeat-dose studies. Please refer to the [Investigator's Brochure](#) for further details.

An open-label (OL) extension (WVE-DMDX51-002) to the Phase 1 study with WVE-210201 is presently ongoing to further assess the safety of WVE-210201 and to provide long-term treatment for patients. Please refer to the [Investigator's Brochure](#) for further details.

2 RATIONALE FOR THE TRIAL

Duchenne muscular dystrophy is caused by mutations (commonly deletions) in the dystrophin gene which lead to the absence of, or significant deficiency in, dystrophin protein. The lack of functional dystrophin protein results in progressive muscle weakness and a corresponding loss of

muscle function. Given its role in the pathology of DMD, measurement of dystrophin protein provides a meaningful pharmacodynamic marker for assessment of response to treatment and the potential for clinical benefit.

All 36 patients in the first-in-human (FIH) Phase 1 clinical study have completed the study and data have been finalized. Analyses of safety and plasma exposure data along with review of preclinical in vivo target engagement studies have led to the selection of two doses (3 and 4.5 mg/kg), to be evaluated further in repeat-dose studies.

Given the expected mechanism of action of WVE-210201, the change from baseline in dystrophin production as measured by Western blot is a primary endpoint for the US and a secondary endpoint in other regions. At Baseline, an open biopsy from the deltoid muscle will be performed per local standard of care. Baseline biopsies will be collected at least 2 weeks prior to the study start to allow some healing prior to functional assessments. The open muscle biopsy will allow for adequate tissue quantity and quality for analysis via Western blot and other pharmacodynamic assessment methods (e.g., immunohistochemistry, reverse transcription polymerase chain reaction [RT-PCR]) at Baseline and post-baseline.

In the EU and Japan, the North Star Ambulatory Assessment (NSAA), a validated instrument to assess functional status, will be used as the primary efficacy endpoint in accordance with regional-specific regulatory guidelines. Therefore, the study will be powered to test for a meaningful effect on this endpoint, in an effort to establish clinical benefit and correlate clinical outcomes with increased dystrophin production.

This Phase 2/3 study includes several planned interim efficacy analyses. Interim analyses of dystrophin will determine if efficacy is demonstrated prior to study conclusion and if adaptations to treatment arm allocation or clinical efficacy analyses are warranted. In the event that an interim dystrophin analysis results in a statistically significant finding in the dystrophin level in favor of WVE-210201, the study will continue and patients will remain in the Double-blind Treatment Period (up to 48 weeks) to assess clinical outcomes and other endpoints.

The lower age requirement (5 years) was chosen to ensure that patients would be definitively diagnosed with DMD and able to comply with required clinical assessments and testing procedures. While patients may first exhibit symptoms at 2.5 years, many are not diagnosed until 5 years of age⁴. In addition, the use of corticosteroids prior to this age is less common and varies greatly by region, impacting the ability to control for this important concomitant medication in this global study. It is known that progressive muscle degeneration in DMD eventually leads to loss of ambulation in most patients by 10 to 12 years of age⁵. Pathologically, the myofiber breakdown, necrosis and inflammation that results from the lack of dystrophin production in DMD gives rise to tissue fibrosis and fat cell replacement⁴³. The Sponsor is proposing to identify a homogenous population of patients for this efficacy and safety study with the intention of enrolling patients aged 5 to 12 years who may putatively have a more limited extent of tissue destruction, thereby maximizing the likelihood that they may benefit from treatment and reducing variability.

Other important outcome assessments in DMD, such as respiratory function tests, muscle function and strength tests, including timed function tests, will be included as additional secondary endpoints.

2.1 Rationale for the Pharmacokinetic Analysis in Japanese Patients

DMD is an orphan disease with an estimated prevalence of <1 in 10,000 persons in Japan⁴⁴. There are currently no approved therapies in Japan and a significant unmet medical need exists for effective treatments for patients with DMD. In an effort to address this critical unmet need, the Sponsor wishes to enroll patients in Japan in the global Phase 2/3 study of WVE-210201 to potentially expedite development and drug accessibility in Japan.

This is a global study that will include study sites in Japan. The PK of WVE-210201 in Japanese patients will be assessed in patients enrolled at clinical sites in Japan. The first 12 patients enrolled in Japan will be randomized in a 1:1:2:2 ratio to placebo 3 mg/kg, placebo 4.5 mg/kg, WVE-210201 3 mg/kg, and WVE-210201 4.5 mg/kg and undergo intensive PK sampling. Enrollment of additional patients at Japanese clinical sites will not occur until the 12 patients have completed at least 2 weeks of follow-up, the PK and safety data have been reviewed, and a decision has been made to proceed.

2.2 Rationale for the Doses and the Dosing Regimen

Two doses, 3 and 4.5 mg/kg were selected based on in vitro and in vivo pre-clinical studies, tolerability profiles in Phase 1, and the safety margin provided by toxicity studies. Based on in vitro and in vivo nonclinical studies, target engagement is expected at both 3 and 4.5 mg/kg in DMD patients. The extrapolation was based on patient plasma concentrations, muscle to plasma ratios in monkeys, differences between healthy and diseased muscle³⁷, and the measured exon skipping in monkeys. The muscle concentrations in DMD patients were predicted to be approximately 0.05 to 0.43 µg/g at 4.5 mg/kg following single-dose. However, it has been demonstrated that oligonucleotides have 4- to 10-fold higher distribution in DMD muscles as compared to normal muscles³⁷. This potential for increased penetration, due to greater permeability of the cell membrane as compared to healthy cynomolgus monkeys with intact muscle tissue integrity, should result in greater target engagement in DMD patients. Therefore, by applying these correction factors, it is anticipated that WVE-210201 concentrations following repeat administration of 4.5 mg/kg would be approximately 0.19 to 1.73 µg/g (4-fold) or 0.47 to 4.31 µg/g (10-fold). Similarly, the concentration at 3 mg/kg would be estimated at 0.13 to 1.2 µg/g (4-fold) or 0.31 to 2.9 µg/g (10-fold). The projected muscle concentrations in DMD patients at 3 and 4.5 mg/kg are similar to or above the ranges at which exon skipping was observed in the monkey and suggest that doses of 3 mg/kg and 4.5 mg/kg in patients with DMD would be predicted to lead to the tissue concentrations needed to engage the target. Due to the semi-quantitative nature of exon skipping measurement, the translation of target engagement to dystrophin protein restoration and to clinical efficacy is to be determined.

Based on Phase 1 tolerability profiles, both 3 and 4.5 mg/kg dose levels are anticipated to be generally well tolerated.

Findings in toxicology studies as well as in the human experience to date are readily monitorable in patients. This study includes weekly renal and hepatic monitoring. Specifically, weekly renal monitoring includes proteinuria, urine RBC and WBC, and serum cystatin C. If urine protein is >0.2 g/L then the dose should be held and 24-hour urine monitoring performed weekly until it returns to the normal range. Evaluation of coagulation parameters is also performed regularly.

2.3 Rationale for the Open-label Treatment Period

This OL treatment period is being conducted to evaluate the long-term safety, tolerability and efficacy of weekly IV doses of WVE-210201 over an additional 48 weeks. All patients who successfully complete the double-blind period of the study WVE-DMDX51-003 will receive treatment with WVE-210201 in the OL treatment period.

3 STUDY OBJECTIVES

3.1 Study Objectives-Double-blind Treatment Period

Primary Objectives

- To evaluate the efficacy of WVE-210201 by assessing changes in dystrophin levels (United States/Other regions as applicable)
- To evaluate the efficacy of WVE-210201 by assessing changes in motor function by North Star Ambulatory Assessment (NSAA) (EU/Japan)

Secondary Objectives

- To evaluate the efficacy of WVE-210201 by assessing changes in upper limb proximal strength
- To evaluate the efficacy of WVE-210201 by assessing changes in lower limb motor function
- To evaluate the efficacy of WVE-210201 by assessing changes in respiratory function
- To evaluate the efficacy of WVE-210201 by assessing changes in stride velocity
- To evaluate the safety of WVE-210201

Exploratory Objectives:

- To evaluate the efficacy of WVE-210201 by assessing changes in quality of life
- To assess the PK of WVE-210201 in plasma
- To evaluate the efficacy of WVE-210201 by assessing changes in upper limb function

- To evaluate the effect of WVE-210201 on dystrophin protein localization
- To evaluate the effect of WVE-210201 on exon-skipping
- To evaluate the efficacy of WVE-210201 by assessing changes in cardiac function (by echocardiogram [ECHO])
- To evaluate the efficacy of WVE-210201 by assessing changes in daily activity as measured by a wearable device
- To evaluate the efficacy of WVE-210201 by time to milestone events

3.2 Study Objective-Open-label Treatment Period

- To evaluate the long-term efficacy, safety and PK of WVE-210201

4 STUDY DESIGN

4.1 Study Design Overview

This is a Phase 2/3, multicenter, randomized, double-blind, placebo-controlled study with an OL extension, to evaluate the safety and efficacy of WVE-210201 in ambulatory male pediatric patients with DMD amenable to exon 51 skipping intervention.

The study will include a screening period (up to 6 weeks), a double-blind treatment period (48 weeks), an OL treatment period (48 weeks), and a safety follow-up.

4.1.1 Screening

Screening evaluations must be completed within 6 weeks of signing the informed consent form (ICF) and these assessments can occur on multiple days, provided they are within the Screening Period. The Investigator will determine whether patients meet eligibility criteria and will collect the demographic and medical data permitting full characterization of the patient. Patients who screen fail may be rescreened once.

A record of patient screen failures will be maintained for patients who do not qualify for enrollment, including the reason for the failure. A baseline open muscle biopsy (from deltoid) will be performed at least 2 weeks prior to the Day 1 visit. This will allow full recovery from the surgery prior to obtaining baseline functional assessments. All attempts should be made to complete all screening assessments and confirm patient eligibility for the study prior to muscle biopsy collection to prevent biopsies from being performed on patients not eligible for the study. The time from signing the ICF to Day 1, including screening and open muscle biopsy collection cannot exceed 6 weeks.

4.1.2 Double-blind Treatment Period

In the Double-blind Treatment Period, patients will receive weekly intravenous (IV) doses of either placebo or WVE-210201. Patients will be randomized in a 1:1:2:2 ratio to placebo 3 mg/kg, placebo 4.5 mg/kg, WVE-210201 3 mg/kg, and WVE-210201 4.5 mg/kg. Patients must be randomized within one day prior to their first dose. Safety and efficacy assessments will be performed over the course of study. All functional assessments, performance of upper limb (PUL), NSAA, myometry, timed function tests, and pulmonary function tests (peak flow rate [PFR], cough peak flow [CPF], and forced vital capacity [FVC]) and completion of the Pediatric Quality of Life questionnaires must be done pre-dose (on the dosing day or up to 24 hours prior to respective dosing day). The ActiMyo wearable device will also be given to patients, and activity data will be collected throughout the study at specified timepoints. To minimize the potential unblinding, functional assessments must be completed by an assessor not involved in administration of study drug or assessment and recording of AEs during the study. The same assessor should perform the functional assessments throughout the study for a given patient to minimize variability of assessments.

A second open muscle biopsy (deltoid) will be collected at 1 of 3 timepoints mentioned below:

- First 30 patients: Week 12
- Next 40 patients: Week 22
- Remaining patients: Week 46, 2 weeks prior to Week 48 visit.

The biopsy timing facilitates interim analyses of dystrophin; all biopsies will be used in the primary efficacy analysis. The open muscle biopsies will be collected to allow for adequate tissue quantity and quality for analysis of dystrophin-related study endpoints via Western blot analysis (dystrophin protein level), and other pharmacodynamic assessment methods (e.g., dystrophin localization by immunohistochemistry, exon skipping via RT-PCR).

In addition, pharmacokinetics of WVE-210201 will be determined. Immunogenicity analysis will also be performed.

Patients and parents will be asked to complete the quality of life questionnaires as applicable.

This Phase 2/3 study includes several planned interim efficacy analyses. Interim analyses of dystrophin will determine if efficacy is demonstrated prior to study conclusion and if adaptations to treatment arm allocation or clinical efficacy analyses are warranted. Interim analyses of the NSAA endpoint will determine if study enrollment can stop based on the predictive probability of success and will be performed at 4 pre-specified enrollment targets. Historical control datasets will be included in the computation of the predicted probability of success and the NSAA efficacy analysis. [Section 11.3.2](#) and [Section 11.5](#) include additional details on the interim analyses and the statistical methods planned.

After the Week 48 efficacy assessments are done pre-dose, all patients will transition to the OL treatment period and receive WVE-210201 (further details in [Section 4.1.2](#)).

The interim dystrophin analyses may serve to provide early evidence of efficacy as established by dystrophin production, which is the expected mechanism of action of WVE-210201. Positive evidence from these interim analyses may support early registration efforts in some regions in consideration of established regulatory policy where increased dystrophin protein levels are accepted as a surrogate endpoint reasonably likely to predict clinical benefit in support of accelerated approval. In the event that either interim dystrophin analysis results in a statistically significant finding in the dystrophin level in favor of WVE-210201, the study will continue and all patients will remain in the Double-blind Treatment Period (up to Week 48) to assess clinical outcomes and other endpoints. However, if a futility boundary is crossed at the second interim analysis, the study may be stopped due to lack of efficacy.

Japanese PK Cohort:

This is a global study that will include study sites in Japan. The PK of WVE-210201 in Japanese patients will be assessed in patients enrolled at clinical sites in Japan. The first 12 patients enrolled in Japan will be randomized in a 1:1:2:2 ratio to placebo 3 mg/kg, placebo 4.5 mg/kg, WVE-210201 3 mg/kg, and WVE-210201 4.5 mg/kg and undergo intensive PK sampling. After the first dose of study drug (WVE-210201 or placebo), Japanese patients in the PK cohort will remain in the clinic for a period of at least 24 hours or longer, based on the Investigator's judgement.

Enrollment of additional patients at Japanese clinical sites will not occur until the 12 patients have completed at least 2 weeks of follow-up, the PK and safety data have been reviewed, and a decision has been made to proceed. The Sponsor will be blinded to the results of these analyses. Patients will be replaced if they drop out before 2 weeks of follow-up.

Except for the intensive PK sampling and additional safety monitoring in the 24-hour period following the first dose of WVE-210201, the schedule of events for the Japanese PK cohort will be the same as for patients not enrolled at Japanese clinical sites, including the biopsy procedures.

Stopping Criteria for Japanese PK Cohort

The Phase 1 study of WVE-210201 did not include patients of Japanese descent. As such, this is the first time Japanese patients will receive WVE-210201 and stopping criteria for the Japanese PK cohort have been established. If any of the stopping criteria, as defined below, are met in the Japanese PK cohort, dosing will be suspended for patients in the Japanese PK cohort and the data will be reviewed by the unblinded Data Monitoring Committee (DMC) to determine whether it is safe to proceed with dosing in the cohort.

- If a single patient experiences a serious AE assessed as related to treatment
- If 2 or more patients experience a treatment emergent adverse event (TEAE) graded by the investigator as "severe" in intensity and assessed as related to treatment.

If a determination is made to resume dosing in the Japanese PK cohort following the review of safety data related to any event(s) that meet the stopping criteria, information will be submitted to the applicable regulatory authorities (in Japan) in accordance with local regulations prior to restarting treatment. If a decision is made to terminate dosing in the Japanese PK cohort, all Investigators in Japan will be informed immediately.

4.1.3 Open-label Treatment Period

After the Double-blind Treatment Period efficacy assessments are completed pre-dose at Week 48, all patients will transition to the OL Treatment Period and receive WVE-210201. Patients randomized to WVE-210201 will continue with the dose administered at the end of the Double-blind Treatment Period. Patients randomized to placebo in the Double-blind period will be treated at the matching WVE-210201 dose level. During the OL Treatment Period, patients will remain blinded to the treatment they received in the Double-blind Treatment Period.

Assessments of safety, efficacy, pharmacokinetics, and immunogenicity will be performed during the OL Treatment Period.

At subsequent visits, all functional assessments, PUL, NSAA, myometry, timed function tests, and pulmonary function tests (PFR, CPF, FVC), must be performed pre-dose (on the dosing day or up to 24 hours prior to the respective dosing day). The pediatric quality of life questionnaires will also be completed.

Assessments of safety, pharmacokinetics, and immunogenicity will also be performed during the OL Period.

To minimize the potential unblinding, functional assessments must be completed by an assessor not involved in administration of study drug or assessment and recording of AEs during the study. The same assessor should perform the functional assessments throughout the study for a given patient to minimize variability of assessments.

4.1.4 Discontinuation and Withdrawal

Patients who discontinue study treatment prior to study completion, will be encouraged to remain in the study to be monitored and to complete all study related procedures until study completion.

Patients withdrawing from the study will be requested to come back to the clinic for an early termination (ET) visit ([Table 1](#) [ET visit for double-blind period] and [Table 2](#) [ET visit for OL period]) to have relevant safety and efficacy assessments performed.

Any patient, for whom consent to participate in the study is withdrawn, will be removed from further treatment and study observation immediately upon the date of request.

4.1.5 Safety Follow-up

A follow-up call approximately 2 weeks after the last visit will be required to ensure that the patients do not have any AEs/SAEs since their last visit.

4.2 Schedule of Assessments

The schedule of assessments is presented in [Table 1](#) and [Table 2](#).

Table 1 Schedule of Assessments-Double-blind Treatment Period

| Assessments | Prestudy Assessments (-6 weeks) | | Weekly Treatment Visit | | | | | | | | ET | | | | | | | | | |
|--|------------------------------------|------------------------------|---|----|----|--|-------|----|----|----|------|--|--|--|--|--|--|--|--|--|
| | | | 1 | 2 | 3 | 4 | 5-11 | 46 | 47 | 48 | | | | | | | | | | |
| Beginning of Week | Screening ^a | Baseline Biopsy ^b | | | | 12 | 13-23 | | | | | | | | | | | | | |
| | | | | | | 24 | 25-35 | | | | | | | | | | | | | |
| | | | | | | 36 | 37-45 | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | D1 | D2 | D8 | D9 (TC) | | | | | D330 | | | | | | | | | |
| Patient informed consent form (ICF) Signed | X | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | | | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | | | | | | | | | |
| Prior or concomitant medications | X | | X | X | X | X | X | X | X | X | X | | | | | | | | | |
| Physical examination ^c | X | | X | | | On Week 4 and every 4 weeks afterwards | | | | X | X | | | | | | | | | |
| Height ^d | X | | X | | | On Week 4 and every 4 weeks afterwards | | | | X | | | | | | | | | | |
| Weight ^d | X | | X | | | On Week 4 and every 4 weeks afterwards | | | | X | | | | | | | | | | |
| Vital signs ^e | X | | X | X | X | X | X | X | X | X | X | | | | | | | | | |
| ECG ^e | | | X | | | | | | | X | X | | | | | | | | | |
| Echocardiogram | X | | | | | | | | | X | X | | | | | | | | | |
| Hematology ^f | X | | X | X | X | X | X | | | X | X | | | | | | | | | |
| Platelets ^g | X | | X | | X | X | X | X | X | X | X | | | | | | | | | |
| Anti-platelet antibody ^h | X | | | | | See Section 6.2.4.2 | | | | | | | | | | | | | | |
| Clinical Chemistry ^f | X | | X | X | | X | | | | X | X | | | | | | | | | |
| Cardiac troponin I ⁱ | X | | X | | | X | X | | | X | X | | | | | | | | | |
| Coagulation parameters | X | | X | X | | X | | | | X | X | | | | | | | | | |
| Urinalysis ^j | X | | X | | X | X | X | X | X | X | X | | | | | | | | | |
| 24-hour urine collection ^j | X | | | | | | | | | | | | | | | | | | | |
| Serum cystatin C ^k | X | | X | | X | X | X | X | X | X | X | | | | | | | | | |
| Complement | | | X | X | X | X | X | | | X | X | | | | | | | | | |
| AE monitoring | X | | X | X | X | X | X | X | X | X | X | | | | | | | | | |
| Open biopsy-deltoid | | | See Section 4.1 for details | | | | | | | | | | | | | | | | | |
| Pharmacokinetics | | | Table 3 and Table 4 | | | | | | | | | | | | | | | | | |
| Immunogenicity sample | | | Table 6 | | | | | | | | | | | | | | | | | |
| NSAA ^l | X | | X | | | | X | | | X | X | | | | | | | | | |
| FVC | X | | | | | | | | | | | | | | | | | | | |
| Pulmonary function testing ^l | | | X | | | X | | | | X | X | | | | | | | | | |
| PUL 2.0 ^l | | | X | | | X | | | | X | X | | | | | | | | | |
| Timed function test-4 stair climb ^l | | | X | | | X | | | | X | X | | | | | | | | | |

| Assessments | Prestudy Assessments (-6 weeks) | | Weekly Treatment Visit | | | | | | | | | ET | | | | |
|--|------------------------------------|------------------------------|------------------------|----|----|------------|-------|----|----|----|------|----|--|--|--|--|
| | | | 1 | 2 | 3 | 4 | 5-11 | 46 | 47 | 48 | | | | | | |
| Beginning of Week | Screening ^a | Baseline Biopsy ^b | | | | 12 | 13-23 | | | | | | | | | |
| | | | | | | 24 | 25-35 | | | | | | | | | |
| | | | | | | 36 | 37-45 | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | | | D1 | D2 | D8 | D9 (TC) | | | | | D330 | | | | | |
| Myometry ^l | | | X | | | | X | | | | X | X | | | | |
| PedsQL-Generic core scale a-child self-report and parent proxy report ^l | | | X | | | | | | | | | X | | | | |
| PedsQL-Neuromuscular Module ^l | | | X | | | | | | | | | X | | | | |
| ActiMyo | | | | | | | | | | | | | | | | |
| Treatment (Placebo or WVE-210201) ^m | | | X | | X | | X | X | X | X | | | | | | |
| Treatment (WVE-210201) ^m | | | | | | | | | | | X | | | | | |

Abbreviations: ECG=electrocardiogram, EOI=end of infusion, ICF=informed consent form, NSAA=North Star Ambulatory Assessments, PedsQL-NMM=Pediatric Quality of Life Inventory-neuromuscular module, PedsQL-GCS= Pediatric Quality of Life Inventory-generic core scale, PUL=performance of upper limb, Pulmonary function tests= Peak flow rate (PFR), cough peak flow (CPF), and forced vital capacity (FVC); TC= telephone call; TFT= Timed function test.

^a Screening assessment completed within 6 weeks of ICF and prior to baseline biopsy.

^b Baseline biopsy performed after eligibility confirmed and ≥ 2 weeks prior to Day 1.

^c Full physical examinations required on Weeks 1 and 48. For all other timepoints (Week 4 and every 4 weeks afterwards), please refer to Section 8.1.3

^d **Weight will be collected pre-dose at screening, Day 1, Week 4 and every 4 weeks afterwards; the most recent weight collected is to be used to determine the infusion volume. Height will also be collected on those timepoints.**

^e Patient must rest quietly ≥ 5 minutes prior to collection of blood pressure (systolic and diastolic), pulse, or ECG. On Day 1 and Week 48 (D330), 12 lead (triplicate) ECG will be done pre-dose (within 24 hours), and 15 minutes (± 5 mins) after EOI.

^f Full panel (Table 9) collected at these time points. Platelets (footnote h), cardiac troponin I (footnote i), serum cystatin c (footnote k), complement, and coagulation parameters to be collected at additional time points as listed in the Schedule of Assessments.

^g Pre-dose platelet samples collected and analyzed locally. Abnormal results repeated locally for confirmation. Concurrent samples collected and sent centrally for analysis (Section 6.2.4.2)

^h Blood samples will be collected at screening and will be repeated if a patient's platelet count falls to $< 75,000$ platelets/ μ L (See Section 6.2.4.2 for details)

ⁱ Cardiac troponin I assessed at screening, baseline (Day 1 pre-dose), Weeks 6, 12 and 48.

^j Twenty-four-hour urine collection performed for all patients during Screening. Urinalysis (local urine dipstick and central quantitative urine) done pre-dose every dosing day. If urine protein on pre-dose quantitative testing is elevated > 0.2 mg/mOsm, dose should be held and a 24-hour urine collection and assessment be done. See Section 6.2.4.1 for all pre-dose parameters to be evaluated, including serum cystatin C.

Table 10

^k See protocol [Section 6.2.4.1](#) for all pre-dose parameters to be evaluated, including serum cystatin c.

^l Functional assessments will be done pre-dose on Weeks 1, 12, 24, 36, and 48 (on the dosing day or up to 24 hours prior to the indicated dosing day) These will not be assessed on Week 4. PedsQL will be collected pre-dose on Week 1 and Week 48 (on the dosing day or up to 24 hours prior to the indicated dosing day). See [Section 8.7.2](#) for sequence and timing of these assessments.

^m Refer to [Section 6.2.2](#)for details regarding study drug administration. Prior to dosing, review of drug withholding criteria should be performed (See [Section 6.2.4](#)). For each dosing day, ± 2 days of window may be allowed. However, administration of Study Drug needs to be separated by a minimum of 5 days between infusions. Starting from Week 48, all patients will receive WVE-210201.

Table 2 Schedule of Assessment-Open-label Treatment Period

| Assessments | Weekly Treatment Visit | | | | | | | | Follow-up ^a |
|--|------------------------|------|------|------|---------------------|----|-------|----|------------------------|
| | | | | | 50-51 | 52 | 53-59 | | |
| | | | | | | 60 | 61-71 | | |
| | | | | | | 72 | 73-83 | | |
| | | | | | | 84 | 85-95 | | |
| | | | | | | | | 96 | ET |
| Prior or concomitant medications | Refer to Table 1 | D330 | D331 | D337 | D338 (TC) | | | | |
| Physical examination ^b | | | X | X | X | X | X | X | X |
| Height ^c | | | | | Every 4 weeks | | | X | X |
| Weight ^c | | | | | Every 4 weeks | | | X | X |
| Vital signs ^d | | | X | X | X | X | X | X | X |
| ECG ^d | | | | | | | | X | X |
| Echocardiogram | | | | | | | | X | X |
| Hematology ^e | | | X | X | X | X | | X | X |
| Platelets ^f | | | | X | X | X | X | X | X |
| Anti-platelet antibody ^g | | | | | See Section 6.2.4.2 | | | | |
| Clinical Chemistry ^e | | | X | | | X | | X | X |
| Cardiac troponin I ^h | | | | | | X | X | X | X |
| Coagulation parameters | | | X | | | X | | X | X |
| Urinalysis ⁱ | | | | X | X | X | X | X | X |
| Serum cystatin C ^j | | | | X | X | X | X | X | X |
| Complement | | | X | X | X | X | | X | X |
| AE monitoring | | | X | X | X | X | | X | X |
| Pharmacokinetics | | | | | Table 5 | | | | |
| Immunogenicity sample | | | | | Table 7 | | | | |
| NSAA ^k | | | | | | X | | X | X |
| Pulmonary function testing ^k | | | | | | X | | X | X |
| PUL 2.0 ^k | | | | | | X | | X | X |
| Timed function test-4 stair climb ^k | | | | | | X | | X | X |
| Myometry ^k | | | | | | X | | X | X |
| PedsQL-Generic core scale a-child self-report and parent proxy report ^k | | | | | | | | X | X |
| PedsQL-Neuromuscular Module ^k | | | | | | | | X | X |
| Treatment (WVE-210201) ^l | | | | X | X | X | X | X | X |

Abbreviations: ECG=electrocardiogram, EOI=end of infusion, ICF=informed consent form, NSAA=North Star Ambulatory Assessments.

PedsQL-NMM=Pediatric Quality of Life Inventory-neuromuscular module, PedsQL-GCS= Pediatric Quality of Life Inventory-generic core scale, PUL=performance of upper limb, TC= telephone call; TFT= Timed function test.

^a A follow-up call approximately 2 weeks after the Week 96 visit (or ET visit) will be required to ensure that the patient does not have any new AEs or serious adverse events (SAEs).

^b Full physical examinations required on Week 96. For all other timepoints, please refer to Section 8.1.3

^c Weight will be collected pre-dose every 4 weeks, and the most recent weight collected is to be used to determine the infusion volume. Height will also be collected on those timepoints.

^d Patient must rest quietly \geq 5 minutes prior to collection of blood pressure (systolic and diastolic), pulse, or ECG. 12 lead (triplicate) ECG will be repeated on Week 96 dosing day 15 minutes (\pm 5 mins) after EOI.

^e Full panel (Table 11) collected at these time points. Platelets (footnote h), cardiac troponin I (footnote h), serum cystatin c (footnote j), complement, and coagulation parameters to be collected at additional time points as listed in the Schedule of Assessments.

^f Predose platelet samples collected and analyzed locally. Abnormal results repeated locally for confirmation. Concurrent samples collected and sent centrally for analysis (Section 6.2.4.2)

^g Blood samples will be collected at screening and will be repeated if a patient's platelet count falls to $<75,000$ platelets/ μ L (See Section 6.2.4.2 for details)

^h Cardiac troponin I assessed on Weeks 54, 60, 96 or ET.

ⁱ Urinalysis (local urine dipstick and central quantitative urine) done predose every dosing day. If urine protein on pre-dose quantitative testing is elevated >0.2 mg/mOsm, dose should be held and a 24-hour urine collection and assessment be done. See Section 6.2.4.1 for all predose parameters to be evaluated, including serum cystatin C.

^j See protocol Section 6.2.4.1 for all predose parameters to be evaluated, including serum cystatin c.

^k Functional assessments will be done pre-dose on Weeks 60, 72, 84 and 96 (on the dosing day or up to 24 hours prior to the indicated dosing day). These will not be assessed on Week 52. PedsQL will be collected pre-dose on Weeks 48 and 96 (on the dosing day or up to 24 hours prior to the indicated dosing day). See Section 8.7.2 for sequence and timing of these assessments.

^l Refer to Section 6.2.2 for details regarding study drug administration. Prior to dosing, review of drug withholding criteria should be performed (See Section 6.2.4). For each dosing day, \pm 2 days of window may be allowed. However, administration of Study Drug needs to be separated by a minimum of 5 days between infusions

Table 3 Schedule of Pharmacokinetic Blood Sample Collection for the Japanese PK Cohort-Double-blind Period

| Week 1 | | | | | | | | Week 2 |
|----------|------------------|----------------------|------------------|-------------------|-------------------|--------------------|--------------------|----------|
| Day 1 | | | | | | | | Day 2 |
| Pre-dose | EOI | 15 minutes after EOI | 1 hour after EOI | 4 hours after EOI | 6 hours after EOI | 12 hours after EOI | 24 hours after EOI | Pre-dose |
| | within 5 minutes | ±5 minutes | ±15 minutes | | | | | |
| X | X | X | X | X | X | X | X | X |

Abbreviations: EOI = end of infusion; PK = pharmacokinetic

Table 4 Schedule of Sparse PK Blood Sample Collection for All Patients-Double-blind Period

| Week 1 | | Week 2 | Week 12 | Week 22 | | Week 46 | |
|----------|------------------|----------|-----------------------|-----------------------|------------------|-----------------------|------------------|
| Pre-dose | EOI | Pre-dose | Pre-dose ^a | Pre-dose ^a | EOI | Pre-dose ^a | EOI |
| | within 5 minutes | | | | within 5 minutes | | within 5 minutes |
| X | X | X | X | X | X | X | X |

Abbreviations: EOI = end of infusion; PK = pharmacokinetic.

^a On biopsy days, pre-dose PK samples should be collected before biopsy procedure.**Table 5 Schedule of Sparse PK Blood Sample Collection for All Patients-Open-label Period**

| Week 60 | Week 72 | Week 96 (or ET) |
|----------|----------|-----------------|
| Pre-dose | Pre-dose | Pre-dose |
| X | X | X |

Table 6 Immunogenicity Sample Collection-Double-blind Period

| Week 1 | Week 12 | Week 22 | Week 48 (or ET) |
|------------------|------------|------------|-----------------|
| Day 1 (Pre-dose) | (Pre-dose) | (Pre-dose) | (Pre-dose) |
| X | X | X | X |

Table 7 Immunogenicity Sample Collection-Open-label Period

| Week 60 | Week 72 | Week 96 (or ET) |
|----------|----------|-----------------|
| Pre-dose | Pre-dose | Pre-dose |
| X | X | X |

Table 8 ActiMyo Device Data Collection- Double-blind Treatment Period

| Beginning of Device Use ^a | End of Device Use ^a | Data Collection Duration |
|--------------------------------------|--------------------------------|-----------------------------------|
| Day when patient signs ICF | Day 1 | ~ 4 to 6 weeks (at least 4 weeks) |
| Dosing day of Week 8 | Dosing day of Week 12 | ~ 4 weeks |
| Dosing day of Week 20 | Dosing day of Week 24 | ~ 4 weeks |
| Dosing day of Week 32 | Dosing day of Week 36 | ~ 4 weeks |
| Dosing day of Week 44 | Dosing day of Week 48 | ~ 4 weeks |

^a Refer to [Section 8.7.2.6.](#) for further instruction regarding wearing the ActiMyo device.

4.3 Study Endpoints

4.3.1 Double-blind Treatment Period

Study Endpoints: The primary and key secondary efficacy endpoints differ by region. All other endpoints are the same across regions.

Primary Efficacy Endpoint

- Change from baseline in dystrophin level (% normal dystrophin) assessed by Western blot of muscle tissue (United States/Other regions, as applicable)
- Change from baseline in North Star Ambulatory Assessment (NSAA) through 48 weeks (EU/Japan)

Secondary Efficacy Endpoints

- Key secondary endpoint - Change from baseline in NSAA through 48 weeks (United States/Other regions, as applicable)
- Key secondary endpoint - Change from baseline dystrophin level (% normal dystrophin) assessed by Western blot of muscle tissue (EU/Japan)
- Change from baseline in upper limb proximal strength assessed by hand held myometry through 48 weeks
- Change from baseline in 4-stair climb (4SC) through 48 weeks
- Change from baseline in the 10-meter walk/run test through 48 weeks

- Change from baseline in forced vital capacity (FVC; % predicted) through 48 weeks
- Change from baseline in the 95th percentile of stride velocity through 48 weeks

Exploratory Efficacy Endpoints

- Change from baseline in Pediatric Quality of Life Inventory (PedsQLTM)-neuromuscular module at 48 weeks
- Change from baseline in Pediatric Quality of Life Inventory (PedsQLTM)-Generic Core Scale module at 48 weeks
- Change from baseline in individual NSAA items through 48 weeks
- Change from baseline in respiratory function (peak flow rate [PFR], cough peak flow [CPF]) through 48 weeks
- Change from baseline in PUL 2.0 through 48 weeks
- Time to milestone events (loss of ambulation, loss of self-feeding, requirement of daytime ventilation on a regular basis)
- Changes from baseline in daily activity as measured by a wearable device measure

Safety, Pharmacokinetic and Pharmacodynamic Endpoints

- Adverse events, laboratory values, physical exams and vital signs
- Changes from baseline in cardiac functions by ECHO
- Concentration of WVE-210201 in plasma
- Concentration of WVE-210201 in muscle
- Exon-skipping by RT-PCR in muscle tissue
- Dystrophin localization by immunofluorescence

4.3.2 *Open-label Treatment Period*

- Long-term efficacy, safety, and PK of WVE-210201

4.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will review unblinded safety data periodically and on an ad hoc basis at least until completion of the Double-blind period. In addition, the DMC will review the results from the planned interim analyses. More details on the DMC are provided in [Section 14.1](#).

5 PATIENT SELECTION AND WITHDRAWAL CRITERIA

Patients will be randomized to study treatment only if they qualify according to all of the following inclusion and exclusion criteria.

5.1 Inclusion Criteria

1. Patient and/or parent or legal guardian must have the ability and be willing to provide written informed consent prior to any study-related procedures
2. Diagnosis of DMD based on clinical phenotype with increased serum creatine kinase
3. Documented mutation in the Dystrophin gene associated with DMD that is amenable to exon 51 skipping
4. Ambulatory male, able to walk independently for at least 10 meters in 10 seconds or less at the time of Screening visit (performed as part of the NSAA)
5. Age of ≥ 5 and ≤ 12 years at time of randomization
6. Willing and able to comply with scheduled visits, drug administration plan, laboratory tests, study restrictions, and all study procedures, including undergoing the biopsy procedures
7. Stable pulmonary and cardiac function, as measured by:
 - a. Reproducible percent predicted forced vital capacity (FVC) $\geq 50\%$
 - b. Left ventricular ejection fraction (LVEF) $>55\%$ in patients <10 years of age and $>45\%$ in patients ≥ 10 years of age, as measured (and documented) by echocardiogram
8. Currently on a stable corticosteroid therapy regimen, defined as initiation of systemic corticosteroid therapy occurred ≥ 6 months prior to Screening, and no changes in dosing ≤ 3 months prior to Screening visit
9. Adequate deltoid muscle at Screening to perform open muscle biopsies
10. Sexually mature males must be willing to use contraception for the duration of the study, if the patient is sexually active
11. Patient and caregivers must agree not to post any study-related information on social media

5.2 Exclusion Criteria

1. Clinically significant medical finding on the physical examination other than DMD that, in the judgment of the Investigator, will make the patient unsuitable for participation in and/or completion of the study procedures.
2. Other prior or ongoing medical conditions including:
 - a. Acute illness within 4 weeks of the initial Screening visit;

- b. Abnormal physical findings, other than those associated with musculoskeletal findings attributable to DMD
- 3. Laboratory abnormality that, in the Investigator's opinion, could adversely affect the safety of the patient, make it unlikely that the course of treatment or follow-up would be completed, or impair the assessment of study results. These include, but are not limited to:
 - a. Renal insufficiency;
 - b. Impaired hepatic function glutamate dehydrogenase (GLDH) $\geq 2.5 \times$ upper limit of normal (ULN) and bilirubin $\geq 2 \times$ ULN (or INR $\geq 1.5 \times$ ULN);
 - c. Activated partial thromboplastin time (aPTT) values above ULN;
 - d. Platelet count $<$ lower limit of normal (LLN).
- 4. Documented positive hepatitis B surface antigen or hepatitis C antibody test.
- 5. Known to be positive for human immunodeficiency virus (HIV).
- 6. Severe mental retardation and/or behavioral problems that, in the opinion of the Investigator, could prohibit participation in this study.
- 7. Cardiac insufficiency:
 - a. Severe cardiomyopathy that, in the opinion of the Investigator, prohibits participation in this study; however, cardiomyopathy that is managed by ACE inhibitors or beta blockers is acceptable provided the patient meets the LVEF inclusion criterion
 - b. Any other evidence of clinically significant structural or functional heart abnormality
 - c. A cardiac troponin I value $> 0.2 \text{ ng/mL}$ on initial and repeat testing if initial test is elevated at screening
- 8. Need for daytime mechanical or non-invasive ventilation OR anticipated need for daytime mechanical or non-invasive ventilation within the next year, in the opinion of the Investigator. Nighttime non-invasive ventilation is permitted.
- 9. Changes in nutritional or herbal supplements or concomitant medications within 1 month prior to Screening visit or plans to modify (dose or regimen) during the study.
- 10. Currently on anticoagulants or drugs that are known to significantly increase the risk of bleeding, such as NSAIDs and heparin.
- 11. Received prior treatment with drisapersen or with an investigational peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO).

12. Received prior treatment with WVE-210201.
13. Received prior treatment with gene therapy for DMD
14. Received treatment with ataluren or eteplirsen within the 14 weeks prior to the planned Baseline biopsy collection.
15. Received any investigational drug within 3 months or 5 half-lives, whichever is longer, prior to the planned Baseline biopsy collection.
16. Known hypersensitivity to any oligonucleotide, as demonstrated by a systemic allergic reaction, such as changes in pulse, blood pressure, breathing function, etc.
17. Parent or legal guardian is directly or indirectly involved in the conduct and administration of this study as an Investigator, sub-investigator, study coordinator, or other study staff member, or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study.

5.3 Additional Study Restrictions

5.3.1 Contraception

The investigator should review the sexual maturity of study patients on a regular basis and provide guidance on the use of contraception, as necessary, while the patient is participating in the study.

Participating patients that are sexually mature and sexually active must be willing to use contraception (ie, condom) for the duration of the study.

5.3.2 Social Media

Patients and caregivers must not post any study-related information on social media. Posting study related information on social media sites may have a negative impact on the study and potentially result in patient discontinuation from the study.

5.4 Withdrawal and Study Treatment Discontinuation

Patients are free to withdraw from the study or discontinue study treatment at any time, upon request, without prejudice to their future medical care by the Investigator or at the study site. See Section 4.1.4 for study specific requirements. Patient participation in the study may also be stopped at any time at the discretion of the Investigator or at the request of the Sponsor, as described below.

5.4.1 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- The patient or patient's legal guardian(s) withdraws consent.
- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation
- Termination of the study by the Sponsor (See Section 15.4 for additional details).

Any patient for whom consent to participate in the study is withdrawn will be removed from further treatment and study observation immediately upon the date of request. These patients should complete the early termination study procedures ([Table 1](#)) and observations at the time of withdrawal. The reason for withdrawal from the study must be recorded in the eCRF and source documentation.

5.4.2 Discontinuation of Study Treatment

A patient may permanently discontinue study treatment for any of the following:

- The patient is withdrawn from the study ([Section 5.4.1](#)).
- The patient experiences a serious or intolerable AE that in the Investigator's opinion requires treatment discontinuation (*e.g., severe or serious reactions during infusion, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of the study drug administration, aggressive symptomatic therapy, and the patient should not be re-challenged.*).
- A change in the patient's medical condition not consistent with the protocol requirements or that justifies withdrawal from the study or study drug.

If a patient discontinues treatment, they will be encouraged to remain in the study to be monitored and to complete all study related procedures, unless consent is withdrawn. Patients who discontinue treatment due to an AE ([Section 9](#)) may require longer follow-up.

The reason for discontinuation of study treatment must be recorded in the eCRF and source documentation.

5.4.3 Lost to Follow-up

Patients who fail to return for study assessments will be contacted by the site in an attempt to have them comply with the protocol. A minimum of three documented contact efforts should be made on different days over the course of 2 weeks. If the patient is unreachable by telephone, a registered letter will be sent to the patient or the caregiver requesting him/her to contact the study center. As part of the informed consent, patients will be asked if they are willing to be contacted at the follow-up time point if they have stopped study participation.

5.4.4 *Replacements*

Patients who withdraw from the study will not be replaced.

6 INVESTIGATIONAL DRUG AND PLACEBO

6.1 Method of Assigning Patients to Investigational Drug or Placebo

Treatment will be assigned through randomization performed using a centralized, interactive voice/web response system (IXRS).

6.1.1 *Double-blind Treatment Period*

Patients will be randomized in a 1:1:2:2 ratio to placebo 3 mg/kg, placebo 4.5 mg/kg, WVE-210201 3 mg/kg, and WVE-210201 4.5 mg/kg. Randomization will be stratified by age (≤ 9 years, > 9 years). Blocks of fixed size will be used within each of the randomization strata.

A separate randomization stratum will be included for the first 12 patients randomized in Japan (the Japanese PK cohort). As 4 patients are needed in each treatment arm in this cohort, these patients will be randomized in a 1:1:2:2 ratio to placebo 3 mg/kg, placebo 4.5 mg/kg, WVE-210201 3 mg/kg, and WVE-210201 4.5 mg/kg. This stratum will not include the age randomization factor. Japanese patients randomized after the Japanese PK cohort will be randomized as described above, but in strata that are separate from the non-Japanese patients.

6.1.2 *Open-label Treatment Period*

Patients randomized to WVE-210201 will continue with the dose level administered at the end of the Double-blind Treatment Period. Patients randomized to placebo will be treated with WVE-210201 at the dose level they had received at the end of the Double-blind Treatment Period. Patients and clinical site staff will remain blinded to the patient's treatment assignment from the Double-blind Treatment Period.

6.2 Dose and Study Drug Administration of Investigational Drug or Placebo

6.2.1 *Identity of Investigational Drug*

6.2.1.1 *WVE-210201*

WVE-210201 will be supplied as an isotonic solution for dilution for IV infusion. Directions on dilution are provided in the Pharmacy manual.

Laboratory Code: WVE-210201

Chemistry: WVE-210201 drug substance may be described chemically as the fully neutralized sodium salt of a 3'→5' linked mixed 2'-fluoro - 2'-deoxy-*2'-O*-methyl- ribonucleic acid oligonucleotide 20 mer containing a prescribed combination of phosphodiester and phosphorothioate linkages.

International Nonproprietary Name (INN): Not yet assigned

United States Adopted Name (USAN): suvodirsen

Molecular Formula (sodium salt form): C₁₉₆H₂₁₁F₁₅N₇₆Na₁₉O₁₀₈P₁₉S₁₅

Average Molecular Weight (sodium salt form): 7150.45 g/mol

Molecular Formula (free acid): C₁₉₆H₂₃₀F₁₅N₇₆O₁₀₈P₁₉S₁₅

Average Molecular Weight (free acid): 6732.80 g/mol

6.2.1.2 *Placebo*

To maintain the blind, a matched placebo will be supplied as the comparator treatment. Matched placebo consisting of a liquid phosphate buffered saline solution will be supplied in single-use glass vials for dilution for IV infusion. The placebo will be visually identical in appearance to WVE-210201 drug product.

6.2.2 *Administration of Study Drug*

The study drug, WVE-210201 or placebo, are supplied as a solution in a single-use vial. Study drug should be diluted with 0.45% Sodium Chloride Injection or 0.9% Sodium Chloride Injection prior to infusion, in accordance with instructions in the Pharmacy Manual. Study drug will be administered at the study site by trained personnel. The route of administration will be IV, and the total volume of the infusion will be 100-500 mL based on patient weight.

The infusion should be administered over a minimum of 60 minutes. However, investigators should consider initiating treatment with longer infusion times (i.e., 3 hours) to potentially enhance tolerability. The prepared infusion solution contains no preservatives and should be administered within 4 hours of preparation. Patients should remain stationary during the infusion. For each dosing day, ± 2 days of window may be allowed. However, administration of Study Drug needs to be separated by a minimum of 5 days between infusions. The Investigator may electively choose to monitor patients in an in-patient setting on any dosing day in order to facilitate careful observation of the patient post-study drug administration. However, any such hospitalizations for observation purposes must be pre-planned before the applicable study drug administration day and clearly documented in the patient's medical record. Please see [Section 9](#) for additional information regarding hospitalization.

6.2.3 *Monitoring for Infusion-Associated Reactions*

As with other IV-infused drugs, infusion-related reactions (e.g., rash, urticaria, erythema, pruritus, bronchospasm, pyrexia, and hypotension) may occur with WVE-210201. Infusion-associated reactions such as pyrexia, vomiting, tachycardia, and chills have been observed in clinical studies of WVE-210201 or placebo. Symptoms such as flushing, pyrexia, skin reactions, dyspnea, lower back pain, hypotension, nausea and/or vomiting, or tachycardia may require

temporary interruption of the infusion or slowing the infusion rate for the subsequent dosing. Patients who experience infusion-associated reactions may be pre-medicated for subsequent infusions to help ameliorate symptoms, as medically appropriate, per local guidelines and clinical practice. However, severe or serious reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of the study drug administration, aggressive symptomatic therapy, and the patient should not be re-challenged.

6.2.4 Monitoring and Criteria for Withholding Study Drug

6.2.4.1 Renal Monitoring and Criteria for Withholding Study Drug

Prior to each dose, the Investigator should review the following:

- Urine dipstick sample results from that day.
- Serum cystatin C results collected predose at the previous visit.
- Quantitative urinalysis collected predose at the previous visit.
- If serum cystatin C or quantitative urinalysis results are available from an unscheduled laboratory sample collected between the weekly visits, those results should be reviewed instead.

Dosing Decisions Based on Urine Testing Parameters

- **All 3 Tests Normal:** if the local dosing-day dipstick is normal, and the previous visit serum cystatin C and quantitative urinalysis are normal, dosing may occur on that day.

Local Dipstick Abnormal:

- If the result (protein, RBC, WBC) is abnormal (1+ or greater) and remains so after hydration and repeat testing, dosing should be held, and a local quantitative urinalysis should be performed. If this result is normal, dosing can proceed.

Local Quantitative Abnormal:

- If local quantitative results are abnormal (protein, RBC, WBC) (protein/osmolality ratio of >0.2 mg/mOsm; RBC or WBC abnormal per local reference ranges), and remains so after hydration and repeat testing, the dose should be held, and the results should be confirmed at the central laboratory. In addition, a 24-hour quantitative urine collection should be obtained, and if this result is normal and the urine dipstick is normal, then dosing can resume at the next scheduled visit day.

Quantitative Urinalysis (central laboratory) and Serum Cystatin C

If quantitative urinalysis is abnormal, and serum cystatin C is within the normal range but elevated by $\geq 50\%$ and $<100\%$ from baseline, dosing should be held until weekly urinalysis (central) is normal and serum cystatin C returns to a level of $<50\%$ elevation from baseline. Dosing can resume at the next scheduled visit day.

If serum cystatin C is within the normal range but elevated by $\geq 50\%$ and $<100\%$ from baseline, and urine protein is normal (according to central quantitative urinalysis and local dipstick) without an increase in RBCs or WBCs, dosing should be held until serum cystatin C returns to a level that represents $<50\%$ elevation from baseline. Dosing can resume at the next scheduled visit day.

- **If quantitative urinalysis (central laboratory) is abnormal, but serum cystatin C is unchanged compared to baseline** and in the normal range, dosing should be held until weekly central urinalysis is normal (and weekly serum cystatin C remains unchanged and in the normal range). Dosing can then resume at the next scheduled visit day.
- **If serum cystatin C is above the normal range and elevated by $>50\%$ and $<100\%$ from baseline, dosing should be held.** The following steps will be taken, depending on the quantitative urinalysis assessment:
 - **If quantitative urinalysis (central laboratory) is normal** (normal protein without an increase in RBCs or WBCs), serum cystatin C assessments will be assessed weekly until values are $<50\%$ elevation from baseline and within the normal range. Dosing can resume at the next scheduled visit day.
 - **If quantitative urinalysis (central) is abnormal**, weekly urine assessments will be performed until values return to normal. In addition, serum cystatin C assessments will be performed weekly until values are $<50\%$ elevation from baseline and within the normal range. Dosing can resume at the next scheduled visit day.
- **If serum cystatin C is elevated by $>100\%$ from baseline**, study drug will be held and a 24-hour urine collection and assessment will be performed.
 - **If the 24-hour urine assessment, including protein, albumin, WBC and RBCs, is normal**, study drug will be held and weekly serum cystatin C assessments will be performed until values are $<50\%$ elevation from baseline and within the normal range. Dosing can resume at the next scheduled visit day.
 - **If the 24-hour urine assessment, including protein, albumin, WBC and RBCs, is abnormal**, study drug will be discontinued and weekly 24-hour urine collections will be repeated until normal. In addition, weekly serum cystatin C assessments will be performed until values are $<50\%$ elevation from baseline and within the normal range. Weekly 24-hour urine collections and serum cystatin C monitoring can be

discontinued at the Investigator's discretion, even if not all values have returned to normal, when at least 2 consecutive assessments have shown stable values; however, the patient should be followed until resolution of abnormal values (according to the local guidelines).

- **If urine protein/osmolality ratio is >0.2 mg/mOsm, then the dose should be held and 24-hour urine monitoring performed weekly until it returns to the normal range. Dosing can then resume at the next scheduled visit day, provided serum cystatin C is at <50% elevation from baseline and in the reference range (other urine parameters and serum cystatin C need to be normal to resume study drug administration).**

6.2.4.2 Monitoring for Thrombocytopenia and Criteria for Withholding Study Drug

Patients will be closely monitored for thrombocytopenia. Prior to each dose, samples for assessments of platelets will be collected and analyzed locally. Abnormal results should be repeated locally for confirmation. Concurrent samples should also be collected and sent to the central laboratory for analysis. Local results should be reviewed against the following criteria:

- If platelet values fall to <100,000 platelets/ μ L and the patient has new clinical signs or symptoms indicative of thrombocytopenia, drug will be held. Dosing can resume when symptoms have resolved and platelets are >150,000 platelets/ μ L.
- If platelet values fall to <50,000 platelets/ μ L, drug administration will be discontinued and the patient will be followed until resolution.
- If a platelet measurement is uninterpretable, a repeat platelet count should be obtained as soon as possible using a sodium citrate tube.
- **Note:** For patients who experience a decrease in platelets to <75,000 platelets/ μ L, an antiplatelet antibody test should be performed. If the result is indeterminate, the test should be repeated. In the case that the anti-platelet antibody test is positive, a repeat test should be performed at end of treatment.

6.3 Management of Clinical Supplies

6.3.1 Study Drug Packaging and Storage

WVE-210201 or placebo solution for infusion is supplied in a single-use 10 mL Type 1 clear glass vial with a Teflon lined rubber stopper, aluminum overseal, and plastic flip-off cap. Each vial contains 20 mg/mL WVE-210201 or placebo. Study drug will be stored at -20°C in a locked area accessible only to the pharmacy personnel. The diluted infusion solution should be stored in accordance with instructions in the Pharmacy Manual.

All study drug will be transported, received, stored, and handled in accordance with the container or product label, the instructions supplied to the pharmacy, the relevant institution's Standard Operating Procedures (SOPs), and applicable regulations. Appropriate storage and transportation

conditions will be maintained for the study drug from the point of manufacture up to delivery of the study drug.

Partially used, unused, or damaged study drug vials should be returned to the Sponsor per instructions included in study-specific manuals.

6.3.2 *Investigational Drug Accountability*

The Investigator will maintain accurate records of receipt of drug supplies, including dates of receipt. In addition, accurate records will be kept regarding when each treatment is administered, which patients received treatment, and the name of the personnel administering the treatment. Reasons for departure from the expected treatment regimen must also be recorded. Only trained site staff are permitted to treat study patients. A study monitor will review the accountability records onsite.

6.3.3 *Other Supplies*

Study sites will be provided with the Investigator's Brochure (IB), study-specific manuals, laboratory kits, and other materials, as appropriate.

7 BLINDING PROCEDURES

7.1 Blinding

This is a randomized, double-blinded, placebo-controlled study with an OL treatment period. During the double-blind period, ALL study personnel will also be blinded to patient treatment assignment (WVE-210201 or placebo). All study personnel will be blinded to assigned dose level for a given patient (i.e. 3 or 4.5 mg/kg WVE-210201 or placebo), with the exception of the pharmacist who will need to prepare study drug (WVE-210201 or matched placebo) for infusion based on dose level and patient weight. However, the pharmacists WILL be blinded as to whether a given patient receives WVE-210201 or placebo. The patient's treatment assignment in this double-blinded period will remain blinded until the end of the study (EOS).

During the OL period, all patients will receive WVE-210201, however, all study personnel will remain blinded to patient's prior treatment assignment until the EOS. Study personnel will also remain blinded to the patient's dose level (i.e., 3 or 4.5 mg/kg WVE-210201) during the OL period, with the exception of the pharmacist who will need to prepare study drug for infusion based on dose level and patient weight.

Physicians, nurses, patients, and any study personnel performing patient assessments must NOT be informed of the patient's treatment assignment except in the event of a medical emergency or as required by regulatory authorities ([Section 7.2](#)). To protect the integrity of the blind functional assessments must be completed by an assessor who has not been involved in administration of the study drug or assessment and recording of AEs at any point during the study. The same assessor should perform the assessments throughout the study for a given patient to minimize variability of assessments.

7.2 Breaking the Blind

7.2.1 *Unblinding for Medical Emergency:*

A patient's treatment assignment should remain blinded until the end of the study. However, in the event of a medical emergency, when the medical treatment of the patient depends on knowing the study treatment the patient received, the treatment blind may be broken through the IXRS system. The Investigator must document the reasons for unblinding in the patient's source documents. *The Investigator is strongly advised not to divulge the patient's treatment assignment to any individual not directly involved in managing the medical emergency nor to personnel involved with the analysis and conduct of the study.*

7.3 Recording the Unblinding

If an unblinding occurs, the date on which the code was broken, together with the identity of the person responsible for breaking the blind, must be documented in the patient's source documents. The unblinded treatment information will not be disclosed to the Sponsor. In consultation with the Medical Monitor and the Sponsor, the patient may be withdrawn from the study if the blind is broken.

The documentation should include, but is not limited to, the following information:

- Patient information
- Reason for unblinding
- Date and time of unblinding
- Name of the person requesting/responsible for unblinding

8 METHODS OF ASSESSMENT AND ENDPOINTS

8.1 Safety Assessments

The safety assessments will include the following:

- Adverse events (Section 9)
- Medical history and demographics
- Prior and concomitant medications
- Physical examinations (including neurological and psychiatric)
- Vital signs

- Height and weight
- 12-lead ECGs
- Clinical laboratory evaluations (including clinical chemistry, hematology, and urinalysis)
- Echocardiogram

Any abnormal laboratory test results (hematology, clinical chemistry, or urine) or other safety assessments (e.g., vital sign measurements), that are assessed as clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

8.1.1 *Medical History and Demographics*

A general medical history will be obtained at the Screening visit. Investigator assessment of past medical history at Screening will include information regarding any significant medical, surgical, psychiatric, and/or neurological conditions and treatments.

8.1.2 *Prior and Concomitant Medications*

Medications with a start date before the first dose of investigational drug will be classified as prior medications. Any medication that the patient began taking after the first dose of investigational drug will be classified as concomitant. Any medication that a patient started before the first dose of investigational drug and continued to take during the study will be classified as both prior and concomitant. Any medication that was stopped on the same day (prior to dosing) as the first dose of investigational drug will be considered a prior medication. If the stop date of a given medication is missing, then the medication will be classified as concomitant.

Any history of steroid and/or investigational drug use will be captured. Prior treatments for DMD (e.g., approved ASO) given at any time in the patient's history should be captured.

The minimum requirement is that the drug name, dose, indication, and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator. It is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF.

8.1.3 *Physical Examination*

A complete physical examination will be performed at the time points noted in the Schedule of Assessments ([Table 1](#) and [Table 2](#)). At Screening, Weeks 48 and 96, the physical examination will include (but is not limited to) an examination of skin, head, eyes, ears, nose, throat,

respiratory, cardiovascular, gastrointestinal, endocrine, metabolic, blood, lymphatic, musculoskeletal, psychiatric, and neurologic (including mental status, cranial nerves, motor system, reflexes, coordination and gait, and sensory system) systems.

At all other time points (approximately every 4 weeks), the physical examination must include (at a minimum) head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, musculoskeletal, psychiatric, and neurologic). Other systems should be evaluated as appropriate.

Physical findings will be recorded in the eCRF and source documents.

8.1.4 *Vital Signs (Blood Pressure, Heart Rate and Temperature)*

Vital sign measurements will be taken as per standard site practice, after the patient has been resting quietly (either lying flat or sitting, whichever is most appropriate for the condition of the patient) for a period of at least 5 minutes. Blood pressure (systolic and diastolic), temperature, and pulse will be measured by medically qualified personnel at the time points described in the Schedule of Assessments ([Table 1](#) and [Table 2](#)) and recorded in the eCRF and source documents. As feasible, the same position (either sitting or lying) should be used for all subsequent blood pressure measurements during the study for an individual patient. If the initial reading is high, the measurements will be repeated twice and the average of the three readings will be used.

8.1.5 *Height and Weight*

The patient's height and weight will be measured at the time points described in the Schedule of Assessments ([Table 1](#) and [Table 2](#)) and recorded in the eCRF and source documents.

8.1.6 *12-Lead ECG*

Computerized, good quality, 12-lead ECGs will be collected in triplicate and recorded at the time points described in the Schedule of Assessments ([Table 1](#) and [Table 2](#)). Recordings will be obtained in the supine position after the patient has rested comfortably for ≥ 5 minutes.

The ECG tracing will be submitted and read by a centralized reviewer (details will be provided in a study-specific manual). The following should be recorded on the trace and eCRF: whether the ECG is normal or abnormal and, if deemed abnormal, whether the abnormality is clinically significant or not clinically significant, including a note of the abnormality.

8.1.7 *Echocardiogram*

A standard 2-dimensional (2D) ECHO will be obtained at the time points specified in [Table 1](#) and [Table 2](#), and the results recorded in the eCRF and source documents.

ECHOs should be performed at a consistent time of day throughout the study. The Investigator will review the results of the ECHO report and determine if the findings are clinically significant. Results will be submitted and read by a centralized reviewer (details will be provided in a study-specific manual).

8.1.8 Clinical Laboratory Evaluations

Clinical laboratory safety testing will be collected at the time points described in the Schedule of Assessments ([Table 1](#) and [Table 2](#)) and recorded in the eCRF and source documents. Safety laboratory samples will be analyzed at a central laboratory. Local testing on these samples may be conducted, as clinically indicated.

The parameters to be assessed are presented in [Table 9](#).

Table 9 Clinical Laboratory Parameters

| Hematology | Coagulation | Clinical chemistry | Urinalysis |
|--|--|--|--|
| <p>Complete blood count, including:</p> <ul style="list-style-type: none"> White blood cell count (with differential) Red blood cell count Hemoglobin Hematocrit Platelet count Reticulocyte count Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration High sensitivity C-reactive protein (hsCRP) Fibrinogen Complement (C3 and Bb)^a | <p>Activated partial thromboplastin time</p> <p>Prothrombin time</p> <p>International Normalized Ratio</p> | <p>Sodium</p> <p>Potassium</p> <p>Chloride</p> <p>Bicarbonate</p> <p>Blood urea nitrogen</p> <p>Creatinine</p> <p>Creatine phosphokinase</p> <p>Alanine aminotransferase</p> <p>Aspartate aminotransferase</p> <p>Alkaline phosphatase</p> <p>Bilirubin</p> <p>Gamma glutamyl transferase</p> <p>GLDH</p> <p>Serum Cystatin C</p> <p>Hepatitis B surface antigen test^b</p> <p>Hepatitis C antibody test^b</p> <p>Cardiac Troponin 1</p> | <p>pH</p> <p>Specific gravity</p> <p>Urine osmolality</p> <p>Glucose</p> <p>Ketones</p> <p>Blood</p> <p>Urobilinogen</p> <p>Bilirubin</p> <p>Microscopic examination for RBCs and WBCs</p> <p>Quantitative analysis of protein</p> |

^a Complement will not be tested at Screening.

^b Tested only at Screening

8.2 Pharmacokinetic Assessments in Japanese PK Cohort Patients

PK blood samples will be collected according to [Table 3](#). Additional PK time points may also be collected from these patients as mentioned in Section [8.3](#).

8.3 Pharmacokinetic Assessments (Overall)

Sparse sampling for all patients will be collected per [Table 4](#) and Table 5. Blood samples will be collected for analysis done by a Sponsor-approved CRO using a validated method. Samples will only be used by the Sponsor and/or a contracted vendor for research related to the development of treatments for DMD, and will be stored for a maximum of 15 years. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited, and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the study-specific manual.

8.4 Immunogenicity

Immunogenicity samples will be collected to assess anti-drug and anti-dystrophin antibodies in serum, according to the Schedule of Assessment ([Table 6](#) and [Table 7](#)).

Samples will only be used by the Sponsor and/or a contracted vendor for research related to the development of treatments for DMD and will be stored for a maximum of 15 years. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited, and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the study-specific manual.

8.5 Pharmacodynamic Assessments

Tissue samples collected from muscle biopsies ([Section 4.1](#)) will be evaluated for changes in dystrophin protein level, dystrophin localization, and presence of exon 51-skipped mRNA transcript following treatment with WVE-210201.

Samples will only be used by the Sponsor and/or a contracted vendor for research related to the development of treatments for DMD and will be stored for a maximum of 15 years. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited, and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the study-specific manual.

8.5.1 *Dystrophin Localization*

Muscle biopsy samples will be used to assess the effect of WVE-210201 on dystrophin protein localization by immunohistochemistry/immunofluorescence.

8.5.2 *Exon 51-Skipped mRNA in Muscle Tissue*

Muscle biopsy samples will be used to evaluate the effect of WVE-210201 on the presence of exon 51-skipped mRNA by RT-PCR.

8.6 Muscle Concentration of WVE-210201

WVE-210201 concentration in muscle tissue by ELISA (if adequate tissue sample is available) may be evaluated.

8.7 Efficacy Assessments

8.7.1 *Dystrophin Quantification by Western Blot*

Levels of dystrophin may be quantified by Western blot in the muscle tissues collected at baseline and at one of three postbaseline time points, according to [Section 4.1](#).

The amount of restored dystrophin protein from muscle tissues will be evaluated using a validated Western blot method, according to a detailed validation protocol.

8.7.2 *Functional Assessments*

Functional assessments that are included in both NSAA and Timed Function Tests, will only be administered once per timepoint.

Functional assessments must be performed pre-dose on: Weeks 1, 12, 24, 36 48, 60, 72, 84 and 96 (on the dosing day or up to 24 hours prior to the indicated dosing day) in the order listed below:

See the [Table 1](#), [Table 2](#) and the Study Manual for additional information

- NSAA (will also be done at screening)
- PUL 2.0
- Timed function test 4-stair climb
- Hand-held myometry
- Pulmonary function tests (PFR, CPF, and FVC); FVC will be done at screening as well.

PedsQL ([Section 8.7.3](#)) assessments must be performed pre-dose on Weeks 1, 48, and 96 (on the dosing day or up to 24 hours prior to indicated dosing day), in the following order:

- PedsQL-NMM and GCS
- NSAA
- PUL 2.0
- Timed function test 4-stair climb

- Hand-held myometry
- Pulmonary function tests (PFR, CPF, and FVC); FVC will be done at screening as well.

8.7.2.1 *North Star Ambulatory Assessment*

The NSAA is a validated unidimensional scale, designed for measuring motor function in ambulatory boys with DMD^{45,46}. The scale is suitable for multicentric global studies and is widely used internationally as a relevant functional assessment for patients with DMD. The scale was specifically designed for ambulant children with DMD. NSAA includes 17 items, ranging from standing (item 1) to running (item 17), that are necessary to remain functionally ambulant. The scale includes items assessing abilities, such as head raise and standing on heels that can be present in the early stages of the disease and other activities such as hopping, or running that are generally never fully achieved in untreated DMD boys⁴⁷.

Each item is scored on a 3-point scale using simple criteria:

2 - Normal; achieves goal without any assistance

1 - Modified method but achieves goal independent of physical assistance from another person

0 - Unable to achieve independently

The total score is the sum of the individual item scores. The score can range from 0, if no activities can be achieved independently, to 34, if all the activities can be achieved without any assistance. The scale is generally completed in a maximum of 15 minutes.

8.7.2.2 *Timed Function Tests*

The time to climb 4 standard-sized stairs will also measure lower limb motor function in ambulatory patients. Other timed-function tests, 10-m walk/run and rise from floor will be performed by the patient only once as part of NSAA, and will not be re-administered. These tests will be recorded on both NSAA and TFT scales.

8.7.2.3 *Performance of Upper Limb (PUL 2.0) Test*

The PUL test is an assessment tool that evaluates upper limb function in ambulatory and non-ambulatory DMD patients and was developed through a collaborative international group including boys with DMD and their families. The PUL test was designed with a conceptual framework reflecting the progression of weakness and the natural history of functional decline in DMD⁴⁸.

8.7.2.4 *Hand-held Myometry*

Upper limb proximal strength will be assessed by handheld myometry^{49,50}.

8.7.2.5 Pulmonary Function Tests

Pulmonary function tests (PFR, CPF, and FVC)⁵¹ will be performed using the Microlab Spirometer.

- Peak flow rate (PFR) and cough peak flow (CPF): Muscle weakness caused by neuromuscular disorders results in reduced values for peak flow rate. This test is effort dependent. The use of CPF can minimize effort-related variation. Thus, for patients with neuromuscular weakness, CPF measured by peak flow meter is a reliable measurement of expiratory muscle strength.
- Forced vital capacity (FVC): During the FVC assessment, the patient takes a maximum breath and fills his lungs to total lung capacity (TLC) and then exhales to the maximum. The total volume of air expelled during forced exhalation after maximum inspiration is the FVC. The values are reduced in patients with neuromuscular disease. Measurements of FVC will be collected while the patient is in the sitting position. If the patient is wearing a thoracolumbar device, the measurements will be taken with the device on, and the patient in a sitting position

8.7.2.6 ActiMyo Wearable Device

ActiMyo is a wearable device that has been developed to quantify a patient's ambulation ability directly and reliably in a continuous manner in the home environment. Data collection will be performed at the time points listed in [Table 7](#) Immunogenicity Sample Collection-Open-label Period

| Week 60 | Week 72 | Week 96 (or ET) |
|----------|----------|-----------------|
| Pre-dose | Pre-dose | Pre-dose |
| X | X | X |

[Table 8](#). The device consists of two sensors: one worn on the ankle and one worn on the wrist. The two sensors must be worn on the same side and must be worn on the chosen side consistently throughout the study. The device is put on in the morning and worn throughout the day, removed at night, and placed in a docking station for charging and data upload. The device will be given to patients during the Screening Period and worn, as instructed ([Table 6](#)). The ActiMyo device will only be used during the double-blind treatment period.

The device recordings will be processed to generate measures of ambulation ability and maximal ambulation performance. These variables include the following:

- percentage of time walking
- distance walked
- median stride velocity

- 95th percentile stride velocity
- median stride length
- 95th percentile stride length
- number of falls

8.7.3 *Quality of Life*

The PedsQL is a brief, standardized, generic assessment instrument that systematically assesses pediatric patients' and parents' perceptions of HRQOL in pediatric patients with chronic health conditions. Considered a clinically important patient-rated outcome (PRO) of patient care, HRQOL characterizes the perceived effect of a disease, condition, illness, injury, or treatment intervention on various health domains (eg, physical, emotional, social). The PedsQL is a modular instrument for measuring HRQOL in children and adolescents aged 2 to 18. The PedsQL 4.0 Generic Core Scales are multidimensional pediatric patient self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL Disease-Specific Modules. A disease specific module of the PedsQL (Pediatric Quality of Life Inventory), the PedsQL 3.0 Neuromuscular Module (NMM), will be administered together with the PedsQL 4.0 Generic Core Scales⁵². This assessment is development-appropriate and will be done according to the Schedule of Assessments ([Table 1](#)). Please refer to Section 8.7 for the sequence of assessments.

8.7.3.1 *Pediatric Quality of Life Inventory (Neuromuscular Module)*

The PedsQL offers a modular approach to measuring health-related quality of life (HRQOL) in healthy children and adolescents and those with acute and chronic health conditions, and is responsive to clinical change over time. PedsQL Neuromuscular Module is a specific module of the PedsQL, and is used for measuring HRQOL in patients with DMD⁵².

8.7.3.2 *Pediatric Quality of Life Inventory (Generic Core Scale)*

Given the importance of HRQOL in patient care, efforts have been directed over the last decade to developing generic PRO instruments to evaluate HRQOL during care. The PedsQL GCS (version 4.0) is a generic PRO instrument that evaluates HRQOL in patients aged 2 to 18 years^{53,54}. Pediatric self-report is measured in children and adolescents aged 5-18 years, and parent proxy-report of child HRQOL is measured for children and adolescents aged 2-18 years. The 23-item PedsQL GCS consists of four subscale scores and two summary scores. The PedsQL GCS subscales include physical functioning (PF, 8 items), emotional-functioning (EF, 5 items), social-functioning (SOF, 5 items), and school-functioning (SCF, 5 items). The total score (TS, 23 items) is a summary score of all subscale scores, and the psychosocial functioning score (PSF, 15 items) is a summary score of the EF, SOF, and SCF subscale scores. Each item is rated on a 5-point Likert scale.

8.7.4 *Milestone Events*

The occurrence of milestone events (loss of ambulation, loss of ability to self-feed and need for day time ventilation) will be derived using observations from the NSAA, PUL 2.0 and pulmonary function tests.

9 ADVERSE EVENTS

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study treatment or their clinical significance.

Adverse event information will be collected from the date of signed informed consent and up to the end of the study. All ongoing AEs at the end of the study will be followed to resolution or until the Investigator and the Sponsor agree that further follow-up is not required.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study treatment. Patients and parents/legal guardians/caregivers will be instructed to contact the Investigator at any time after the patient/parent/legal guardian signs informed consent, if any symptoms develop while the patient is in the study.

If a patient is hospitalized for a pre-planned elective medical or surgical procedure, or is admitted as an in-patient for a pre-planned observation period post-study drug administration (refer to [Section 6.2.2](#)) this will not be recorded as an SAE unless associated with an untoward medical occurrence that meets the definition of a serious event as outlined in [Section 9.3.1](#) (e.g. bleeding event after surgery that prolongs hospitalization). Such hospitalization must be documented in advance in the patient's medical record and the reason should be described in detail.

A TEAE is defined as any event not present before exposure to study treatment or any event already present that worsens in either intensity or frequency after exposure to study treatment.

9.1 Eliciting and Documenting Adverse Events

All AEs reported or observed during the study, including AEs resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states, will be recorded on the AE page in the eCRF and in the site source notes. The eCRFs used to document AEs are designed to help ensure this information is collected in a standard way. Information to be collected includes the as-reported event term, date and time of onset, date and time of resolution, Investigator-specified assessment of severity and relationship to study treatment, action taken with respect to study treatment, seriousness, any required treatment or evaluations, and outcome. All AEs will be followed to adequate resolution. The sites will be provided completion guidelines for the eCRF, which will further guide them on how to record the data, including AEs. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient/parent/legal guardian signs informed consent but does not worsen should not be reported as an AE. However, if it worsens at

any time during the study, it must be recorded as an AE. This includes any spontaneously reported worsening of depression, i.e., not based on the study rating scales.

In addition to observations of the patient, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG changes) or identified from review of other documents, that are considered clinically significant will be documented on the AE page in the eCRF. Worsening of symptoms that are only detected on clinical effects rating scales will not be reported as AEs.

Adverse events will be assessed at each visit by direct questioning of the patient/parent/caregiver as well as elicited from physical examination by site staff. In addition, all sites in the study must ensure patients/parents/caregivers have a 24-hour telephone number to contact medical site staff for the duration of the study, in case of emergent AEs or SAEs.

If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

9.2 Definitions of Adverse Event Severity and Relationship to Study Drug

9.2.1 Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. Adverse event severity will be evaluated using the criteria in [Table 10](#).

Table 10 Definitions of AE Severity Criteria

| AE Severity | Definition |
|-----------------|---|
| Mild | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| Moderate | Moderate; of sufficient severity to make the patient uncomfortable; minimal, local, or noninvasive intervention indicated. |
| Severe | Severe or medically significant, of sufficient severity to cause the patient severe discomfort; may cause cessation of treatment; treatment of event symptoms/intervention may be required. |

Abbreviations: AE = adverse event;

Changes in the severity of an AE should be documented in the eCRF to allow an assessment of the duration of the event at each level of intensity.

9.2.2 Relationship to Study Drug

The Investigator's assessment of an AE's relationship to study treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. All AEs, regardless of relationship, will be recorded in the eCRF. In addition, SAEs will be reported to regulatory authorities as required by local regulation ([Section 9.3.4](#)).

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the classification and criteria presented in [Table 11](#).

Table 11 Guidelines for Determining the Relationship (if any) Between Adverse Event and the Study Drug

| AE Relationship | Definition |
|-------------------------|--|
| Definite | This relationship suggests that a definite causal relationship exists between treatment administration and the AE, and that other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study treatment is re-administered. |
| Probable | This relationship suggests that a reasonable temporal sequence of the event with treatment administration exists and, based upon the known pharmacological action of the treatment, known or previously reported adverse reactions to the treatment or class of treatment, or judgment based on the Investigator's clinical experience, the association of the event with the study treatment seems likely. The event disappears or decreases on cessation of study treatment. |
| Possible | This relationship suggests that the study treatment caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of treatment administration or follows a known response pattern to the study treatment, but could also have been produced by other factors. |
| Unlikely Related | This relationship suggests an improbable (but not impossible) association between the study medication and the reported event. |
| Not Related | This relationship suggests no association between the study treatment and the reported event. |

Abbreviations: AE = adverse event.

9.3 Serious Adverse Events

9.3.1 Serious Adverse Event Criteria

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A life-threatening event does not include an AE that, had it occurred in a more severe form, might have caused death.

Serious AEs must be reported (Section 9.3.4) and will be followed through the follow-up visit. An SAE that occurs after the final follow-up visit need not be reported unless the Investigator or the Sponsor considers it related to study drug.

The Sponsor pharmacovigilance risk management physician will provide a Sponsor causality statement for all SAEs.

9.3.2 Suspected, Unexpected Serious Adverse Reaction

A suspected, unexpected, serious adverse reaction (SUSAR) is an SAE for which there is a reasonable possibility that the drug caused the event, and this SAE has not been previously identified as an expected/listed AE. If an investigational agent is early in development all SAEs may be considered unexpected. Later phase investigational agents may have an identified list of expected AEs. A list of expected AEs (if applicable) is provided in the current version of the Investigator's Brochure and is considered the Reference Safety Information (RSI) for the study. Generally, the indication for which a product is intended would not be on the list of expected AEs, but if it did occur, would not be considered "unexpected" for SUSAR reporting. As an example, a flare-up of symptoms consistent with the underlying disease under treatment that required hospitalization would constitute an SAE; however, the event would not be considered unexpected. An exception would be if the reporter believed that study drug worsened the underlying condition.

9.3.3 Serious Adverse Event Follow-up

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs regardless of relationship to study drug will be followed by the Investigator until resolution. Clinical, laboratory, and diagnostic measures should be employed by the Investigator, as needed, to adequately determine the etiology of the event.

9.3.4 Serious Adverse Event Reporting

9.3.4.1 Reporting Requirements

Any AE that meets SAE criteria (Section 9.3.1) must be reported to the Sponsor and/or designee immediately (i.e., within 24 hours) after the time site personnel first learn about the event. The SAE Report Form provided for the study must be used. Regardless of causality, all SAEs must be reported and will be collected and recorded from the time the patient/parent/legal guardian signs the ICF until completion of the final follow-up visit. All SAEs must also be recorded in the patient's source documentation and on the AE page of the patient's eCRF.

The initial report should include at least the following information:

- Study Number
- Patient's identification number

- Description of the event
- Date and time of onset of the event
- Seriousness criteria
- Causality assessment to study drug

If follow-up is obtained, or requested by the Sponsor and/or designee, the additional information should be e-mailed on an SAE Report Form to WAVE and/or designee, in a timely manner according to the procedures outlined above. Copies of discharge summaries, consultant reports, autopsy reports, and any other relevant documents may also be requested.

The Investigator will be responsible for reporting all SAEs to the Institutional Review Board (IRB) or Ethics Committee (EC). The Sponsor will be responsible for reporting to the regulatory authorities and Central Ethics Committees, as per local requirements.

9.3.4.2 *SAE Contact Information*

Serious adverse event contact information is provided in the [Study Identification Table](#).

9.4 Overdose

The study drugs are planned to be administered by trained study staff. Administration will be performed in accordance with the IB and instructions in a study-specific manual. Any incidence of overdose should be recorded as an SAE.

No clinical data are available regarding overdose with WVE-210201. As with any agent, if overdose occurs, general supportive measures and close observation should be instituted. Misuse of the study drug for illegal purposes is not expected in this study as patients have no direct access to the study drugs.

10 PREGNANCIES

Not applicable.

11 STATISTICAL METHODS

11.1 Sample Size Determination

Approximately 150 patients are planned to be enrolled in this study. This study was designed to demonstrate the efficacy of WVE-210201 compared to placebo on a clinical endpoint, NSAA.

The sample size determination for the NSAA endpoint was based on the following assumptions:

- Two-sample t-test to test for statistical significance of treatment difference

- 1:1:2:2 placebo 3 mg/kg, placebo 4.5 mg/kg, WVE-210201 3 mg/kg, and WVE-210201 4.5 mg/kg randomization ratio
- Standard deviation of change in NSAA from baseline to 48 weeks⁵⁵ of 4.5
- Treatment difference of change in NSAA from baseline to 48 weeks of 3.0 between WVE-210201 and placebo
- Dropout rate of 10%
- Two-sided significance level of 5%

With these assumptions, a sample size of 150 patients provides 88% power to detect a difference of 3 in the change in NSAA from baseline to 48 weeks. The treatment difference of 3 was selected as it is equal to the average 1-year decline observed in longitudinal natural history studies^{55,56}.

The power of the dystrophin endpoint was based on the following assumptions:

- Two-sample t-test to test for statistical significance of treatment difference
- 150 patients randomized 1:1:2:2 placebo 3 mg/kg, placebo 4.5 mg/kg, WVE-210201 3 mg/kg, and WVE-210201 4.5 mg/kg
- Standard deviation of change in dystrophin protein level from baseline to 46 weeks of 3.0%
- Treatment difference of change in dystrophin protein level from baseline to 46 weeks of 4.0% between WVE 210201 and placebo
- Dropout rate of 10%
- Two-sided significance level of 5%

With these assumptions, the power is greater than 99% to detect a difference of 4% in the change in dystrophin level from baseline to 46 weeks.

11.2 Disposition of Patients

Screened patients are defined as any patient who signed informed consent.

Randomized patients are defined as all patients, with a signed informed consent, randomized via the IXRS.

The number and percentage of patients screened, randomized, and included in the analyses, and those who complete the study, will be presented by treatment group. The number and percentage

of randomized patients who withdraw prior to completion, and the primary reason for withdrawal, will be summarized by treatment group.

Study completion information will be presented by patient in a data listing. A by-patient listing of patients who are screen failures, and the reason for screen failure, will also be presented.

11.2.1 Analysis Populations

The primary efficacy analysis population will be the intent-to-treat (ITT) population, which consists of all randomized patients. All patients will be analyzed according to the treatment to which they are randomized.

The safety population will include all randomized patients who have received at least one dose of the study drug. All patients will be analyzed according to the treatment they have actually received.

The pharmacokinetic population will be a subset of the safety population and include subjects with evaluable pharmacokinetics data.

11.3 Statistical Methods

11.3.1 Study Drug Exposure and Compliance

The extent of study treatment exposure and compliance will be summarized for the safety population. The duration of study drug exposure is defined as [last dose date – first dose date + 1 day] regardless of unplanned intermittent discontinuations. Treatment compliance is defined as the number of infusions received compared to the scheduled number of infusions. Treatment compliance, the number of infusion interruptions, and the percentage of subjects with compliance <80% will be summarized.

11.3.2 Analyses of Efficacy Endpoints

11.3.2.1 Analysis of dystrophin protein level

A primary objective of this Phase 2/3 study is to evaluate the efficacy of WVE-210201 by assessing changes in dystrophin protein levels. Therefore, the primary efficacy endpoint for the United States and Other regions, as applicable, and the key secondary endpoint for the EU and Japan is the change in dystrophin protein level (% normal) from baseline. The treatment policy estimand, which assesses the effect of treatment initially assigned at baseline (regardless of adherence to the planned course of treatment), will be used. The analysis population will be the ITT population. The main estimator is a Bayesian analysis of covariance (ANCOVA). The model will include fixed effects for mean change from baseline in dystrophin levels at each time point for placebo and fixed effects for the increase or decrease in dystrophin compared to placebo for each treatment arm at each time point.

Let the change from baseline in dystrophin level at time point j for patient i be Y_{ij} , for $j = 1, 2, 3$ and $i = 1, \dots, n$. Time periods $j = 1, 2$, and 3 , refer to the post-baseline visits at 12, 22 and 46 weeks; each patient will have one Y_{ij} with either $j = 1, 2$, or 3 . The ANCOVA model is

$$Y_{ij} = \alpha_j + \theta_{t(i),j} + \epsilon_{ij};$$

$$\epsilon_{ij} \sim N(0, \sigma_{t(i),j}^2).$$

The $\alpha_j, j = 1, 2, 3$, parameters represent the mean change from baseline in dystrophin level at each time point for placebo-treated patients. For patient i , the treatment arm is labelled $t(i)$ with 0 for placebo, 1 for WVE-210201 3 mg/kg and 2 for WVE-210201 4.5 mg/kg. The effect of treatment T at time j is the parameter $\theta_{T,j}, T = 0, 1, 2$ and $j = 1, 2, 3$. For placebo, the effect is assumed to be 0 ($\theta_{0,j} = 0$). Thus, the treatment effect parameter for treatment T at time j represents the mean difference in the change from baseline in dystrophin at time j compared to placebo. The errors for the individual observations, ϵ_{ij} , are assumed independent and follow a normal distribution. The standard deviation, $\sigma_{T,j}, T = 0, 1, 2$ and $j = 1, 2, 3$, is specific to treatment arm and visit.

Summaries of the posterior distribution for the treatment difference in dystrophin compared to placebo at each time point for each arm will be provided including the probability that each treatment is superior to placebo at each time point, $\Pr(\theta_{T,j} > 0)$, as well as mean and 95% credible intervals.

The dystrophin analysis will be supplemented with dystrophin data from the ongoing Open-label extension study to the Phase 1 trial (WVE-DMDX51-002). These results will be available at the time of the first dystrophin interim analysis.

Missing dystrophin data can result from intercurrent events which include discontinuation of the study and non-evaluable biopsies. Previous pivotal studies in DMD, including exon skipping therapies, have had low study discontinuation rates (e.g. 0.6% and 2.7%) so it is anticipated that missing data resulting from study discontinuation will be limited (^{57,58}). With the selected estimand, missing dystrophin results due to study discontinuation will be handled using baseline imputation. Non-evaluable dystrophin will be addressed using imputation under the assumption of missing-at-random (MAR). The regression method for monotone missing data will be used for the multiple imputation with baseline dystrophin as a covariate and imputation stratified by treatment arm.

There will be two interim dystrophin efficacy analyses and a final dystrophin efficacy analysis. The dystrophin treatment effects will be declared significant at the interim or final analyses using a gatekeeping strategy where the WVE-210201 4.5 mg/kg arm is assessed first and, if significant, the WVE-210201 3 mg/kg arm is assessed. To account for the three possible analyses of the dystrophin treatment effects, a Bonferroni-level adjustment will be applied. A one-sided, significance threshold of $1 - (0.025/3) = 0.991667$ will be used for the Bayesian posterior probability of superiority of each dose compared to placebo. If successful for WVE-

210210 4.5 mg/kg, the same threshold will be used for WVE-210210 3 mg/kg. Specifically, success will be declared for WVE-210201 4.5 mg/kg if

1. $\Pr(\theta_{2,1} > 0) > 0.991667$ at the first dystrophin interim analysis,
2. $\Pr(\theta_{2,2} > 0) > 0.991667$ at the second dystrophin interim analysis, or
3. $\Pr(\theta_{2,3} > 0) > 0.991667$ at the final dystrophin analysis.

With this plan, the 12-week WVE-210201 4.5 mg/kg treatment effect is assessed at the first dystrophin interim analysis, the 22-week WVE-210201 4.5 mg/kg treatment effect is tested at the second dystrophin interim analysis and the 46-week WVE-210201 4.5 mg/kg treatment effect is tested at the final dystrophin interim analysis. Similar comparisons will be made for the WVE-210201 3 mg/kg treatment effect if the 4.5 mg/kg treatment effect is significant.

11.3.2.2 Analysis of North Star Ambulatory Assessment (NSAA)

Another primary objective is to evaluate the efficacy of WVE-210201 by assessing changes in the NSAA. Therefore, the primary efficacy endpoint for the EU and Japan and the key secondary endpoint for the United States and Other regions is the change in NSAA from baseline over 48 weeks. The treatment policy estimand which assesses the effect of treatment initially assigned at baseline (regardless of adherence to the planned course of treatment) will be used. The analysis population will be the ITT population. The main estimator will be a Bayesian progression model (BPM) to compare the change in NSAA between patients treated with WVE-210201 and placebo treated patients^{59,60}. The placebo data from this study will be augmented with historical control data via a Bayesian meta-analytic approach.

The BPM assumes a non-parametric rate of progression of the NSAA for placebo patients and a proportional rate of slowing NSAA progression for the treated patients relative to the placebo patients at each time point. The model will include covariate effects to measure differences in the rates of progression based on patient-specific baseline covariates. Additionally, random patient variability will be accounted for using patient-level random effects of the rate of NSAA progression. Borrowing from historical control data to augment the placebo arm information will entail including a random data source effect to model the between-source variability in NSAA progression rates.

The NSAA analysis will be independent of the dystrophin analysis described in [Section 11.3.2.1](#). Let the NSAA at visit j for patient i be Y_{ij} , for $j = 0, \dots, 4$ and $i = 1, \dots, n$. The Y_{i0} observation corresponds to the baseline visit. Visits $j = 1, 2, 3, 4$ refer to the post-baseline visits (each separated by 12 weeks). Let X_i be a vector of dimension C of baseline covariates for patient i that have been standardized. The DPM is

$$Y_{ij} = \gamma_i + \exp(\theta_{t(i)} + \eta_i + \alpha X_i + \delta_{s(i)}) \sum_{k=0:j} \beta_k + \epsilon_{ij}; \\ \epsilon_{ij} \sim N(0, \sigma_{t(i),s(i)}^2).$$

Patient-specific random effects, $\gamma_i, i = 1, \dots, n$, represent the patient-specific mean NSAA at the time of randomization.

It is assumed that $\beta_0 = 0$ and the decline in NSAA per each 12-week period for a placebo patient in this study with average baseline covariates is modelled as $\beta_k, k = 1, \dots, 4$, with the sum of all β_k equal to the total decline over 48 weeks. Each β_k is assumed to be less than or equal to zero to ensure a monotonic decline.

For patient i , the treatment arm is labelled $t(i)$ with 0 for placebo, 1 for WVE-210201 3 mg/kg and 2 for WVE-210201 4.5 mg/kg. The disease rate ratio (DRR) for treatment T is the parameter $\exp(\theta_T), T = 0, 1, 2$. For a placebo-treated patient, the DRR is assumed to be 1 ($\theta_0 = 0$). Thus, the DRR parameter for treatment T represents the multiplicative change to the mean decline of a placebo-treated patient. If the DRR is less than 1, the rate of decline for treatment T is slower than placebo; the DRR value represents the proportional slowing of NSAA progression. For example, a DRR = 0.75 corresponds to a 25% slowing in the rate of NSAA progression. The WVE-210201 treatment arms will be pooled for the NSAA analysis and the restriction that $\theta_1 = \theta_2$ incorporated into the DPM. However, if the randomization to the WVE-210201 3 mg/kg arm is stopped after an interim analysis (Section 11.5), the WVE-210201 treatment arms will not be pooled. Summaries of the posterior distribution for the DRR ($\exp(\theta_T)$) for each arm will be provided including the probability that each treatment is superior to placebo, $Pr(\exp(\theta_T) < 1)$, as well the mean and 95% credible intervals for each DRR.

Patient-specific multiplicative random effects in the slope, $\exp(\eta_i), i = 1, \dots, n$, represent the patient-specific proportional increase or decrease in the rate of progression. Covariate effects are modelled as $\alpha_c, c = 1, \dots, C$, and account for explained variability in the rate of NSAA progression due to subject-specific baseline covariates.

Random data source effects to account for the between-source variability in NSAA progression rates are modelled as $\delta_{s(i)}$, where the source of each patient is labelled $s(i)$ with 0 for this study and 1:S for the historical data sources. These source effects account for the variability in the rate of progression of NSAA between placebo and historical controls in the different data sources that are not explained by baseline covariates. For a patient randomized in this study, the source effect is assumed to be 1 ($\delta_0 = 0$).

The residual errors for the individual observations, $\epsilon_{ij}, i = 1, \dots, n$ and $j = 0, \dots, 4$, are modelled as independent normal distributions with a treatment arm and source-specific standard deviation of $\sigma_{t(i),s(i)}$.

Missing NSAA data can result from intercurrent events which include discontinuation of the study and loss of ability to complete any NSAA activities. With the selected primary estimand, missing NSAA assessments or NSAA assessments collected after randomized therapy discontinuation will be imputed using a control-based imputation strategy for treated patients. Placebo patients will have missing observations imputed assuming MAR. The loss of the ability

to complete any NSAA activities will be recorded as 0 on the case report forms and used in the analysis.

The posterior probability that the DRR is less than 1 will be assessed to determine significance of the WVE-210201 NSAA treatment effect. Superiority on slowing the rate of decline on NSAA will be declared if the posterior probability that either 1) the pooled WVE-210201 treatment effect ($\theta_1 = \theta_2$; if the low dose has not been dropped) or 2) the WVE-210201 treatment effect θ_2 (if randomization to the WVE-210201 3 mg/kg has been stopped) is superior to placebo and slows the rate of NSAA progression is greater than 0.975:

$$\Pr(\exp(\theta_2) < 1) > 0.975.$$

11.3.2.3 Secondary Efficacy Analyses

The secondary efficacy endpoints will be analyzed in the ITT population using a Bayesian progression model analogous to the model described for the analysis of the NSAA endpoint.

11.3.2.4 Analysis of Open-label Treatment Period

Extensions to the BPM described above will be used to perform efficacy analyses of the extended follow-up in the OL Treatment Period.

11.3.3 Multiplicity considerations

The overall type I family-wise error rate for the primary and key secondary efficacy endpoint comparisons will be controlled at the one-sided, 2.5% error rate.

In the United States/Other regions, the dystrophin and NSAA efficacy analyses will be conducted as described in [Section 11.3.2](#). Simulations have demonstrated that the type I error rate is maintained across a range of parameterizations.

In the EU/Japan, the NSAA endpoint will be compared first and if the efficacy threshold is crossed, the dystrophin endpoint will be compared.

11.3.4 Analysis of Safety Data

The summary of safety results will be presented by treatment group. All safety analyses will be performed on the safety population using the following common rules:

- The baseline value is defined generally as the last available value before randomization.
- Adverse event observation periods are defined as follows:
 - Pretreatment AEs are AEs that developed or worsened prior to the first dose of study drug

- On-treatment AEs are AEs that developed or worsened from the first dose of study drug to study completion/discontinuation. Summaries of TEAEs will include all on-treatment AEs.
- For quantitative safety parameters based on central laboratory/reading measurements descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group.

11.3.4.1 *Adverse Events*

Treatment-emergent AEs, TEAEs assessed as related to study drug or to study procedures, and treatment-emergent SAEs will be summarized for each treatment group based on MedDRA coding of verbatim terms reported by Investigators.

Adverse event incidence tables will present, by system organ class (SOC) and preferred term, the number and percentage of patients experiencing an AE. Multiple occurrences of the same event will be counted once in the tables. The denominator for computation of percentages is the safety population within each treatment group.

Adverse event incidence tables will present, by SOC and preferred term, the number and percentage of patients experiencing an AE by severity and by relationship to treatment. In tabulating the severity of AEs, the highest severity will be assigned to a subject with more than one occurrence of the same AE. The highest level of association will be reported in subjects with differing relationships for the same AE.

Listings of all AEs, SAEs, deaths, and AEs leading to study discontinuation will be provided.

11.3.4.2 *Clinical Laboratory Evaluations*

Summary statistics of laboratory variables will be calculated for each visit or study assessment by treatment group. Shift tables showing the pattern of change from baseline to postbaseline visit(s) will be provided. Listings of laboratory data will be provided. For hematology and chemistry variables, the normal ranges will be provided, and abnormal laboratory values flagged and clinical significance indicated. A listing of clinically significant hematology and chemistry findings will be provided.

11.4 Analysis of Pharmacokinetic and Pharmacodynamic Variables

11.4.1 *Pharmacokinetic Analyses*

The individual patient plasma concentration-time data following the first dose for Japanese intensive PK subjects will be listed and displayed graphically on linear and log scales. The plasma concentration-time data will be summarized descriptively in tabular and graphical formats (linear and log scales).

For Japanese intensive PK subjects, the plasma WVE-210201 concentration data following the first dose will be analyzed by noncompartmental PK analysis (NCA). The parameters listed in [Table 12](#) will be determined if there are sufficient data. Additional PK parameters may be evaluated if deemed appropriate. The PK parameters will be summarized by treatment group.

For sparse PK concentrations, the data will be summarized by treatment week and treatment group. All subjects will be included in the summary for the sparse time points, including intensive PK subjects.

Table 12 Pharmacokinetic Parameters

| Parameter | Definition |
|---------------------|--|
| C_{\max} | Maximum observed concentration |
| AUC_{last} | Area under the plasma concentration-time curve from time zero to the last quantifiable concentration |
| AUC_{∞} | Area under the plasma concentration-time curve from time zero to infinity |
| $T_{1/2}$ | Terminal half-life |
| CL | Total body clearance |
| V_{dss} | Volume of distribution at steady state |

11.4.2 Immunogenicity

Immunogenicity analyses will be performed for all patients. Summary statistics will be provided as appropriate.

11.4.3 Muscle tissue concentration of WVE-210201

If performed, for all subjects, the tissue concentration of WVE-210201 will be summarized by treatment group.

11.5 Interim Analyses

Multiple interim efficacy analyses are planned for the Double-blind Treatment Period in this Phase 2/3 study and will include analysis of dystrophin and NSAA data.

The interim analyses will be performed by an independent statistical center (ISC) and the results will be reviewed by the DMC. Sponsor personnel responsible for the conduct of this trial will not be unblinded at the time of the interim analyses and will not have access to the interim analysis results. Procedures pertaining to the ISC and its communication with the DMC are described in an ISC Charter and Data Access Plan.

11.5.1 Dystrophin Interim Analyses

Interim analyses of dystrophin will determine if efficacy is demonstrated prior to study conclusion and may allow for stopping randomization to the WVE-210201 3 mg/kg arm. The

first interim dystrophin analysis will compare dystrophin protein levels between WVE-210201 and placebo using the Week 12 open biopsies collected from up to the first 30 patients randomized. The second interim dystrophin analysis will compare dystrophin protein levels between WVE-210201 and placebo from approximately 40 patients with Week 22 open biopsies (collected from the 31st through 70th patient). The dystrophin interim analyses will be supplemented with dystrophin data from the ongoing OL extension study to the Phase 1 trial (WVE-DMDX51-002). A final analysis of dystrophin will occur when up to 80 patients (collected from the 71st through a maximum of the 150th patient) have Week 46 open biopsies. The significance thresholds for the dystrophin analyses are described in [Section 11.3.2.1](#). If the first or second interim dystrophin analysis results in a significant WVE-210201 treatment effect, randomized patients will continue to complete 48 weeks of follow-up to assess clinical outcomes and other endpoints.

Randomization to the WVE-210201 3 mg/kg treatment arm may be stopped based on the interim analysis of dystrophin. Specifically, randomization to the WVE-210201 3 mg/kg treatment arm will stop, if there is a high posterior probability that the high dose is effective, and the low dose is less efficacious of the high dose. The specific thresholds are included in the SAP.

If randomization to the 3 mg/kg treatment arm is stopped, patients originally randomized to the 3 mg/kg treatment arm will be transitioned to the WVE-210201 4.5 mg/kg treatment arm and all future patients will be randomized to WVE-210201 4.5 mg/kg or placebo at a 2:1 ratio. For clinical endpoint analyses, including the NSAA, patients originally randomized to the WVE-210201 3 mg/kg arm who transition to the WVE-210201 4.5 mg/kg treatment arm will not be included in WVE-210201 4.5 mg/kg treatment effect estimation.

11.5.2 NSAA Interim Analyses

In addition to comparing dystrophin levels between the WVE-210201 and placebo treatment arms, there will be interim analyses for NSAA sample size re-estimation at 4 pre-specified enrollment targets. The enrollment targets are included in the DMC charter and SAP. A final NSAA analysis will take place when all randomized patients have been followed for 48 weeks. The purpose of these interim analyses is to potentially stop enrollment based on the predicted success of the 48-week NSAA analysis assuming the current trial sample size.

The predictive probability of success (PPS_{NSAA}) for 48-week NSAA given the current enrollment will be estimated at each NSAA interim analysis and based on the posterior probability that the estimated DRR, $\exp(\theta_T)$, is less than or equal to a target DRR. If the DRR meets a threshold, enrollment will stop as the probability of NSAA success is high enough not to warrant additional randomization of patients. All enrolled patients will continue in the study until completion. The target DRR and the specific thresholds are included in the SAP. If none of the thresholds are reached, the sample size of 150 will be enrolled.

12 REGULATORY, ETHICAL, AND LEGAL OBLIGATIONS

12.1 Declaration of Helsinki

The Sponsor and Investigator(s) will ensure that this Study is conducted in accordance with the most recent revision of the Declaration of Helsinki.

12.2 Good Clinical Practice

The Study will be conducted according to the study protocol and SOPs that meet the guidelines provided by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) in clinical studies, and any other applicable local regulatory requirements.

12.3 Institutional Review Boards/Ethics Committees

Federal regulations and ICH guidelines require that approval be obtained from an IRB or EC before participation of human patients in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/EC. Documentation of all IRB/EC approvals and of the IRB/EC compliance with ICH guideline E6(R2): GCP will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/EC approvals should be signed by the chairman or designee and must identify the IRB/EC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted. The study protocol, appendices, and ICFs must be approved by the IRB/EC.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding one year, or otherwise specified, by the IRB/EC. The Investigator must promptly supply the Sponsor or its designee, the IRB/EC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

12.4 Informed Consent Forms

Signed ICFs in compliance with the Declaration of Helsinki, current ICH and GCP guidelines, US Title 21 Code of Federal Regulations (CFR) Part 50, and applicable local regulations will be obtained from each patient or the patient's legal guardian before enrolling the patient in the study or performing any unusual or non-routine procedure that involves risk to the patient.

Informed consent form templates will be provided by the Sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the ICF(s) must be reviewed by the Sponsor, its designee, or both before IRB/EC submission. Once reviewed, the ICF(s) will be submitted by the Investigator to his or her IRB/EC for review and approval before the start of the study. If the ICF(s) is revised during the course of the study,

all actively participating patients must sign the revised form after it has received IRB/EC approval.

Before Screening, each prospective patient or the patient's legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the appropriate ICF.

The Investigator will retain the signed original ICF(s) and give a copy of the signed original form(s) to the patient/legal guardian.

12.5 Minor Assent

Written assent will be obtained from each minor patient, as applicable, in accordance with 21 CFR 50.55. When applicable, patients will be reconsented at the appropriate age per local law.

13 INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study in accordance with GCP guidance. These items may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB/EC but will not result in protocol amendments.

13.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient/legal guardian, except as necessary for monitoring and auditing by the Sponsor, its designee, applicable regulatory agencies, or the IRB/EC.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.2 Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/EC approval.
- A fully executed Clinical Trial Agreement.

- Curriculum vitae for the Investigator and each sub-investigator listed on the IRB/EC application.
- Financial disclosure information, as applicable.
- IRB/EC-approved ICF, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient/parent/legal guardian.
- Laboratory certifications and normal ranges for any local laboratories used by the site.

13.3 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical study registers in accordance with all national, state, and local laws or regulations.

13.4 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

13.5 Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the IRB/EC as appropriate.

13.6 Investigator's Final Report

Where applicable, the Investigator should inform the institution of study completion; the Investigator/institution should provide the IRB/EC with a summary of the study outcome and the Sponsor and regulatory authority(ies) with any reports required.

13.7 Records Retention

The Investigator/institution will retain essential documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational drug. However, these documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

13.8 Publications

All information regarding WVE-210201 supplied by the Sponsor to the Investigator or generated as a result of any clinical study is privileged and confidential information belonging to the Sponsor. The Investigator agrees to use Sponsor's confidential information solely to accomplish the study and will not use such information for any other purposes without the prior written consent of the Sponsor. The Investigator is obligated to provide the Sponsor with complete and accurate data obtained during the study. The information obtained from the clinical study will be used toward the development of WVE-210201 and may be disclosed by the Sponsor to regulatory authority(ies), other Investigators, corporate partners, and consultants as required.

It is anticipated that the results of this study may be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. The Clinical Advisory Committee (Section 14.2) will oversee any publication or presentation of the study results. Subsequently, individual Investigators may publish results from the study in compliance with their agreements with the Sponsor. A pre-publication manuscript is to be provided to the Sponsor at least 45 days prior to the submission of the manuscript to a publisher.

14 STUDY COMMITTEES

14.1 Data Monitoring Committee

A DMC will oversee the safety of patients during the study. Unblinded safety data will be reviewed periodically and on an ad hoc basis by the DMC, at least during the Double-blind period. In addition, the DMC will review the results from the planned interim analyses.

Unblinded information will be reviewed in a closed session without the Sponsor present.

Further details regarding the DMC, including committee membership, will be provided in a DMC Charter.

14.2 Clinical Advisory Committee

A Clinical Advisory Committee, consisting of a Principal Investigator and other experts in DMD, will be formed to provide advice regarding protocol and study conduct. Members of this committee will oversee any publication or presentation of the study results, which will reflect the experience of all participating sites. Authorship on the initial publications that result from the study will consist of members of the Clinical Advisory Committee, top study enrollers, and employees of the Sponsor as appropriate. Further details regarding the Clinical Advisory Committee, including committee membership, will be provided in a Clinical Advisory Committee Charter.

15 STUDY MANAGEMENT

15.1 Monitoring

15.1.1 *Monitoring of the Study*

Monitoring and auditing procedures developed by the Sponsor or designee will be followed in order to comply with ICH GCP guidelines.

During the study, a monitor from the Sponsor or designee will have regular contact with the study center for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being recorded accurately in the source documents and eCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. Verification will require direct access to all original records for each patient (eg, clinic charts), or as appropriate per local regulations.
- Record and report any protocol deviations not sent to the Sponsor or designee previously.
- Confirm AEs and SAEs have been documented properly in the eCRFs and confirm any SAEs have been forwarded to the Sponsor, and those SAEs that met criteria for reporting (ie, serious adverse drug reactions) have been forwarded to the IRB/EC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.2 Data Quality Assurance

15.2.1 *Electronic Case Report Forms and Data Management*

Subject data will be captured in an electronic data capture (EDC) system, Medidata RAVE®, provided by the Sponsor or designee. Data will be entered directly from the source documents to the eCRFs following the CRF Completion Guidelines. Source documents should be clear, complete and accurate and should include all the details of study assessments performed per the protocol. The investigator is responsible for ensuring the data entered on the eCRFs are accurate and complete and all data are entered in a timely manner.

The final eCRF data and audit trails will be archived in an electronic media and placed in the Investigator's Study File.

15.2.2 *Inspection of Records*

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/EC review, and regulatory inspections by providing direct access to all study records, or as appropriate per local regulations. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or regulatory authorities access to all study records.

The Investigator should notify the Sponsor promptly of any audits scheduled by any regulatory authorities and will promptly forward copies of any audit reports received to the Sponsor.

15.3 Management of Protocol Amendments and Deviations

15.3.1 *Modification of the Protocol*

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol, other than minor clarifications and typographical corrections, must be submitted in writing to the Investigator's IRB/EC and regulatory authorities for approval before patients can be enrolled into an amended protocol.

15.3.2 *Protocol Deviations*

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/EC. A major protocol deviation is any deviation that impacts the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

The Investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from the protocol to eliminate an immediate hazard to study patients without prior IRB/EC approval. As soon as possible after such an occurrence, the implemented deviation, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/EC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

Protocol deviations will be documented by the clinical monitor in the clinical study management system and on monitoring reports throughout the course of monitoring visits. Investigators will be notified of deviations in writing by the monitor. As required by local regulatory authorities, the Investigator will notify the IRB/EC of any applicable protocol deviations in a timely manner.

15.4 Study Termination

Although the Sponsor has every intention of completing the study, the Sponsor may terminate the study, or close an individual study site at any time for any reason. Some reasons for terminating a study or closing a site may include, but are not limited to, the following:

- The research can no longer meet its stated scientific purpose, and this assessment has been confirmed by the medical ethical review committee which has given a positive assessment of the research
- Severe non-compliance to this protocol as judged by the Investigator and/or the Sponsor
- Due to unforeseen circumstances that prevent continuation of the research

The end of the study is defined as the date on which the last patient completes the last visit (includes follow-up visit).

Upon completion or termination of the study, the medical monitor will conduct site closure activities with the Investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and SOPs.

15.5 Final Report

Whether the study is completed or terminated prematurely, the Sponsor will ensure that a final report is prepared and provided to the regulatory agency(ies), as applicable. The Sponsor will also ensure that the clinical study reports (CSRs) in marketing applications meet the standards of the ICH Guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, a Principal Investigator will be identified for the approval and signoff of the CSR. The Principal Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

The Investigator is encouraged to share the summary results with the study patients, as appropriate. The results will be posted on publicly available clinical study registers.

16 REFERENCES

1. Emery AE. Population frequencies of inherited neuromuscular diseases--a world survey. *Neuromuscul Disord*. 1991;1(1):19-29.
2. Mah JK, Korngut L, Dykeman J, Day L, Pringsheim T, Jette N. A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. *Neuromuscul Disord*. 2014;24(6):482-491.
3. Mendell JR, Shilling C, Leslie ND, et al. Evidence-based path to newborn screening for Duchenne muscular dystrophy. *Ann Neurol*. 2012;71(3):304-313.
4. Ciafaloni E, Fox DJ, Pandya S, et al. Delayed diagnosis in duchenne muscular dystrophy: data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). *J Pediatr*. 2009;155(3):380-385.
5. Kim S, Campbell KA, Fox DJ, Matthews DJ, Valdez R, STARnet MD. Corticosteroid Treatments in Males With Duchenne Muscular Dystrophy: Treatment Duration and Time to Loss of Ambulation. *J Child Neurol*. 2015;30(10):1275-1280.
6. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol*. 2010;9(1):77-93.
7. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *Lancet Neurol*. 2010;9(2):177-189.
8. Barber BJ, Andrews JG, Lu Z, et al. Oral corticosteroids and onset of cardiomyopathy in Duchenne muscular dystrophy. *J Pediatr*. 2013;163(4):1080-1084 e1081.
9. Mah JK. Current and emerging treatment strategies for Duchenne muscular dystrophy. *Neuropsychiatr Dis Treat*. 2016;12:1795-1807.
10. Manzur AY, Kinali M, Muntoni F. Update on the management of Duchenne muscular dystrophy. *Arch Dis Child*. 2008;93(11):986-990.
11. Eagle M, Bourke J, Bullock R, et al. Managing Duchenne muscular dystrophy--the additive effect of spinal surgery and home nocturnal ventilation in improving survival. *Neuromuscul Disord*. 2007;17(6):470-475.
12. Hoffman EP, Brown RH, Jr., Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell*. 1987;51(6):919-928.
13. Koenig M, Monaco AP, Kunkel LM. The complete sequence of dystrophin predicts a rod-shaped cytoskeletal protein. *Cell*. 1988;53(2):219-228.
14. Kole R, Krieg AM. Exon skipping therapy for Duchenne muscular dystrophy. *Adv Drug Deliv Rev*. 2015;87:104-107.
15. Wallace GQ, McNally EM. Mechanisms of muscle degeneration, regeneration, and repair in the muscular dystrophies. *Annu Rev Physiol*. 2009;71:37-57.
16. Nallamilli BR, Ankala A, Hegde M. Molecular diagnosis of Duchenne muscular dystrophy. *Curr Protoc Hum Genet*. 2014;83:9 25 21-29.
17. Muntoni F, Wood MJ. Targeting RNA to treat neuromuscular disease. *Nat Rev Drug Discov*. 2011;10(8):621-637.
18. Sardone V, Zhou H, Muntoni F, Ferlini A, Falzarano MS. Antisense Oligonucleotide-Based Therapy for Neuromuscular Disease. *Molecules*. 2017;22(4).

19. Muntoni F, Torelli S, Ferlini A. Dystrophin and mutations: one gene, several proteins, multiple phenotypes. *Lancet Neurol.* 2003;2(12):731-740.
20. Dominski Z, Kole R. Restoration of correct splicing in thalassemic pre-mRNA by antisense oligonucleotides. *Proc Natl Acad Sci U S A.* 1993;90(18):8673-8677.
21. Kole R, Leppert BJ. Targeting mRNA splicing as a potential treatment for Duchenne muscular dystrophy. *Discov Med.* 2012;14(74):59-69.
22. Echigoya Y, Aoki Y, Miskew B, et al. Long-term efficacy of systemic multiexon skipping targeting dystrophin exons 45-55 with a cocktail of vivo-morpholinos in mdx52 mice. *Mol Ther Nucleic Acids.* 2015;4:e225.
23. Holloway SM, Wilcox DE, Wilcox A, et al. Life expectancy and death from cardiomyopathy amongst carriers of Duchenne and Becker muscular dystrophy in Scotland. *Heart.* 2008;94(5):633-636.
24. Aartsma-Rus A, Fokkema I, Verschueren J, et al. Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations. *Hum Mutat.* 2009;30(3):293-299.
25. Exondys 51™ [package insert]. Cambridge MST, Inc; 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206488s006lbl.pdf. Accessed 28 February 2018. .
26. EMFLAZA® [package insert]. South Plainfield NPT, Inc. 2017. Available at: <http://www.emflaza.com/wp-content/uploads/2017/10/Prescribing-Information.pdf>. Accessed 28 February 2017.
27. Eckstein F. Phosphorothioate oligodeoxynucleotides: what is their origin and what is unique about them? *Antisense Nucleic Acid Drug Dev.* 2000;10(2):117-121.
28. Eckstein F. Phosphorothioates, essential components of therapeutic oligonucleotides. *Nucleic Acid Ther.* 2014;24(6):374-387.
29. Geary RS, Norris D, Yu R, Bennett CF. Pharmacokinetics, biodistribution and cell uptake of antisense oligonucleotides. *Adv Drug Deliv Rev.* 2015;87:46-51.
30. Juliano RL, Ming X, Carver K, Laing B. Cellular uptake and intracellular trafficking of oligonucleotides: implications for oligonucleotide pharmacology. *Nucleic Acid Ther.* 2014;24(2):101-113.
31. Liang XH, Sun H, Shen W, Crooke ST. Identification and characterization of intracellular proteins that bind oligonucleotides with phosphorothioate linkages. *Nucleic Acids Res.* 2015;43(5):2927-2945.
32. Miller TM, Pestronk A, David W, et al. An antisense oligonucleotide against SOD1 delivered intrathecally for patients with SOD1 familial amyotrophic lateral sclerosis: a phase 1, randomised, first-in-man study. *Lancet Neurol.* 2013;12(5):435-442.
33. Cheruvallath ZS, Wyrzykiewicz TK, Cole DL, Ravikumar T. Diastereomeric Process Control in the Synthesis of Oligodeoxyribonucleotide Phosphorothioates. *Nucleosides and Nucleotides.* 1999;18(6-7):1191-1194.
34. Iwamoto N, Butler DCD, Svrzikapa N, et al. Control of phosphorothioate stereochemistry substantially increases the efficacy of antisense oligonucleotides. *Nat Biotechnol.* 2017;published online 21 August 2017.
35. Ravikumar T, Vasulinga T, Cole DL. Development of 2'-O-Methoxyethyl Phosphorothioate Oligonucleotides as Antisense Drugs under Stereochemical Control. *Organic Process Research & Development.* 2002;6(6):798-806.

36. Stec WJ, Cierniewski CS, Okruszek A, et al. Stereodependent inhibition of plasminogen activator inhibitor type 1 by phosphorothioate oligonucleotides: proof of sequence specificity in cell culture and in vivo rat experiments. *Antisense Nucleic Acid Drug Dev.* 1997;7(6):567-573.
37. Heemskerk H, de Winter C, van Kuik P, et al. Preclinical PK and PD Studies on 2'-O-Methyl-phosphorothioate RNA Antisense Oligonucleotides in the mdx Mouse Model. *Mol Ther.* 2010;18(6):1210-1217.
38. Shen L, Frazer-Abel A, Reynolds PR, et al. Mechanistic understanding for the greater sensitivity of monkeys to antisense oligonucleotide-mediated complement activation compared with humans. *J Pharmacol Exp Ther.* 2014;351(3):709-717.
39. Frazier KS. Antisense oligonucleotide therapies: the promise and the challenges from a toxicologic pathologist's perspective. *Toxicol Pathol.* 2015;43(1):78-89.
40. Zanardi TA, Kim TW, Shen L, et al. Chronic Toxicity Assessment of 2'-O-Methoxyethyl Antisense Oligonucleotides in Mice. *Nucleic Acid Ther.* 2018;28(4):233-241.
41. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York (NY): McGraw-Hill Medical Publication Division; 2001.
42. Henry SP, Beattie G, Yeh G, et al. Complement activation is responsible for acute toxicities in rhesus monkeys treated with a phosphorothioate oligodeoxynucleotide. *Int Immunopharmacol.* 2002;2(12):1657-1666.
43. Klingler W, Jurkat-Rott K, Lehmann-Horn F, Schleip R. The role of fibrosis in Duchenne muscular dystrophy. *Acta Myol.* 2012;31(3):184-195.
44. Theadom A, Rodrigues M, Roxburgh R, et al. Prevalence of muscular dystrophies: a systematic literature review. *Neuroepidemiology.* 2014;43(3-4):259-268.
45. Mazzone ES, Messina S, Vasco G, et al. Reliability of the North Star Ambulatory Assessment in a multicentric setting. *Neuromuscul Disord.* 2009;19(7):458-461.
46. Scott E, Eagle M, Mayhew A, et al. Development of a functional assessment scale for ambulatory boys with Duchenne muscular dystrophy. *Physiother Res Int.* 2012;17(2):101-109.
47. De Sanctis R, Pane M, Sivo S, et al. Suitability of North Star Ambulatory Assessment in young boys with Duchenne muscular dystrophy. *Neuromuscul Disord.* 2015;25(1):14-18.
48. Mayhew A, Mazzone ES, Eagle M, et al. Development of the Performance of the Upper Limb module for Duchenne muscular dystrophy. *Dev Med Child Neurol.* 2013;55(11):1038-1045.
49. Beenakker EA, van der Hoeven JH, Fock JM, Maurits NM. Reference values of maximum isometric muscle force obtained in 270 children aged 4-16 years by hand-held dynamometry. *Neuromuscul Disord.* 2001;11(5):441-446.
50. Hyde SA, Steffensen BF, Floytrup I, et al. Longitudinal data analysis: an application to construction of a natural history profile of Duchenne muscular dystrophy. *Neuromuscul Disord.* 2001;11(2):165-170.
51. Sharma GD. Pulmonary function testing in neuromuscular disorders. *Pediatrics.* 2009;123 Suppl 4:S219-221.
52. Davis SE, Hynan LS, Limbers CA, et al. The PedsQL in pediatric patients with Duchenne muscular dystrophy: feasibility, reliability, and validity of the Pediatric Quality of Life Inventory Neuromuscular Module and Generic Core Scales. *J Clin Neuromuscul Dis.* 2010;11(3):97-109.

53. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr*. 2003;3(6):329-341.
54. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. *Med Care*. 1999;37(2):126-139.
55. Mazzone ES, Pane M, Sormani MP, et al. 24 month longitudinal data in ambulant boys with Duchenne muscular dystrophy. *PLoS One*. 2013;8(1):e52512.
56. Ricotti V, Ridout DA, Pane M, et al. The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials. *J Neurol Neurosurg Psychiatry*. 2016;87(2):149-155.
57. Bushby K, Finkel R, Wong B, et al. Ataluren treatment of patients with nonsense mutation dystrophinopathy. *Muscle Nerve*. 2014;50(4):477-487.
58. Goemans N, Mercuri E, Beloussova E, et al. A randomized placebo-controlled phase 3 trial of an antisense oligonucleotide, drisapersen, in Duchenne muscular dystrophy. *Neuromuscul Disord*. 2018;28(1):4-15.
59. Quintana M, Shrader J, Slota C, et al. Bayesian model of disease progression in GNE myopathy. *Stat Med*. 2018.
60. Wang G, Berry S, Xiong C, et al. A novel cognitive disease progression model for clinical trials in autosomal-dominant Alzheimer's disease. *Stat Med*. 2018;37(21):3047-3055.