Official Title: A Randomized, Double-Blind, Placebo controlled, Global Phase 3 Study of Edasalonexent in Pediatric Patients with Duchenne Muscular Dystrophy

NCT Number: NCT03703882

Applicant/MAH: Catabasis Pharmaceuticals Inc.

Version Date: 16 April 2020

CLINICAL STUDY PROTOCOL

CAT-1004-301

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, GLOBAL PHASE 3 STUDY OF EDASALONEXENT IN PEDIATRIC PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

Sponsor:	Catabasis Pharmaceuticals, Inc. 100 High Street, 28th Floor Boston, MA 02110 Tel: PI Fax: PI
Product:	Edasalonexent (CAT-1004)
IND Number:	123319
EudraCT Number:	2018-000464-29
Protocol Version:	Protocol Amendment 1 Original Protocol, 09 July 2018
Version Date:	16 April 2020

CONFIDENTIAL

Investigator's Agreement

This protocol was designed and will be conducted, recorded, and reported in accordance with the Protocol and in compliance with the principles of Good Clinical Practice (GCP), and any other applicable regulatory requirements. GCP principles are stated in "Guidance for Good Clinical Practice," International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

I have read and agree to abide by the requirements of this protocol.

Principal Investigator Signature Date

Principal Investigator Name (please print or type)

SPONSOR'S AGREEMENT

This Clinical Trial Protocol was subject to critical review and has been approved by the Sponsor. The following Personnel contributed to writing and/or approving this protocol.

PI

PI M.D., Ph.D.

PI

PI abasis Pharmaceuticals, Inc.

April 16, 2020

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Clinical Study Manager	PI Senior, Clinical Research Associate Catabasis Pharmaceuticals, Inc.	PI (office) PI (mobile) PI
Clinical Study Leader	PI, MHP Vice President, Clinical Operations Catabasis Pharmaceuticals, Inc.	PI (office) PI (mobile) PI
Study Medical Monitor	PI, MBBS Medical Monitor Orphan Reach Ltd.	PI (mobile) PI
Sponsor Medical Monitor	PI, M.D., Ph.D. Chief Medical Officer Catabasis Pharmaceuticals, Inc.	PI (office) PI (mobile) PI
Pharmacovigilance	PI Head of Pharmacovigilance and Safety Orphan Reach Ltd.	PI (office) (direct) (mobile) (fax) PI <u>Toll Free Numbers</u> Germany: PI Sweden: PI Israel: PI Ireland: PI Australia: PI Canada: PI USA: PI

1. SYNOPSIS

Name of Sponsor/Company:
Catabasis Pharmaceuticals, Inc.

Name of Investigational Product:
Edasalonexent

Name of Active Ingredient:
Edasalonexent

Title of Study:
A Randomized, Double-Blind, Placebo-Controlled, Global Phase 3 Study of Edasalonexent in Pediatric Patients with Duchenne Muscular Dystrophy

Phase of Development: 3

Objectives:

Primary

- To assess the efficacy of edasalonexent as measured by change from Baseline (CFB) on North Star Ambulatory Assessment (NSAA) Total Score in pediatric patients with Duchenne muscular dystrophy (DMD)

Secondary

- To assess the safety and tolerability of edasalonexent in pediatric patients with DMD
- To assess the effects of edasalonexent on physical function as measured by the 10-meter walk/run test (10MWT), time to stand from supine, and the 4-stair climb in pediatric patients with DMD

Methodology:

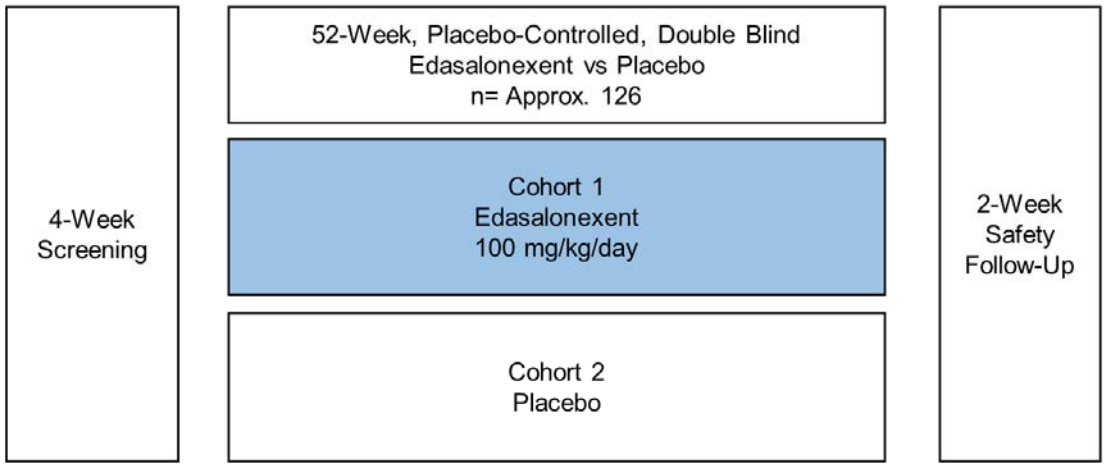
This is a randomized, double-blind, placebo-controlled, Phase 3, multisite study of edasalonexent in pediatric patients with DMD. Approximately 126 patients will be enrolled.

Eligible patients will be ambulatory boys from ≥4.0 to <8.0 years of age with a confirmed diagnosis of DMD who have not used steroids within 24 weeks prior to treatment initiation (Day 1).

As shown in the figure below, the study includes a 52-week, double-blind, placebo-controlled period comparing 1 dose level of edasalonexent with placebo, followed by a 2-week follow-up.

Following completion of the treatment period and Primary Endpoint evaluation, patients may elect to continue in the open-label extension study, pending approval by appropriate ethics committees and regulatory authorities. Patients who choose not to participate should complete the safety follow-up within 2 weeks.

CAT-1004-301 – Overview of Study Design



Double-Blind Placebo-Controlled Study

Following a Screening period to determine eligibility, approximately 126 patients will be randomized 2:1 to receive edasalonexent 100 mg/kg/day (administered as approximately 33 mg/kg 3 times per day [TID]) or placebo in double-blind fashion daily for 52 weeks. Randomization will be stratified by Baseline age (≤6.0 years or >6.0 years), time to stand from supine (≤5 seconds or >5 seconds), treatment with eteplirsen (yes or no), and region (North America or Europe/Asia/Australia). If siblings are enrolled, they will be assigned to the same treatment group.

Screening procedures should be performed within 4 weeks prior to the start of treatment on Day 1. At the discretion of the Investigator, informed consent, collection of medical history and demographic data, and collection of laboratory Screening assessments may be completed remotely by a qualified medical professional at an alternative site setting.

After Screening, eligible patients will complete Baseline procedures and begin receiving study drug (edasalonexent or placebo) on Day 1. Study drug will be orally administered as soft-gel capsules in divided doses taken with food containing at least 8 grams of fat. Patients and their families will be provided with written and verbal instructions for study drug administration, and subsequent doses will be administered remotely, except for on scheduled site visits as specified in the Schedule of Assessments (SOA).

Patients will have site visits approximately every 13 weeks with site calls in between as specified in the SOA.

The efficacy and safety of edasalonexent will be assessed at the timepoints specified in the SOA.

Efficacy assessments will include: the NSAA; timed function tests (TFTs) including the 10MWT, time to stand from supine, and the 4-stair climb; muscle strength testing; Performance of Upper Limb (PUL) entry item assessment; and assessment of health-related physical functioning as measured by the PODCI.

Safety assessments will include collection of adverse events (AEs), serious adverse events (SAEs), growth parameters, vital signs, physical examinations, clinical laboratory testing (including chemistry, hematology, and urinalysis), assessment of adrenal function (adrenocorticotrophic hormone [ACTH] and cortisol levels), and electrocardiogram (ECG).

For analysis of pharmacokinetics (PK), blood samples will be obtained for determination of edasalonexent and its metabolite concentrations.

Additionally, blood samples will be drawn to evaluate gene expression, micro-RNA, and protein biomarkers that might predict the course of disease and/or responses to treatment.

Additional cardiac ECG monitoring will be performed via a wearable cardiac monitoring device if approved for use in the participating country.

Lateral thoracolumbar spine radiography and dual energy X-ray absorptiometry (DXA) scan will be performed if approved by the appropriate governing bodies at each site or country.

A safety follow-up should occur within 2 weeks of the last dose of study drug for collection of AEs.

Inclusion / Exclusion Criteria:

The eligibility criteria are designed to include only patients with an established diagnosis of DMD based on clinical, laboratory and genetic findings who are sufficiently well (both in terms of DMD and in terms of concomitant illness) to safely participate in study procedures and provide interpretable results.

Inclusion Criteria

A patient must meet all the following criteria to be eligible for this study.

1. Written consent/assent by patient and/or legal guardian as per regional and/or Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements
2. Diagnosis of DMD based on a clinical phenotype with increased serum creatine kinase (CK) and documentation of mutation(s) in the dystrophin gene known to be associated with a DMD phenotype
3. Male sex by birth
4. Age ≥4.0 to <8.0 years (at the time of consent)
5. Able to perform stand from supine without assistance in ≤ 10 seconds
6. Able to perform the 10MWT and 4-stair climb
7. Able to swallow placebo capsules at the Screening Visit
8. Followed by a doctor or medical professional who coordinates Duchenne care on a regular basis and willingness to disclose patient's study participation with medical professionals

Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study.

1. Use of corticosteroids within 24 weeks prior to Day 1; use of inhaled, intranasal, and topical corticosteroids is permitted
2. Use of an investigational drug, idebenone, or dystrophin-focused therapy within 4 weeks or a period of 5 half-lives duration prior to Day 1 (whichever is longer) or ongoing participation in any other therapeutic clinical trial. *Exception: Patients who have received at least 24 weeks of a stable dose of eteplirsen prior to Day 1, and expected to continue treatment, will be eligible.*
3. Use of the following within 4 weeks prior to Day 1: immunosuppressive therapy, warfarin, phenytoin, S-mephenytoin, cyclosporine, dihydroergotamine, ergotamine, fentanyl, alfentanil, pimozide, quinidine, sirolimus, tacrolimus, or paclitaxel
4. Use of human growth hormone within 3 months prior to Day 1
5. Documented positive hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) or a known risk factor for hepatitis such as a blood transfusion within 12 weeks prior to Day 1
6. Hemoglobin <10.5 g/dL
7. Abnormal gamma-glutamyl transferase (GGT) (>laboratory's upper limit of normal [ULN])
8. Other prior or ongoing medical condition, known hypersensitivity to omega-3 fatty acids, physical findings, ECG findings, or laboratory abnormality (including but not limited to renal insufficiency or impaired hepatic function) 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 (e.g., a gastrointestinal condition that would impair fat absorption)

9. In the Investigator's opinion, unwilling or unable for any reason (e.g., attentional or behavioral issues) to complete all study assessments and laboratory tests and comply with scheduled visits, administration of drug, and all other study procedures

Note: Patients may be re-tested or re-screened for eligibility after discussion with the Medical Monitor.

Number of Patients:

Approximately 126 patients will be enrolled in a 2:1 ratio to receive edasalonexent or placebo.

Investigational Product, Dosage and Mode of Administration:

Edasalonexent 100 mg/kg/day (administered as approximately 33 mg/kg TID). The Sponsor will supply edasalonexent soft-gel capsules at a dose strength of 250 mg for oral administration; 100-mg capsules will be available should patients need a smaller size capsule to facilitate swallowing. An Interactive Web Response System (IWRS) will determine each patient's weight-based dosing; the total daily dose will be within 80% to 125% of each target dose. Study drug will be taken with food containing at least 8 grams of fat.

Duration of treatment:

The approximate duration of participation for each patient will be 58 weeks, including the 4-week Screening period, the 52-week dosing period, and the 2-week follow-up.

Reference therapy, dosage and mode of administration:

The Sponsor will supply placebo capsules for oral administration for assessment of swallowing prior to initiation of treatment and for administration during the study. The appearance and administration of placebo will be identical to that of the investigational product.

Criteria for evaluation:

Efficacy

The primary efficacy assessment is the NSAA Total Score.

Secondary efficacy assessments will include the following:

- 10MWT
- Stand from supine
- 4-stair climb

Additional efficacy assessments will include the following:

- Muscle strength testing
- PUL entry item assessment
- PODCI Transfer and Basic Mobility scale

Safety:

Safety will be evaluated in terms of all treatment-emergent adverse events (TEAEs) and SAEs, as well as physical examination, growth parameters, vital signs, clinical laboratory parameters (including chemistry, hematology and urinalysis), adrenal function (ACTH and cortisol levels), and ECG. Data from ECGs will be locally read and centrally evaluated.

Additional Analyses:

Plasma and urine PK will be evaluated in terms of concentrations of edasalonexent and its metabolites.

PD evaluations may include gene expression, micro-RNA, and circulating protein biomarkers to evaluate the course of disease and/or responses to treatment.

In addition, deoxyribonucleic acid (DNA) samples may be collected to permit pharmacogenomics analysis of potential markers of clinical risk/benefit as well as drug metabolizing enzyme and/or transporter analysis.

To measure heart rate and heart rate variability, additional cardiac monitoring will be performed for approximately 48 hours via a wearable cardiac monitoring device if approved for use in the participating country.

To measure bone health, lateral thoracolumbar spine radiography and DXA scan will be performed if approved by the appropriate governing bodies at each site or country. Bone radiography will be locally read and centrally evaluated.

Statistical Methods:

Analysis Populations:

The Randomized Population consists of all patients who are randomized into the study.

The Safety Population will consist of all patients who receive at least 1 dose of study drug.

The Full Analysis Population for efficacy analyses will be a modified intent to treat (mITT) population and will consist of all patients in the Randomized Population who receive at least 1 dose of study drug and provide at least 1 valid post Baseline NSAA efficacy assessment.

The Per Protocol (PP) Population will consist of all patients in the Full Analysis Population who complete the study, without any significant protocol violations.

The PK Population will consist of all patients in the Safety Population who receive at least 1 dose of edasalonexent and have at least 1 measured plasma concentration.

Other analysis populations may be defined in the statistical analysis plan (SAP).

General Considerations:

Descriptive characteristics for continuous variables will be summarized using mean, median, standard deviation, minimum and maximum values. For categorical variables, the number and percentage of patients (or observations) will be reported.

Unless otherwise defined for a particular endpoint, a patient's baseline value is the last measurement prior to initiation of study drug.

Demographics, Baseline characteristics, and DMD-specific medical history will be listed by patient, and summarized by treatment group.

Results of efficacy assessments will be listed by patient, and summarized by treatment group and timepoint as applicable. Descriptive statistics will be calculated for efficacy data as well as for CFB and differences between groups as applicable.

Results of safety assessments will be listed by patient, and summarized by treatment group and timepoint as applicable. Descriptive statistics will be calculated for safety assessments by treatment group and timepoint as applicable. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary and will be categorized by system organ class and preferred term. Abnormal clinical laboratory values will be identified as outside (above or below) the normal range and will be evaluated for clinically notable abnormalities. Reference (normal) ranges for laboratory parameters will be included in the clinical study report. Shift tables will be implemented as applicable. Concomitant medications will be listed by treatment and coded using the World Health Organization (WHO) Drug dictionary. Medical history will be listed and coded by patient using the MedDRA® dictionary.

Results of PK and PD assessments will be listed by patient and summarized by treatment group and timepoint as applicable.

Efficacy Endpoints and Analyses:

The primary efficacy endpoint will be the CFB in the NSAA Total Score at Week 52.

The CFB in NSAA Total Score will be analyzed using a mixed-model repeated-measures (MMRM) analysis of covariance (ANCOVA), implemented using SAS® Proc Mixed. The factors in the model will be Baseline age (≤6.0 years or >6.0 years), time to stand from supine (≤5 seconds or >5 seconds), region (North America

or Europe/Asia/Australia), visit, treatment group, Baseline value, Baseline value by visit, and treatment group by visit.

The primary analysis will test the treatment difference at Week 52 via the MMRM model at the 2-sided 0.05 level. The primary efficacy analysis will be performed on the Full Analysis Population with exclusions that may be defined in the SAP, such as excluding patients receiving treatment with eteplirsen.

Secondary efficacy endpoints will include the CFB on the following:

- 10MWT speed
- Stand from supine speed
- 4-stair climb speed

The secondary efficacy endpoints will be analyzed in a similar manner to the primary efficacy endpoint analysis.

Additional efficacy endpoints will include CFB on the following:

- Muscle strength testing
- PUL entry item assessment
- PODCI Transfer and Basic Mobility scale

Determination of Sample Size

Approximately 126 patients will be randomized to either edasalonexent or placebo in a 2:1 ratio. Based on Phase 1/2 data of changes in NSAA in this age group, an effect size of 0.625 is assumed. With this effect size, and assuming a dropout rate of approximately 20%, the study has approximately 80% power to show a difference between the treatment groups at a 2-sided type I error rate of 0.05.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and terms are used in this study protocol.

Abbreviation	Definition
10MWT	10-meter walk/run test
ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BID	twice a day
BMI	body mass index
CA	Competent Authorities
CFB	change from Baseline
C_{last}	last quantifiable plasma concentration
C_{max}	maximum plasma concentration
CK	creatine kinase
DHA	docosahexaenoic acid
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DXA	dual energy X-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GRMD	golden retriever muscular dystrophy
HEENT	head, eyes, ears, nose, throat
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LPS	lipopolysaccharide

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MMP9	matrix metalloproteinase 9
MMRM	mixed-model repeated-measures
MRI	magnetic resonance imaging
MuRF1	muscle RING finger protein 1
n	sample size
NCS	not clinically significant
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
NOAEL	no-observed-adverse-effect level
NSAA	North Star Ambulatory Assessment
PD	pharmacodynamic
PK	pharmacokinetic(s)
PODCI	Pediatric Outcomes Data Collection Instrument
PUL	Performance of Upper Limb
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDHM	Study Drug Handling Manual
SOA	Schedule of Assessments
SOC	System Organ Class
SOCS3	suppressor of cytokine signaling 3
SRM	Study Reference Manual
TID	3 times per day
TEAE	treatment emergent adverse event
TFT	Timed Function Test
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
WHO	World Health Organization

2. INTRODUCTION

The purpose of this multisite, Phase 3 study is to confirm the efficacy and safety of edasalonexent (CAT-1004) on ambulatory male pediatric patients with a confirmed diagnosis of Duchenne muscular dystrophy (DMD). The study is a 52-week, double-blind, placebo-controlled study comparing 100 mg/kg/day of edasalonexent (administered as approximately 33 mg/kg 3 times per day [TID]) with placebo.

Duchenne Muscular Dystrophy

DMD is a progressively debilitating and ultimately fatal inherited neuromuscular disorder affecting approximately 1 in 3,500 to 5,000 live male births worldwide. It is caused by mutations in the gene encoding dystrophin, a critical part of the protein complex that connects the cytoskeletal actin of a muscle fiber to the extracellular matrix. In the absence of dystrophin, the stress of repeated muscle contractions damages the sarcolemma resulting in repeated cycles of cellular degeneration, progressively failing regeneration, and inflammation (Blake, 2002; Emery, 2002). Over time, muscle is replaced by fibrotic tissue and fat. Of note, while a lack of dystrophin is the primary cause of DMD, it is not sufficient for disease progression, as evidenced by the heterogeneity in disease progression among different muscles (Porter, 2003; Hu, 2015).

Affected children are usually diagnosed between the ages of 3 to 5 years when they begin to show lordosis, waddling gait, toe walking, calf hypertrophy, and have difficulty climbing stairs. By 8 years of age, most patients are losing the ability to rise from the floor and climb stairs, have an increasingly labored gait, and often fall while walking. By 10 to 14 years of age, most are wheelchair-dependent. Upper limb, cardiac, and diaphragmatic muscles continue to progressively weaken during adolescence, and patients often require ventilation support in their teens. In recent years, use of ventilation support and glucocorticoids have increased life span by several years (Kohler, 2009); however, DMD still has an early mortality rate of 100%.

There is no cure for DMD and those drug treatments that have recently been approved for the disease, i.e., ataluren, which received conditional approval in the European Union, and eteplirsen (Exondys51™), which received accelerated approval in the United States, demonstrate limited efficacy and are appropriate for only a subset of patients. Current standard of care guidelines include the administration of glucocorticoids (Birnkrant, 2018a; Birnkrant, 2018b), which can delay the time to respirator dependence and the onset of scoliosis, and improve performance on measures of clinical function in patients with DMD (Manzur, 2009). However, they do not fully ameliorate symptoms or halt disease progression. Moreover, their use is often limited by numerous side effects, including growth inhibition, delay of pubertal changes, weight gain, behavioral changes, osteoporosis resulting in fractures, Cushingoid facies and habitus, cataracts, and myopathy, a particularly serious concern for patients with DMD (Manzur, 2009; Schakman, 2009; Hanaoka, 2012).

Thus, even though there are a handful of treatment options available, those options are inadequate and a significant need remains for safer and more effective treatments for patients affected by this fatal disease.

Rationale for Edasalonexent as a Potential Therapy for the Treatment of DMD

Edasalonexent, an orally administered small molecule containing covalently linked salicylic acid and docosahexaenoic acid (DHA), synergistically leverages the ability of both compounds to intracellularly inhibit activated nuclear factor kappa light chain enhancer of activated B cells

(NF-κB) to reduce NF-κB-mediated inflammation and muscle degeneration and facilitate muscle regeneration (Kopp, 1994; Yin, 1998; Cai, 2004; Zwart, 2010). Following its cellular uptake, edasalonexent is hydrolyzed into its constituents by endogenous fatty acid amide hydrolase (FAAH), simultaneously delivering salicylic acid and DHA to key intracellular targets where they significantly inhibit activated NF-κB.

In vitro, edasalonexent inhibits NF-κB and downstream cytokines known to be increased in DMD (Vu, 2016). Edasalonexent inhibits lipopolysaccharide (LPS)-stimulated pro-inflammatory gene expression (TNFα, IL-6, IL-1β, SOCS3, MMP9) in RAW264.7 macrophages and this effect is greater than that produced by DHA or the combination of DHA and salicylic acid. In addition, studies in mouse C2C12 myotubes showed that edasalonexent blocks cytokine-induced reductions in MyoD to a greater degree than dexamethasone and blunts cytokine-induced upregulation of MuRF1 and MMP9, both of which promote the degradation of key intracellular proteins and the extracellular matrix (Cai, 2004; Li, 2009). These data are consistent with selective inhibition of activated NF-κB by edasalonexent having a more positive and favorable effect on muscle degeneration and regeneration than that produced by the concomitant NF-κB inhibition and activation of the glucocorticoid receptor by glucocorticoids.

In vivo, edasalonexent inhibits NF-κB, and has positive effects in the *mdx* and golden retriever muscular dystrophy (GRMD) models of DMD. Edasalonexent reduced LPS-stimulated release of TNFα levels in normal mice, and reduced muscle inflammation and muscle fiber degeneration, preserved muscle mass, and increased the number of regenerating fibers per field in the *mdx* mouse model of muscular dystrophy (Hammers, 2016). Moreover, a single treatment with edasalonexent inhibited basal NF-κB p65 deoxyribonucleic acid (DNA) binding as well as LPS-stimulated NF-κB p65 activity and induction of TNFα protein in the GRMD dog model. Similarly, administration of CAT-1041, a closely related analog of edasalonexent that differs only in the omega-3 fatty acid moiety, significantly improved muscle endurance, increased muscle mass, and reduced fibrosis in the *mdx* mouse, and improved pulmonary function in the GRMD model of DMD.

By reducing inflammation and muscle degeneration while simultaneously facilitating muscle regeneration, pharmacological inhibition of NF-κB with edasalonexent has the potential to provide disease-modifying benefits to patients of all mutations beyond those afforded by glucocorticoids, but without their negative side effects, which are largely independent of their anti-inflammatory properties (Schacke, 2004; Newton, 2007).

2.1. Summary of Edasalonexent Nonclinical Data

In nonclinical studies, edasalonexent demonstrated reduction of NF-κB activation in vitro and in vivo, and disease-modifying effects in 2 established animal models of DMD, the *mdx* mouse and the GRMD models. To support single- and repeat-dose oral administration in healthy subjects, edasalonexent has been assessed in a series of nonclinical studies including safety pharmacology, genotoxicity, and general toxicity studies in rats and dogs, with durations of repeat dose oral administration up to 6 and 9 months, respectively.

Detailed information on all edasalonexent nonclinical studies conducted to date can be found in the Investigator's Brochure.

2.2. Summary of Edasalonexent Clinical Experience

Edasalonexent was evaluated in three Phase 1 studies in adults (Donovan, 2017). Across the 3 studies, 79 adult subjects received single doses of edasalonexent up to 6000 mg and multiple doses up to 4000 mg/day for 14 days (~100 and 67 mg/kg/day, respectively), with no identified safety concerns. Single-dose exposures of 2000 mg (~33 mg/kg) edasalonexent significantly reduced ex vivo LPS-stimulated NF-κB activity and NF-κB p65 DNA binding, while 14 days of dosing with edasalonexent reduced basal expression of NF-κB target genes in patients with type 2 diabetes with mild inflammation.

Edasalonexent is currently being evaluated in ambulatory boys with DMD from ≥4 to <8.0 years of age at enrollment who are not receiving corticosteroids in a multipart, Phase 1/2 clinical study, CAT-1004-201. Phase 1, which has been completed, was a 1-week, open-label study to assess the safety and pharmacokinetics (PK) of 3 sequential ascending doses (33, 67, or 100 mg/kg/day administered as 17 mg/kg twice daily [BID], 33 mg/kg BID, or 33 mg/kg TID) of edasalonexent under low- or high-fat conditions. Results from Phase 1 indicate that 7 days of treatment with edasalonexent at doses up to 100 mg/kg/day were safe and generally well tolerated. There were no serious adverse events (SAEs), discontinuations, or dose reductions, and the most common adverse events (AEs) were gastrointestinal, primarily mild diarrhea. Pharmacokinetic data collected showed daily exposures projected to be within the range observed in adults (on a mg/kg basis), with only modest differences between dosing after a high- or low-fat meal at the 67 mg/kg/day dose. Importantly, clinical exposure at 100 mg/kg/day was 4 times lower than exposures at the no-observed-adverse-effect level (NOAEL) in the 13-week postnatal day (PND) 21 rat study, and 2 times lower than those at the NOAEL in the 13-week dog study.

Phase 2, which has also been completed, included patients from Phase 1 as well as additional patients (total N = 31) and was a randomized, placebo-controlled study to evaluate the efficacy, safety, PK, and PD of the 2 higher doses edasalonexent (67 and 100 mg/kg/day) over 12 weeks. Both doses were safe and generally well tolerated. There were no dose-dependent safety findings and, as in Phase 1, the majority of AEs were mild in nature and the most common treatment-related AEs were gastrointestinal, primarily mild and transient diarrhea. There were no treatment-related SAEs, drug discontinuations, or dose reductions, nor were there any concerning trends in chemistry, hematology, coagulation, or adrenal function assessments. Edasalonexent plasma exposures were consistent with those observed in Phase 1. The 100 mg/kg/day dose level demonstrated numerical improvement versus placebo across multiple efficacy measures, though not statistically significant. The 67 mg/kg/day dose group had mixed efficacy results compared with both the 100 mg/kg/day dose group and placebo, which in each case were not statistically significant.

In the open-label extension, which is currently ongoing, all patients (including those who received placebo in Phase 2) were to receive open-label edasalonexent at dose levels of 67 or 100 mg/kg for up to 124 weeks. Based on results from Phase 2 and the recommendation of the Data Safety Monitoring Board (DSMB), all patients in the 67 mg/kg/day dose group were switched to the 100 mg/kg/day dose group (which was already ongoing at the time the Phase 2 results were analyzed).

In an interim analysis conducted with all data through December 31, 2017, patients on edasalonexent at 100 mg/kg/day over 60 weeks of treatment showed a slower decline in timed function test speeds (10-meter walk/run test [10MWT], 4-stair climb, and time to stand) and North Star Ambulatory Assessment (NSAA) when compared to declines in the prior off-treatment control period. In addition to the muscle function assessments, supportive changes in measures of muscle health were observed,

consistent with positive edasalonexent treatment effects. Four muscle enzymes (creatine kinase, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase) were significantly lower compared to Baseline following 12 weeks of edasalonexent treatment and at later time points, consistent with a slowing of muscle degeneration and an improvement in muscle integrity. A composite of magnetic resonance imaging (MRI) T2 rates of change in five lower leg muscles was also significantly improved through 48 weeks of 100 mg/kg/day edasalonexent treatment compared to the off-treatment control period, consistent with a reduction of inflammation in the muscle. Improvements were also seen in rates of change in both soleus and vastus lateralis magnetic resonance spectroscopy (MRS) fat fraction through 48 weeks of edasalonexent treatment compared to the off-treatment control period, consistent with a reduction of fat in the muscle. Edasalonexent remained well tolerated and no safety signals were observed. The most common adverse events, gastrointestinal, were typically mild and transient. Based on emerging safety and efficacy data, all patients moved to 133 mg/kg/day (33/33/67 mg/kg in 3 divided doses) in the open-label extension.

As of June 2018, 32 pediatric patients had received up to 112 weeks of active dosing with edasalonexent at doses up to 133 mg/kg/day, with a total combined exposure of over 45 years, with no safety concerns. More detailed information on clinical studies and potential clinical risks of edasalonexent can be found in the Investigator's Brochure.

2.3. Dose Selection Rationale

Selection of the 100 mg/kg/day dose of edasalonexent for this Phase 3 study is supported by interim results from the ongoing Phase 1/2 study of edasalonexent in same aged boys with DMD (CAT-1001-201), which showed:

- The plasma exposure of edasalonexent at the NOAEL in the 26-week rat study (2000 mg/kg/day) is approximately 4-fold higher than that expected with the anticipated clinical dose utilized in CAT-1004-201 of 100 mg/kg/day. The plasma exposure of edasalonexent at the NOAEL in the 13-week and 9-month dog studies (1000 mg/kg/day) is approximately 2-fold higher, than that expected with the anticipated clinical dose for this study of 100 mg/kg/day.
- Treatment with edasalonexent at doses of 67 mg/kg/day for up to 47 weeks, at 100 mg/kg/day for up to 84 weeks, and at 133 mg/kg/day for up to 32 weeks was safe and generally well tolerated with no dose-dependent safety findings, treatment-related SAEs, drug discontinuations, or dose reductions, and no concerning trends in chemistry, hematology, coagulation, or adrenal function assessments.
- Treatment with 100 mg/kg/day edasalonexent resulted in numerical improvements across multiple efficacy measures compared to placebo. In contrast, the 67 mg/kg/day dose group had mixed efficacy results compared with both the 100 mg/kg/day dose group and placebo. Compared to declines in the prior off-treatment control period, patients on 100 mg/kg/day edasalonexent showed a slower decline in timed function test speeds and NSAA scores over 60 weeks of treatment.

3. TRIAL OBJECTIVES

3.1. Primary

- To assess the efficacy of edasalonexent as measured by change from Baseline (CFB) on NSAA Total Score in pediatric patients with DMD

3.2. Secondary

- To assess the safety and tolerability of edasalonexent in pediatric patients with DMD
- To assess the effects of edasalonexent on physical function as measured by the 10MWT, time to stand from supine, and the 4-stair climb in pediatric patients with DMD

3.3. Overall Study Design

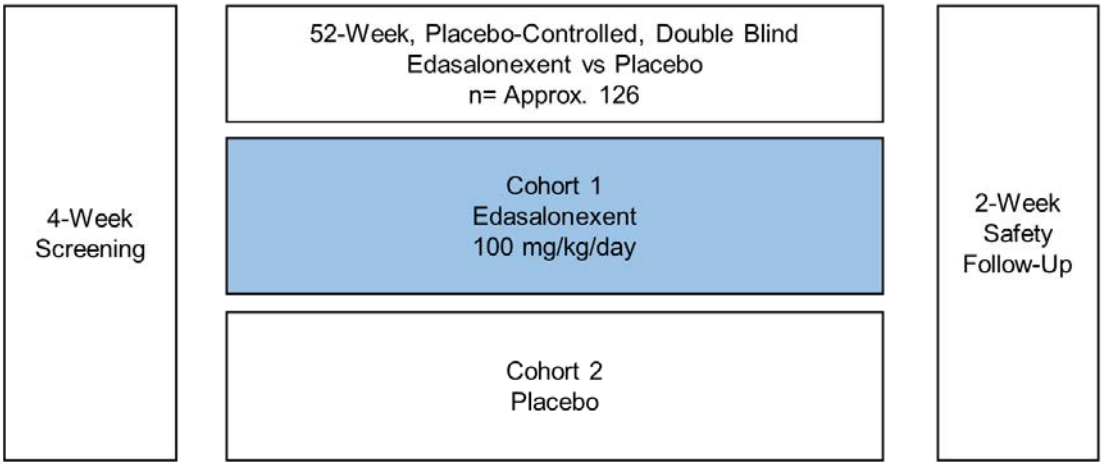
This is a randomized, double-blind, placebo-controlled, Phase 3, multisite study of edasalonexent in pediatric patients with DMD. Approximately 126 patients will be enrolled.

Eligible patients will be ambulatory boys ≥4.0 to <8.0 years of age with a confirmed diagnosis of DMD who have not used steroids within 24 weeks prior to treatment initiation (Day 1). In regions where eteplirsen is approved or there is an established access program, patients who have received at least 24 weeks of treatment with eteplirsen prior to Day 1 will be eligible for the study.

As shown in Figure 1, this is a 52-week, double-blind, placebo-controlled study comparing one dose level of edasalonexent with placebo.

Following completion of the treatment period and Primary Endpoint evaluation, patients may elect to continue in the open-label extension study, pending approval by appropriate ethics committees and regulatory authorities. Patients who choose not to participate should complete the safety follow-up within 2 weeks of the last dose of study drug.

Figure 1: CAT-1004-301 – Overview of Study Design



3.3.1. Double-Blind Placebo-Controlled Study Design

As shown in Figure 1, following a Screening period to determine eligibility, approximately 126 patients will be randomized 2:1 to receive edasalonexent 100 mg/kg/day (administered as approximately 33 mg/kg TID) or placebo in double-blind fashion daily for 52 weeks. The exact capsule count per dose will be provided. Randomization will be stratified by Baseline age (≤6.0 years or >6.0 years), time to stand from supine (≤5 seconds or >5 seconds), treatment with eteplirsen (yes or no), and region (North America or Europe/Asia/Australia). If siblings are enrolled, they will be assigned to the same treatment group.

All Screening procedures will be performed within 4 weeks prior to the start of treatment (Day 1). At the discretion of the Investigator, informed consent, collection of medical history and demographic data, and collection of laboratory Screening assessments may be completed remotely by a qualified medical professional at an alternative site setting.

After Screening, eligible patients will complete Baseline procedures and begin receiving study drug (edasalonexent or placebo) on Day 1. Study drug will be orally administered as soft-gel capsules in divided doses taken with food containing at least 8 grams of fat as detailed in Section 5.1.1. Patients and their families will be provided with written and verbal instructions for study drug administration, and subsequent doses will be administered remotely, except for on scheduled site visits as specified in the Schedule of Assessments (SOA) in Appendix 1. Nutritional guidance will be provided at Baseline. Patient compliance with nutritional guidance will be confirmed throughout treatment.

Efficacy and safety will be assessed at site visits at the timepoints specified in the SOA in Appendix 1. Efficacy assessments will include: the NSAA; timed function tests (TFTs) including the 10MWT, time to stand from supine, and the 4-stair climb; muscle strength testing; the Performance of Upper Limb (PUL) scale; and assessment of physical functioning as measured by the PODCI.

Safety assessments will include collection of AEs, SAEs, growth parameters (height and weight), vital signs, physical examinations, clinical laboratory testing (including chemistry, hematology, and urinalysis), assessment of adrenal function (adrenocorticotrophic hormone [ACTH] and cortisol levels), and electrocardiogram (ECG). To measure heart rate and heart rate variability, additional cardiac monitoring will be performed for approximately 48 hours via a wearable cardiac monitoring device if approved for use in the participating country. To measure bone health, lateral spine radiography and dual energy X-ray absorptiometry (DXA) scan will be performed if approved by the appropriate governing bodies at each site or country.

For analysis of PK, blood and urine samples will be obtained for determination of edasalonexent and its metabolite concentrations. Blood samples will be drawn for analysis of PD.

To assess acceptability and palatability of edasalonexent, caregivers will complete a study drug questionnaire.

A safety follow-up should occur within 2 weeks of the last dose of study drug for collection of AEs.

3.3.2. Study Conduct during the COVID-19 Pandemic

Ensuring the safety of patients is paramount especially during a pandemic so modifications have been made to the original study procedures and schedule of assessments to reduce the patient's risk or exposure to COVID-19 while ensuring the integrity of the study. Changes to the study visit schedule which should be considered, or deemed necessary per the local situation at each site during the

COVID-19 pandemic are captured in Appendix 2. Patients may not be able to come on-site for visits as specified in Appendix 1 or patients may be able to come on-site for visits however for a reduced amount of time to minimize risk or exposure to COVID-19, so considerations for modifying the schedule of assessments are captured in Appendix 2.

Investigators must document how restrictions or institutional requirements during the COVID-19 pandemic led to the changes in study conduct and duration of those changes and indicate which patients were impacted and how those patients were impacted.

3.3.3. Completion of a Patient's Participation in the Study and Overall Study Completion

3.3.3.1. Completion of a Patient's Participation in the Study

The length of a patient's participation in the study will be from the time the informed consent form is signed through the Week 52 visit. A patient will be considered to have completed the study when they have completed the Week 52 assessments. Patients who do not participate in the open-label extension study will be considered to have completed the study after they complete the safety follow-up.

3.3.3.2. Premature Patient Discontinuation from the Study

Parents/guardians and patients (as applicable according to site and regional regulations) are free to withdraw consent and/or discontinue participation in the study at any time, without prejudice to further treatment. A patient's participation in the study may also be discontinued at any time at the discretion of the Investigator, Medical Monitor, or Sponsor.

The reasons indicated in Section 5.2.5 for withdrawing a patient from treatment may also be justifiable reasons for the Investigator, Medical Monitor, or Sponsor to remove a patient from the study. Patients also may be discontinued from the study if the study is terminated by the Sponsor (see Section 10.3.5).

Patients who are prematurely withdrawn from the study (i.e., those who leave the study prior to completing the Week 52 assessments) will be asked to complete an early termination (ET) visit prior to their last dose of study drug and are not permitted to re-enroll in the study.

Post-study SAEs will be reported according to Section 7.6. A patient will be considered discontinued due to an AE if they discontinued due to any AE, regardless of whether the AE is considered related to investigational product. If the patient withdraws from the study due to an AE, the Investigator should arrange for the patient to be followed appropriately until the AE has resolved or stabilized (in the opinion of the Investigator).

At the end of the patient's participation in the study, the Investigator will document the reason(s) for study discontinuation in the electronic case report form (eCRF).

3.3.3.3. Overall Study Completion

The study will be considered complete when the last patient has completed their last assessment.

3.4. Discussion of Study Design, Including Choice of Control Group

This is a Phase 3 study to evaluate the efficacy, safety, PK, and PD of edasalonexent in ambulatory, male, pediatric patients with a confirmed diagnosis of DMD. This is a randomized, double-blind,

placebo-controlled study in which patients will receive either edasalonexent or placebo daily for 52 weeks.

The rationale for the dose levels and dosing regimen used in the study is provided in Section 2.3.

Population

The study's eligibility criteria are designed to include only patients with an established diagnosis of DMD who are sufficiently well (both in terms of DMD and in terms of concomitant illness) to safely participate in study procedures and provide interpretable results. Diagnostic criteria will include demonstration of a classic DMD clinical phenotype, increased serum creatine kinase (CK), and the presence of a mutation in the dystrophin gene consistent with DMD.

Eligible patients will be ambulatory boys ≥4.0 to <8.0 years of age. These gender and age criteria are intended to facilitate enrollment (as DMD is much more common in boys), and ensure that the enrolled patients will be able to complete the timed function tests included in the study as efficacy assessments. In addition, eligible patients must have not used steroids within the 24 weeks prior to initiation of study treatment (Day 1). It is important to evaluate the effects of edasalonexent in the absence of concomitant steroid use since the positive effects of glucocorticoids are thought to be at least partially mediated by their anti-inflammatory action via modulation of NF-κB, and edasalonexent is proposed to work through the same pathway (but without the negative side effects). While it is also important to evaluate the efficacy and safety of edasalonexent in the absence of other disease-modifying therapies, recent nonclinical data have shown that administration of edasalonexent in combination with eteplirsen results in increased dystrophin expression and does not reveal any increased risk. Therefore, patients who have received at least 24 weeks of treatment with eteplirsen prior to Day 1 will be eligible for the study.

For detailed information on prohibited concomitant medications, please refer to Section 5.3.

To minimize the risk for practice effects (which could mask potential treatment effects), decrease the heterogeneity of the patient population with respect to disease state, and ensure that patients are not at high risk for imminent loss of ambulation, patients will be required to do the following to enroll: stand from supine in ≤10 seconds, and complete the 10MWT and 4-stair climb.

It is strongly recommended that all patients receive annual vaccinations for influenza virus.

Safety Monitoring

The safety measures used in this study are standard and reflect appropriate monitoring of pediatric patients receiving an investigational drug. Although no adrenal abnormalities have been observed in the Phase 1/2 study, CAT-1004-201 (see the Investigator's Brochure), since weight loss and adverse effects on adrenal glands were observed in 13-week juvenile rat toxicology studies at plasma exposures higher than anticipated in humans, monitoring of adrenal function will be included in this study as a precaution. In addition to monitoring by the Investigators, sub-Investigators and Medical Monitors, a DSMB will provide oversight of the study.

Efficacy

The selection of efficacy endpoints was based on consideration of the primary clinical manifestations of DMD, namely a progressive loss of muscle strength and the associated impact of this loss on function. The potential effects of edasalonexent on muscle strength and function are assessed by

means of widely used and accepted measures of these constructs including NSAA, TFTs, muscle strength testing, PUL entry item assessment, and the PODCI Transfer and Basic Mobility scale.

4. PATIENT POPULATION AND SELECTION

4.1. Inclusion Criteria

A patient must meet all the following criteria to be eligible for this study.

1. Written consent/assent by patient and/or legal guardian as per regional and/or Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements
2. Diagnosis of DMD based on a clinical phenotype with increased serum creatine kinase (CK) and documentation of mutation(s) in the dystrophin gene known to be associated with a DMD phenotype
3. Male sex by birth
4. Age ≥4.0 to <8.0 years (at the time of consent)
5. Able to perform stand from supine without assistance in ≤10 seconds
6. Able to perform the 10MWT and 4-stair climb
7. Able to swallow placebo capsules at the Screening Visit
8. Followed by a doctor or medical professional who coordinates Duchenne care on a regular basis and willingness to disclose patient's study participation with medical professionals

4.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study.

1. Use of corticosteroids within 24 weeks prior to Day 1; use of inhaled, intranasal, and topical corticosteroids is permitted
2. Use of an investigational drug, idebenone, or dystrophin-focused therapy within 4 weeks or a period of 5 half-lives duration prior to Day 1 (whichever is longer) or ongoing participation in any other therapeutic clinical trial. *Exception: Patients who have received at least 24 weeks of a stable dose of eteplirsen prior to Day 1, and expected to continue treatment, will be eligible.*
3. Use of the following within 4 weeks prior to Day 1: immunosuppressive therapy, warfarin, phenytoin, S mephenytoin, cyclosporine, dihydroergotamine, ergotamine, fentanyl, alfentanil, pimozide, quinidine, sirolimus, tacrolimus, or paclitaxel
4. Use of human growth hormone within 3 months prior to Day 1
5. Documented positive hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) or a known risk factor for hepatitis such as a blood transfusion within 12 weeks prior to Day 1
6. Hemoglobin <10.5 g/dL
7. Abnormal gamma glutamyl transferase (GGT) (>laboratory's upper limit of normal [ULN])
8. Other prior or ongoing medical condition, known hypersensitivity to omega 3 fatty acids, physical findings, ECG findings, or laboratory abnormality (including but not limited to renal insufficiency or impaired hepatic function) 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 (e.g., a gastrointestinal condition that would impair fat absorption)

9. In the Investigator's opinion, unwilling or unable for any reason (e.g., attentional or behavioral issues) to complete all study assessments and laboratory tests and comply with scheduled visits, administration of drug, and all other study procedures

Note: Patients may be re-tested or re-screened for eligibility after discussion with the Medical Monitor.

5. TREATMENTS

5.1. Treatments Administered

5.1.1. Double-Blind Placebo-Controlled Treatment

Eligible patients will be randomly assigned 2:1 to receive either edasalonexent 100 mg/kg/day (administered as approximately 33 mg/kg TID) or placebo in double-blind fashion daily for 52 weeks. The exact capsule count per dose will be provided. All doses of study drug will be orally administered in divided doses with food containing at least 8 grams of fat. Nutritional guidance will be provided at Baseline. Patient compliance with the nutritional guidance will be confirmed throughout treatment. The acceptability and palatability of edasalonexent will be explored in this study; data will be collected from patients and caregivers.

5.1.2. Investigational Product(s) Description

Description of edasalonexent capsules:

- 100-mg capsules (Size 3 oval) containing 100 mg edasalonexent formulated with the following excipients: polysorbate-80, glyceryl monooleate (type 40), PEG-400, and dl-alpha-tocopherol, with imprint "####" using black iron oxide ink
- 250-mg capsules (Size 7.5 oval) containing 250 mg edasalonexent formulated with the following excipients: polysorbate-80, glyceryl monooleate (type 40), PEG-400, and dl-alpha-tocopherol, with imprint "####" using black iron oxide ink

Description of placebo capsules:

- Placebo 100-mg match capsules (Size 3 oval) containing the following excipients: polysorbate-80, glyceryl monooleate (type 40), PEG-400, and dl-alpha-tocopherol, with imprint "####" using black iron oxide ink
- Placebo 250-mg match capsules (Size 7.5 oval) containing the following excipients: polysorbate-80, glyceryl monooleate (type 40), PEG-400, and dl-alpha-tocopherol, with imprint "####" using black iron oxide ink

5.1.3. Packaging and Labeling

The investigational products described in Section 5.1.2 will be provided to the site by the Sponsor or designee. Refer to the Study Drug Handling Manual (SDHM) for additional details. The Sponsor or designee will provide the Investigator with packaged investigational product labeled in accordance with country-specific regulatory requirements.

5.1.4. Storage

The investigational products must be stored refrigerated at 2°C to 8°C (36°F to 46°F) at the site. Single bottles dispensed to patients may be stored at up to 25°C (77°F; controlled room temperature) for up to 30 days. Refer to the SDHM for additional details.

5.1.5. Preparation and Administration

Refer to the SDHM for additional details.

5.2. Dosing Considerations

5.2.1. Dose Selection Rationale

See Section 2.3 for details on dose rationale.

5.2.2. Dose Modification or Reduction

Temporary or persistent dose reductions may be made for safety or tolerability at any time during the study. Refer to Section 7.9 for additional details.

5.2.3. Safety Monitoring

Safety will be monitored on an ongoing basis by the Investigator, Medical Monitor, and Sponsor. In addition, the DSMB will review relevant study data (as defined in the DSMB charter) to decide on the continuation, termination, or modification of the trial (also see Section 8.4).

5.2.4. Treatment Compliance

Throughout the study, patients and their parents/caregivers will complete a diary documenting investigational product administration, and diet compliance. Upon completion of data entry, the database will undergo a quality review to ensure acceptable accuracy and completeness. In addition, site calls, which will occur throughout the study as noted in the SOA (Appendix 1), will include a compliance check on investigational product administration and diet. Detailed information regarding the study-specific dietary requirements and the process for monitoring compliance to the diet are provided in the Study Reference Manual (SRM).

5.2.5. Treatment Discontinuation

A patient's study treatment may be discontinued at any time at the patient's/parent/legal guardian's request or at the discretion of the Investigator, Medical Monitor or Sponsor. The following may be justifiable reasons for the Investigator, Medical Monitor or Sponsor to discontinue a patient from treatment:

- The patient experiences an intolerable or unacceptable AE
- The patient is unable to comply with the requirements of the protocol
- The patient participates in another investigational study without the written authorization of the Sponsor

Discontinuation of treatment does not imply withdrawal from the study.

Patients who discontinue treatment prematurely will be asked to complete the early termination visit prior to their last dose of study drug as noted in the SOA in Appendix 1.

5.3. Prior and Concomitant Medications and Therapeutic Procedures

In general, disease-modifying drugs, investigational drugs, immunosuppressive therapy, and drugs with narrow therapeutic indices metabolized by CYP3A4, CYP2C8, CYP2C9, and CYP2C19 are prohibited for at least 4 weeks prior to Day 1 and during the study (Table 2). Recent nonclinical data have shown that administration of edasalonexent in combination with eteplirsen results in increased dystrophin expression and does not reveal any increased risk. In regions where eteplirsen is approved

or there is an established access program, patients who have received at least 24 weeks of treatment with eteplirsen prior to Day 1 will be eligible for the study.

Throughout the study, Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care to patients.

Treatment with corticosteroids is prohibited within 24 weeks prior to Day 1 and during the study (Table 2).

All medications should be taken as prescribed, per Investigator judgment, even when blood samples are planned to be drawn. In addition, all concomitant medications, including supplements must be recorded in the source documentation and in the eCRF.

Note: Annual vaccination for influenza is strongly recommended for all patients.

Table 2: Prohibited Prior and Concomitant Medications

Medication	Prohibited within 24 weeks prior to Day 1	Prohibited within 4 weeks prior to Day 1[a]	Initiation prohibited throughout the study
Corticosteroids [b]	X	X	X
Deflazacort (Emflaza™)	X	X	X
Ataluren (Translarna™)		X	X
Idebenone (Raxone®)		X	X
Other investigational drugs		X	X
Immunosuppressive therapy		X	X
Warfarin, phenytoin, S mephenytoin, cyclosporine, dihydroergotamine, ergotamine, fentanyl, alfentanil, pimozide, quinidine, sirolimus, tacrolimus, paclitaxel		X	X
Eteplirsen (Exondys 51™) [c]			X

a If 5 half-lives of the drug is >4 weeks, drug is prohibited for 5 half-lives prior to Day 1.

b Use of inhaled, intranasal, and topical corticosteroids is permitted.

c Use of eteplirsen is permitted if on a stable dose for at least 24 weeks prior to Day 1.

5.4. Method of Assigning Patients to Treatment

During the study, patients will be randomly assigned in a 2:1 ratio to receive edasalonexent or placebo in double-blind fashion.

5.5. Blinding and Randomization

5.5.1. Blinding and Randomization

Approximately 126 patients will be randomized 2:1 to receive edasalonexent or placebo in double-blind fashion daily for 52 weeks. Randomization will be stratified by Baseline age (≤6.0 years or >6.0 years), time to stand from supine (≤5 seconds or >5 seconds), treatment with eteplirsen (yes or no), and region (North America or Europe/Asia/Australia).

If siblings are enrolled, only one sibling will be included in the Randomized Population, the second sibling will be assigned to the same treatment group as the randomized sibling (see Section 9.3). If both siblings meet the inclusion/exclusion criteria, the sibling to be included in the Randomized Population will be the first sibling randomized.

5.5.2. Scheduled Unblinding

After completion of the study, patients, monitors, Investigators, study center personnel, and the Sponsor will remain blinded to treatment assignments until results from the study are available.

5.5.3. Emergency Unblinding

Prior to scheduled unblinding (see Section 5.5.2), if an emergency where the identity of the investigational product must be known by the Investigator to provide appropriate medical treatment occurs, the Investigator will be allowed to unblind using the Interactive Web Response System (IWRS). Before doing this, the Investigator should make every effort to discuss the situation with the Medical Monitor.

The treatment assignment should only be unblinded when knowledge of the treatment assignment will impact the clinical management of the patient. Every reasonable attempt should be made to complete the final treatment assessment procedures prior to unblinding, as knowledge of the treatment assignment could influence patient assessment.

6. STUDY ASSESSMENTS

6.1. Study Schedule of Events

The SOA for the study is provided in Appendix 1.

The modified SOA for this study during the COVID-19 pandemic is provided in Appendix 2.

6.2. Screening and Baseline Assessments and Start of Treatment

Once written informed consent, and when appropriate, written assent is obtained, patients will be screened for eligibility for entry into the study based on the inclusion and exclusion criteria detailed in Sections 4.1 and 4.2. A full medical/surgical history will be obtained, including information relating to any prior or existing medical conditions/surgical procedures that may be relevant to the patient's experience in the study. Demographic data and DMD-specific medical history information will also be recorded. Patients will undergo a full physical examination, including vital signs (see Sections 6.4.1 and 6.4.2), safety labs, a 12-lead ECG tracing will be obtained, and body weight will be measured. Additional cardiac monitoring will be performed via a wearable cardiac monitoring device to measure heart rate and heart rate variability if approved for use in the country. The laboratory assessments shown in Appendix 3 will be performed.

Screening assessments should be completed within 4 weeks of Day 1.

At Baseline, patient eligibility for the study will be reconfirmed and the patient will be randomized. Patients will undergo a full physical examination. Height and body weight will be measured and body mass index (BMI) will be calculated. Any AEs or changes in concomitant medications since Screening will be recorded. Patients will undergo Baseline efficacy evaluations as specified in Appendix 1, and blood samples will be drawn for safety, ACTH/cortisol, biomarkers and gene expression. Bone evaluations (spine radiography and DXA scan) will be performed if approved by the appropriate governing bodies at each site or country. Patients and their families will be provided with written and verbal instructions for study drug administration. Nutritional guidance will also be given and study drug will be dispensed.

6.3. Efficacy Assessments

Efficacy will be assessed at the timepoints specified in Appendix 1.

6.3.1. North Star Ambulatory Assessment (NSAA)

The NSAA is a clinician-reported outcome instrument designed to measure ambulatory function in males with DMD (Scott, 2012). During this assessment, patients are asked to perform 17 different functional activities, including a 10MWT, rising from supine, rising from a sit to stand, standing on 1 leg, e.g., climbing and descending a step, rising from the floor, lifting the head, standing on heels, and jumping. The NSAA has undergone detailed psychometric evaluations based on traditional (reliability and validity) and modern (Rasch analysis) methods, and has been included in international clinical trials (Kinali, 2009). In addition, 36-month longitudinal data are available in patients with DMD (Mazzone, 2011; Pane, 2014b). The NSAA will be administered by trained evaluators; every effort will be made to have the same evaluator perform all assessments for a given child at the same time of day. Completion of this test is expected to take approximately 20-30 minutes.

Additional details on the performance of the NSAA are provided in the Clinical Evaluator Manual.

6.3.2. Timed Function Testing

TFTs will include the 10MWT and the stand from supine (as measured in the NSAA) as well as the 4-stair climb. These tests have been used as clinical trial endpoints in DMD and have shown response to therapeutic intervention with steroids (Mendell, 1989; Griggs, 1990; Beenakker, 2005; Manzur, 2009). TFTs will be performed by trained evaluators; every effort will be made to have the same evaluator perform all assessments for a given child at the same time of day. Completion of TFTs is expected to take approximately 10 minutes.

Additional details on the performance of the TFTs is provided in the Clinical Evaluator Manual.

6.3.3. Muscle Strength Testing

Muscle strength testing will include assessment of knee extension and elbow flexion. Muscle testing will be performed using a hand-held dynamometer. Knee myometry will be performed while the patient is in a sitting position. Elbow myometry will be performed while the patient is positioned supine. Muscle testing will be performed by trained evaluators; every effort will be made to have the same evaluator perform all assessments for a given child at the same time of day. Completion of each muscle test is expected to take approximately 10-15 minutes, for a total of 20-30 minutes.

Additional details on the assessment of muscle strength are provided in the Clinical Evaluator Manual.

6.3.4. Performance of Upper Limb (PUL) Scale

The PUL was specifically designed by an international Clinical Outcomes Group consisting of clinicians, scientists, patient advocacy groups and industries representative to assess upper limb function in ambulant and non-ambulant DMD patients (Mercuri, 2012; Mayhew, 2013b). The PUL is made up of a 6-point entry item (based on the modified Brooke Upper Extremity Scale) to define the starting functional level, and 22 items subdivided into shoulder level (6 items), middle level (9 items) and distal level (7 items) dimension (Pane, 2018). Loss of full overhead reach occurs at median age 9.6 with some boys losing the ability as early as age 5 or 6 (McDonald, 2018). Patients will perform the PUL entry item assessment as specified in Appendix 1. Based on the age of patients in this study, most patients will score a 6 on the 6-point entry item assessment. Those patients who score a 6 on the 6-point entry item assessment will not be required to perform the additional items. Patients who score below a 6 on the 6-point entry item assessment will perform a subset of the PUL battery including the shoulder level dimension and supination, consisting of 7 items with a maximum score of 14. In boys with DMD, the PUL has robust internal reliability, validity, and hierarchical scalability (Mayhew, 2013a), excellent interobserver and intra-observer reliability (Pane, 2014a), and is sensitive to changes over time (Seferian, 2015) and in response to steroid treatment (Pane, 2015). It may be most suitable for DMD patients 5 years of age and above. Completion of the 6-point entry item assessment is expected to take approximately 5 minutes. Completion of the battery of PUL assessments is expected to take approximately 20 minutes.

Additional details on the PUL scale are provided in the Clinical Evaluator Manual.

6.3.5. The Pediatric Outcomes Data Collection Instrument (PODCI)

The PODCI is a well-validated tool for assessment of health-related functioning in children, and has been used in a study of boys with DMD (Henricson, 2013). It is designed to be completed by the parent/caregiver of children aged 10 or younger, contains 86 questions, takes approximately 20-30 minutes to complete, and provides information on the following 6 scales:

- Upper Extremity and Physical Function Scale: Measures difficulty encountered in performing daily personal care and student activities.
- Transfer and Basic Mobility Scale: Measures difficulty experienced in performing routine motion and motor activities in daily activities.
- Sports and Physical Functioning Scale: Measures difficulty or limitations encountered in participating in more active activities or sports.
- Pain/Comfort Scale: Measures the level of pain experienced during the past week.
- Happiness Scale: Measures overall satisfaction with personal looks and sense of similarity to friends and others of own age.
- Global Functioning Scale: A general combined scale calculated from the first 4 scales listed above.

Parents/caregivers will complete the PODCI listed in Appendix 5 at timepoints listed in Appendix 1.

6.3.6. Assessor Training and Ensuring Compliance with Protocol-Specified Test-Administration.

The following efficacy assessments will be administered by trained evaluators: NSAA, TFTs, muscle strength testing, and PUL. To help ensure proper and consistent test administration across evaluators/sites, all evaluators will undergo training on the proper administration of these assessments prior to the study. As part of this training, therapists will administer each assessment to boys with DMD who are not participating in the study; test administrations will be videotaped, reviewed for adherence and inter-rater consistency, and feedback will be provided as applicable.

To help ensure proper and consistent test administration over the course of the study, administration of NSAA, TFTs, and muscle strength testing may be videotaped and reviewed for each patient at Screening and Week 52 and may also be required at Baseline as specified in Appendix 1.

Additional information on the training and monitoring of the administration of these tests is provided in the Clinical Evaluator Manual.

6.4. Safety Assessments

Safety will be assessed for all enrolled patients from Screening through the safety follow-up, as specified in Appendix 1. Safety parameters include physical examinations, growth parameters, vital signs, clinical laboratory tests (including chemistry, hematology, urinalysis, and tests for adrenal function), ECGs, and concomitant medication monitoring as described in Section 6.4.5 and AEs as described in Section 7. A list of all required clinical laboratory assessments is provided in Appendix 3.

6.4.1. Physical Examination and Growth Parameters

The physical examinations will include an assessment of the patient's general appearance; skin; head, ears, eyes, nose, throat (HEENT); lymph nodes; heart; lungs; abdomen; extremities/joints; and neurological and mental status. Physical examinations should be performed by the same person when possible. Height and weight will be measured at the timepoints specified in Appendix 1 and BMI will be calculated.

6.4.2. Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be measured at the timepoints specified in Appendix 1. Systolic and diastolic blood pressure (preferably assessed on the same arm each time) will be measured only after the patient is positioned in a semi-supine position and resting for at least 5 minutes.

6.4.3. Clinical Laboratory Tests

Blood and urine samples will be collected for clinical laboratory evaluations (see Appendix 3 for a complete list of analytes).

The clinical laboratory tests to be done at Screening include hematology with differential, chemistry, and urinalysis.

Blood samples for ACTH and cortisol will be obtained at Baseline before initiation of treatment.

Chemistry, hematology, and ACTH/cortisol assessments done during the treatment period will be performed in the morning when possible.

A central laboratory will provide collection supplies, arrange collection, and perform analysis of clinical laboratory evaluations indicated in Appendix 3. Using the central laboratory for unscheduled clinical laboratory evaluations and repeat testing is recommended. Procedures for the handling and shipment of all central laboratory samples will be included in the Laboratory Manual. Specimens will be appropriately processed by the central laboratory facility and laboratory reports will be made available to the Investigator in a timely manner to ensure appropriate clinical review.

The enrolling Investigator is responsible for reviewing and signing all laboratory reports unless the patient is transferred to another site for all subsequent visits. The clinical significance of each value outside of reference range will be assessed by the Investigator and documented as either not clinically significant (NCS) or clinically significant. All clinically significant values require a comment and the out-of-range value or the overlying diagnosis (or value if the diagnosis is unknown) must be captured as an AE.

Clinical laboratory reports will serve as source documents.

6.4.4. Electrocardiogram

The 12-lead ECGs will be performed only after the patient is positioned supine, resting, and quiet for a minimum of 5 minutes. If findings are abnormal, the Investigator is responsible for indicating

whether the ECG tracing is NCS or clinically significant. In addition, ECGs will be centrally evaluated.

6.4.5. Concomitant Medications and Therapies

Concomitant medications and therapies are to be assessed at all visits. Reasonable efforts will be made to determine all treatments (pharmacological and non-pharmacological) received by the patient.

A medication/therapy is considered concomitant if it is taken/administered at any time from Screening through the final study evaluation.

Data on pharmacological and non-pharmacological treatments will be recorded on an eCRF page, to include: drug name/name of procedure, dose, route, regimen, start date, stop date, and indication. At each study visit, the parent or caregiver will be asked about any additional treatments or any changes in regimen or dosages since the last visit. Indications for any new medications or therapies during the study period will be recorded as an AE.

Patients and their parents/caregivers will be contacted by the site between scheduled visits to assess concomitant medications and AEs (as indicated in Appendix 1).

For detailed information on prohibited concomitant medications please refer to Section 5.3.

6.5. Pharmacokinetic Assessments

Samples for determination of edasalonexent and its metabolite concentrations will be drawn at selected visits as detailed in Appendix 1.

In addition to the PK analyses described, any of the collected PK plasma and urine samples from study patients may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of study drug with plasma constituents.

6.6. Pharmacodynamic Assessments

Blood samples will be obtained at selected visits as indicated in Appendix 1. Assessments may include:

- Circulating protein biomarkers to evaluate course of disease and/or response to treatment
- DNA, RNA (ribonucleic acid), and micro-RNA samples may be collected and used for pharmacogenomic analyses that might predict the course of disease and/or responses to treatment as well as analysis of drug metabolizing enzyme and/or transporters.

Details of blood collection procedures will be provided in the Laboratory Manual.

6.7. Cardiac Monitoring

Patients with DMD are known to have resting tachycardia even in the age range in this clinical study (Thomas, 2012). Additionally, decreases in heart rate variability have been observed (Thomas, 2015). Since decreases in heart rate to age-normative values were observed in a previous clinical study (CAT-1004-201), measures of heart rate and variability will be collected for approximately 48 hours via a wearable cardiac monitoring device if approved for use in the participating country. In addition, the results from the patient's last cardiac assessment should be documented as part of

medical history. Prospective cardiac assessments performed should also be documented as part of ongoing procedures.

6.8. Bone Evaluations

Patients with DMD have a deficiency of bone mineral density and increased incidence of bone fractures which becomes more severe when taking corticosteroids. Patients who use corticosteroids have over two times as many fractures as steroid naïve patients (King, 2007). Fractures that occur in lower extremities can lead to early loss of ambulation. Bone evaluations will be performed through lateral thoracolumbar spine radiography and DXA scan. In Germany, bone assessment will not be performed until the respective approvals from the German Federal Office for Radiation Protection (Bundesamt für Strahlenschutz) become available. A qualified medical professional will review the results of the lateral thoracolumbar spine radiography and DXA scan and designate the findings as normal or abnormal; if abnormal, the Investigator will indicate whether the scans are NCS or clinically significant. In addition, bone radiography will be centrally evaluated.

6.9. Study Drug Acceptability

To evaluate the acceptability and palatability of edasalonexent, caregivers will complete the study drug questionnaire listed in Appendix 4 at timepoints indicated in Appendix 1.

6.10. Total Volume of Blood Collected

The total number of venipunctures and the total volume of blood collected during the study will be limited to that needed for safety monitoring, PK, and PD measurement. Refer to the SRM and/or laboratory manual for the collection preparation and procedures as well as the estimated total volume of blood to be collected during the study. The total blood volume collected from each patient for the entire study is within the guidelines set forth by the World Health Organization (WHO) (Howie, 2011).

7. ADVERSE EVENTS AND ADVERSE EVENT REPORTING

At each study visit, patients will be evaluated for new AEs and the status of existing AEs. The Investigator may elicit symptoms using an open-ended question, followed by appropriate questions that clarify the patient's verbatim description of AEs or change in concomitant medications. The enrolling Investigator is responsible for safety oversight of data for all visits unless the patient is transferred to another site for all subsequent visits. All AEs from the time of signing the informed consent through follow-up will be recorded on the eCRF.

7.1. Timeframe for Collection of Adverse Events

7.1.1. Adverse Events Occurring Prior to Study Treatment

All AEs that occur between the time informed consent is provided and the patient's receipt of the first dose of investigational product will be considered pretreatment AEs.

7.1.2. Adverse Events Occurring After Study Treatment

All AEs that occur from the time of the administration of the first dose of investigational product through the end of the safety follow-up will be considered treatment-emergent AEs (TEAEs).

7.1.3. Adverse Events Occurring Following Patient Discontinuation of Treatment

For patients who prematurely discontinue study treatment (see Section 5.2.5), but who are not withdrawn from the study, AEs will continue to be recorded until the patient completes the study (see Section 3.3.3.1 for definition of patient completion). See Section 7.6 for reporting requirements after the patient completes the study.

7.2. Definitions

7.2.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient, which does not necessarily have a causal relationship with the investigational product (active or placebo drug, biologic, or device). An AE can, therefore, be any unfavorable and unintended symptom, sign, disease or condition, or test abnormality, whether considered related to the investigational product.

Adverse events include:

- Symptoms described by the patient or signs observed by the Investigator or medical staff
- Test abnormalities (laboratory tests, ECG, X-rays, etc.) that result in an alteration in medical care (diagnostic or therapeutic)

Adverse events do not include:

- Changes that are characteristic of disease progression in Duchenne

Abnormalities present at Baseline are considered AEs only if they reoccur after resolution or they worsen during the study.

7.2.2. Definition of a Serious Adverse Event

Seriousness of an AE serves as a guide for defining regulatory reporting obligations. An SAE is any AE that results in any of the following:

Death: The patient died as the result of the event.

Life-threatening event: Any AE that places the patient, in the view of the Investigator, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that had it occurred in a more severe form, might have caused death.

Required or prolonged inpatient hospitalization: The AE resulted in an initial inpatient hospitalization or prolonged an existing hospitalization of the patient. Note: Planned hospital admissions, or surgical procedures for an illness or disease that existed before the administration of the study treatment or before the patient was enrolled in the study, will not be captured as SAEs unless they occur at a time other than the planned date.

Persistent or significant disability/incapacity: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.

Congenital anomaly/birth defect: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the investigational product.

Important medical events: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.3. Evaluation of Adverse Events/Serious Adverse Events

7.3.1. Relationship to Study Treatment

Assessment of the association between the AE and study drug exposure is important for regulatory reporting. For each AE/SAE, the Investigator will determine whether there is a reasonable possibility that the AE may have been caused by the study drug according to the following categories:

Not Related: The AE is clearly not related to study drug.

Unlikely Related: There is no evidence of a causal relationship between study drug and the AE; although such relationship cannot be ruled out.

Possibly Related: There is some evidence supporting the possibility of a causal relationship between study drug and the AE.

Related: There is strong evidence that there is a causal relationship between study drug and the AE.

A relationship to the investigational product must be given for each AE/SAE recorded, even if there is only limited information at the time. The Investigator may change his/her opinion of causality in light of follow-up information, amending the AE/SAE report accordingly.

7.3.2. Severity Grading of Adverse Event Scoring

Note that severity is not the same as "seriousness," which is defined in Section 7.2.2.

The Investigator will grade the severity of all AEs/SAEs as mild, moderate, or severe, based on the following definitions (developed from Clinical Data Interchange Standards Consortium [CDISC] Study Data Tabulation Model [SDTM] standard terminology v3.1.1):

Mild: An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: An AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

Severe: An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

7.3.3. Outcome

Outcome describes the status of the AE. The Investigator will provide information regarding the patient outcome of each AE.

Possible results of an AE outcome are defined as follows:

Fatal: The termination of life as a result of an AE.

Not recovered/not resolved: The patient has not recuperated or the AE has not improved.

Recovering/resolving: The patient is recuperating or the AE is improving.

Recovered/resolved: The patient has recuperated or the AE has resolved.

Recovered with sequelae/resolved with sequelae: The AE has resolved, but the patient has been left with symptoms or pathology.

Unknown: Not known, not observed, not recorded, or refused.

7.3.4. Action Taken Regarding the Investigational Product

The Investigator will be required to provide the action taken regarding investigational product (e.g., active, comparator) in response to the AE according to the following categories:

Dose not changed: No change in administration of the investigational product.

Dose reduced: Reduction in the frequency, strength or amount of investigational product administered.

Drug (investigational product) interrupted: Temporary interruption (termination) in administration of the investigational product.

Drug (investigational product) withdrawn: Administration of the investigational product terminated (no further dosing).

Not applicable: Determination of a value is not relevant in the current context.

Unknown: Not known, not observed, not recorded, or refused.

7.4. Recording of Adverse Events/Serious Adverse Events

All AEs/SAEs experienced by the patient will be recorded on the eCRF. The following information will be recorded: a concise description of the event; date and time of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, and relationship to investigational product; and, action taken regarding the investigational product. Abnormal vital signs, laboratory results, or other abnormal safety assessments noted in Section 6.4 will be recorded as an AE if they meet the definition of an AE (see Section 7.2). When possible, a diagnosis should be recorded as an AE rather than symptoms or isolated laboratory abnormalities related to that diagnosis. A medical or surgical procedure is not an AE; rather the condition leading to the procedure should be recorded as the AE. If the condition is not known, the procedure must be reported as an AE instead. Similarly, death is not an AE, but rather is the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then death must be reported as an AE.

All SAEs experienced by the patient will be recorded on the AE eCRF and reported to the Sponsor or its designee according to Section 7.6.

7.5. COVID-19 Adverse Events and/or Serious Adverse Events

For any study participants exhibiting symptoms consistent with COVID-19, these need to be captured as adverse events or serious adverse events according to the established safety reporting system specified in the study protocol. In the event a participant tests positive for COVID-19, or if no testing is available, ensure appropriate documentation of the AE and/or SAE of COVID-19 is reflected in the eCRF and the study specific SAE report form.

7.6. Reporting of Serious Adverse Events

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria in Section 7.2.2). SAEs that the Investigator considers related to study drug that occur after the 30-Day follow-up period must also be reported.

All SAEs should be reported immediately within 24 hours of site awareness of the event. The Investigator should complete the paper study SAE report form and send the initial SAE report within 24 hours to PV department via email/fax as per contact details below.

Safety Contact Information:

E-mail: PI

Office: PI

Direct: PI P I

Mobile: PI

Fax: PI

The Investigator is required to submit SAE reports to the IRB or IEC in accordance with local requirements. All Investigators involved in trials using the same investigational product will receive

any safety alert notifications for onward submission to their local IRB/IEC as required. All reports sent to Investigators will be blinded.

The Investigator must continue to follow the patient until the SAE has resolved or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the patient dies. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to contacts above via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

7.7. Follow-up of Adverse Events/Serious Adverse Events

All AEs/SAEs documented at a previous visit/contact that are designated as not recovered/not resolved or recovering/resolving will be reviewed by the Investigator at subsequent visits/contacts.

All AEs will be followed until the parameter returns to its Baseline status, resolution of AE, completion of the patient's participation, agreement is reached between the Investigator and Sponsor that the event no longer requires follow-up, or study termination, whichever occurs first. SAEs will be followed until resolution, the condition stabilizes, or the Investigator and Medical Monitor agree that follow-up is no longer necessary. Rules for AE/SAE follow-up apply to all patients, including those withdrawn prematurely to the extent allowed by the patient's consent. The Investigator will ensure that follow-up includes further investigations consistent with appropriate medical management and patient consent to elucidate the nature and/or causality of the AE/SAE.

7.8. Pregnancy Reporting

Not applicable for this study.

7.9. Temporary or Persistent Dose Reductions

Temporary or persistent dose reductions may be made for safety or tolerability reasons in the judgment of the Principal Investigator. If at any time after initiation of treatment the patient experiences a clinically significant AE indicative of drug intolerance, the patient will undergo clinical assessment as soon as reasonably possible. The Principal Investigator should discuss any potential dose modifications or reduction with the Medical Monitor.

7.10. Monitoring of Abnormal Laboratory Values

Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are common in patients with DMD, so exclusion of patients with abnormal Baseline values is not feasible. Patients with abnormal GGT will be excluded.

During the study, liver function tests will be monitored, including ALT, AST, GGT, alkaline phosphatase, glutamate dehydrogenase, and bilirubin. If increases in ALT or AST are noted, the relationship of these to CK will be determined, as well as to GGT and measures of liver synthetic function. Trends in these parameters will be monitored. Safety alert flags for the Investigator and Medical Monitor will include an alert for increases in ALT >150 U/L with stable or decreased CK, as well as for total bilirubin, glutamate dehydrogenase, or GGT parameters greater than the ULN.

Additional information on safety alert flags will be included in the Laboratory Manual.

7.11. Stopping Rules

Either the Investigator or Medical Monitor may stop dosing in individual patients based on tolerability or AEs.

7.12. Restriction on the Lifestyle of Patients

Not applicable.

8. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

8.1. Recording of Data

The Investigator must provide the Sponsor or its designee direct access to each patient's source documents. Source documents may include, but are not limited to, the following original documents, data, and records where information is first recorded.

- Hospital records
- Medical histories and narrative statements relating to the patient's progress
- Clinical and office charts (electronic or paper)
- Operative reports
- Laboratory notes/reports
- Project-specific worksheets (e.g., for study visits), including all worksheets developed specifically for this study
- X-ray, MRI, and computed tomography (CT) reports
- Cardiac ultrasound, echocardiogram

Required data for this study will be captured using eCRFs via EDC unless otherwise specified in this document, below.

Clinical data that are not recorded on the eCRF will be captured and transferred to the Sponsor or its designee.

8.2. Data Quality Assurance

The eCRFs will be reviewed by the Sponsor's clinical monitor or designee for completeness and accuracy. Source document verification will be performed. The data will also be reviewed internally by the Sponsor's Data Management department or its designee and, if necessary, the investigational sites will be queried for corrections and/or clarifications. Upon completion of data entry and reconciliation, all EDC user access privileges will be changed to read only. Upon completion of data entry, the database will undergo a quality review to ensure acceptable accuracy and completeness.

8.3. Data Management

The format and content of the eCRF will be approved by the Sponsor or its designee prior to the start of the study. The Sponsor or its designee will be responsible for database creation, data entry if applicable, and management of data from sources other than the clinical database (e.g., laboratory data). Once all patients have completed all study visits, the database will be cleaned, locked, unblinded and the statistical analysis will be performed.

8.4. Data Safety Monitoring Board

External oversight for this trial will be provided by a DSMB, which will include physicians experienced in treating DMD and a biostatistician experienced in clinical trials. The primary

responsibility of the DSMB is to protect the safety and welfare of patients participating in this clinical trial and to ensure the integrity of the clinical trial.

Specifically, for this study, the DSMB will be responsible for examining accumulated safety data, PK, and compliance data to make recommendations concerning the continuation, termination, or modification of the trial based on the safety of the interventions under study throughout the study. The DSMB will meet with a frequency as defined in the DSMB charter.

Further information regarding the DSMB review process will be provided in the DSMB charter.

9. STATISTICAL METHODS AND PLANNED ANALYSES

9.1. General Considerations

A Statistical Analysis Plan (SAP), in compliance with the International Council for Harmonisation (ICH) and Food and Drug Administration's Guidance for Industry: "Statistical Principles for Clinical Trials", will be written and finalized prior to database lock and unblinding providing greater detail on the statistical analysis methodology.

All eCRF data, as well as any outcomes derived from the data, will be displayed in data listings.

Descriptive characteristics for continuous variables will be summarized using mean, median, standard deviation, minimum and maximum values. For categorical variables, the number and percentage of patients (or observations) will be reported.

Unless otherwise defined for a particular endpoint, a patient's baseline value is the last measurement prior to initiation of study drug.

9.2. Determination of Sample Size

Approximately 126 patients will be enrolled and assigned to either edasalonexent or placebo in a 2:1 ratio. Based on Phase 1/2 data of changes in NSAA in this age group, an effect size of 0.625 is assumed. With this effect size, and assuming a dropout rate of approximately 20%, the study has approximately 80% power to show a difference between the treatment groups at a 2-sided type I error rate of 0.05.

The number of enrolled patients on eteplirsen should not exceed their representation in the Duchenne population.

9.3. Analysis Sets

The following are the analysis populations for this study:

Randomized Population: The Randomized Population consists of all patients who are randomized into the study.

Note: If a randomized patient has a sibling assigned to the same treatment group, the non-randomized sibling (i.e., the sibling assigned to the same treatment as the randomized sibling) will not be included in the randomized population (see Section 5.5.1).

Safety Population: The Safety Population will consist of all patients who receive at least 1 dose of study drug. This will include the set of patients who were assigned the same treatment as their randomized sibling.

Full Analysis Population: The Full Analysis Population for efficacy analyses will be a modified intent to treat (mITT) population and will consist of all patients in the Randomized Population who receive at least 1 dose of study drug, and provide at least 1 valid post Baseline NSAA efficacy assessment.

Per Protocol Population: The Per Protocol (PP) Population will consist of all patients in the Full Analysis Population who complete the study, without any significant protocol violations.

PK Population: The PK Population will consist of all patients in the Safety Population who receive at least 1 dose of edasalonexent and have at least 1 measured plasma concentration.

Other analysis populations may be defined in the SAP.

9.4. Demographics and Baseline Characteristics

Demographics, including age at Baseline considered as a continuous variable, frequency of age by year, age at Baseline (≤6.0 years or >6.0 years) and Baseline characteristics, including time to stand from supine (≤5 seconds or >5 seconds) treatment with eteplirsen (yes or no), and region (North America or Europe/Asia/Australia) will be listed by patient, and summarized by treatment group and overall.

9.5. Concomitant Medications

Concomitant medications will be listed by treatment and coded using the WHO Drug dictionary.

9.6. Medical History

Medical history will be listed and coded by patient using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary Version 21.0.

9.7. DMD-Specific Medical History

DMD-specific medical history, including age at symptom onset and diagnosis, will be listed by patient, and summarized by treatment group and overall.

9.8. Patient Disposition

All patients who sign the informed consent will be included in a summary(s) of patient disposition. The number of patients randomized, and the number and percentage of patients discontinuing and completing treatment, will be presented. The number of patients discontinuing before study completion (including reason for discontinuation), and the number of patients completing the study will be presented as well. The number and percentage of patients in the various analysis populations will be presented separately.

9.9. Study Treatment Usage and Compliance

For the Safety Population, treatment duration, number of administrations, and compliance will be summarized by treatment group and overall.

9.10. Efficacy Analyses

Results of efficacy assessments will be listed by patient, and summarized by treatment group and timepoint, as applicable. For the TFTs, both the times to complete in seconds and their speed (i.e., the reciprocals) will be tabulated (in the case of the 10MWT, in units of 10 meters per second; in the case of the stand from supine and 4-stair climb in units of task per second). Descriptive statistics will be calculated for quantitative efficacy data as well as for the CFB, and differences between groups as applicable.

9.10.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be the CFB in the NSAA Total Score at Week 52.

The CFB in NSAA Total Score will be analyzed using a mixed-model repeated-measures (MMRM) analysis of covariance (ANCOVA), implemented using SAS® Proc Mixed. The factors in the model will be Baseline age (≤6.0 years or >6.0 years), time to stand from supine (≤5 seconds or >5 seconds), region (North America or Europe/Asia/Australia), visit, treatment group, Baseline value, Baseline value by visit, and treatment group by visit.

The primary analysis will test the treatment difference at Week 52 via the MMRM model at the two-sided 0.05 level. Details of the MMRM model will be provided in the SAP. The primary analysis will be performed on the Full Analysis Population with exclusions that may be defined in the SAP, such as excluding patients receiving treatment with eteplirsen.

9.10.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints will be the CFB to Week 52 on the 10MWT, stand from supine, and 4-stair climb.

The Baseline values and CFB in each will be summarized by treatment group and timepoint using descriptive statistics. The CFB will be analyzed using the same MMRM ANCOVA model as described above for the primary efficacy endpoint. The secondary efficacy analyses will be performed on the Full Analysis Population with exclusions that may be defined in the SAP, such as excluding patients receiving treatment with eteplirsen.

9.10.3. Controlling for Multiplicity

The method for controlling the overall Type I Family-wise error rate at the two-sided 0.05 level will be provided in the SAP.

9.10.4. Sensitivity Analyses of the Primary and Secondary Efficacy Endpoints

Sensitivity analyses of the primary and secondary efficacy endpoints will be specified in the SAP.

While the MMRM analysis represents the primary method for incorporating patients with missing data (i.e., observed case analyses), a multiple imputation method for addressing missing data will be applied using the primary and secondary analysis methods.

Additional details on the methods to assess the impact of missing data will be provided in the SAP.

9.10.5. Additional Efficacy Endpoints

Additional efficacy endpoints will include CFB on the following endpoints:

- Muscle strength testing
- PUL entry item assessment
- PODCI Transfer and Basic Mobility scale

The analysis methods for these endpoints will be defined in the SAP. Additional efficacy endpoints may also be defined in the SAP.

9.11. Pharmacokinetic Analyses

Serial plasma concentration time data collected for edasalonexent and its metabolites will be analyzed using non-compartmental methods for all patients with evaluable data. Actual sample and dosing times will be used for pharmacokinetic analyses. Pharmacokinetic parameters, as data permit, will be reported for individual patients and summarized using descriptive statistics by visit. Trough concentrations will be summarized separately, along with other single time-point plasma concentration data by visit. Exploratory PK-PD analyses may be performed as deemed necessary.

In addition to non-compartmental analyses or when the data do not lend to a non-compartmental approach, pharmacokinetic data will be analyzed using non-linear mixed-effects modeling approach for population pharmacokinetic analyses. For population PK analyses, data from this clinical study will be pooled with data from other clinical studies with extensive and/or sparse sampling. The population PK analyses will characterize the inter- and intra-subject variability in pharmacokinetic parameters and evaluate the effect of covariates such as but not limited to, demographics (e.g., age, body weight, race), disease status on oral clearance and volume. Exploratory population PK-PD analyses may also be performed to evaluate and characterize exposure-response relationships.

As an exploratory analysis, urine samples will be analyzed in terms of concentrations of edasalonexent and/or metabolites.

Raw and derived data will be summarized using descriptive statistics and presented graphically, as appropriate. Plasma PK parameters will be estimated from plasma concentration-versus-time data using noncompartmental analyses.

The following noncompartmental PK parameters will be calculated from plasma samples:

- Area under concentration time curve from time 0 to time of last quantifiable concentration (AUC_{last})
- Area under concentration time curve from time 0 to 4 hours post dosing (AUC_{0-4})
- Maximum plasma concentration (C_{max})
- Last quantifiable plasma concentration (C_{last})
- Time of C_{max} (T_{max})
- Time of C_{last} (T_{last})
- Time between the time of dosing and time of appearance of plasma concentration (T_{lag})

The detailed methodology will be described in the SAP.

9.12. Safety Analyses

Safety will be assessed using the incidence of treatment-emergent AEs and SAEs, physical examination findings, growth parameters, vital signs, clinical laboratory evaluations, and ECGs.

Results of all safety assessments will be listed by patient, and summarized by treatment group and timepoint as applicable.

These safety analyses will be compared qualitatively between groups; however, there will be no inferential statistical comparisons between groups.

9.12.1. Physical Examination, Growth Parameters, Electrocardiograms, and Vital Signs

Physical examination (general appearance, skin, HEENT, etc.) abnormal results will be summarized. Physical examination results will also be summarized in a shift table from Baseline.

Growth parameters (height, weight, BMI) will be compared to age-normative percentiles.

ECG results will be summarized at each timepoint, and also using shift tables from Baseline.

Vital signs (temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure), and changes from Baseline in vital signs, will be summarized descriptively at Baseline and other study timepoints. Data listings will be provided.

9.12.2. Clinical Laboratory Tests

Values at all study timepoints and changes from Baseline to post Baseline timepoints in clinical chemistry, hematology and urinalysis results will be summarized descriptively. Shift tables from Baseline to each timepoint and from Baseline to each patient's final visit will be produced by cohort and overall.

Abnormal clinical laboratory values will be identified as outside (above or below) the normal range and will be evaluated for clinically notable abnormalities. Reference (normal) ranges for laboratory parameters will be included in the clinical study report.

9.12.3. Adverse Events

Adverse events will be coded using the MedDRA® dictionary and will be categorized by system organ class (SOC) and preferred term.

An overall summary of TEAEs will include the number and percentage of patients in each cohort and overall reporting:

- Any TEAEs
- Treatment-related TEAEs
- Severe TEAEs
- Serious TEAEs, including any events resulting in death
- Treatment-related serious TEAEs
- TEAEs (and treatment-related TEAEs) leading to discontinuation of study drug

TEAEs will be summarized by SOC and preferred term, with each patient counted only once for each AE reporting level. TEAEs will also be summarized by SOC, preferred term, and severity and by SOC, preferred term, and relatedness. The most severe occurrence of a TEAE, as well as the most extreme relationship of the TEAE to the study procedures or treatment, will be used in tabulations of severity and relatedness in cases of multiple occurrences of the same TEAE.

9.13. Pharmacodynamic Analyses

Pharmacodynamic analyses may include evaluation of gene expression as well as circulating protein and micro-RNA biomarkers that help inform target engagement and efficacy. These will be assessed at the times specified in Appendix 1. Blood samples will also be collected at times specified in

Appendix 1 for pharmacogenomic studies that might predict the course of disease and/or response to treatment as well as analysis of drug metabolizing enzyme and/or transporters.

9.14. Cardiac Monitoring

Measures of cardiac autonomic dysfunction, including heart rate variability, will be measured at the times specified in Appendix 1. Results will be summarized by treatment group and timepoint as applicable.

The detailed analyses will be provided in the SAP.

9.15. Bone Evaluations

Lateral thoracolumbar spine radiography scans and DXA scans will be performed at the times specified in Appendix 1. Bone radiography will be locally read and centrally evaluated.

Results will be summarized by treatment group and timepoint as applicable.

The detailed analyses will be provided in the SAP.

9.16. Other Statistical Issues

9.16.1. Missing or Invalid Data

For the primary and secondary efficacy analyses, the MMRM analyses will be observed case analyses. Multiple imputation will be used as a sensitivity analysis to address missing data (see Section 9.10.4); additional methods will be specified in the SAP.

If a patient is not able to complete a TFT, a value of 0 tasks/second will be assigned.

If a patient initiates corticosteroid therapy or discontinues study treatment, all observations from a patient after these events will be censored from the primary and secondary efficacy analyses. Sensitivity analyses which incorporate these observations will be defined in the SAP.

9.16.2. Multisite Issues

Summary statistics for the primary and secondary efficacy endpoints will be presented by investigative site.

9.16.3. Subgroup Analyses

The SAP will address analyses of additional subgroups.

10. SPECIAL REQUIREMENTS AND PROCEDURES

This protocol was designed and will be conducted, recorded, and reported in compliance with the ICH/Good Clinical Practice (GCP) guideline. These requirements are stated in the ICH Guideline Topic E6 entitled "Guideline for Good Clinical Practice".

10.1. Institutional and Ethics Review

This protocol and a patient informed consent form, participant-facing information sheets, and any proposed advertising materials, must be reviewed and approved by an IRB/IEC, applicable regulatory authorities, and host institution(s) for written approval (where applicable) before enrollment of patients and release of investigational product. Documentation of IRB/IEC approval and the approved consent form must be received by the Sponsor or its designee prior to obtaining the patient's informed consent. These documents will also be submitted to and approved by the above parties for all substantial amendments to the original approved documents, where applicable.

10.2. Changes to the Conduct of the Study or Protocol

Any changes in the study protocol, such as changes in the study design, objectives or endpoints, inclusion and exclusion criteria, and/or procedures (except to eliminate an immediate hazard) will be implemented only after the mutual agreement of the Investigator and the Sponsor or designee. All protocol changes must be documented in protocol amendment(s). Protocol amendment(s) must be signed by the Investigator and approved by the IRB/IEC and Competent Authorities (CA), if applicable, prior to implementation. Any changes in study conduct that result from a pending amendment will be considered protocol deviations until required IRB/IEC/CA approvals are granted. Documentation of IRB/IEC/CA approval (as applicable) must be returned to the Sponsor or designee.

10.3. Investigator's Responsibilities

10.3.1. Patient Informed Consent

Investigators must adhere to GCP, which includes ethical principles that have their origin in the Declaration of Helsinki, when developing the patient informed consent form and when obtaining consent from the patient. Written informed consent from the parent or legal guardian of the patient (and written assent for pediatric patients as per regional and/or IRB/IEC requirements) is required prior to enrollment in the study. It is the responsibility of the Investigator to document the consent process within the source documents and obtain consent using an IRB-/IEC-approved consent form.

10.3.2. Case Report Forms

Copies of pertinent records relevant to the study, including all source documents, will be made available to the Sponsor or its designee on request with due precaution towards protecting the privacy of the patient.

Data will be entered by the site onto the eCRFs in the EDC system. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the eCRFs should be corrected. Changes made to the data after initial entry into the eCRF will be captured via an electronic audit trail, and should include the reason for change. Incomplete entries or entries needing additional explanation will be highlighted or queried to the Investigator for clarification.

10.3.3. Record Retention

The enrolling Investigator is responsible for oversight and maintenance of the study records and patient source documents unless the patient is transferred to another site for all subsequent visits. These records must be readily available for audit or inspection.

The Investigator must retain study records for at least 2 years after the last marketing approval has been granted, or at least 2 years have elapsed since the formal discontinuation of clinical program. However, these documents should be retained for a longer period, if required by other applicable requirements (e.g., applicable local regulatory requirement) or by an agreement with the Sponsor or its designee. The Investigator should contact the Sponsor or its designee prior to any record destruction.

Patient records or other source data must be kept for the maximum period of time mandated by the hospital, institution, or private practice, but not less than 15 years.

If off-site archiving is used, all records should be retrieved and made available for review at the time of an audit or regulatory authority inspection.

10.3.4. Monitoring

A representative of the Sponsor or its designee will visit the Investigator periodically for the purpose of monitoring the progress of this study in accordance with the protocol, GCP, and local regulations. Noncompliance with the protocol, GCP, and local regulations will be documented and corrective actions implemented, as necessary. It is the responsibility of the Investigator to be present or available for consultation during monitoring visits. During these routine visits, all data pertaining to a patient's participation in this clinical investigation must be made available to the monitor.

Monitoring during the COVID-19 pandemic is subject to Investigator and/or local restrictions. It is possible that after local restrictions are lifted, monitoring may resume with more intense pace to clean all data accumulated during the pandemic.

At any time prior to, during, or after completion of the clinical study, an audit may be performed by the Sponsor or its designee or a representative of a national regulatory agency may choose to inspect a study site. Investigators should notify the Sponsor or its designee upon notification of inspection by a representative of a national regulatory agency. A Sponsor or designee representative will be available to assist in the preparation for study site inspections. All pertinent study data should be made available for verification, audit, or inspection purposes.

10.3.5. Study or Site Termination

If the Sponsor, the Investigator, or regulatory authorities discover any conditions during the study that indicate that the study or study site should be terminated, this action may be taken after appropriate consultation between the Sponsor and the Investigator. The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, which may include the following:

- The incidence and severity of AEs in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

- Data recording is inaccurate or incomplete.
- Investigator(s) does not adhere to the protocol or applicable regulatory guidelines in conducting this study
- Submission of knowingly false information from the study site to the Sponsor or regulatory authorities

In the event that the study is terminated early, the Sponsor will provide specific guidance to investigational sites regarding the end-of-study procedures.

10.3.6. Investigational Product Control

10.3.6.1. Receipt of Investigational Product

A proof of receipt, which details the quantity and description of the investigational product, will accompany the shipment from the Sponsor or designee to the Investigator. The site must acknowledge each shipment of investigational product in the IWRS system once received. The Investigator must ensure that the investigational product is maintained in a controlled location, with limited access, and under adequate storage conditions (as described in Section 5.1.4).

10.3.6.2. Disposition of Unused Investigational Product

All unused investigational products must be maintained under adequate storage conditions in a limited-access area. If any unused material is remaining upon completion of the study, the material will be returned to the Sponsor or destroyed only after the following has been completed:

- Accountability has been performed by a representative of the Sponsor.
- Approval to return or destroy unused Investigational Product. Refer to the SDHM for further details.

10.3.6.3. Product Handling and Complaints Reporting

If there are any issues during the study related to the quality of the Investigational Product, the clinical site pharmacist or pharmacy designee should contact the Sponsor.

10.3.7. Disclosure of Data

All details related to the disclosure and publication of study data will be addressed in the Investigator's study contract.

10.3.8. Confidentiality and Data Privacy

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation (GDPR 25May2018) in European Union Member States.

Sponsor affirms the patient's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is more stringent). Sponsor requires the Investigator to permit sponsor representatives (monitor) and when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws (any copies of patients' records must be duly anonymised to protect patients' confidentiality).

Should direct access to medical records require a waiver or authorisation separate from the patient's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual. Representative of the sponsor may be required to have access to patient's medical records for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

Representative of sponsor must maintain the confidentiality of all patient's data and will not disclosed information by which patients may be identified to any third party other than those directly involved in the treatment and organization for which the patient has given explicit consent for data transfer.

11. REFERENCES

Arpan, I., R. J. Willcocks, et al. (2014). Examination of effects of corticosteroids on skeletal muscles of boys with DMD using MRI and MRS. Neurology **83**(11): 974-980.

Beenakker, E. A., N. M. Maurits, et al. (2005). Functional ability and muscle force in healthy children and ambulant Duchenne muscular dystrophy patients. Eur J Paediatr Neurol **9**(6): 387-393.

Birnkrant, D. J., K. Bushby, et al. (2018a). Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. The Lancet Neurology.

Birnkrant, D. J., K. Bushby, et al. (2018b). Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. The Lancet Neurology **17**(3): 251-267.

Blake, D. J., A. Weir, et al. (2002). Function and genetics of dystrophin and dystrophin-related proteins in muscle. Physiol Rev **82**(2): 291-329.

Cai, D., J. D. Frantz, et al. (2004). IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. Cell **119**(2): 285-298.

Donovan, J. M., M. Zimmer, et al. (2017). A Novel NF-kappaB Inhibitor, Edasalonexent (CAT-1004), in Development as a Disease-Modifying Treatment for Patients With Duchenne Muscular Dystrophy: Phase 1 Safety, Pharmacokinetics, and Pharmacodynamics in Adult Subjects. J Clin Pharmacol **57**(5): 627-639.

Emery, A. E. (2002). The muscular dystrophies. Lancet **359**(9307): 687-695.

Griggs, R. C., R. T. Moxley, 3rd, et al. (1990). Randomized, double-blind trial of mazindol in Duchenne dystrophy. Muscle Nerve **13**(12): 1169-1173.

Hammers, D. W., M. M. Sleeper, et al. (2016). Disease-modifying effects of orally bioavailable NF-kappaB inhibitors in dystrophin-deficient muscle. JCI Insight **1**(21): e90341.

Hanaoka, B. Y., C. A. Peterson, et al. (2012). Implications of glucocorticoid therapy in idiopathic inflammatory myopathies. Nat Rev Rheumatol **8**(8): 448-457.

Henricson, E., R. Abresch, et al. (2013). The 6-minute walk test and person-reported outcomes in boys with duchenne muscular dystrophy and typically developing controls: longitudinal comparisons and clinically-meaningful changes over one year. PLoS Curr **5**.

Howie, S. R. (2011). Blood sample volumes in child health research: review of safe limits. Bull World Health Organ **89**(1): 46-53.

Hu, X. and S. S. Blemker (2015). Musculoskeletal simulation can help explain selective muscle degeneration in duchenne muscular dystrophy. Muscle Nerve.

Kinali, M., V. Arechavala-Gomeza, et al. (2009). Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study. Lancet Neurol **8**(10): 918-928.

King, W., R. Ruttencutter, et al. (2007). Orthopedic outcomes of long-term daily corticosteroid treatment in Duchenne muscular dystrophy. Neurology **68**(19): 1607-1613.

Kohler, M., C. F. Clarenbach, et al. (2009). Disability and survival in Duchenne muscular dystrophy. J Neurol Neurosurg Psychiatry **80**(3): 320-325.

Kopp, E. and S. Ghosh (1994). Inhibition of NF-kappa B by sodium salicylate and aspirin. Science **265**(5174): 956-959.

Li, H., A. Mittal, et al. (2009). Matrix metalloproteinase-9 inhibition ameliorates pathogenesis and improves skeletal muscle regeneration in muscular dystrophy. Hum Mol Genet **18**(14): 2584-2598.

Manzur, A. Y., T. Kintzer, et al. (2009). Glucocorticoid corticosteroids for Duchenne muscular dystrophy. The Cochrane Library.

Mayhew, A., E. S. Mazzone, et al. (2013a). Development of the Performance of the Upper Limb module for Duchenne muscular dystrophy. Developmental Medicine & Child Neurology **55**(11): 1038-1045.

Mayhew, A. G., S. J. Cano, et al. (2013b). Detecting meaningful change using the North Star Ambulatory Assessment in Duchenne muscular dystrophy. Dev Med Child Neurol **55**(11): 1046-1052.

Mazzone, E., G. Vasco, et al. (2011). Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study. Neurology **77**(3): 250-256.

McDonald, C. M., E. K. Henricson, et al. (2018). Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. The Lancet **391**(10119): 451-461.

Mendell, J. R., R. T. Moxley, et al. (1989). Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. N Engl J Med **320**(24): 1592-1597.

Mercuri, E., C. McDonald, et al. (2012). International workshop on assessment of upper limb function in Duchenne Muscular Dystrophy: Rome, 15-16 February 2012. Neuromuscul Disord **22**(11): 1025-1028.

Newton, R. and N. S. Holden (2007). Separating transrepression and transactivation: a distressing divorce for the glucocorticoid receptor? Mol Pharmacol **72**(4): 799-809.

Pane, M., G. Coratti, et al. (2018). Upper limb function in Duchenne muscular dystrophy: 24 month longitudinal data. PLOS ONE **13**(6): e0199223.

Pane, M., L. Fanelli, et al. (2015). Benefits of glucocorticoids in non-ambulant boys/men with Duchenne muscular dystrophy: A multicentric longitudinal study using the Performance of Upper Limb test. Neuromuscul Disord **25**(10): 749-753.

Pane, M., E. S. Mazzone, et al. (2014a). Reliability of the Performance of Upper Limb assessment in Duchenne muscular dystrophy. Neuromuscular Disorders **24**(3): 201-206.

Pane, M., E. S. Mazzone, et al. (2014b). Long term natural history data in ambulant boys with Duchenne muscular dystrophy: 36-month changes. PLoS One **9**(10): e108205.

Porter, J. D., A. P. Merriam, et al. (2003). Dissection of temporal gene expression signatures of affected and spared muscle groups in dystrophin-deficient (mdx) mice. Hum Mol Genet **12**(15): 1813-1821.

Schacke, H., A. Schottelius, et al. (2004). Dissociation of transactivation from transrepression by a selective glucocorticoid receptor agonist leads to separation of therapeutic effects from side effects. Proc Natl Acad Sci U S A **101**(1): 227-232.

Schakman, O., H. Gilson, et al. (2009). Mechanisms of muscle atrophy induced by glucocorticoids. Horm Res **72 Suppl 1**: 36-41.

Scott, E., M. Eagle, et al. (2012). Development of a functional assessment scale for ambulatory boys with Duchenne muscular dystrophy. Physiother Res Int **17**(2): 101-109.

Seferian, A. M., A. Moraux, et al. (2015). Upper limb strength and function changes during a one-year follow-up in non-ambulant patients with Duchenne Muscular Dystrophy: an observational multicenter trial. PLoS One **10**(2): e0113999.

Thomas, T. O., J. L. Jefferies, et al. (2015). Autonomic dysfunction: a driving force for myocardial fibrosis in young Duchenne muscular dystrophy patients? Pediatr Cardiol **36**(3): 561-568.

Thomas, T. O., T. M. Morgan, et al. (2012). Correlation of heart rate and cardiac dysfunction in Duchenne muscular dystrophy. Pediatr Cardiol **33**(7): 1175-1179.

Vu, C. B., J. E. Bemis, et al. (2016). Synthesis and Characterization of Fatty Acid Conjugates of Niacin and Salicylic Acid. J Med Chem **59**(3): 1217-1231.

Willcocks, R. J., I. A. Arpan, et al. (2014). Longitudinal measurements of MRI-T2 in boys with Duchenne muscular dystrophy: effects of age and disease progression. Neuromuscul Disord **24**(5): 393-401.

Yin, M. J., Y. Yamamoto, et al. (1998). The anti-inflammatory agents aspirin and salicylate inhibit the activity of I(kappa)B kinase-beta. Nature **396**(6706): 77-80.

Zwart, S. R., D. Pierson, et al. (2010). Capacity of omega-3 fatty acids or eicosapentaenoic acid to counteract weightlessness-induced bone loss by inhibiting NF-kappaB activation: from cells to bed rest to astronauts. J Bone Miner Res **25**(5): 1049-1057

APPENDIX 1. SCHEDULE OF ASSESSMENTS

	Screen [a]	BL [b]	Double Blind, Placebo-Controlled Treatment (Weeks 1 - 52)								Safety F/U [c]
Study Week(s)	**-4 - 0**	**0**	**6**	**13**	**19**	**26**	**32**	**39**	**45**	**52/ET[d]**	
Informed Consent/Assent	X										
Site Visit [e]	X	X		X		X		X		X	
Site Call [e, f]			X		X		X		X		X
Med History/Demographics	X										
Confirm Eligibility	X	X									
Randomization [g]		X									
Vital Signs	X	X		X		X		X		X	
Weight	X	X		X		X		X		X	
Height		X				X				X	
Physical Examination	X	X		X		X		X		X	
AEs/Con Meds[h]	X	*Continuous*									
12-Lead ECG[i]	X					X				X	
Cardiac Monitoring [j]	X					X				X	
Hematology/Chemistry [k]	X	X		X		X		X		X	
ACTH/Cortisol [k]		X		X		X		X		X	
Urinalysis	X					X				X	
DNA Sample [l]		X									
Biomarkers, Gene Expression [k]		X		X		X		X		X	
NSAA, Stand from Supine, 10MWT, 4-Stair Climb, Muscle Strength [m]	X	X		X		X		X		X	
PUL [n]		X				X				X	
Videotape Functional Assessments [o]	X	X								X	
PODCI [p]		X								X	
Lateral Spinal Radiography, DXA [q]		X								X	
Study Drug Questionnaire						X					
Nutritional Guidance [r]		X									
Drug Dispensation		X		X		X		X			
Drug Accountability				X		X		X		X	
PK (plasma and urine) [s]				X		X				X	

[a] Per Investigator's discretion, informed consent, medical history/demographic data and lab assessments may be completed remotely by a qualified medical professional.

[b] The first day of study drug is "Day 1"; unless otherwise specified, all assessments should be completed within a 4 week window prior to Day 1.

[c] Safety follow-up should occur within 2 wks. after last dose of study drug. Patients continuing in the open-label extension study are not required to perform the safety follow-up.

[d] If patient discontinues treatment early, patient will be asked to return for early termination (ET) visit prior to their last dose of study drug. Functional assessments performed within 6 weeks of discontinuing treatment do not need to be repeated at the ET visit. If the ET visit occurs after drug has been discontinued, certain assessments may be omitted per Sponsor discretion.

[e] Weeks 6-19 should be conducted within the study week with a ±4-day window. Weeks 26-54 have a ±10-day window.

[,f] Per Investigator discretion, site calls may occur by telephone or use of other technology.

[g] Randomization occurs after Screening assessments have been completed and eligibility is confirmed.

[h] AEs and concomitant medication/therapy will be assessed at all visits and during site calls.

[i] ECGs will be performed predose at all timepoints. At Week 26, ECG will per performed predose and 2 hours postdose (+/-15 min).

[j] Cardiac monitoring will be performed for approximately 48 hours remotely via a wearable cardiac monitoring device if approved for use in the participating country.

[k] Blood samples will be drawn in the morning when possible.

[l] DNA sample may be collected at Baseline for drug metabolizing enzyme and/or transporter analysis as well as pharmacogenomic analysis of potential markers of clinical risk/benefit.

[m] Assessments should be performed in the order listed and in the morning when possible. Time to stand from supine and 10MWT will be recorded as measured in the NSAA.

[n] The PUL 6-point entry item scale will be performed at all timepoints. If a patient scores a 6 on the PUL entry item scale, no further PUL testing is required for the visit.

[o] Videotaping at Baseline is required if Screening video did not pass QC.

[p] PODCI will be performed when feasible.

[q] These assessments should be collected within 2 months prior to Day 1. In Germany, bone assessment will not be performed until the respective approvals from the German Federal Office for Radiation Protection (Bundesamt für Strahlenschutz) become available.

[r] Patient compliance with the nutritional guidance will be confirmed throughout the trial.

[s] Urine PK collection will be performed at Week 13. Plasma PK collection will be performed predose at Week 13 and Week 52. At Week 26 plasma PK collection will be performed predose, 1 hour (+/- 5 min), 2 hours (+/-15 min), and 4 hours (+/- 15 min) postdose.

APPENDIX 2. POTENTIAL MODIFICATIONS TO THE SCHEDULE OF ASSESSMENTS DURING THE COVID-19 PANDEMIC

At the time of the COVID-19 pandemic, all enrolled patients had completed at least Week 26 so the implementation of alternative means to complete study assessments is intended for Week 39 and Week 52 only.

If the Investigator is able to perform the scheduled visit without impact to the safety of the patients and their families because of the COVID-19 pandemic, the Investigator should perform study assessments on site according to Appendix 1.

If the Investigator is unable or unwilling to perform the scheduled Week 52 visit within window without impact to the safety of the patients and their families because of the COVID-19 pandemic, the Investigator, along with the patient/caregiver may decide to conduct the visit out of window (but in no case should the projected target date be changed by more than 2 months).

The COVID-19 pandemic has impacted study sites variably, so individual situations at each site may impact the capabilities of sites to perform certain study assessments. The purpose of Appendix 2 is to outline considerations for sites to perform study procedures either on site or remotely by using alternative approaches to collect study assessments. While some study assessments can be performed remotely, it is acknowledged that others are not feasible to be conducted remotely.

As the top priority is safety, assessing for AE and concomitant medications is the highest priority to continue, which will occur remotely at intervals specified in Appendix 1. Based on the safety profile of edasalonexent to date, and consideration that all patients in this study have been on study drug for 6 months, other safety assessments, including physical examinations, chemistry and hematology labs and urinalysis can be deferred for six-month intervals if not feasible given the COVID-19 pandemic.

The next priority is study integrity, which requires continued administration of study drug and efficacy assessments. Drug dispensation can take place according to local site procedures, including secured, temperature-controlled shipments to the patients' homes. Study drug accountability can be assessed remotely as well.

Remote collection of efficacy measurements may occur if not feasible on site. Efficacy measurements collected remotely will be administered and monitored by trained evaluators. Additional details on the remote collection of efficacy measurements are provided in the Remote Efficacy Assessment Clinical Evaluator Manual developed for Duchenne clinical trials during the COVID-19 pandemic. Functional assessments may be limited by the remote testing environment.

Some study assessments from Appendix 1 may be not included in Appendix 2 due to the Sponsor's assessment of patient safety vs. criticality during the COVID-19 pandemic.

In the situation where the Investigator is able to perform study procedures on site but requires prioritization of study assessments to minimize patient time on site or exposure to certain locations within the study location, the Investigator should prioritize according to the outline

below. If a prioritized assessment cannot be performed, that does not preclude other assessments for the specific Visit in Appendix 1 if feasible and without additional risk.

- **Week 39 Visit**: **performed on-site**, priorities listed below
  - Assess AE and Concomitant Medications
  - Measure weight (to re-supply study drug), perform study drug accountability, re-supply Study Drug
  - Perform Primary and Secondary Efficacy Assessments (NSAA, TFTs, PUL)
  - Physical examination and vital signs
  - Lab assessments: chemistry, hematology, UA and PK (drawn at the same time)
- **Week 39 Visit: on-site visit is cancelled**, priorities listed below
  - Reconsent/assent for remote efficacy assessments
  - Assess AE and Concomitant Medications
  - Measure weight by home scale (to re-supply study drug), assess drug accountability as appropriate, re-supply Study Drug via courier service
  - Perform Primary and Secondary Efficacy Assessments (NSAA, TFTs, PUL) remotely requires videotaping. More detail can be found in the Remote Efficacy Assessment Clinical Evaluator Manual
- **Week 52 Visit**: **performed on-site**, priorities listed below
  - Assess AE and Concomitant Medications
  - Perform Primary and Secondary Efficacy Assessments (NSAA, TFTs, PUL)
  - Physical examination and vital signs, including height and weight
  - Lab assessments: chemistry, hematology, UA and PK and biomarkers (drawn at the same time)
  - ECG
  - PODCI (if time limitations, provide and collect at next opportunity)
  - DXA and lateral spine films (recognizing that traveling to other parts of the clinic or hospital) may not be conducive at this time)
- Week 52 Visit: **on-site visit is cancelled**, priorities listed below
  - Reconsent/assent for remote efficacy assessments
  - Assess AE and Concomitant Medications
  - Perform Primary and Secondary Efficacy Assessments (NSAA, TFTs, PUL) remotely requires videotaping. More detail can be found in the Remote Efficacy Assessment Clinical Evaluator Manual

- Measure weight by home scale and height as feasible.
- Perform drug accountability as appropriate
- Lab assessments: chemistry, hematology, UA to be considered via local labs but defer to Investigators' judgement and interval since most recent assessments
- PODCI (provide electronically and collect at next opportunity

APPENDIX 3. LIST OF CLINICAL LABORATORY ASSESSMENTS

For timing of laboratory assessments, see Schedule of Assessments in Appendix 1

Clinical Safety Assessments		
Clinical Chemistry	**Urinalysis**	**Hematology**
Sodium Potassium Chloride Bicarbonate Total protein Albumin Creatine kinase Calcium Phosphorus Glucose Blood urea nitrogen Creatinine Uric Acid Lactate dehydrogenase Total bilirubin (direct if above ULN) Alkaline phosphatase AST ALT GGT Cystatin C Cortisol (AM) ACTH Glutamate dehydrogenase	Specific gravity pH Protein Glucose Ketones Bilirubin Blood RBCs WBCs Epithelial cells Bacteria Casts Crystals	WBC count RBC count Hemoglobin Hematocrit MCV, MCH, and MCHC Platelet count WBC differential (% and absolute) • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils

ACTH=adrenocorticotropic hormone; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transferase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; ULN=upper level of normal; WBC=white blood cell

APPENDIX 4. STUDY DRUG QUESTIONNAIRE

STUDY DRUG QUESTIONNAIRE

Protocol CAT-1004-301

Patient Initials

|___|___|___|

Patient Study ID

|__|__|__| - |__ |__|__|

Patient Initials _____ Subject ID: _____ - _____ Date: _____

This questionnaire should be completed by the caregiver of the patient. Please circle the answer that most closely reflects **the patient's opinion** of the study drug. Circle only one answer per question.

1. The taste and aftertaste (a taste that remains in your mouth after swallowing) of the study drug capsules are acceptable:

1	2	3	4	5
Strongly Agree	Agree	Neither Agree Nor Disagree	Disagree	Strongly Disagree

2. The smell of the study drug capsules is acceptable:

1	2	3	4	5
Strongly Agree	Agree	Neither Agree Nor Disagree	Disagree	Strongly Disagree

3. The size and shape of the study drug capsules are acceptable:

1	2	3	4	5
Strongly Agree	Agree	Neither Agree Nor Disagree	Disagree	Strongly Disagree

APPENDIX 5. PEDIATRIC OUTCOMES QUESTIONNAIRE (PODCI)

Pediatric

Outcomes Questionnaire

Developed by:

American Academy of Orthopaedic Surgeons®

Pediatric Orthopaedic Society of North America

American Academy of Pediatrics

Shriner's Hospitals

To be completed by the parent for children 2 – 10 years old

Based on the Version 2.0 Pediatrics-Parent/Child Outcomes Intrument

Also commonly referred to as the PODCI ("Pediatric Outcomes Data Collection Instrument")

Revised, renumbered, reformatted August 2005

FOR OFFICE USE ONLY

Clinic ID _____ First six letter of patient's last name _____

Physician ID _____ Office Chart # _____

	Diagnosis & ICD-9 Code*	Procedure & CPT Code	CPT Date	Side of body procedure was performed on:
Primary DX	DX _____ ICD-9	Tx _____ ICD-9		☐ Right ☐ Left ☐ Both ☐ N/A
Secondary DX	DX _____ ICD-9	Tx _____ ICD-9		☐ Right ☐ Left ☐ Both ☐ N/A
Secondary DX	DX _____ ICD-9	Tx _____ ICD-9		☐ Right ☐ Left ☐ Both ☐ N/A
Secondary DX	DX _____ ICD-9	Tx _____ ICD-9		☐ Right ☐ Left ☐ Both ☐ N/A
Secondary DX	DX _____ ICD-9	Tx _____ ICD-9		☐ Right ☐ Left ☐ Both ☐ N/A

Pediatric Health Assessment (parent-reported)

Today's Date / /

Thank you for completing this questionnaire!

This questionnaire will help us to better understand your general health and any problems related to bone and muscle conditions.

Your completion of this questionnaire is completely voluntary and your responses will be held in the strictest confidence.

Please answer every question. Some questions may look like others, but each one is different.

There are no right or wrong answers. If you are not sure how to answer a question, just give the best answer you can. You can make comments in the margin. We do read all your comments, so feel free to make as many as you wish.

Your Child's Birth Date / /

Your Child's Social Security Number _____

Your Social Security Number _____

Pediatric Health Assessment (parent-reported)

Some kind of problems can make it hard to do many activities, such as eating, bathing, school work, and playing with friends. We would like to find out how your child is doing. (Circle one response on each line.)

During the **last week** was it easy or hard for your child to:

		Easy	A little hard	Very hard	Can't do at all	Too young for this activity
1.	Lift heavy books?	1	2	3	4	5
2.	Pour a half gallon of milk?	1	2	3	4	5
3.	Open a jar that has been opened before?	1	2	3	4	5
4.	Use a fork and spoon?	1	2	3	4	5
5.	Comb his/her hair?	1	2	3	4	5
6.	Button buttons?	1	2	3	4	5
7.	Put on his/her coat?	1	2	3	4	5
8.	Write with a pencil?	1	2	3	4	5

9. On average, **over the last 12 months**, how often did your child miss school (preschool, day care, camp, etc.) because of his/her health?

1. Rarely
2. Once a month
3. Two or three times a month
4. Once a week
5. More than once a week
6. Does not attend school, etc.

During the **last week** how happy has your child been with: (Circle one response on each line.)

		Very happy	Somewhat happy	Not sure	Somewhat unhappy	Very unhappy	Child is too young
10.	How he/she looks?	1	2	3	4	5	6
11.	His/her body?	1	2	3	4	5	6
12.	What clothes or shoes he/she can wear?	1	2	3	4	5	6
13.	His/her ability to do the same things his/her friends do?	1	2	3	4	5	6
14.	His/her health in general?	1	2	3	4	5	6

Pediatric Health Assessment (parent-reported)

During the **last week**, how much of the time:
(Circle one response on each line.)

		Most of the time	Some of the time	A little of the time	None of the time
15.	Did your child feel sick and tired?	1	2	3	4
16.	Were your child full of pep and energy?	1	2	3	4
17.	Did pain or discomfort interfere with your child's activities?	1	2	3	4

During the **last week**, has it been easy or hard for your child to:
(Circle one response on each line.)

		Easy	A little hard	Very hard	Can't do at all	Too young for this activity
18.	Run short distances?	1	2	3	4	5
19.	Bicycle or tricycle?	1	2	3	4	5
20.	Climb three flights of stairs?	1	2	3	4	5
21.	Climb one flight of stairs?	1	2	3	4	5
22.	Walk more than a mile?	1	2	3	4	5
23.	Walk three blocks?	1	2	3	4	5
24.	Walk one block?	1	2	3	4	5
25.	Get on and off a bus?	1	2	3	4	5

26. How often does your child need help from another person for walking and climbing? (Circle one response.)

1 Never 2 Sometimes 3 About half the time 4 Often 5 All the time

27. How often does your child use assistive devices (such as braces, crutches, or wheelchair) for walking and climbing? (Circle one response.)

1 Never 2 Sometimes 3 About half the time 4 Often 5 All the time

During the **last week**, has it been easy or hard for your child to:
(Circle one response on each line.)

		Easy	A little hard	Very hard	Can't do at all	Too young for this activity
28.	Stand while washing his/her hands and face at a sink?	1	2	3	4	5
29.	Sit in a regular chair without holding on?	1	2	3	4	5
30.	Get on and off a toilet or chair?	1	2	3	4	5
31.	Get in and out of bed?	1	2	3	4	5
32.	Turn door knobs?	1	2	3	4	5
33.	Bend over from a standing position and pick up something off the floor?	1	2	3	4	5

34. How often does your child need help from another person for sitting and standing? (Circle one response.)

1 Never 2 Sometimes 3 About half the time 4 Often 5 All the time

35. How often does your child use assistive devices (such as braces, crutches, or wheelchair) for sitting and standing? (Circle one response.)

1 Never 2 Sometimes 3 About half the time 4 Often 5 All the time

36. Can your child participate in **recreational outdoor activities** with other children the same age? (For example: bicycling, tricycling, skating, hiking, jogging) (Circle one response.)

1 Yes, easily 2 Yes, but a little hard 3 Yes, but very hard 4 No

If you answered "no" to Question 36 above, was your child's activity limited by: (Circle yes to all that apply)

	Yes
37. Pain?	1
38. General Health?	1
39. Doctor or parent instructions?	1
40. Fear the other kids won't like him/her?	1
41. Dislike of recreational outdoor activities?	1
42. Too young?	1
43. Activity not in season?	1

44. Can your child participate in **pickup games or sports** with other children the same age? (For example: tag, dodge ball, basketball, soccer, catch, jump rope, touch football, hop scotch) (Circle one response.)

1 Yes, easily 2 Yes, but a little hard 3 Yes, but very hard 4 No

If you answered "no" to Question 44 above, was your child's activity limited by: (Circle yes to all that apply)

	Yes
45 Pain?	1
46. General Health?	1
47. Doctor or parent instructions?	1
48. Fear the other kids won't like him/her?	1
49. Dislike of pickup games or sports?	1
50. Too young?	1
51. Activity not in season?	1

52. Can your child participate in **competitive level sports** with other children the same age? (For example: hockey, basketball, soccer, football, baseball, swimming, running [track or cross country], gymnastics, or dance) (Circle one response.)

1 Yes, easily 2 Yes, but a little hard 3 Yes, but very hard 4 No

If you answered "no" to Question 52 above, was your child's activity limited by: (Circle yes to all that apply)

	Yes
53. Pain?	1
54. General Health?	1
55. Doctor or parent instructions?	1
56. Fear the other kids won't like him/her?	1
57. Dislike of pickup games or sports?	1
58. Too young?	1
59. Activity not in season?	1

60. How often in the **last week** did your child get together and do things with friends? (Circle one response.)

1 Often 2 Sometimes 3 Never or rarely

If you answered "sometimes" or "never or rarely" to Question 60 above, was your child's activity limited by: (Circle yes to all that apply)

	Yes
61. Pain?	1
62. General Health?	1
63. Doctor or parent instructions?	1
64. Fear the other kids won't like him/her?	1
65. Friends not around?	1

66. How often in the **last week** did your child participate in **gym/recess**? (Circle one response.)

1 Often 2 Sometimes 3 Never or rarely 4 No gym or recess

If you answered "sometimes" or "never or rarely" to Question 63 above, was your child's activity limited by: (Circle yes to all that apply)

	Yes
67. Pain?	1
68. General Health?	1
69. Doctor or parent instructions?	1
70. Fear the other kids won't like him/her?	1
71. Dislike of gym/recess?	1
72. School not in session?	1
73. Does not attend school?	1

74. Is it easy or hard for your child to make friends with children his/her own age? (Circle one response.)

1 Usually easy 2 Sometimes easy 3 Sometimes hard 4 Usually hard

Pediatric Health Assessment (parent-reported)

75. How much pain has your child had during the **last week**? (Circle one response.)

1 None 2 Very mild 3 Mild 4 Moderate 5 Severe 6 Very severe

76. During the **last week**, how much did pain interfere with your child's normal activities (including at home, outside of the home, and at school)? (Circle one response.)

1 Not at all 2 A little bit 3 Moderately 4 Quite a bit 5 Extremely

What expectations do you have for your child's treatment?
As a result of my child's treatment, I expect my child:
(Circle one response on each line.)

		Definitely yes	Probably yes	Not sure	Probably not	Definitely not
77.	To have pain relief.	1	2	3	4	5
78.	To look better.	1	2	3	4	5
79.	To feel better about himself/herself.	1	2	3	4	5
80.	To sleep more comfortably.	1	2	3	4	5
81.	To be able to do activities at home.	1	2	3	4	5
82.	To be able to do more at school.	1	2	3	4	5
83.	To be able to do more play or recreational activities (biking, walking, doing things with friends).	1	2	3	4	5
84.	To be able to do more sports.	1	2	3	4	5
85.	To be free from pain or disability as an adult.	1	2	3	4	5

86. If your child had to spend the rest of his/her life with his/her bone and muscle condition **as it is right now**, how would you feel about it? (Circle one response.)

1 Very satisfied 2 Somewhat satisfied 3 Neutral 4 Somewhat dissatisfied 5 Very dissatisfied

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Global Phase 3 Study of Edasalonexent in Pediatric Patients with Duchenne Muscular Dystrophy
Protocol Number:	CAT-1004-301
Original Version Date:	09 July 2018
Amendment:	1

Summary and Rationale for Changes

The following information summarizes the changes captured in Amendment 1 reflective of study conduct during the COVID-19 pandemic:

- As patients may not be able to come on-site for visits or for a reduced amount of time, modifications have been made to the original study procedures and schedule of assessments to reduce the patient's risk or exposure to COVID-19 for Week 39 and Week 52 study visits. These include:
  - Allowance for the Week 52 visit to be conducted out of the visit window (but in no case should the projected target date be changed by more than 2 months).
  - Ability to perform study procedures either on site or remotely by using alternative approaches to collect study assessments.
  - As the top priority is safety, assessing for AE and concomitant medications is the highest priority to continue, which will occur remotely at intervals.
  - Based on the safety profile of edasalonexent to date, and consideration that all patients in this study have been on study drug for 6 months, other safety assessments, including physical examinations, chemistry and hematology labs and urinalysis can be deferred for six-month intervals if not feasible.
  - Drug dispensation can take place according to local site procedures, including secured, temperature-controlled shipments to the patients' homes
  - A prioritized list of assessments has been included in Appendix 2 of the protocol.

- Clarification that post the COVID-19 pandemic, clinical monitoring may resume with more intense pace to clean all data accumulated.