Effects of sevasemten (EDG-5506) on safety, biomarkers, and functional measures in adults with Becker muscular dystrophy: results of a phase 1b, open-label study

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Summary

Background Sevasemten (EDG-5506) is an orally administered, investigational small molecule that selectively modulates fast muscle fibre contraction by inhibiting fast myosin ATPase. In animal models of Duchenne and Becker muscular dystrophy (DMD and BMD, respectively), sevasemten reduced the muscle contraction injury that leads to inflammation, fibrosis and muscle loss without affecting function. The aim of this study was to evaluate the long-term safety, tolerability, and pharmacokinetics (PK)/pharmacodynamics of sevasemten in adult participants with BMD who had already experienced a decline in function and would be anticipated to continue to decline based on natural history.

Methods This open-label, dose escalation, phase 1 b study (NCT05160415) was conducted at a single site and enrolled ambulatory adults with BMD aged 18–55 years; the study is completed. Eligible participants received 10 mg of sevasemten once daily (QD) for 8 weeks, followed by 15 mg QD for 4 months, 20 mg QD for 9 months, and 10 mg QD for 9 months. The primary objective was to assess the safety and tolerability of sevasemten in adults with BMD; endpoints included adverse events (AEs), PK, change from baseline in circulating biomarkers of muscle injury, as well as physical function measures.

Findings The study enrolled 12 adults with BMD. Sevasemten was well tolerated; all AEs were mild or moderate in severity and there were no serious AEs or AEs leading to discontinuation. Treatment with sevasemten was associated with reductions in circulating biomarkers of muscle injury that were evident within 4 weeks and sustained for up to 24 months. Physical function, as assessed by North Star Ambulatory Assessment (NSAA), was stable over 24 months.

Interpretation Sevasemten treatment for up to 24 months in adults with BMD was well tolerated and associated with durable reductions in muscle injury biomarkers, consistent with preclinical studies and near maximal with the 10 mg dose, as well as functional stabilisation. Further clinical development is ongoing.

Funding Edgewise Therapeutics, Inc.

Keywords: Becker muscular dystrophy; Contraction-induced injury; Sevasemten; EDG-5506; Fast myosin inhibitor

Introduction

Individuals with Becker muscular dystrophy (BMD) or Duchenne muscular dystrophy (DMD) have mutations in the gene encoding dystrophin (*DMD*), which lead to production of truncated, partially functional (BMD) or absent (DMD) dystrophin protein. In individuals with BMD or DMD, the lack of fully functional dystrophin leads to increased contraction-induced injury along muscle fibres, activation of stress channels, calcium influx, and muscle damage.[1–3] Prolonged muscle injury and stress promotes inflammation and muscle degeneration, ultimately resulting in loss of muscle function, severe disability and death.[4,5]

Contraction-induced injury occurs in unaffected individuals following strenuous exertion, whereas in both DMD and BMD, contraction-initiated fast fibre injury occurs with everyday activity.[3,6,7] In BMD loss of ambulation can occur as early as the third decade, and

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Research in context

Evidence before this study

Dystrophin is a critical structural protein that links the contractile elements of the sarcomere to the basement membrane of the myofibres. Without fully functional dystrophin, muscle contraction in Becker and Duchenne muscular dystrophy (BMD and DMD, respectively) causes ongoing muscle fibre degeneration that eventually leads to increased fibrosis, cardiac dysfunction, and the progressive loss of skeletal muscle function, all of which can result in severe disability and early death. Clinically, individuals with BMD often present with symptoms of symmetrical, proximal limb weakness, notable in the quadriceps, and calf hypertrophy, with 90% of individuals presenting symptoms by age 20. While the age of onset of functional decline is variable in BMD, once the decline begins, it is progressive, with muscle deterioration resulting in limited ambulation at an average age of 30 years old, increased need for assistive devices for individuals in their 40's, and ultimately, loss of ambulation in many. Progression of BMD has been assessed with the North Star Ambulatory Assessment (NSAA), a 17-item test of measures of ambulatory function. Importantly, multiple natural history studies have demonstrated that once function begins to be impaired, individuals with BMD show an NSAA average score decline of 1·0–1·7 points per year. As a result, NSAA has emerged as a sensitive assessment to measure disease progression in ambulatory individuals with BMD with evident functional impairment. In preclinical animal models, modest inhibition of fast muscle fibre contraction with sevasemten protected muscle while preserving function. In a prior phase 1 study, sevasemten treatment for up to 14 days in healthy volunteers and a small cohort of individuals with BMD was generally well tolerated and associated with decreases in biomarkers of muscle injury, supporting further clinical development. We searched PubMed for clinical trials of therapies for patients with BMD published through March 28, 2026. Search terms included "Becker muscular dystrophy", therapy, clinical trial, muscle injury biomarkers, and functional assessments. This search yielded only our prior phase 1 study described above.

Added value of this study

This study provides evaluation of the long-term safety, tolerability, pharmacokinetics (PK)/pharmacodynamics (PD), and functional effects of sevasemten, an investigational small molecule, in adults with BMD. The results of the study indicate that sevasemten treatment for up to 24 months was well tolerated and associated with sustained reductions in muscle injury biomarkers that were near maximal with a 10 mg dose. Importantly, sevasemten treatment resulted in functional stabilisation, suggesting potential benefit in a progressive disease with no approved therapies. The presented data support the clinical hypothesis that selective inhibition of fast muscle myosin is a potential approach to preserving function in BMD and other muscular dystrophies.

Implications of all the available evidence

Combined with our preclinical and initial phase 1 data, the results of this study support further clinical development of sevasemten for the treatment of BMD and support selection of the 10 mg dose for ongoing studies.

use of mobility assistive devices including full-time wheelchair usage, is common after age 40 with a median age of losing ambulation of 60 years.[8–12] While the age of onset of functional decline is variable, once decline begins it is progressive, with loss of muscle resulting in functional impairment and disability. Despite the seriousness of the disease, considerable unmet medical need remains for BMD, with no specifically authorised therapies. Disease progression has been assessed with the North Star Ambulatory Assessment (NSAA), a 17-item test of measures of ambulatory function.[13] Importantly, multiple natural history studies have demonstrated that once function begins to be impaired, individuals with BMD show an NSAA average score decline of 1·0 to 1·7 points per year.[14–18] As a result, NSAA has emerged as a sensitive assessment to measure disease progression in ambulatory individuals with BMD with evident functional impairment.

Sevasemten (EDG-5506) is an orally administered, investigational small molecule designed to selectively modulate fast muscle fibre contraction by modestly inhibiting fast skeletal muscle myosin adenosine triphosphatase (ATPase).[19] Sevasemten is highly selective for fast skeletal myosin as compared to cardiac or smooth muscle myosin. In preclinical studies in *mdx* mice, sevasemten treatment prevented stress injury to dystrophic muscles and reduced exercise-induced creatine kinase (CK) release.[19] Further, muscle protection occurred with minimal contraction inhibition (<15%), which did not impact strength, endurance, or coordination. Long-term treatment with sevasemten reduced fibre size variation and fibrosis in the diaphragm of *mdx* mice and also reversed circulating muscle injury biomarkers and increased activity in dystrophic golden retrievers.[19]

In the phase 1 study EDG-5506-001,[20] sevasemten was well tolerated in healthy volunteers at daily doses up to 40 mg and in a small group of adults with BMD at a dose of 20 mg. Circulating biomarker analyses were suggestive of reduced muscle injury. In healthy volunteers, the half-life of sevasemten is approximately 22 days, whereas in participants with BMD the half-life

is approximately 7 days. This difference is likely related to observations that the sevasemten is ~100-fold more concentrated in muscle than plasma in conjunction with the substantial loss of muscle mass in BMD.[20] Therefore, for this outpatient study, an initial dose of 10 mg was chosen to produce steady state exposures predicted to be similar to those observed in participants with BMD in the first phase 1 study.[20]

The aim of this study was to test the clinical hypothesis that sevasemten, by limiting injurious contraction of fast skeletal muscle fibres, could limit muscle injury and hence disease progression in individuals with dystrophic muscle.

Methods

Study design

Study EDG-5506-002 (ARCH) was an open-label, non-randomised, dose-escalation study conducted at a single centre (Rare Disease Research, Atlanta, GA). Study participants received sevasemten 10 mg as an oral, once daily (QD) dose for 8 weeks, followed by 15 mg QD for 4 months, 20 mg QD for the subsequent 9 months, before returning to the identified target dose of 10 mg QD for the following 9 months (Fig. S1). Of the 12 study participants, 5 had received study drug in Study EDG-5506-001 and 7 were treatment naïve, of which 2 received placebo in Study EDG-5506-001 and 5 were newly enrolled (Fig. 1). For participants who previously received sevasemten in Study EDG-5506-001, there was a washout period of at least 12 weeks prior to receiving sevasemten in Study EDG-5506-002. Eleven of 12 participants were subsequently enrolled into the EDG-5506-203 open-label extension study. The study protocol was amended 5 times between October 2021 and March 2023 to optimise and refine study dosing and treatment duration and update and clarify study procedures. With respect to dosing of study drug, initial dosing levels of 10 and 15 were planned, and 20 mg was added as additional data did not identify safety concerns. The dose was readjusted to 10 mg as emerging biomarker data indicated that the biomarker response was essentially maximal with the 10 mg dose.

Study objectives

The primary objective of this study was to assess the safety and tolerability of sevasemten in adults with BMD. Secondary objectives included the assessment of changes in individual safety parameters and PK profile of sevasemten; exploratory objectives included the effects of sevasemten on biomarkers of muscle injury, functional measures, and self-reported outcomes.

Ethics

The study was conducted in compliance with the principles of Good Clinical Practice (GCP), the Declaration of Helsinki, and the International Council for Harmonisation. Participants were recruited nationally with the

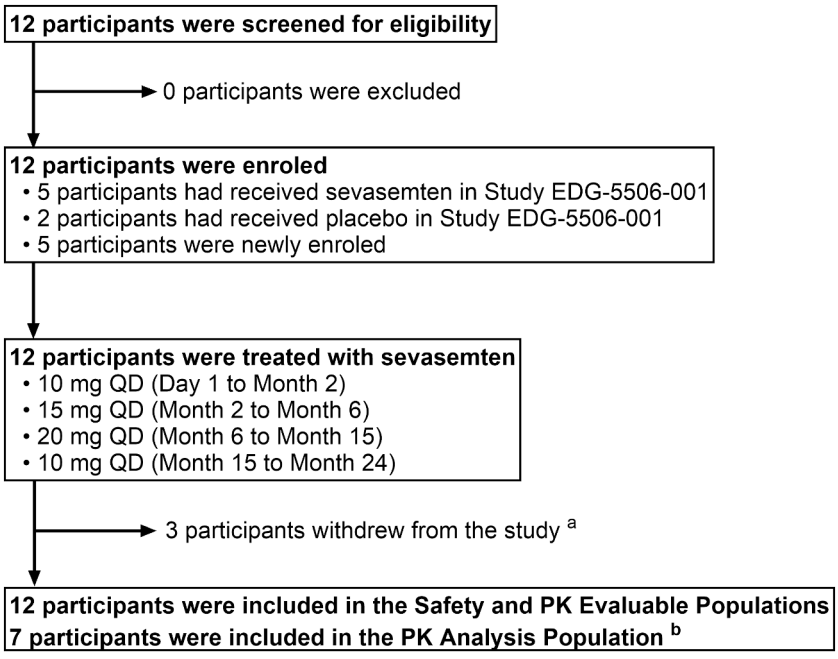

Fig. 1: Study Profile. AE = adverse event; QD = once daily. [a] 2 participants withdrew for family planning and were subsequently enroled into a separate open-label extension study (EDG-5506-203 [NCT06066580]); 1 participant withdrew for non-AE-related reasons. [b] The PK Analysis Population included treatment-naïve participants only.

help of patient advocacy organisations (Muscular Dystrophy Association [MDA], Chicago, IL and Parent Project Muscular Dystrophy [PPMD], Washington, DC). All participants provided written informed consent prior to participation. The Investigator received approval from the Institutional Review Board (Advarra Inc., Columbia, MD) prior to initiating the study (11/24/2021; SSU00170416). An Independent Data Monitoring Committee (IDMC) was established to enhance the safety of trial participants by providing an independent quarterly review of the study data as well as prior to dose escalation. The IDMC included 2 physicians specialised in neurology with experience in clinical trials and experienced in the treatment of muscular dystrophy, a biostatistician, and a community patient advocate. The recommendation of the IDMC was to continue the study after each data review. The study was registered with ClinicalTrials.gov (NCT05160415) and is completed.

Participants

Eligible participants were adult males (18–55 years, inclusive) with a confirmed diagnosis of BMD based on genetic testing and clinical phenotype, and were ambulatory at screening, with the ability to complete a 100-m timed test with or without assistive devices. There was no time limit for completion of the 100-m timed test. Participants were required to have body weight ≥50 kg and body mass index (BMI) between 20 and 34 kg/m^2, inclusive, at the screening visit. Key exclusion criteria were significant cardiac dysfunction (left ventricular ejection fraction <45% or New York Heart Association Class III/IV heart failure), significant pulmonary impairment (forced vital capacity <65% predicted or use of mechanical ventilation), moderate or severe renal or hepatic impairment, or a history of substance abuse. Participants could not have received oral corticosteroids for >5 days in the previous 6 months at a dose of >5 mg equivalent per day. Complete inclusion and exclusion criteria are shown in Table S1.

Study drug administration

Sevasemten was administered orally as 2·5 mg or 10 mg tablets with or without food. For participants who previously received sevasemten in Study EDG-5506-001, study drug administration was performed at the site on Day 1 for PK assessments, with continued at-home dosing thereafter. Treatment-naïve participants received the first dose of sevasemten on Day 1 and returned to the site on Day 2 to complete the last PK timepoint before taking the second dose, with continued at-home dosing starting on Day 3. Compliance was monitored via participant diaries and tablet counts at each study visit. Because the most common adverse events (AEs) observed in Study EDG-5506-001 were mild and transient somnolence and dizziness,[20] participants were instructed to take sevasemten at night prior to bedtime. Dose modifications were permitted following discussion with the Medical Monitor. This may have included changes to dose or frequency of administration.

Safety assessments

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (v24·1). Treatment-emergent adverse events (TEAEs) were defined as any AE that emerged on or after administration of the study drug or any pre-existing AE that worsened upon treatment. Additional safety assessments included physical examinations, vital signs, spirometry, clinical safety laboratory assessments, 12-lead ECGs, echocardiographic examinations, and muscle strength testing. See the Supplementary Methods for additional detail.

Pharmacokinetics and biomarkers of muscle injury

Samples for PK evaluation and analysis of biomarkers of muscle injury were collected from all participants in this study; see the Supplementary Methods for additional information. Biomarker samples were used for the analysis of fast skeletal muscle troponin I (TNNI2), CK, and myoglobin. SomaScan® 7 K proteomics analyses (SomaLogic, Inc., Boulder, CO) were performed to identify potential biomarkers and included evaluation of association under exploratory endpoints. See the Supplementary Methods for additional information.

Functional assessments

The NSAA is a 17-item test that grades performance of various functional skills as 0 (unable to perform), 1 (completes independently but with compensation), and 2 (complete without compensation).[13] The NSAA also includes 2 timed functional tests: rise-from-floor and 10-m walk/run. Additional functional assessments included the North Star Assessment for Limb Girdle Type Muscular Dystrophies (NSAD),[21] the 4-stair climb test, and the 100-m timed test. Functional assessments were administered by clinical evaluators who were trained in established methods by ATOM International (Gateshead, UK). See the Supplementary Methods for additional information.

Sample size justification

The sample size of 12 participants was considered sufficient to provide reasonable estimates of PK measures and assessment of safety and tolerability for this early-stage clinical trial.

Statistics

Safety, biomarker, and functional analyses were performed on all participants; PK analysis populations are described in the Supplementary Methods. Baseline was defined as the last measurement prior to the first dose of study drug. Change from baseline was calculated by

subtracting the baseline value from the individual post-dose value. Missing data were not imputed. For biomarkers, data were log-transformed for analysis and the mean change from baseline and 95% CIs were back-transformed to percent scale as described in the Supplementary Methods. No formal hypothesis testing was performed. The longitudinal analysis of NSAA and muscle injury biomarkers was performed by mixed model for repeated measures (MMRM); methodological details are provided in the Supplementary Methods.

Statistical analyses were performed using Phoenix WinNonlin (version 8·3) for PK analysis, SAS v9·4 (SAS Institute, Cary, NC) for the analysis of safety, physical function, and SAS and Python (with numpy, pandas, and statsmodels modules) for the analysis of muscle injury biomarkers. See the Supplementary Methods for additional information.

Role of funders

The study sponsor (Edgewise Therapeutics, Inc.) was responsible for study design, data collection, data analysis, data interpretation, and manuscript preparation.

Results

The study enrolled 12 male participants with confirmed genetic diagnosis of BMD (Fig. 1) between December 2021 (first participant's first visit) and March 2024 (last participant's last visit), of whom 7 (58%) had completed Study EDG-5506-001 (for these 7 participants, 5 received active drug and 2 received placebo in the prior trial), with a last dose of study drug at least 12 weeks prior to enrolment. Nine (75%) participants completed the study, and 3 (25%) participants discontinued Study EDG-5506-002. For the 3 participants who withdrew, 2 withdrew for family planning and were subsequently enrolled into a separate open-label extension study (EDG-5506-203 [NCT06066580]) and the other participant withdrew for non-AE-related reasons. None of these 3 participants had a decrease in total NSAA score compared to baseline prior to discontinuation. The median (range) age was 32·0 (20–46) years, median weight was 80·9 (57–93) kg, and median body mass index (BMI) was 25·1 (21–32) kg/m^2 (Table 1). Baseline functional measures showed a range of functional impairment, with all participants having evidence of impaired muscle function (Table 1). At baseline, median total NSAA and NSAD scores were 15·5 points and 26·0 points, respectively.

Ten participants had deletion exon 45-x pathogenic variants, including 5 participants with exon 45–47, 4 participants with exon 45–48, and 1 participant with exon 45–53; all were in-frame variants. One participant had a single nucleotide variant, which would be in-frame, identified in multiple family members with a Becker phenotype, and 1 participant had a deletion of multiple exons, with the report noting a Becker phenotype.[20] None of the participants had mutations that have been reported to have slow disease progression.[14]

	Total (N = 12)
Age (years)	32·0 (20–46)
Race	–
White	12 (100%)
Ethnicity	–
Hispanic or Latino	1 (8%)
Not Hispanic or Latino	11 (92%)
Weight (kg)	80·9 (57–93)
BMI (kg/m^2)	25·1 (21–32)
Medical History[a]	–
BMD	12 (100%)
Seasonal allergy	2 (17%)
Concomitant Medications[b]	–
Ibuprofen	6 (50%)
Paracetamol	5 (42%)
Vitamins	4 (33%)
Calcium	3 (25%)
Diphenhydramine hydrochloride	3 (25%)
Lisinopril	3 (25%)
Prednisone	3 (25%)
Functional Characteristics	–
Total NSAA score (out of 34)	15·5 (2–31)
Total NSAD score (out of 52)	26·0 (7–49)
Maximum hand grip strength (kg)	29·2 (2·9–39·9)
Velocity of 4-stair climb (1/seconds)	0·17 (0·0–0·5)
Velocity of 10-m walk/run test (meters/seconds)	1·20 (0·2–2·2)
Velocity of 100-m timed test (meters/seconds)	1·10 (0·2–2·2)
Velocity of rise-from-floor test (1/seconds)	0·10 (0·0–0·6)

Values are reported as median (range) or n (%). BMI = body mass index; NSAA = North Star Ambulatory Assessment; NSAD = North Star Assessment for Limb Girdle Type Muscular Dystrophies. [a]Reported in 2 or more participants. [b]Reported in 3 or more participants.

Table 1: **Demographics and baseline characteristics (Safety Population).**

Over the 2-year trial, sevasemten was well tolerated at all dose levels, with no evidence of dose-dependent AEs. All TEAEs were mild or moderate in severity and there were no serious AEs or AEs leading to discontinuation (Table 2). Overall, the most-frequently reported TEAE was COVID-19 (5 [42%] participants), followed by fall, dizziness, and arthralgia (4 [33%] participants for each). The TEAEs of fall were not associated with dizziness in any participant. Dizziness (4 [33%]) and somnolence (3 [25%]) were generally reported within the first few days of dosing, or with escalation in dose, and resolved within a few days. Of note, fewer participants reported somnolence during the later 15 mg dosing period than during the initial 10 mg dosing period; there were no reports of somnolence during the subsequent 20 mg dosing period. TEAEs of arthralgia and myalgia were only reported when participants were receiving the 20 mg dose.

Given the mechanism of action, safety assessments were performed to monitor muscle strength, including

	10 mg (N = 12)	15 mg (N = 12)	20 mg (N = 12)	Total (N = 12)
Any TEAE [Upper Bound of the 1-sided 95% CI[a]]	10 (83%) [97%]	9 (75%) [93%]	12 (100%) [100%]	12 (100%) [100%]
Any TEAE by Maximum Severity				
Mild	10 (83%)	7 (58%)	12 (100%)	10 (83%)
Moderate	0	2 (17%)	0	2 (17%)
Severe	0	0	0	0
Any Related TEAE	5 (42%)	3 (25%)	0	7 (58%)
Any Related TEAE by Maximum Severity				
Mild	5 (42%)	2 (17%)	0	6 (50%)
Moderate	0	1 (8%)	0	1 (8%)
Severe	0	0	0	0
Any SAE	0[b]	0[b]	0[b]	0[b]
Any TEAE Leading to Discontinuation of Study Drug	0	0	0	0
Any TEAE Leading to Death	0	0	0	0
Any Elicited TEAE	0[b]	0[b]	0[b]	0[b]
Swallowing difficulties	0	0	0	0
Visual changes	0	0	0	0
TEAEs Reported in >1 Participant by System Organ Class and Preferred Term				
Infections and Infestations	5 (42%)	3 (25%)	10 (83%)	12 (100%)
COVID-19	1 (8%)	1 (8%)	3 (25%)	5 (42%)
Influenza	1 (8%)	0	2 (17%)	3 (25%)
Nasopharyngitis	1 (8%)	1 (8%)	1 (8%)	3 (25%)
Viral upper respiratory tract infection	0	0	3 (25%)	3 (25%)
Sinusitis	0	1 (8%)	1 (8%)	2 (17%)
Injury, poisoning and procedural complications	5 (42%)	4 (33%)	3 (25%)	8 (67%)
Fall	2 (17%)	2 (17%)	3 (25%)	4 (33%)
Procedural pain	2 (17%)	0	1 (8%)	3 (25%)
Nervous system disorders	4 (33%)	6 (50%)	3 (25%)	8 (67%)
Dizziness	2 (17%)	3 (25%)	1 (8%)	4 (33%)
Headache	0	3 (25%)	2 (17%)	3 (25%)
Somnolence	2 (17%)	1 (8%)	0	3 (25%)
Musculoskeletal and connective tissue disorders	1 (8%)	1 (8%)	5 (42%)	6 (50%)
Arthralgia	0	0	4 (33%)	4 (33%)
Gastrointestinal disorders	3 (25%)	1 (8%)	3 (25%)	5 (42%)
Gastroesophageal reflux disease	1 (8%)	0	2 (17%)	3 (25%)

Values are reported as n (%). CI = confidence interval; COVID-19 = Coronavirus Disease 2019; SAE = serious adverse event; TEAE = treatment emergent adverse event. [a]1-sided 95% Clopper-Pearson upper confidence interval. [b]For "Any SAE" and "Any Elicited TEAE", the value of the 1-sided 95% Clopper-Pearson upper confidence interval is 22%.

Table 2: **Overall summary of treatment-emergent adverse events (Safety Population).**

hand grip and elbow flexor strength (Fig. S2). Measures of upper body strength showed considerable within-subject variability typical of handheld dynamometry within the error of the measurement.[22] There were no clinically significant findings or trends for other safety evaluations, including physical examinations, vital signs, ECGs, spirometry, or echocardiography.

Sevasemten was rapidly absorbed after a single, 10 mg dose in treatment-naïve participants, with a median (range) T_{max} of 1·5 (0·50–2·00) hours, a C_{max} of 23·2 (11·0–81·5) ng/mL, and an $AUC_{0\text{-}inf}$ of 335 (226–516) ng·hr/mL (Table 3). As was seen in Study EDG-5506-001,[20] sevasemten concentration at steady state was dose-dependent following dose adjustments (Fig. S3).

Treatment with sevasemten was associated with reductions in circulating biomarkers of muscle injury (CK, TNNI2, and myoglobin), all of which were near maximal within the first 4 weeks of treatment and were sustained for up to 24 months (Fig. 2 and Fig. S4). More specifically, median circulating TNNI2 levels were markedly decreased by Month 1 (Fig. 2A), with reductions from baseline observed at all treatment timepoints (Fig. 2B). Of note, TNNI2 is elevated in BMD and, as it is specific to fast muscle, indicates target engagement.[23] Similarly, circulating CK and myoglobin levels were consistently decreased over the duration of the 24-month treatment period (Fig. S4A and C, respectively), with reductions from baseline observed for most timepoints (Fig. S4B and D, respectively).

SomaScan plasma proteomics has been used to identify a 26-protein universal signature of skeletal muscle injury after strenuous exercise in individuals with BMD and Limb-Girdle muscular dystrophies

	$AUC_{0\text{-}t}$ (ng*hr/mL)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	$AUC_{\%extrap}$ (%)	C_{max} (ng/mL)	t_{max} (hr)	K_{el} (1/hr)	CL/F (L/hr)	V_z/F (L)
n	7	5	5	7	7	5	5	5
Mean	176·4	344·7	39·2	37·6	1·4	0·04	31·7	935·2
SD	64·0	117·2	15·0	26·9	0·7	0·01	10·2	260·9
CV%	36·3	34·0	38·3	71·6	50·8	41·4	32·3	27·9
SEM	24·2	52·4	6·7	10·2	0·3	0·01	4·6	116·7
Minimum	98·8	226	15·2	11·0	0·5	0·02	19·4	608
Median	174·5	334·8	41·5	23·2	1·5	0·03	29·9	971·9
Maximum	302	516	55·8	81·5	2·0	0·06	44·3	1210
Geom Mean	167·4	329·4	36·1	29·6	1·2	0·03	30·4	904·2
Geom CV%	35·7	34·5	53·6	89·9	70·0	39·5	34·5	30·3

AUC = area under the plasma concentration–time curve; C_{max} = maximum plasma concentration; CL/F = apparent oral clearance; CV = coefficient of variation; K_{el} = elimination rate constant; SD = standard deviation; SEM = standard error of the mean; t_{max} = time to maximum plasma concentration; V_z/F = apparent volume of distribution during the terminal phase.

***Table 3*: Summary of plasma sevasemten pharmacokinetic parameters following the administration of a single oral dose (10 mg) on day 1 in treatment-naïve participants (PK Analysis Population).**

(LGMD) types R9 and R12.[24] Consistent with this prior study, the average baseline levels of these proteins were elevated in individuals with BMD as compared to healthy volunteers, and treatment with sevasemten lowered most of the injury signature proteins with similar results across timepoints (Fig. S5A and Table S2). Analysis of the change from baseline for this signature (Fig. S5B) revealed an overall mean decrease of 25·8% (95% CI: –11% to –38·2%) across timepoints.

Over the 24-month treatment period, the median change in total NSAA score was generally positive (Fig. 3A), with no apparent difference across the dose levels. More specifically, for the overall population, the median change from baseline at Month 24 was an increase of 2·0 points; of note, 9 of 12 participants (75%) had a stable or increased total NSAA score at their last evaluation, and stabilisation was observed even in participants with the lowest function at baseline (Fig. 3B). Evaluation of the total NSAD score, 100-m timed test, 4-stair climb, 10-m walk/run, rise-from-floor, activity limitations for patients with upper and/or lower limb impairments (ACTIVLIM), and Patient-Reported Outcomes Measurement Information System—57 items (PROMIS-57) generally showed stabilisation or improvement over time and across sevasemten doses (Tables S3 and S4).

Discussion

Sevasemten has a unique and somewhat counterintuitive approach to the treatment of muscular dystrophies; by modestly *inhibiting* contraction of fast muscle fibres, sevasemten is designed to protect against the ongoing contraction-induced injury that ultimately leads to loss of muscle and functional impairment.[19] Inherent in this approach is the need to identify a sevasemten dose that can protect muscle from contraction-induced injury while preserving muscle function. Thus, this study employed a measured dose escalation strategy to evaluate the long-term safety, tolerability, PK/PD, and functional effects in adults with BMD; indeed, we have observed near-maximal decreases in circulating biomarkers of muscle injury after treatment with 10 mg, while muscle function was preserved, resulting in BMD disease progression that diverged from predicted natural history over 2 years.[14–18]

Sevasemten was well tolerated over two years, with no SAEs or AEs leading to discontinuation of study drug. Overall, reported AEs were relatively few, mild, and consistent with those seen in the phase 1 study.[20] Dizziness and somnolence were seen primarily early in the study at the 10 mg dose. A possible explanation is that by partially inhibiting fast skeletal muscle myosin sevasemten may affect proprioception, i.e., transiently changing the relationship of initiating muscle contraction to the degree of actual contraction, which is perceived as dizziness. The mechanism for somnolence is less clear, but some adaptation with time is observed.

In a previous phase 1 study, sevasemten treatment for 14 days was shown to result in trends of reductions in biomarkers of muscle injury (TNNI2 and CK) in 5 adults with BMD.[20] In this dose-ranging study, sevasemten dosing was initiated at 10 mg once daily with steady state anticipated to be reached over 4–5 weeks. As sevasemten was well-tolerated at the 10 mg dose, the dose was escalated sequentially to 15 mg once daily and then to 20 mg once daily, with median trough sevasemten plasma concentrations rising in an approximately linear fashion. Consistent with preclinical observation that partial inhibition of myosin ATPase could protect from contraction-induced muscle damage without inhibition to the point of decreasing function, the aim was to identify a dose that protected muscle injury without compromising function. As emerging biomarker data indicated that the biomarker response was essentially maximal with the 10 mg dose, this dose was chosen for further investigation and the dose in this study was decreased to 10 mg.

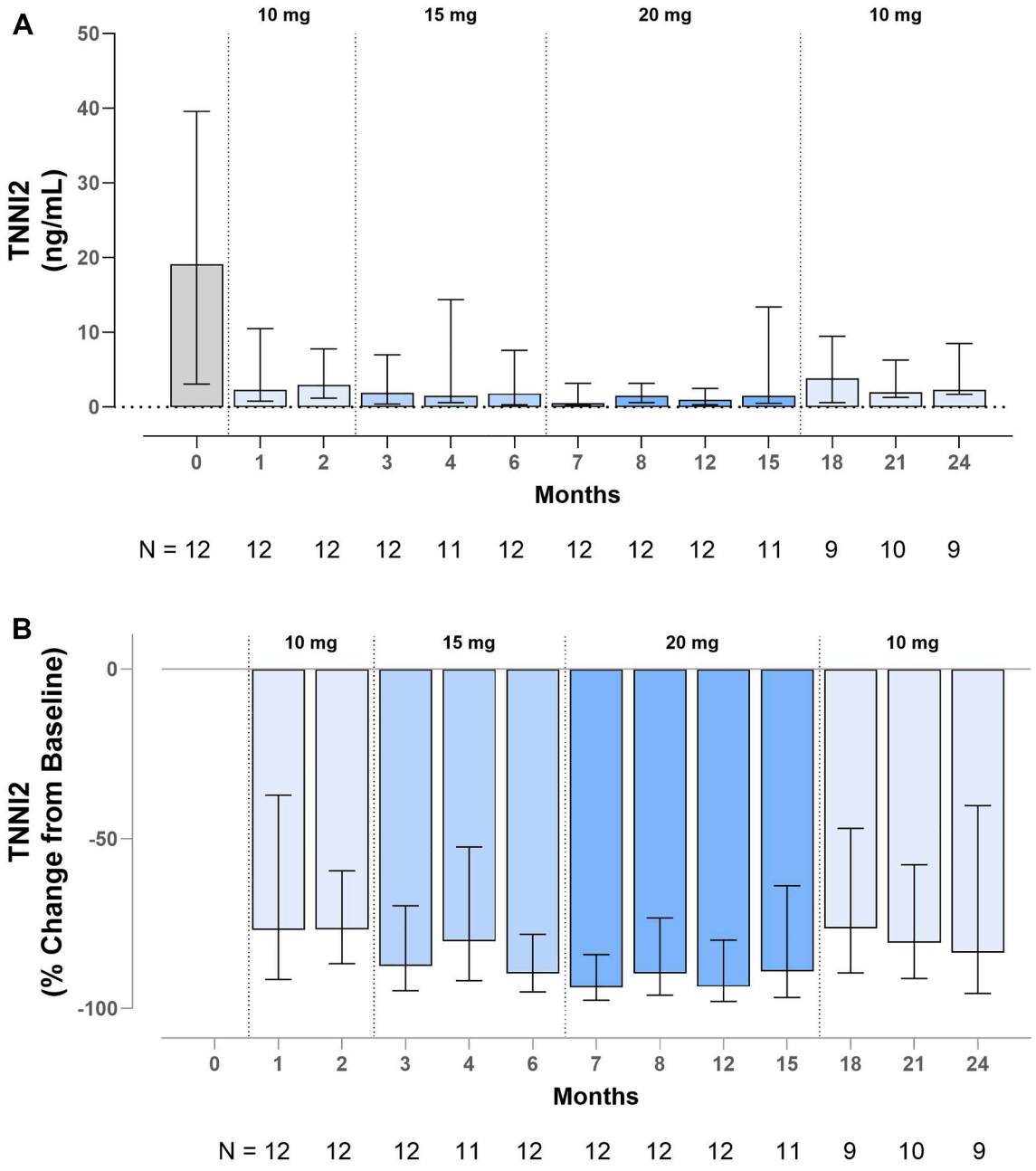

Fig. 2: Sevasemten Treatment Reduces TNNI2. (Panel A) TNNI2 values presented as median (IQR); (Panel B) TNNI2% change from baseline presented as mean (95% CI). TNNI2 = fast skeletal muscle troponin I.

Consistent with ongoing muscle injury and previous reports for individuals with BMD,[25] circulating biomarkers of muscle injury (TNNI2, CK, and myoglobin) were elevated at baseline compared to previous observations in healthy volunteers.[20] With sevasemten treatment, circulating levels of all 3 biomarkers were reduced within the first 4 weeks of treatment at a dose of 10 mg and remained suppressed through 24 months. With dose escalation, further reductions in biomarkers of muscle injury were not observed despite higher exposures. It is also noteworthy that while plasma exposures at the 20 mg dose exceeded those seen at 10 mg, we did not record decreases in NSAA or other functional metrics, demonstrating the broad therapeutic index of this approach.

Biomarker data were further supported by analysis of plasma proteomics using the SomaScan platform. We previously performed a study using controlled

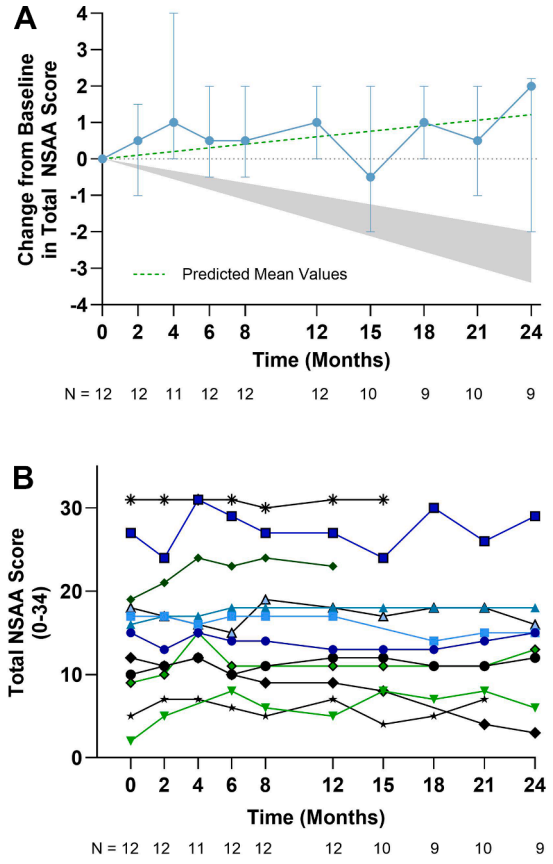

Fig. 3: Total NSAA Score Over Time. (Panel A) Change from baseline in total NSAA score. Data presented as median (IQR). Predicted mean values derived from MMRM regression analysis with fixed and random slope terms for time. Total NSAA Score Slope (change/year): 0·61 (95% CI: −0·93, 2·14). Grey shaded area represents predicted change from baseline based on natural history data.[14-18] (Panel B) NSAA total score over time for individual participants. Sevasemten was administered at a dose of 10 mg daily orally until Month 2 (Day 57), followed by a dose of 15 mg daily to Month 6, a dose of 20 mg daily to Month 15, and a dose of 10 mg daily to Month 24. Of note, 1 participant (black diamond/line) had a meniscal tear and surgery at Month 15. MMRM = mixed model repeated measures; NSAA = North Star Ambulatory Assessment.

strenuous exercise in individuals with BMD to better link circulating protein signatures to a specific exercise intervention designed to yield controlled muscle injury.[24] This signature contained TNNI2 and CK in addition to other structural and metabolic proteins enriched or exclusive to skeletal muscle. Results here show that sevasemten treatment was rapidly followed by a notable reduction in the entire muscle injury signature induced by exercise, suggesting a comprehensive change in the ability of muscle to resist injury with sevasemten. As far as we are aware, this is the only intervention documented to achieve this in muscular dystrophy and supports the clinical hypothesis that sevasemten can be protective against the contraction-induced injury that is the basic defect in BMD.

Estimated steady-state muscle concentrations at the 10 mg dose corresponded to preclinical muscle concentrations at which inhibition of contraction was modest (~10–15%).[19,20] Together with observations of near-maximal reductions of circulating biomarkers of muscle injury, this supported a target dose of 10 mg to maximise protective effects against ongoing muscle injury while minimising potential negative effects on function (e.g., strength loss) associated with excessive, on-target pharmacology.

The ultimate goal for a treatment in BMD is to prevent ongoing muscle damage and loss leading to further loss of functions relevant to everyday life, such as walking, stair climbing, and rising from a seated or supine position, all of which are assessed by the NSAA. As such, the NSAA is considered a clinically meaningful measure, i.e., the test or result shows a real and important change in a person's health or abilities. Contemporary natural history reports following patients for an average of up to 6 years show mean annual declines in total NSAA scores ranging from 1·0 to 1·7.[14–18] In the present 2-year study, NSAA scores were stable or improved, including those who discontinued for reasons unrelated to AEs, with a median improvement in total score of 2·0 at Month 24. Natural history data would suggest that over that time period, total NSAA score would be expected to decline by approximately 2·0 to 3·4 points. Of particular note was that participants with more advanced disease, as evidenced by low NSAA and muscle strength at baseline, remained stable over the duration of the study.

Together, these observations support the hypothesis that modest inhibition of fast skeletal muscle contraction provides protection against the contraction-induced muscle injury that drives disease progression in dystrophinopathies. Further, this unique mechanism could be useful in other muscular dystrophies with defects in the dystroglycan complex and consequent contraction-induced muscle injury.

As this was an open-label trial with no placebo control, caution is required in interpretation. Additional limitations of this study include the small sample size and the lack of diversity in enrolled participants (100% White). The small sample size in particular is an inherent challenge in clinical studies involving rare diseases like BMD that affect fewer than 1 in 15,000 males.[26] While this study used natural history comparisons from multiple sources to provide context for observed treatment effects, these natural history comparisons are inherently limited by the difficulty in deriving the expected decline from published studies, including site-specific differences and other factors which are difficult to quantify.

Overall, the results of this study indicate that once daily sevasemten was well tolerated for up to 2 years in adults with BMD and was associated with reductions in biomarkers of muscle injury that were evident within 4 weeks and sustained to 24 months, as well as functional stability that diverged from the expected decline based on available natural history data.[14–18] On the strength of these findings, additional studies are in progress, including a global, placebo-controlled pivotal study in adults with BMD (NCT05291091), which has been fully enrolled with a sevasemten dose of 10 mg once daily.

Contributors

HP served as the principal investigator for the study and contributed to study design, study enrolment, and study oversight, and was able to access to the raw data. JD and AJR designed the study, provided study oversight, and drafted the manuscript. AB, LT, NRK, and MA contributed to study design, study recruitment, study enrolment, and study conduct. JD, M. Massaro, and JM had access to the raw data and verified the data and all analyses. BB had access to the muscle injury biomarker raw data and verified all plasma proteomics analyses. M. Madden and JAS had access to the raw PK data and performed all PK analyses. All authors participated in the preparation, review, and critical revision of the report. All authors read and approved the final version of the manuscript. JD was responsible for submission of the manuscript. All authors vouch for the completeness and accuracy of the data, for the full reporting of adverse events, and for the fidelity of the trial to the protocol.

Data sharing statement

The data collected in this study, including de-identified individual participant data, will be made available upon reasonable request and after signing an appropriate data sharing agreement. Data access requests should be sent to the corresponding author (jdonovan@edgewisetx.com). Such requests must be approved by the relevant ethics committee(s).

Declaration of interests

HP serves as principal investigator for Edgewise Therapeutics, Avidity, Takeda, RegenixBio, Insamed, Ultragenyx, NS Pharma, Biogen, and Biohaven. JD, BB, M. Madden, JAS, AB, LT, NRK, MA, M. Massaro, JM, and AJR are employees of the study sponsor, Edgewise Therapeutics, Inc., and own stock and/or stock options in the company.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2026.106335.

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