CLINICAL STUDY PROTOCOL

A Phase 1b, Open-label Study of the Safety and Pharmacokinetics of EDG-5506 in Adults with Becker Muscular Dystrophy

Protocol Number:	EDG-5506-002
Version Number:	Amendment 5 (Protocol Version 6)
Compound:	EDG-5506
Brief Title:	Phase 1b Study of EDG-5506 in Becker Muscular Dystrophy
Study Phase:	1b
Sponsor Name:	Edgewise Therapeutics
Legal Registered Address:	3415 Colorado Avenue Boulder, CO 80303 Phone: 720-262-7002
Regulatory Agency Identifier Number(s):	IND 148144
Approval Date:	08-MAR-2023

Confidentiality Statement

Sponsor Signature Page

Study Title: A Phase 1b, Open-label Study of the Safety and Pharmacokinetics of EDG-5506 in Adults with Becker Muscular Dystrophy

Protocol No.: EDG-5506-002

By signing below, I affirm that this protocol and the attachments are approved by the clinical trial Sponsor, Edgewise Therapeutics, Inc.

Signature	Date
[redacted]	09 March 2023

Medical Monitor Name and Contact Information

[redacted]

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Amendment 5 (Version 6.0)	08-MAR-2023
Amendment 4 (Version 5.0)	11-OCT-2022
Amendment 3 (Version 4.0)	02-JUN-2022
Amendment 2 (Version 3.0)	03-FEB-2022
Amendment 1 (Version 2.0)	20-DEC-2021
Original Protocol (Version 1.0)	25-OCT-2021

Amendment 5 (Version 6.0)

Section # and Name	Description of Change	Brief Rationale
Section 1.3: Schedule of Activities	Addition of 3- and 6-month follow-up blood sample collection for those who withdraw prior to the Month 24 visit.	To follow the time course of biomarker response following treatment withdrawal
Section 3: Objectives and Endpoints	Inclusion of Efficacy and Clinical Outcomes as Tertiary/Exploratory Objectives	To align with statistical analysis defined in Section 9
Section 4.3: Justification for Dose Section 6.1: Study Intervention Administered	Dose will be reduced from 20 mg to 10 mg starting at Visit 21	To determine biomarker and functional response at a lower dose based on emerging data.
Section 7.2: Participant Discontinuation/Withdrawal from the Study	Allow re-enrollment for participants who withdraw due to non-safety reasons	Those who withdraw for a non-safety reason (e.g., for family planning due to contraceptive requirement within the study) may return at a later date (e.g., once able to comply with contraceptive requirements again)
Global	In addition, minor changes have been made to the text (addition of detail and for clarification), consistent with standard practices, which do not significantly change the intent of the document.	

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 1b, Open-label Study of the Safety and Pharmacokinetics of EDG-5506 in Adults with Becker Muscular Dystrophy

Brief Title:

Phase 1b Study of EDG-5506 in Becker Muscular Dystrophy

Rationale:

EDG-5506 selectively modulates fast muscle myosin to reduce muscle stress caused by the absence of dystrophin. By protecting fast muscle fibers, EDG-5506 can potentially limit muscle breakdown and disease progression in Becker muscular dystrophy (BMD). This open-label study will evaluate the safety and pharmacokinetics (PK) of EDG-5506 in participants with BMD.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of EDG-5506 in adults with BMD	• Incidence, frequency, and severity of AEs and SAEs in those treated with EDG-5506
Secondary	
• To assess the change in individual safety parameters	• Incidence of treatment-emergent abnormal laboratory test results (clinical chemistry, hematology, coagulation, and urinalysis) • Change from baseline in: – Safety laboratory parameters – Vital signs – Physical and neurological examination – ECG parameters – Cardiac function as assessed by an echocardiogram – Pulmonary function as assessed by FEV_1, FVC – C-SSRS
• To assess the PK of EDG-5506 in adults with BMD	• PK of EDG-5506
Tertiary/Exploratory	
• To investigate the effect of EDG-5506 on biomarkers of muscle fiber damage in adults with BMD	• Change from baseline in: – Serum creatine kinase – Serum cardiac troponin I – Serum myoglobin

Objectives	Endpoints
	– Serum cardiac troponin T – Serum NT-proBNP – Plasma troponin I tissue-specific isoforms (fast skeletal, slow skeletal) – Plasma SomaScan® proteomics
• To assess the effect of EDG-5506 on functional measures in adults with BMD	• Change from baseline in: – NSAA – NSAD – 4-stair climb – 100-meter timed test
• To assess the effect of EDG-5506 treatment on self-reported outcomes in adults with BMD	• Change from baseline in: – PROMIS-57 – ACTIVLIM

ACTIVLIM = activity limitations for participants with upper and/or lower limb impairments; BMD = Becker muscular dystrophy; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NSAA = North Star Ambulatory Assessment; NSAD = North Star Assessment for Limb-Girdle Type Muscular Dystrophies; PROMIS-57 = Patient-Reported Outcomes Measurement Information System; PK = pharmacokinetics; SAE = serious adverse event; AE = adverse event

Overall Design:

This is an open-label, single-center, Phase 1b study to assess the safety and PK of EDG-5506 in adults with BMD. This study will enroll participants who completed (through Day 42) the first-in-human study, EDG-5506-001. If necessary, additional (treatment-naïve) participants from outside the EDG-5506-001 study may be enrolled to meet the target sample size.

Number of Participants:

Enrollment target is based on approximately 8 evaluable participants.

Intervention Groups and Duration:

As this is an open-label study all participants will receive EDG-5506. EDG-5506 will be administered at a dose of 10 mg orally until Visit 8, a dose of 15 mg to Visit 13, a dose of 20 mg to Visit 21, followed by a dose of 10 mg to Visit 27.

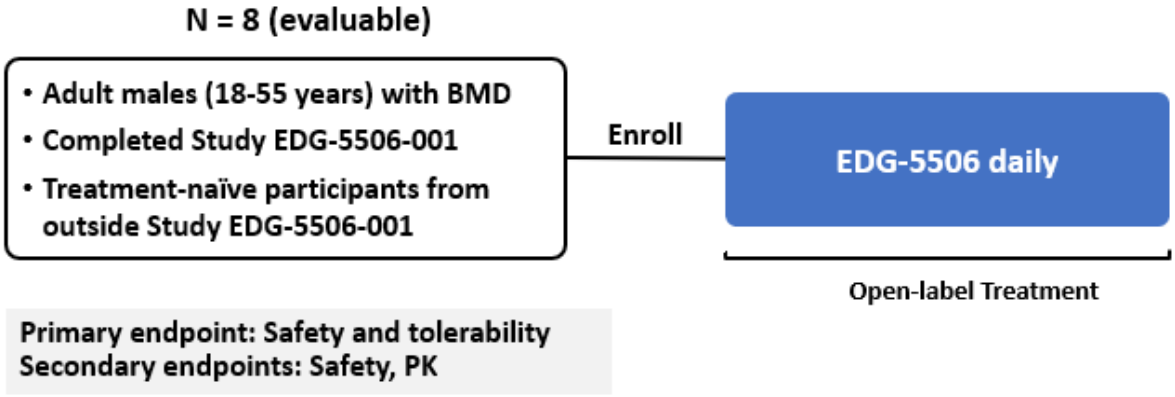
Data Monitoring Committee:

An Independent Data Monitoring Committee (DMC) is being established to enhance the safety of trial participants by providing an independent review of the study data.

1.2. Schema

The study schema is shown in Figure 1.

Figure 1 Study Schema



1.3. Schedule of Activities

The Schedule of Activities (SoA) is provided in Table 1.

Table 1 Schedule of Activities

	Screen	Open-label Treatment Period																		CSP Section | Appendix
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	
	Days									**Months**										
Study Day / Month	**-1**	**1**	**2**	**8**	**15**	**29**	**43**	**57**	**71**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Window (Days)	**-2**	**0**	**0**	**±1**	**±1**	**±3**	**±1**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
Site visit [a]	X	X	X			X		X		X	X		X	X	X		X		X	NA
Telemedicine video call				X	X		X		X			X				X		X		NA
Informed consent	X																			A.3
Demography and Medical Hx	X																			NA
Physical and neuro exam	X					X		X		X	X		X		X		X		X	8.2.1
Weight	X									X									X	NA
Height	X																		X	NA
Vital signs [c]	X	X	X			X		X		X	X		X	X	X		X		X	8.2.2
Hematology/Chemistry [d]	X					X		X		X	X		X	X	X		X		X	8.2.3
Coagulation [d]	X									X									X	8.2.3
Urinalysis	X									X	X		X		X		X		X	8.2.3
Serology [e]	X																			8.2.3
PK sampling [f]		X	X			X		X		X	X		X	X	X		X		X	8.4
Urine PK	X					X				X	X									8.4
Biomarker collection	X					X		X		X	X		X	X	X		X		X	8.6
SomaScan® collection	X					X		X		X	X		X	X	X				X	NA
Dispensing		X				X		X		X	X		X	X	X		X		X	NA
Dose administration		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	6.1.1
Accountability						X		X		X	X		X	X	X		X		X	6.2
NSAA and NSAD	X	X						X			X		X		X				X	8.1.1.1
4-stair climb, 100-m timed test	X	X						X			X		X		X				X	8.1.1.2, 8.1.1.3
Muscle strength and Hand grip	X	X				X		X			X		X		X				X	8.1.1.4
Pedometer		X				X		X		X	X	X	X	X	X	X	X	X	X	8.1.1.5
DXA assessment	X																		X	8.2.6
Cardiac assessment - Echo	X										X								X	8.2.5
Spirometry	X					X		X			X				X				X	8.2.7

	Screen	Open-label Treatment Period																		CSP Section | Appendix
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	
	Days									**Months**										
Study Day / Month	**-1**	**1**	**2**	**8**	**15**	**29**	**43**	**57**	**71**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Window (Days)	**-2**	**0**	**0**	**±1**	**±1**	**±3**	**±1**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
12-lead electrocardiogram	X					X		X		X	X		X		X		X		X	8.2.4
C-SSRS		X				X					X				X				X	8.2.9
ACTIVLIM, PROMIS-57		X						X			X		X		X				X	8.1.2.1, 8.1.2.2
Contraception check	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	NA
Concomitant medications	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	6.8
SAE and AE monitoring	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	8.3

	Open-label Treatment Period											CSP Section | Appendix
Visit Identifier	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**F/U [g]**	**ET 3m[i]**	**ET 6m[i]**	
Study Month[h]	**13.5**	**15**	**16.5**	**18**	**19.5**	**21**	**22.5**	**24/ET [b]**	**25**			
Visit Window (Days)	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	
Site visit		X		X		X		X		X	X	NA
Telemedicine video call	X		X		X		X		X			NA
Physical and neuro exam		X		X		X		X				8.2.1
Weight								X				NA
Height								X				NA
Vital signs		X		X		X		X				8.2.2
Hematology/Chemistry [d]		X		X		X		X				8.2.3
Coagulation [d]								X				8.2.3
PK sampling		X		X		X		X		X		8.4
Biomarker collection		X		X		X		X		X	X	8.6
SomaScan® collection		X		X		X		X		X	X	NA
Dispensing		X		X		X						NA
Dose administration	→	→	→	→	→	→	→					6.1.1
Accountability		X		X		X		X				6.2
NSAA and NSAD		X		X		X		X				8.1.1.1
4-stair climb, 100-m timed test		X		X		X		X				8.1.1.2, 8.1.1.3
Muscle strength and Hand grip		X		X		X		X				8.1.1.4
DXA assessment								X				8.2.6
Cardiac assessment - Echo								X				8.2.5
Spirometry				X				X				8.2.7
12-lead electrocardiogram				X				X				8.2.4
C-SSRS				X				X				8.2.9
ACTIVLIM, PROMIS-57		X		X		X		X				8.1.2.1, 8.1.2.2
Contraception check	→	→	→	→	→	→	→	→	→			NA
Concomitant medications	→	→	→	→	→	→	→	→	→			6.8
SAE and AE monitoring	→	→	→	→	→	→	→	→	→			8.3

AE = adverse event; ACTIVLIM = measure of activity limitations for patients with upper and/or lower limb impairments; CSP = clinical study protocol; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; DXA = dual-energy X-ray absorptiometry; ET = early termination; m = meter; NA = not applicable; NSAA = North Star Ambulatory Assessment; NSAD = North Star Assessment for Limb Girdle Type Muscular Dystrophies; PK = pharmacokinetics; PROMIS-57 = Patient-Reported Outcomes Measurement Information System – 57 items; SAE = serious adverse event; "X" = in-clinic; "→"=continuously
Screening assessments may be performed over 2 days.

[a] Day 2 Site visit for **Treatment-naïve participants only**
[b] Early termination laboratory tests and assessments should mimic those of Month 24 however Medical Monitor discretion may be utilized especially if assessments were recently completed. Participants who withdraw prior to the Month 24 visit for non-safety reasons may re-enroll under the current protocol, or based on availability, the planned open-label extension study.
[c] For treatment-naïve participants vital signs should be assessed 1, 2, 4, and 6 hours post-dose on Day 1
[d] All laboratory tests must be performed before functional assessments
[e] Serology only collected for participants enrolling from outside EDG-5506-001
[f] Single PK to be collected at each visit, except for Day 1. For treatment-naïve participants Day 1 is a serial collection at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 24 hours post-dose. The last timepoint is on Day 2. The dose on Day 2 should be administered only after the 24 hour timepoint. For treatment experienced, Day 1 is pre-dose only.
[g] Based on availability, participants may roll over to the planned open-label extension prior to the Month 24 visit after completion of the ET visit. They are not required to perform the safety follow-up.
[h] Starting at visit 10, study months are defined as 30 days. Monthly visits will be separated by 30 days +/- the visit window.
[i] Laboratory collections for participants who withdraw prior to the Month 24 visit.

2. Introduction

EDG-5506, a first-in-class orally bioavailable, small molecule that selectively inhibits type II fast skeletal muscle myosin is being developed for the treatment of Becker muscular dystrophy (BMD).

2.1. Study Rationale

EDG-5506 selectively modulates fast muscle myosin to reduce muscle stress caused by the absence of dystrophin. By protecting fast muscle fibers, EDG-5506 can potentially limit muscle breakdown and disease progression in muscular dystrophies such as Duchenne muscular dystrophy (DMD) and BMD. This open-label study will evaluate the safety, tolerability, and pharmacokinetics (PK) of EDG-5506 in participants with BMD who completed the first-in-human study, EDG-5506-001 and if necessary, additional (treatment-naïve) participants from outside the EDG-5506-001 study to meet the target sample size.

2.2. Background

2.2.1. Disease Background

BMD is an inherited condition that causes progressive weakness and wasting of the skeletal and cardiac muscles. Structural impairment of muscle from the genetic truncation of the dystrophin protein leads to myofiber membrane stress, hypercontraction, and subsequent degeneration with muscle use. Biomarkers of myofiber degeneration can be assessed in vivo with an elevation of creatine kinase (CK) and troponin in the blood. Human skeletal muscle consists of both fast (type IIa, IIx) and slow (type I) myofibers defined by myosin isoform, a protein integral for muscle contraction. In muscular dystrophy, fast (type II) myofibers appear to be particularly susceptible to early myofiber degeneration that ultimately proceeds to irreversible loss of muscle function with severe disability and early death (Webster 1988). Preventing hypercontraction of fast myofibers and therefore circumventing the loss of dystrophin's structural function may prevent myofiber degeneration and preserve skeletal muscle function in BMD.

2.2.2. Overview of EDG-5506

EDG-5506, which is an allosteric, selective, fast myofiber (type IIa and IIx) myosin inhibitor (half-maximal inhibitory concentration [IC_{50}] of 0.4 μM), has been designed to limit the number of fast skeletal myosin heads engaged in hypercontraction. EDG-5506 is inactive against slow myofiber (type I) myosin (IC_{50} >100μM), which is present in both skeletal muscle and the heart. It is also inactive against the more distantly-related myosin in smooth muscle.

Nonclinical studies have shown acute prevention of ex vivo muscle injury upon treatment with EDG-5506. In dystrophic mouse muscle (*mdx*), modest force reduction secondary to fast myofiber inhibition is coupled to protect against hypercontraction induced force loss, membrane rupture, calcium entry, and myofiber degeneration. Single doses of EDG-5506 reduce circulating CK after strength or exercise tolerance tests in *mdx* mice without reducing performance. In chronic dosing studies using *mdx* mice, EDG-5506 reduces exercise-induced CK, decreases the appearance of fibrosis in the diaphragm and increases grip strength. In the more fibrotic DBA/2 *mdx* mouse (Fukada 2010), chronic administration of EDG-5506 reduces fibrosis in multiple

muscle types including the heart. Finally, in dystrophinopathy dogs, a nonclinical model that more closely mimics human disease (Kornegay 2017), EDG-5506 reversibly decreases circulating CK and increases physical activity, as measured by a wearable device, in short term (2-week) dosing studies.

Overall, results from the first-in-human Phase 1 study, EDG-5506-001, demonstrated that EDG-5506 was well tolerated at doses up to 40 mg once daily for 14 days in healthy volunteers (n=90) and 20 mg once daily for 14 days in adults with BMD (n=5). In participants treated with EDG-5506, reductions in CK and myoglobin were observed.

A detailed description of the chemistry, pharmacology, efficacy, and safety of EDG-5506 is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of EDG-5506 may be found in the IB.

2.3.1. Risk Assessment

As of May 8th, 2022, 90 healthy adult volunteers and 12 adults with BMD have received at least one dose of EDG-5506. EDG-5506 was well tolerated with no withdrawals due to treatment-related AEs. The most common AEs were dizziness, drowsiness, and blurred vision. These were self-limiting and generally occurred more frequently early in dosing despite continued increase in circulating levels of EDG-5506 later in dosing. No AE in BMD patients resulted in withdrawal or dose-adjustment. There were no SAEs or severe AEs.

[redacted]

2.3.2. Benefit Assessment

A substantial unmet need remains for people diagnosed with BMD. Nonclinical data with EDG-5506 have demonstrated improvements in biomarkers and function in mouse and dog models of muscular dystrophy, including reduced levels of CK and improved activity. In addition, treatment also demonstrated reduced fibrosis of the diaphragm and heart muscles. These results suggest that people diagnosed with BMD may benefit from treatment with EDG-5506, however, clinical benefit has not yet been investigated in humans. Refer to the IB for details.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with EDG-5506 are justified by the anticipated benefits that may be afforded to participants with BMD.

3. Objectives and Endpoints

The study objectives and endpoints are summarized in Table 2.

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of EDG-5506 in adults with BMD	• Incidence, frequency, and severity of AEs and SAEs in those treated with EDG-5506
Secondary	
• To assess the change in individual safety parameters	• Incidence of treatment-emergent abnormal laboratory test results (clinical chemistry, hematology, coagulation, and urinalysis) • Change from baseline in: – Safety laboratory parameters – Vital signs – Physical and neurological examination – ECG parameters – Cardiac function as assessed by an echocardiogram – Pulmonary function as assessed by FEV_1, FVC – C-SSRS
• To assess the PK of EDG-5506 in adults with BMD	• PK of EDG-5506
Tertiary/Exploratory	
• To investigate the effect of EDG-5506 on biomarkers of muscle fiber damage in adults with BMD	• Change from baseline in: – Serum creatine kinase – Serum myoglobin – Serum cardiac troponin I – Plasma troponin I tissue-specific isoforms (fast skeletal, slow skeletal) – Serum cardiac troponin T – Serum NT-proBNP – Plasma SomaScan® proteomics
• To assess the effect of EDG-5506 on functional measures in adults with BMD	• Change from baseline in: – NSAA – NSAD – 4-stair climb – 100-meter timed test
• To assess the effect of EDG-5506 treatment on self-reported outcomes in adults with BMD	• Change from baseline in: – PROMIS-57 – ACTIVLIM

ACTIVLIM = activity limitations for participants with upper and/or lower limb impairments; BMD = Becker muscular dystrophy; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NSAA = North Star Ambulatory Assessment; NSAD = North Star Assessment for Limb-Girdle Type Muscular Dystrophies; PROMIS-57 = Patient-Reported Outcomes Measurement Information System; PK = pharmacokinetics; SAE = serious adverse event; AE = adverse event.

4. Study Design

4.1. Overall Design

This is an open-label, single-center, Phase 1b study to assess the safety and PK of EDG-5506 in adults with BMD. This study will enroll participants diagnosed with BMD who completed (through Day 42) the first-in-human study, EDG-5506-001. If necessary, additional participants (treatment naïve) from outside the EDG-5506-001 study may be enrolled to meet the target enrollment of 8 evaluable participants (see Section 9.2 for details).

4.2. Scientific Rationale for Study Design

Prior to the start of this study, EDG-5506 had been administered to a total of 90 healthy volunteers and 5 adults with BMD and demonstrated to be well tolerated at doses administered up to 40 mg once daily for 14 days in healthy volunteers and 20 mg once daily for 14 days in adults with BMD. The half-life of EDG-5506 is estimated to be approximately 18 days in healthy volunteers and approximately 7 days in adults with BMD. Pharmacokinetic modeling predicts that, in the healthy volunteer population, approximately one half of the steady state plasma concentrations are reached after approximately 2 weeks, which was the duration of the EDG-5506-001 multiple dose cohorts. In the Becker population approximately seventy five percent of steady state concentrations were reached on Day 14 in EDG-5506-001. This study aims to characterize the PK up to and including steady state, confirming the safety and tolerability observed at higher doses for 14 days, now in the setting of an extended dosing period.

The study has an open-label design and will enroll participants who completed EDG-5506-001, which was randomized and placebo-controlled. In addition, to meet target enrollment, treatment-naïve participants from outside EDG-5506-001 may be enrolled. Participants will be in clinic on Day 1 for initial dosing and assessments. Those participants who were randomized to placebo in EDG-5506-001 and treatment-naïve participants from outside the EDG-5506-001 study will undergo an additional day of on-site dosing to provide additional observation and PK assessments. All participants will continue dosing at home and will be instructed to take EDG-5506 at night prior to bedtime.

4.3. Justification for Dose

In EDG-5506-001, EDG-5506 was well tolerated in healthy volunteers at single doses of up to 90 mg and once-daily doses of 40 mg for 14 days. All treatment emergent AEs were mild (Grade 1 based on DAIDS AE Grading) in multiple dose cohorts receiving up to 40 mg once-daily for 14 days. In adults with BMD, 20 mg once-daily for 14 days was well-tolerated with the most common AEs being dizziness or somnolence.

Adults with BMD enrolled in Study EDG-5506-001, had an apparent terminal half-life of approximately 7 days, suggesting approximately 75% of the steady state concentration was reached after 14 days of dosing. Therefore, exposures at steady state with a daily dose of 15 mg in this study are anticipated to be similar to exposures observed in the Study EDG-5506-001 in participants with BMD or healthy adult volunteers, at which exposures EDG-5506 was well-tolerated with an acceptable safety profile. Participants will initially dose at 10 mg followed by 15 mg daily starting at Visit 8 and 20 mg starting at Visit 13. Dosing at 15 mg once-daily

continues to be well tolerated in all participants, including dosing of up to 3 months. Therefore, dose will be increased to 20 mg to further explore the safety, PK and effects on biomarkers at higher exposures. Data was also reviewed by the independent DMC who supported increase to 20 mg at Visit 13.

All doses were well tolerated. A near maximal reduction in biomarkers of muscle injury (creatine kinase, myoglobin and TNNI2) was seen after treatment with 10 mg, without further meaningful reductions observed on escalation to 15 mg or 20 mg. This is consistent with the 10 mg dose providing plasma exposures within or above the target therapeutic range observed in animal models of disease. Therefore, at the 15-month visit, participants dose will be changed to 10 mg once-daily, and safety, biomarkers and functional measures will continue to be collected and analyzed to inform dosing in future trials.

Since the most common AEs observed in the EDG-5506-001 were somnolence and dizziness, participants will be instructed to take EDG-5506 at night prior to bedtime.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in Table 1 Schedule of Activities (SoA) for the last participant in the study.

5. Study Population

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

5.1. Inclusion Criteria

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

1. Type of Participant and Disease Characteristics

Participants who have completed Study EDG-5506-001.

Participants who were not from Study EDG-5506-001 must meet the following:

a. Male sex at birth and aged 18 to 55 years inclusive at time of consent.
b. Documented dystrophin mutation with phenotype consistent with BMD.
c. Ambulatory at Screening (defined as ability to complete 100 meter [m] timed test, with or without assistance).
d. Body weight ≥ 50 kg at the Screening visit.
e. Body mass index (BMI) between 20 and 34 kg/m^2 inclusive.

2. Sex and Contraceptive/Barrier Requirements

Female sexual partners of male participants must use highly effective contraception (<1% failure rate per year) through 6 months after last dose.

f. Participants must agree to not donate sperm during the study and for at least 6 months after last dose.

3. Informed Consent

Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Any clinically significant changes during or following the completion of Study EDG-5506-001 that would affect the potential safety of the participant to receive EDG-5506.
2. Cardiac echocardiogram ejection fraction <45% or New York Heart Association (NYHA) Class III or Class IV.
3. Baseline 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results.
4. Forced vital capacity (FVC) predicted <65% or using daytime (mechanical or noninvasive) ventilatory support.
5. Moderate or severe renal or hepatic impairment (eGFR <60 mL/min/1.73 m^2).

6. Positive test for hepatitis C antibody (unless negative HCV PCR), hepatitis B surface antigen, or human immunodeficiency virus (HIV) antibody at screening.

Prior/Concomitant Therapy

7. History of substance abuse or dependency.
8. Receipt of oral corticosteroids for >5 days in the previous 6 months at a dose of >5 mg equivalent per day. Lower oral doses or inhaled/intranasal steroids are permitted.
9. Receiving moderate or strong cytochrome P450 CYP3A4 inhibitors or inducers.
10. Participation in any other investigational drug study or use of use of an investigational drug within 30 days or 5 half-lives (whichever is longer) of dosing in the present study.

Other Exclusions

11. Participants who are unlikely to comply with the study protocol or, in the opinion of the Investigator, would not be a suitable candidate for participation in the study.
12. Medical history or other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory result or abnormality that may increase the risk of study participation or, in the Investigator's judgment, make the participant inappropriate for the study. Includes venous access that would be too difficult to facilitate repeated blood sampling.

5.3. Lifestyle Considerations

EDG-5506 may cause dizziness or drowsiness and so may impair the mental and/or physical ability required for the performance of potentially hazardous tasks. Participants should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely. Initial advice is to not drive a motor vehicle or undertake potentially dangerous work. This will be reassessed based on discretion of the Investigator at the Day 29 visit. However, participants should be reminded not to drive if, at any time, they feel impaired during the study.

[redacted]

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study may be retested or rescreened.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as the investigational intervention, EDG-5506, intended to be administered to a study participant according to this study protocol.

6.1. Study Intervention Administered

Intervention name	EDG-5506
Type	Drug
Dose formulation	Tablet
Unit dose strengths	2.5 mg or 10 mg
Dosage level(s)	10 mg daily until Visit 8 followed by 15 mg daily until Visit 13 followed by 20 mg until Visit 21 followed by 10 mg daily
Route of administration	Oral
Use	Investigational
Packaging and labeling	Provided in HDPE containers with child-resistant screw caps
Storage	15ºC to 30ºC

HDPE = high density polyethylene

6.1.1. Administration of EDG-5506

EDG-5506 will be provided as a 2.5 mg or 10 mg tablet. It should be taken at night prior to bedtime, with or without food. Time of dose will be recorded in the participant diary through the Month 12 visit, at that point only time of dose the night prior to PK collections are required.

Refer to the Pharmacy Manual for information about missed doses.

Treatment-experienced participants will take the first dose of EDG-5506 at the site, in the morning on Day 1 to support the PK collection. Participants will continue dosing at home, starting in the evening on Day 2.

Treatment-naïve participants will take the first dose of EDG-5506 at the site in the morning on Day 1 and return to the site on Day 2 to complete the last PK timepoint before taking the second dose. Participants will remain at the site on Day 2 to be observed for a minimum of 2 hours post dose. Participants will continue dosing at home, starting in the evening on Day 3 after travel home from the site has been completed.

6.2. Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; hence, there will be no randomization or blinding. The participant will be assigned EDG-5506 using interactive response technology (IRT). The site will contact the IRT prior to the start of study intervention administration for each participant.

6.4. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance will be assessed at each site visit. Compliance will be assessed by direct questioning and counting returned tablets and will be documented in the source documents and relevant forms. Deviation(s) from the prescribed dosage regimen will be recorded. In addition to each site visit, telehealth calls, which will occur throughout the study as noted in the SoA, will include a compliance check on EDG-5506 administration.

A record of the quantity of EDG-5506 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5. Dose Modification

Dose modifications will be permitted following discussion with the Medical Monitor. This may include changes to dose or frequency of administration.

6.6. Continued Access to Study Intervention after the End of the Study

Following completion of the treatment period, an open-label extension study may be available for participants to continue receiving treatment with EDG-5506, pending approval by appropriate ethics committees and regulatory authorities.

6.7. Treatment of Overdose

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be reviewed by the Investigator and recorded in the source documents along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Use of strong or moderate CYP3A4 inhibitors or inducers, and examples, not intended to be exhaustive, are listed in Table 3. Potential interactions of EDG-5506 metabolites with transporters have not been studied, so narrow therapeutic index sensitive substrates of transporters are prohibited during the study. All medications will be recorded as concomitant medications.

Table 3 Examples of Prohibited Concomitant Medications

Enzyme	Strong	Moderate
CYP Inhibitors		
CYP3A4	Echinacea, grapefruit juice, itraconazole, ketoconazole, voriconazole, clarithromycin, nefazodone, milk thistle	Ciprofloxacin, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, verapamil, cimetidine
CYP Inducers		
CYP3A4	Carbamazepine, phenytoin, rifampin, St. John's wort, barbiturates, modafinil	Etravirine, phenobarbital, primidone

[redacted]

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Individual dosing may be stopped until safety information can be reviewed in the event that:

- A subject experience an SAE that is considered related to EDG-5506

Because the transaminases ALT and AST that are typically followed to detect hepatotoxicity are elevated in BMD, the liver specific transaminase glutamate dehydrogenase will be followed (Schomaker 2020). The following criteria will be used.

Dosing will be paused for an individual until safety information is reviewed and drug induced liver injury is ruled out in the event that:

- Total bilirubin > 2.0 X ULN, or if baseline bilirubin is > ULN, an increase from baseline value by an amount of at least 1 X ULN

AND either

- GLDH is > 2.5 X ULN (10 U/L)

OR

- ALT is increased by an absolute amount equal to 2.5 X the ULN with no corresponding increase in CK to suggest muscle origin

The participant should be further evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include detailed history, physical assessment, and laboratory assessments, including at least AST, ALT, albumin, CK, direct and indirect bilirubin, GGT, PT/INR, and alkaline phosphatase.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. Discontinuation of study intervention does not imply withdrawal from the study. If study intervention is permanently discontinued, the participant may remain in the study to be evaluated. See the SoA (Table 1) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of study discontinuation, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 1). See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time. However, participants who withdraw for non-safety reasons may re-enroll (e.g., for family planning due to contraceptive requirement within the study)

and may return at a later date (e.g., once able to comply with contraceptive requirements again).

- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Discontinuation of specific sites or of the study as a whole is described in Appendix A.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not permitted.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Efficacy and Clinical Outcome Assessments

Planned time points for all efficacy and clinical outcome assessments are provided in the SoA (Table 1).

8.1.1. Functional Assessments

The functional assessments are briefly described below. Refer to the Clinical Evaluator Manual for details.

8.1.1.1. NSAA and NSAD

The North Star Ambulatory Assessment (NSAA) and North Star Assessment for Limb Girdle Type Muscular Dystrophies (NSAD) have substantial overlap, with almost all NSAA assessments being included in the NSAD. The NSAD includes assessments that are harder than the most difficult NSAA assessments and that are easier than the easiest NSAA assessments, and therefore decreases the likelihood of either a ceiling or a floor effect for the NSAA. To maintain the integrity of the NSAA, the assessments will be performed as a single sequence following the order of the NSAA so identical assessments will not be repeated. Assessments that are unique to the NSAD, starting with the easiest, will be performed after all NSAA assessments are complete.

NSAA

The NSAA is a 17-item test that grades performance of various functional skills from 0 (unable to perform), 1 (completes independently but with modifications), and 2 (complete without compensation) (Mazzone 2009). The NSAA also includes 2 timed functional tests: rise from floor and run 10 meters. The NSAA has been found to correlate with the 6-minute walk test and other functional outcomes in boys with DMD (Mazzone 2009).

NSAD

The NSAD is a functional scale specifically designed to measure motor performance in individuals with limb-girdle muscular dystrophy and is being evaluated in BMD due to the similar limb-girdle pattern of weakness (Jacobs 2021). The NSAD consists of 29 items that are considered clinically relevant items from the adapted NSAA and the Motor Function Measure 20 with a maximum score of 54 and higher scores indicating higher functional abilities.

8.1.1.2. 4-Stair Climb

The 4-stair climb test (with or without the use of handrails) quantifies in seconds the time required for a participant to ascend 4 standard steps. The method the participant uses (e.g., using the handrails) to climb the stairs is recorded to understand any change in technique that occurs over time, however, at no time is the participant instructed on the preferred method (with or without the use of handrails) used to perform this test.

8.1.1.3. 100-Meter Timed Test

The participant will be asked to complete 4 laps on a 25 meter track, for a total of 100 meters as quickly and safely as possible, running if able, and the time recorded in seconds.

8.1.1.4. Muscle Strength Testing and Hand Grip Strength

Muscle strength testing will include assessment of knee extension and flexion and elbow extension and flexion and hand grip strength. Muscle testing will be performed using a hand-held dynamometer. Knee myometry will be performed while the participant is in a sitting position with knee and hip flexed at 90 degrees. Elbow myometry will be performed while the participant is positioned supine with arm at the side and elbow flexed at 90 degrees.

8.1.1.5. Pedometer

To measure daily activity, participants will wear a pedometer daily during waking hours as listed the SoA. The pedometer will be returned to the site at each visit for data upload and returned to the participant for wear through the open-label treatment period to Visit 19. Data may also be collected during telemedicine video calls in between site visits. Participants will be instructed to document daily step count in the participant diary.

8.1.2. Clinical Outcome Assessments

8.1.2.1. ACTIVLIM

This patient-reported measure of activity limitations is to assess individuals with upper and/or lower limb impairments (ACTIVLIM), which measures the ability to perform daily activities.

8.1.2.2. PROMIS-57

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a set of 57 patient-reported measures developed by a National Institute of Health and evaluates physical, mental, and social health.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1. Physical and Neurological Examinations

A physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung, lymph nodes, and gastrointestinal and musculoskeletal systems. A neurological examination will also be conducted to include upper and lower limb tone, power, reflexes and examination of cranial nerves II-XII (excluding ophthalmoscopy).

Abnormal findings will be further characterized as clinically significant or not clinically significant for the purposes of reporting as AEs.

8.2.2. Vital Signs

Supine blood pressure (BP), pulse rate, respiratory rate, and temperature will be measured. Unscheduled collection times will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mmHg after at least 5 minutes of rest. Whenever possible, the same arm (preferably the dominant arm) should be used throughout the study.

Wherever possible, the same size blood pressure cuff, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring blood pressure and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

8.2.3. Clinical Safety Laboratory Assessments

Refer to Appendix B for the list of clinical laboratory tests to be performed.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory tests, as defined in Appendix B, must be conducted in accordance with the laboratory manual and the SoA (Table 1).

If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically

significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.4. Electrocardiograms

Triplicate 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

8.2.5. Echocardiograms

Echocardiographic examinations will be performed by a qualified individual (sonographer) at the site to evaluate left-ventricular systolic and diastolic function, geometry, and mass, as well as left-atrial and right-ventricular function and geometry via two-dimensional, doppler, and/or speckle-tracking imaging techniques. Valvular competence, including presence or absence of regurgitation, will be evaluated and quantified, while overall cardiac health will be qualitatively evaluated (e.g., presence/absence of pericardiac effusion). Echocardiograms will be read locally at the site to satisfy inclusion requirements and ensure the safety of the participants; however, examinations may also be stored, reviewed, and/or analyzed centrally.

8.2.6. DXA Assessment

Dual-energy X-ray absorptiometry (DXA) will collect measures of total lean body mass, fat mass, and bone mineral density. The DXA assessment should be performed consistent with clinical practice.

8.2.7. Spirometry

Spirometry will be performed using a calibrated spirometer device to measure the forced vital capacity percentage (FVC%) predicted for the participant.

The predicted FVC% and the largest FVC will be recorded at each time point. The predicted FVC% will be pulled against the third National Health and Nutrition Examination Survey (NHANES III) (Centers for Disease 1994).

8.2.8. Oculofacial Assessments

Examination of cranial nerves II-XII will be performed as part of the neurological examination at the time points specified in the SoA.

8.2.9. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire used for suicide assessment developed by multiple institutions, including Columbia University, with National Institute of Mental Health support. The scale is evidence-supported and is part of a national and international public health initiative involving the assessment of suicidality.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix C.

Adverse events will be reported by the participant.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

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

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

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Table 1).

All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Table 1).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix C. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor within 24 hours of awareness.

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, the participant is lost to follow-up, or until the condition becomes chronic in nature (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix C.

8.3.4. Regulatory Reporting Requirements for SAEs

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

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review Investigator Site Files and notify the IRB/IEC, if appropriate, according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. Expedited reporting within 7 days will be made for events deemed life threatening or death. For all other serious events, reporting shall occur within 15 days.

8.3.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until the time period for reporting pregnancies aligns with the time period for post-intervention contraception determined in Section 5.1.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy of the female partner of the participant (after obtaining the necessary signed informed consent from the female partner).
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The pregnant female partner of the participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants' pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

8.4. Pharmacokinetics

Samples will be collected for measurement of concentrations of EDG-5506 and metabolites of EDG-5506 as specified in the SoA (Table 1).

8.5. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.6. Biomarkers

- Samples for biomarker research will be collected from all participants in this study as specified in the SoA.
- Biomarker samples will be used for analysis of fast and slow skeletal troponin I, cardiac troponin I, cardiac troponin T, NT-proBNP, myoglobin, and creatine kinase.
- In addition, these biomarker samples will be stored and used for biomarker research related to pathophysiology of muscular dystrophies.
- No samples for genetic, genomic, or RNA analysis will be taken.
- SomaScan® proteomics analysis will be performed to identify potential biomarkers and include evaluation of association under exploratory endpoints.

8.7. Immunogenicity Assessments

Not applicable.

8.8. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

No hypothesis testing is planned for this study.

9.2. Sample Size Determination

Sample size has been set empirically based on the number of participants who completed (through Day 42) the first-in-human study, EDG-5506-001. If necessary, additional (treatment-naïve) participants from outside the EDG-5506-001 study may be enrolled to meet the target enrollment of approximately 8 evaluable participants to provide reasonable estimates of PK and important safety/tolerability for this early stage of clinical development. No formal statistical hypothesis testing is planned. An evaluable participant is defined as a participant who completes the open-label treatment period without significant protocol deviations.

9.3. Analysis Sets

The analysis populations are described in Table 4.

Table 4 Analysis Sets

Participant Analysis Set	Description
Safety Population	All participants who received at least one dose of study intervention
PK Evaluable Population	All participants who received at least one dose of study intervention and have a sufficient PK profile to derive at least one PK parameter

PK = pharmacokinetics.

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

9.4. Statistical Analyses

The SAP will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

9.4.2. Safety Analyses

All safety analyses will be made on the Safety Population. Safety data will be summarized in tables and listings.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Incidence rates for treatment-emergent adverse events (TEAEs), will be summarized

overall, by maximum severity, and by relationship to EDG-5506. Serious adverse events will also be summarized.

The change from baseline in the following safety endpoints will be summarized at each scheduled assessment time point using descriptive statistics:

- Safety laboratory parameters
- Vital signs
- Physical and neurological examination
- ECG parameters
- LVEF as assessed by cardiac echogram
- Pulmonary function as assessed by FEV_1, FVC
- C-SSRS

9.4.3. Efficacy Endpoints

The change from baseline in the following efficacy endpoints will be summarized at each scheduled assessment time point using descriptive statistics:

- NSAA
- NSAD
- 4-stair climb
- 100-meter timed test
- Muscle strength testing

9.4.4. Clinical Outcome Endpoints

The change from baseline in the following efficacy endpoints will be summarized at each scheduled assessment time point using descriptive statistics:

- ACTIVLIM
- PROMIS-57

9.4.5. Biomarkers

The change from baseline in the following efficacy endpoints will be summarized at each scheduled assessment time point using descriptive statistics:

- Serum CK
- Serum cardiac troponin I
- Serum myoglobin
- Serum cardiac troponin T
- Serum NT-proBNP

- Plasma troponin I tissue-specific isoforms (fast skeletal, slow skeletal)
- Plasma SomaScan® proteomics

9.4.6. Pharmacokinetics

Treatment-experienced participants: Exposures will be summarized using descriptive statistics at each time point collected. Additional PK analysis may be done outside of the clinical study report (CSR).

Treatment-naïve participants: For Day 1, standard PK parameters endpoints will be estimated and summarized using descriptive statistics based on the PK Evaluable Population.

Exposures will be summarized using descriptive statistics at each time point collected. Additional PK analysis may be done outside of the CSR.

9.5. Interim Analysis

No formal interim analysis is planned.

10. Supporting Documentation and Operational Considerations

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval (per local regulations) prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

A.2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

A.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of

21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

A.4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A.5 Data Monitoring Committee

The Sponsor is establishing a DMC to enhance the safety of trial participants by providing an independent review of study data.

The DMC shall be comprised of a minimum of 3 experts, including a neurologist, who are independent of the Sponsor study team.

The DMC Charter for this study will define the exact membership, and who should be present for decisions to be made, how reviews will be performed, and how discussions will be documented.

A.6 Dissemination of Clinical Study Data

A description of this clinical study will be available on clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A.7 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRF/eCRF) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in Case Report Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

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

A.9 Study and Site Start and Closure

First Act of Recruitment

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

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

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

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor 's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

A.10 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Clinical Laboratory Tests

Chemistries	**Hematology (CBC)**	**Biomarkers**
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Cholesterol Creatine phosphokinase Creatinine Cystatin C Gamma-glutamyl transferase Glucose Glutamate dehydrogenase Lactate dehydrogenase Magnesium Phosphorus Potassium Sodium Total bilirubin (Reflex: Direct, indirect bilirubin) Total protein Triglycerides Uric acid **Coagulation** Prothrombin time/Partial thromboplastin time	Reticulocytes (%) Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count White blood cell differential (Percentage and absolute): Basophils Eosinophils Lymphocytes Monocytes Neutrophils **Urinalysis (UA)** Bilirubin Color and appearance Glucose Ketones Leukocytes Microscopic[a] (includes RBC and WBC) Nitrite Occult blood pH Protein Specific gravity Urobilinogen	Proteomics platform assessment (SomaScan® Assay) Troponin I (cardiac, slow skeletal, and fast skeletal) Myoglobin, and CK Cardiac Troponin T NT-proBNP **Other Tests (Participants from outside EDG-5506-001 only):** HBsAg HCVAb (reflex if positive HCV RNA) HIVAb

CBC = complete blood count; CK = creatine kinase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCVAb = hepatitis C virus antibody; HIVAb = human immunodeficiency virus antibody; RBC = red blood cell; RNA = ribonucleic acid; WBC = white blood cell

[a] Urine microscopy will be conducted only as a reflex test following abnormal urinalysis results.

Appendix C AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

C.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant and not related to underlying disease progression, in the medical and scientific judgment of the Investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Laboratory Test Result Abnormalities

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms;

  and/or

- Test result requires additional diagnostic testing or medical/surgical intervention;

  and/or

- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy;

  and/or

- Test result is considered to be an AE by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

C.2 Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

C.3 Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medpace Clinical Safety in lieu of completion of the CRF/required form in the electronic data collection tool.
- There may be instances when copies of medical records for certain cases are requested by Medpace Clinical Safety. In this case, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission to Medpace Clinical Safety.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Medpace Clinical Safety. However, it is very important that the Investigator always assess causality for every event before the initial transmission of the SAE data to Medpace Clinical Safety.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor/Medical Monitor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to Medpace Clinical Safety within 24 hours of receipt of the information.

C.4 Reporting of SAEs

SAE Reporting to Medpace Clinical Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Medpace Clinical Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see SAE Reporting to Medpace Clinical Safety via Paper Data Collection Tool) or to the Medpace Clinical Safety by telephone.
- The Investigator is required to submit SAE reports to the IRB in accordance with local requirements

Please update EDC as applicable and send responses to Medpace Safety, as listed below:

[redacted]

SAE Reporting to Medpace Clinical Safety via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medpace Clinical Safety.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

Appendix D Abbreviations

Abbreviation	Definition/Explanation
µM	micromolar
ACTIVLIM	activity limitations for patients with upper and/or lower limb impairments
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC0-24	Area under the plasma concentration-time curve from time zero to 24 hours
BMD	Becker muscular dystrophy
BMI	body mass index
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CK	creatine kinase
CRF	case report form
CSP	clinical study protocol
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
D	day
DAIDS	Division of Allergy and Infectious Diseases
DMC	Data Monitoring Committee
DMD	Duchenne muscular dystrophy
DXA	dual-energy X-ray absorptiometry
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ET	end of treatment
ECG	electrocardiogram
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
FVC%	forced vital capacity percentage
GCP	Good Clinical Practice
GLDH	glutamate dehydrogenase
GGT	gamma-glutamyl transferase

Abbreviation	Definition/Explanation
HBsAg	hepatitis B surface antigen
HDPE	high density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
HIVAb	human immunodeficiency virus antibody
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
kg	kilogram
LVEF	left ventricular ejection fraction
m	meter
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
min	minute
mL	milliliter
ng	nanogram
NHANES III	Third National Health and Nutrition Examination Survey
NSAA	North Star Ambulatory Assessment
NSAD	North Star Assessment for Limb Girdle Type Muscular Dystrophies
NT-proBNP	N-terminal prohormone brain natriuretic peptide
NYHA	New York Heart Association
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PR	PR interval
PROMIS-57	Patient-Reported Outcomes Measurement Information System – 57 items

Abbreviation	Definition/Explanation
PT	prothrombin time
QRS	QRS complex
QT	QT interval
QTc	QT interval corrected
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAD	single ascending dose
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
TEAE	treatment-emergent adverse event
U/L	units per liter
ULN	upper limit of normal
WBC	white blood cell

Appendix E Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

Amendment 4 (Version 5.0): 11 October 2022

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Treatment period has been extended from 12 months to 24 months	To support continued access with long-term data collection of safety and biomarker data with EDG-5506
Section 6.1 Study Intervention Administered	Addition of 10 mg tablet strength	To reduce tablet burden by minimizing the quantity to achieve the dose
Global	In addition, minor changes have been made to the text (addition of detail and for clarification), consistent with standard practices, which do not significantly change the intent of the document.	

Amendment 3 (Version 4.0): 02 June 2022

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Intervention Groups and Duration Section 4.3 Justification for Dose Section 6.1 Study Intervention Administered	Dose will be escalated from 15 mg to 20 mg starting at Visit 13.	To further explore the safety, PK and effects on biomarkers at higher exposures.
Section 1.3 Schedule of Activities	Visit 14 telemedicine video call becomes a site visit. Functional measure and clinical outcome assessment collection added at Visit 13	To collect 1 month safety, PK, and biomarker data after 20 mg dose escalation. To assess change from 20 mg dose escalation
Global	In addition, minor changes have been made to the text (addition of detail and for clarification), consistent with standard practices, which do not significantly change the intent of the document.	

Amendment 2 (Version 3.0): 03 February 2022

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Intervention Groups and Duration Section 4.3 Justification for Dose Section 6.1 Study Intervention Administered	Dose will be escalated from 10 mg to 15 mg starting at Visit 8.	Based on additional PK data from the Phase 1 Study EDG-5506-001, exposures at steady state with a daily dose of 15 mg in this study are anticipated to be similar to well-tolerated exposures observed in the Study EDG-5506-001 in participants with BMD or healthy adult volunteers, which supports an increase from 10 mg to 15 mg QD at Visit 8 (after 2 months at 10 mg).
Section 6.8 Concomitant Medications	Removal of the requirement for concomitant medications to be approved by the Medical Monitor to allow review to be performed by the Investigator.	Permit assessment to be completed by the Investigator.
Section 1.3 Schedule of Activities Section 8.1.1.5 Pedometer	Add pedometer data collection during telemedicine video calls starting at Visit 12.	Permit pedometer data to be collected in-between site visits during telemedicine video calls to account for larger visit windows.
Global	In addition, minor changes have been made to the text (addition of detail and for clarification), consistent with standard practices, which do not significantly change the intent of the document.	

Amendment 1 (Version 2.0): 20 December 2021

Section # and Name	Description of Change	Brief Rationale
Section 1.3: Schedule of Activities	The PK collection and biomarker labs have been removed from visits: V5, V7, V9	To align with site visits
	Height added at V1	To allow BMI calculation and forced vital capacity percentage
	Spirometry moved from V2 to V1	To use for eligibility
	Treatment period has been extended from 3 months to 12 months	To support long-term data collection of safety and biomarker data with EDG-5506
Section 4.2: Scientific Rationale for Study Design Section 4.3: Justification for Dose Section 6.1: Study Intervention Administered	Dose has been updated from loading dose of 10 mg and maintenance dose of 7.5 mg to dose of 10 mg throughout open-label treatment period	Based on emerging data from the EDG-5506-001 study, the half-life of EDG-5506 is shorter in adults with BMD, approximately 7 days compared with 18 days in healthy volunteers. Steady-state concentrations at a dose of 10 mg are anticipated to be less than those previously evaluated at 20 mg once daily for 14 days in EDG-5506-001 in participants with BMD.
Section 5.1, 5.2: Inclusion/Exclusion Criteria	Updated Sex and Contraceptive Requirements to include sperm donation restrictions	To provide more robust guidance around contraceptive requirements
	Removed reference to Day 42 labs for those previously enrolled in EDG-5506-001.	Screening labs will be used to determine eligibility for all participants
Global	In addition, minor changes have been made to the text (addition of detail and for clarification), consistent with standard practices, which do not significantly change the intent of the document.	

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