Edgewise THERAPEUTICS

Corporate Presentation

September 2021

NASDAQ: EWTX

Forward-Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties of Edgewise Therapeutics, Inc. ("Edgewise" or the "Company"). All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, results of operations, business strategy and plans, and objectives of management for future operations, as well as statements regarding industry trends, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "estimate," "intend," "may," "plan," "potentially" "will" or the negative of these terms or other similar expressions.

We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: negative impacts of the COVID-19 pandemic on Edgewise's operations, including clinical trials; risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and operating as an early clinical stage company; Edgewise's ability to develop, initiate or complete preclinical studies and clinical trials for, obtain approvals for and commercialize any of its product candidates; changes in Edgewise's plans to develop and commercialize EDG-5506 or any other product candidates; the potential for clinical trials of EDG-5506 or any other product candidates to differ from preclinical, preliminary or expected results; Edgewise's ability to enroll patients in its ongoing and future clinical trials; operating results and business generally; Edgewise's ability to raise funding it will need to continue to pursue its business and product development plans; regulatory developments in the United States and foreign countries; Edgewise's reliance on third parties, contract manufacturers and contract research organizations; Edgewise's ability to obtain and maintain intellectual property protection for its product candidates; risks associated with access to capital and credit markets; the loss of key scientific or management personnel; competition in the industry in which Edgewise operates; Edgewise's ability to develop a proprietary drug discovery platform to build a pipeline of product candidates; general economic and market conditions; and other risks. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

This presentation concerns product candidates that are under clinical investigation, and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). It is currently limited by federal law to investigational use, and no representation is made as to its safety or effectiveness for the purposes for which it is being investigated.

Edgewise Therapeutics is a Clinical–Stage Company Focused on Advancing Innovative Treatments for Severe, Rare Muscle Disorders

- Developing lead program, EDG-5506, to become the ***de facto* standard of care** for all dystrophinopathies supported by a **strong preclinical data package**
- Leveraging **development capabilities** to advance an additional **three** preclinical programs, that address therapeutic areas of **considerable unmet need**, to IND
- Plan to enhance portfolio by leveraging **internal research platform** and **external business development**
- Led by an **experienced management team** with deep expertise in muscle physiology/biophysics and rare disease drug development
- Well-capitalized to execute **important value-driving milestones** across both EDG-5506 and pipeline programs

"Our vision is to improve the lives of patients and families suffering from rare muscle disorders"

World-Class Team of Experienced Rare Disease Drug Developers with a Track Record of Success

Leadership Team

Kevin Koch, PhD
President and Chief Executive Officer

Biogen · OrbiMed · AMGEN · ARRAY BIOPHARMA

Alan Russell, PhD
Co-Founder and Chief Scientific Officer

GlaxoSmithKline · Cytokinetics

R. Michael Carruthers
Chief Financial Officer

BrickellBio · Nivalis · ARRAY BIOPHARMA

Joanne Donovan MD, PhD
Chief Medical Officer

catabasis · SANOFI GENZYME

John Moore
General Counsel

Peloton Therapeutics · ARRAY BIOPHARMA · WILSON SONSINI

Behrad Derakhshan, PhD
Chief Business Officer

ALEXION · Therachon · VectivBio

Board of Directors

Peter Thompson, MD
Co-Founder and Chairman

Kevin Koch, PhD
President and Chief Executive Officer

Alan Russell, PhD
Co-Founder and Chief Scientific Officer

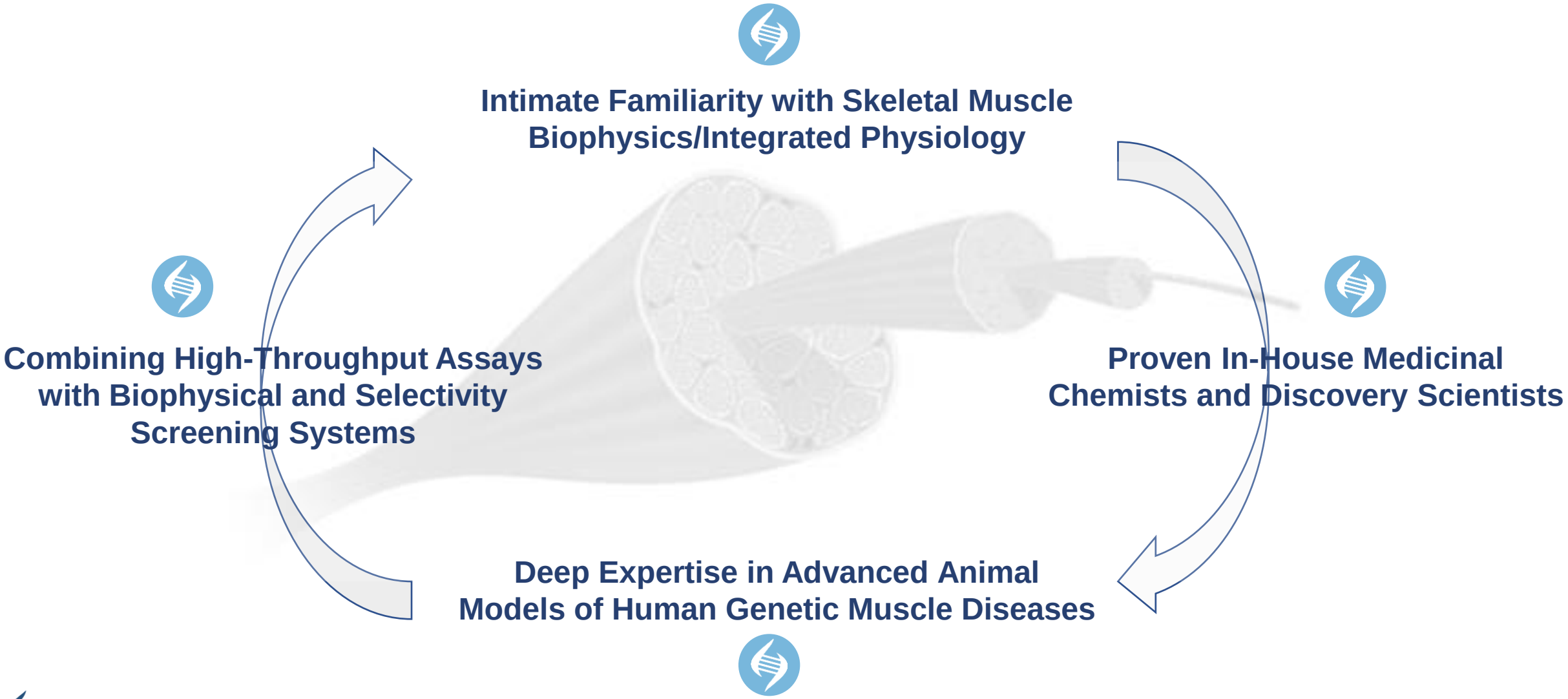
Ken Harrison, PhD
Partner, Novo Ventures

John Root, MD
General Partner, U.S. Venture Partners

Badreddin Edris, PhD
Co-Founder and Chief Operating Officer, SpringWorks Therapeutics

Laura Brege
Senior Advisor, BridgeBio; Former Chief Operating Officer, Onyx Pharma

We Focus Our Small Molecule Precision Platform on Discovering Novel Disease Modifying Therapies for Inherited Muscle Disorders



Our Precision Medicine Muscle Platform has Generated **One Clinical Stage** and **Three Research** Programs

	Target	Indications	Preclinical	Phase 1	Phase 2	Phase 3	Upcoming Milestones	Commercial Rights
Clinical Programs								
EDG-5506 *Skeletal muscle*	*Myosin ATPase*	• DMD • BMD • LGMD					• MAD data in HVs • BMD biomarker and functional data • FDA feedback on DMD and BMD registrational trial design	Edgewise THERAPEUTICS
Preclinical Programs								
EDG-6289 *Skeletal muscle*	*Myosin ATPase*	• Spasticity and other neuromuscular disorders					• IND-enabling studies	Edgewise THERAPEUTICS
EDG-002 Program *Cardiac muscle*	*Muscle Desensitizer*	• Cardiac indications					• Preclinical proof-of-concept • Clinical lead selection • IND-enabling studies	Edgewise THERAPEUTICS
EDG-003 Program *Skeletal muscle*	*Muscle Desensitizer*	• Neuromuscular disorders					• Preclinical proof-of-concept	Edgewise THERAPEUTICS

Strong Execution in 2020 Has Positioned Edgewise for **Multiple Value-Driving Milestones** in the Next 12-24 Months

	2020	2021 / 2022	
EDG-5506	✓ Selection of EDG-5506 as drug candidate ✓ Completed 3-month GLP toxicology ✓ Novel biomarker data supporting MOA ✓ Filed IND in 2Q20 ✓ Dosed first healthy volunteer in Phase 1	• Complete Phase 1 in healthy volunteers • Biomarker and functional data in BMD • Exploratory POC work in other inherited myopathies • DMD registrational trial start date	MAD (**2H21**) **2022** **2022** **2022**
Pipeline	✓ Pushed several early program opportunities to near drug candidate selection stage	• Preclinical POC with a faster onset alternative to EDG-5506 • Candidate selection of a novel cardiac modulator for inherited cardiac disorders • Selection of a novel selective fast skeletal muscle modulator candidate	**2H21** **2H21** **1H22**

Muscular Dystrophies

EDG-5506

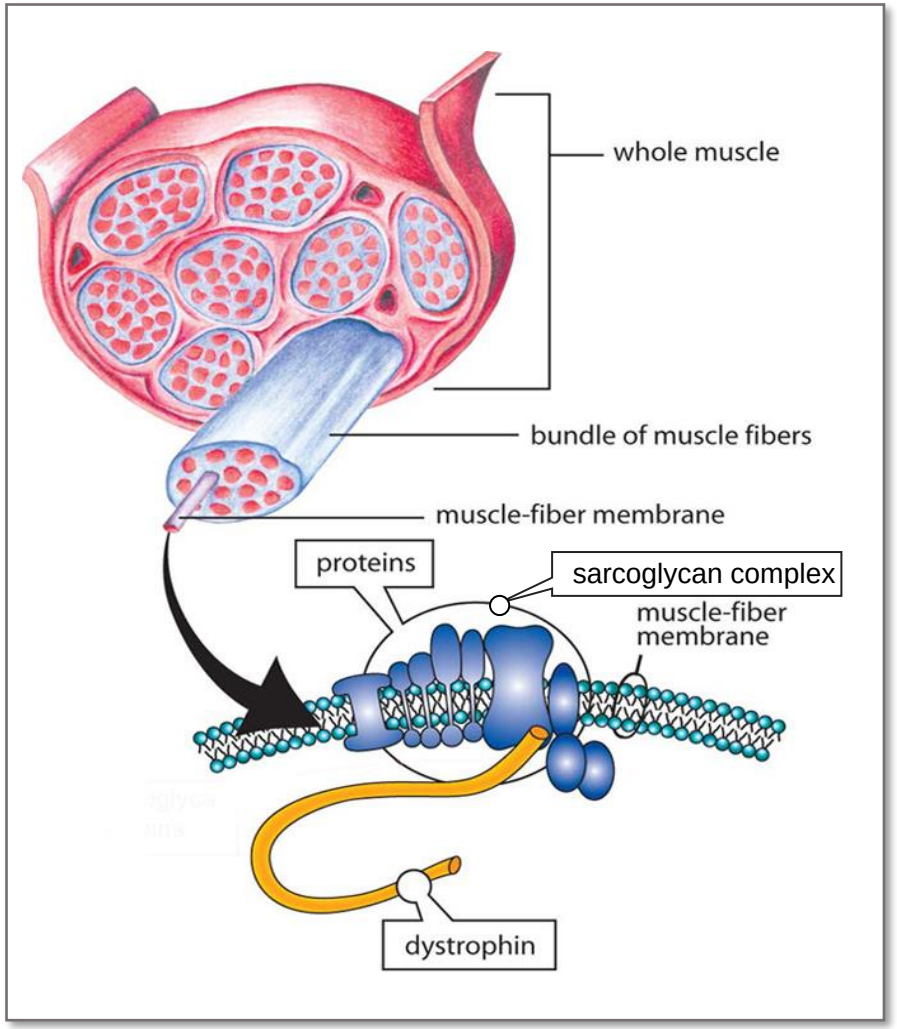
Mutations in Dystrophin or Proteins of the Sarcoglycan Complex Lead to a Family of Severe Myopathies

DMD – non-functional dystrophin

- 12,000-15,000 patients in the US
- Muscle damage from birth; functional deficit by 4-6 yrs.
- Nearly all patients will be wheelchair-bound by early teen yrs.
- Death by respiratory/cardiac failure at 20-30 yrs. old

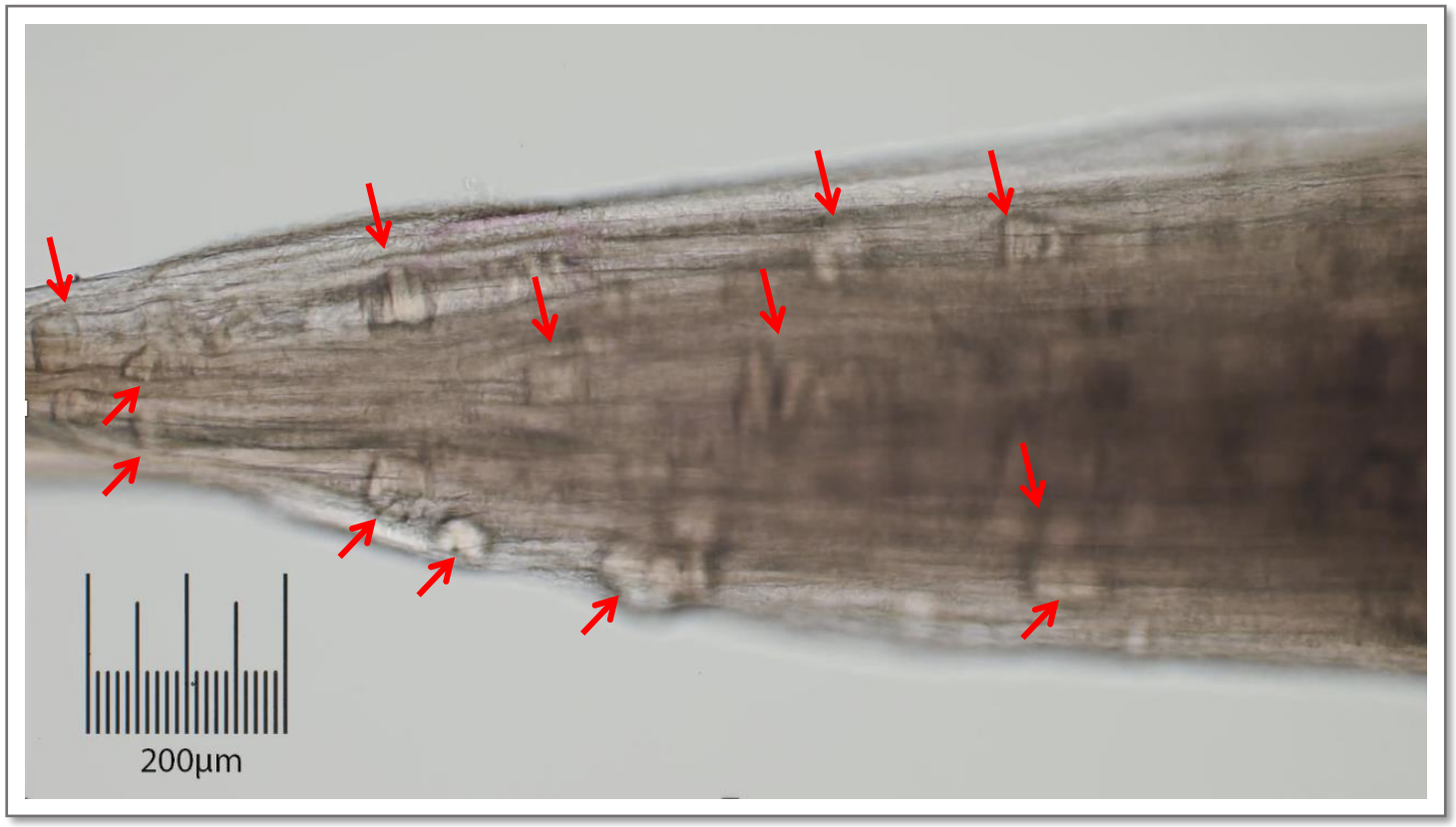
BMD – partially functional protein

- 4,000-5,000 patients in the US
- Later onset versus DMD, typically 8-15 yrs.
- Variable progression for mobility (late 30s) and cardiomyopathy



Contraction Leads to Injury in Dystrophic Muscle

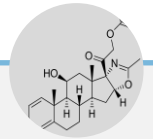
DMD Muscle in an *mdx* Mouse



Dystrophin primarily provides protection from damage **NOT enhanced function**

Current Competitive Landscape Predominantly Focused on Gene and RNA Therapies that are Unlikely to Address the Unmet Needs in DMD

Standard of Care



Steroids

- ~70% of patients are treated with steroids, either EMFLAZA® (deflazacort) or prednisone
- Serious side effects, particularly with long-term use
- Use limited to a relatively narrow age range; initiation of treatment prior to age four is generally not recommended

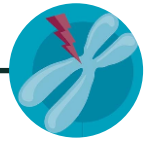
Mutation Specific Therapies

- Exondys51, VyonDys53, Viltepso, Casimersen; Ataluren (EU only); 8-13% of patients are eligible for each therapy
- Biomarker supported provisional approvals; full approvals require further studies demonstrating functional benefit
- Cumbersome weekly infusions

Competitive Pipeline

Gene Therapies

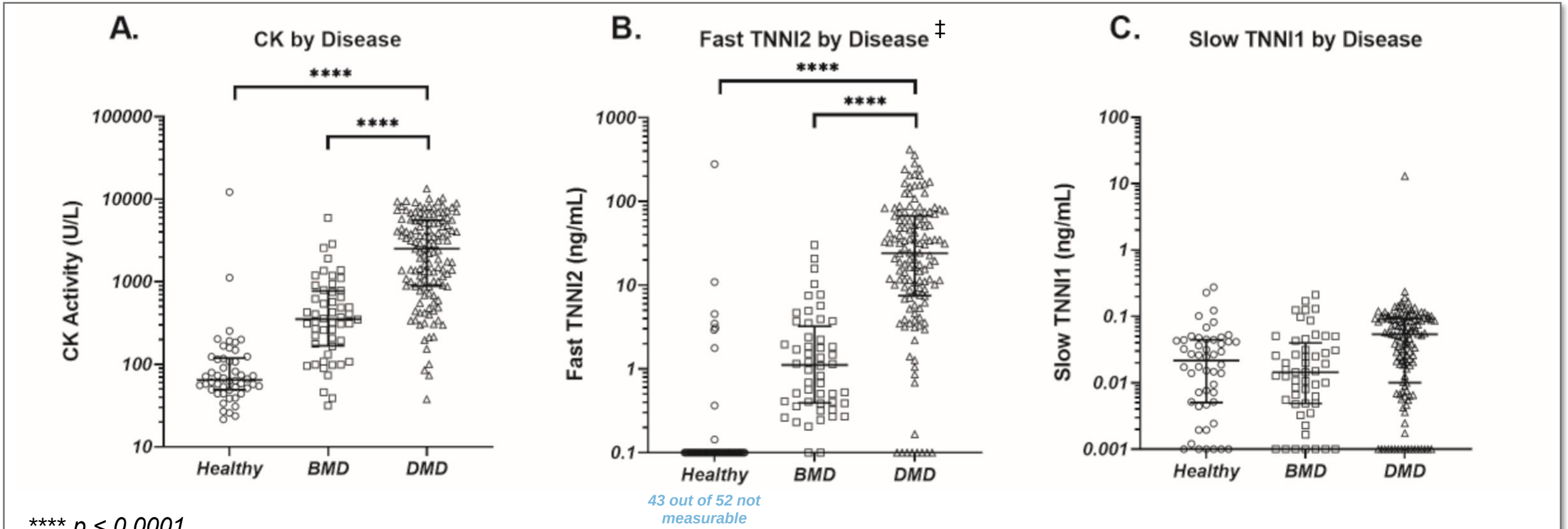
- Delivery of micro-dystrophin (20% of full length), **NOT full dystrophin**
- Muscle injury biomarker data (creatine kinase) restored to upper levels of BMD patients. **NOT to normal levels**
- Dilution with patient growth and injury. **Durability over time unknown**



Next Generation RNA Therapeutics

- First generation compounds showed low dystrophin
- Many next generation approaches still in early preclinical development
- **No evidence of functional benefit**
- **Mutation specific**

Susceptible Fast Fiber Muscle Biomarkers are Elevated in BMD and DMD



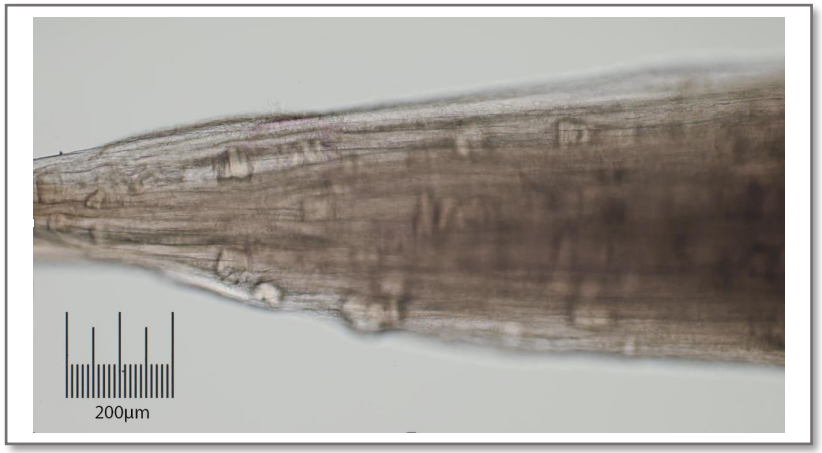
**** $p < 0.0001$

‡ The majority of healthy volunteers (83%) had TNNI2 levels below the lower level of detection of the ELISA (<0.1 ng/ml), while only 4% of BMD and 6% of DMD patients had non-measurable levels of TNNI2

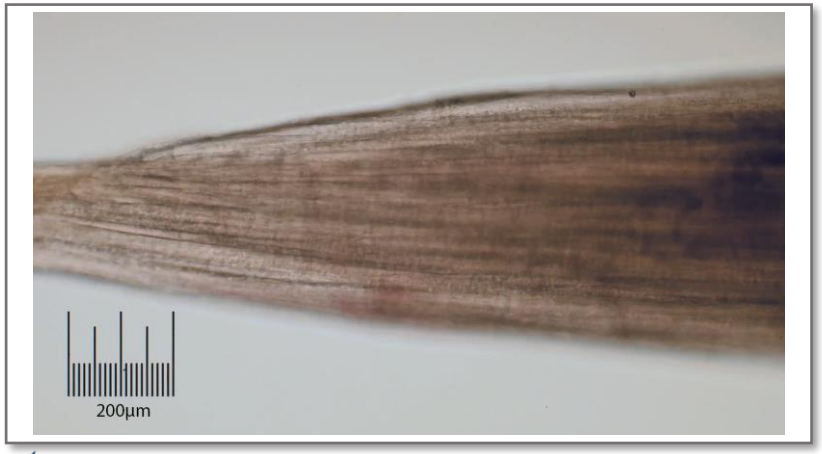
132 DMD samples from Newcastle University Biobank, 49 BMD samples from the CINRG consortium and 50 healthy volunteers from Chen collaboration

Edgewise's Therapeutic Hypothesis: **Selectively Limiting Contraction in Susceptible Fast Muscle Fibers Can Preserve Muscle Function**

Untreated DMD Muscle (*mdx* mouse)



DMD Muscle (*mdx* mouse)
Treated with 0.3 µM EDG-5506

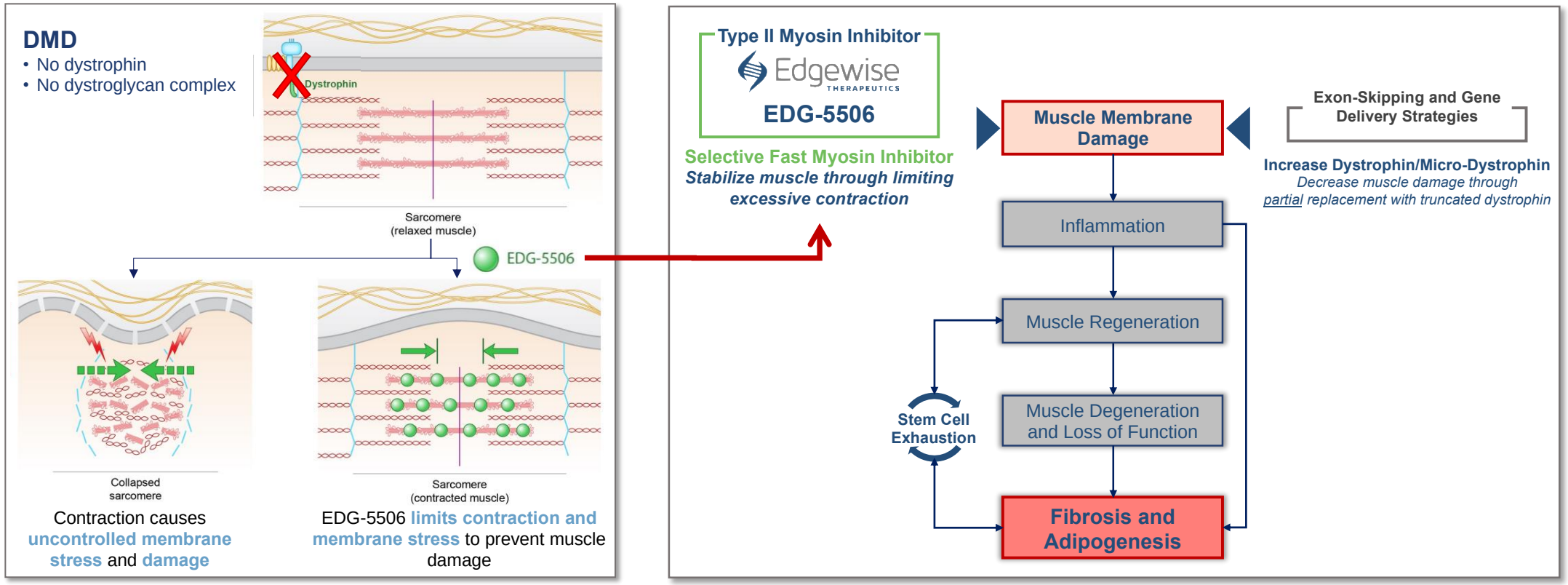


Goal: a 5-20% reduction of muscle contraction in susceptible type II (fast) muscle fibers with a **selective myosin inhibitor**

This reduction in fast fiber contraction is **sufficient to prevent muscle breakdown**

Reduced muscle breakdown will result in **preservation or enhancement of physical function** in DMD patients

EDG-5506's Novel MOA is Potentially Disease Modifying for DMD and BMD Patients



Orthogonal MOA allows for potential **combination with ALL major classes of drugs** currently in development for DMD and is **mutation agnostic**

Preclinical Data

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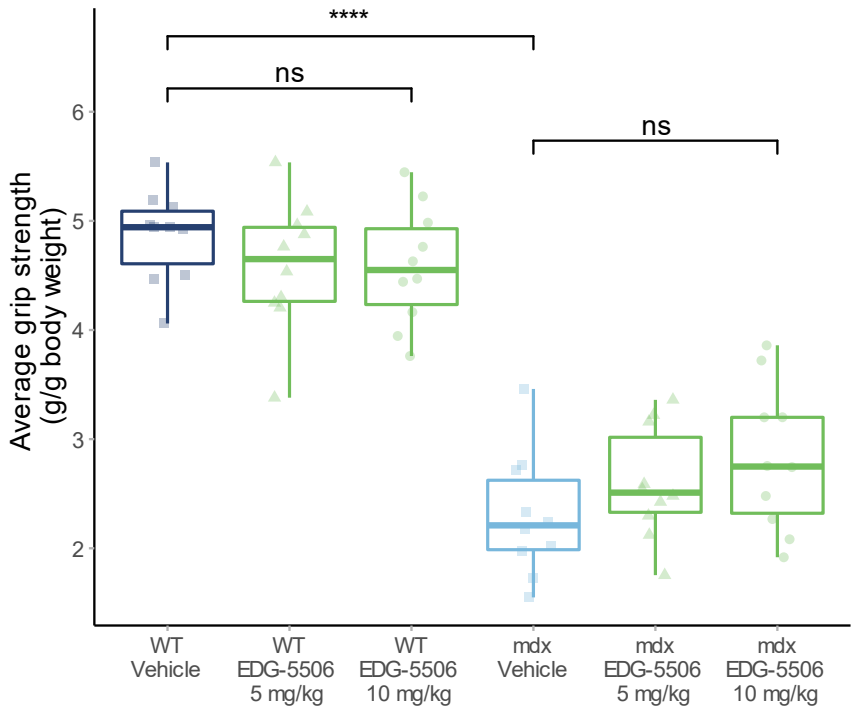
EDG-5506 Has Demonstrated Improvement in a Variety of DMD Clinical Manifestations in Numerous Disease Models

Disease Model	Setting	Clinical Manifestation Tested	EDG-5506 Demonstrated Significant Improvement
***mdx* Mice**	*Ex vivo*, *in-situ*	Contraction-induced injury	✓
	In vivo	Circulating biomarker post-exercise	✓
	In vivo	Muscle fibrosis	✓
DBA/2J-*mdx* Mice	*In vivo*	Fibrosis, scoliosis and strength	✓
	In vivo	Cardiac fibrosis and hypertrophy	✓
GRMD	*In vivo*	Circulating biomarkers	✓
	In vivo	Habitual activity levels	✓

EDG-5506 Reduced *mdx* Mouse Creatine Kinase Response After Strength-Testing without Altering Performance

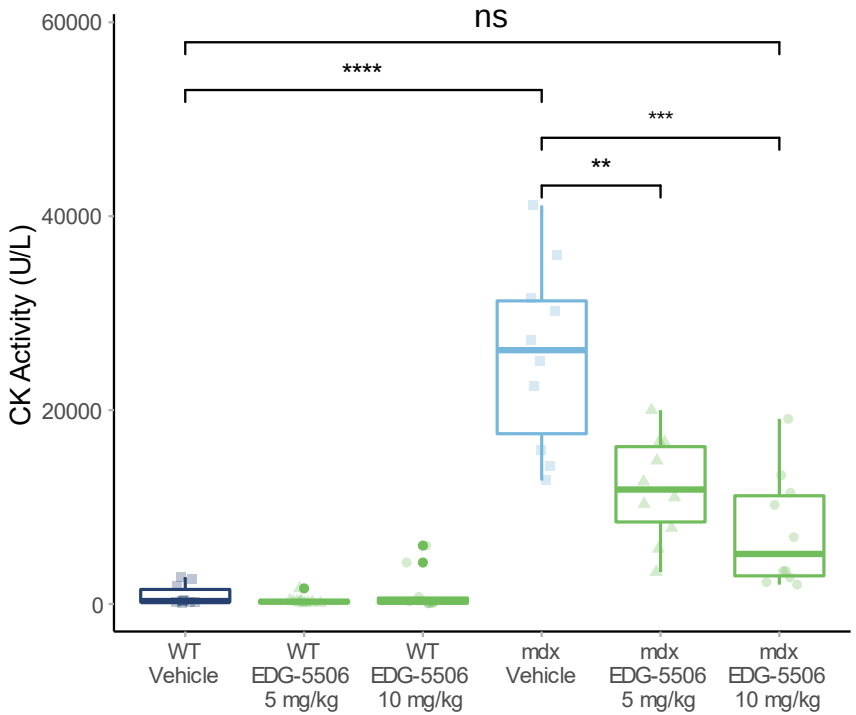
Physical Performance

Grip strength (best of 5) 4 hours post-PO dose



Circulating Biomarker

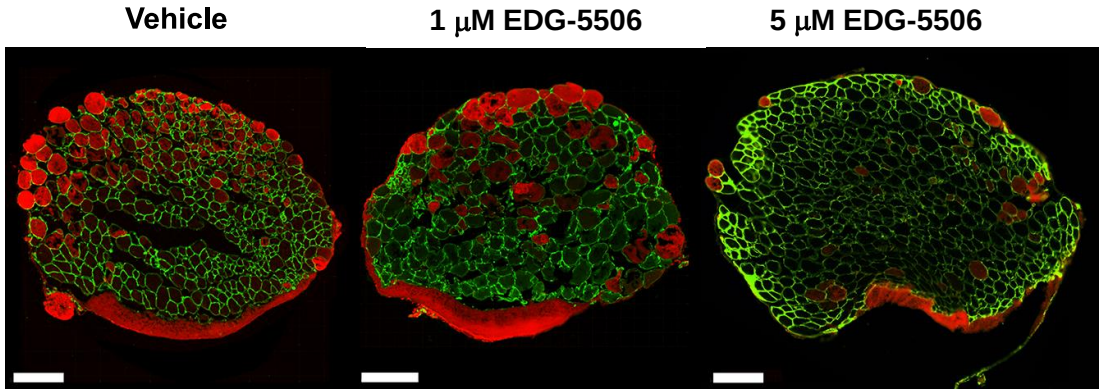
Plasma CK activity 1-hour post-grip strength test



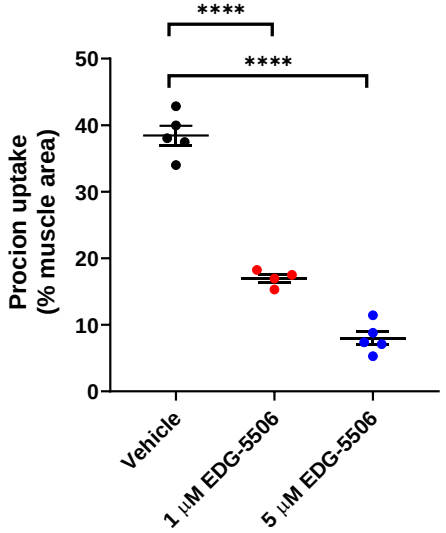
Graphs show mean +/- 1 SEM. Significance calculated by one-way ANOVA with Dunnet's multiple comparison: ns: p > 0.05, **: p <= 0.01, ***: p <= 0.001, ****: p <= 0.0001.

EDG-5506 Protects Muscles from Membrane Disruption in *mdx* Mice

Ex vivo Dye Uptake by Contracting Muscle

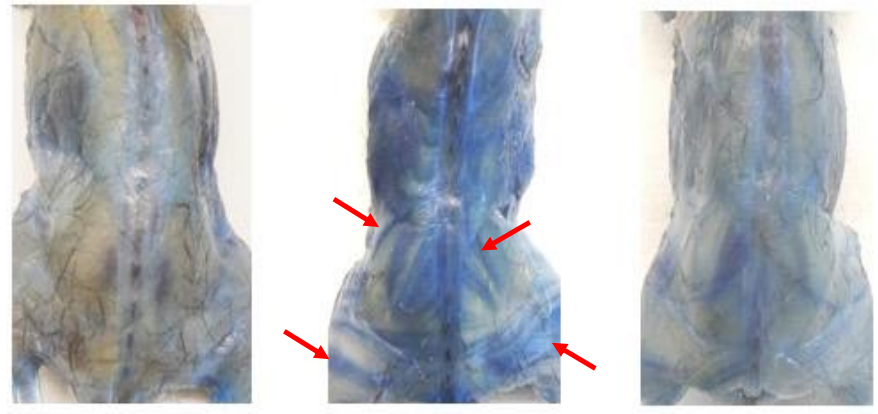


Red = fluorescent procion orange. Taken up by leaky muscle fibers
Green = wheat germ agglutinin (outlines fibers)



In vivo Dye Uptake by Leaky Muscle Fibers

Evans blue uptake in non-exercised mdx mice after 3 weeks of treatment



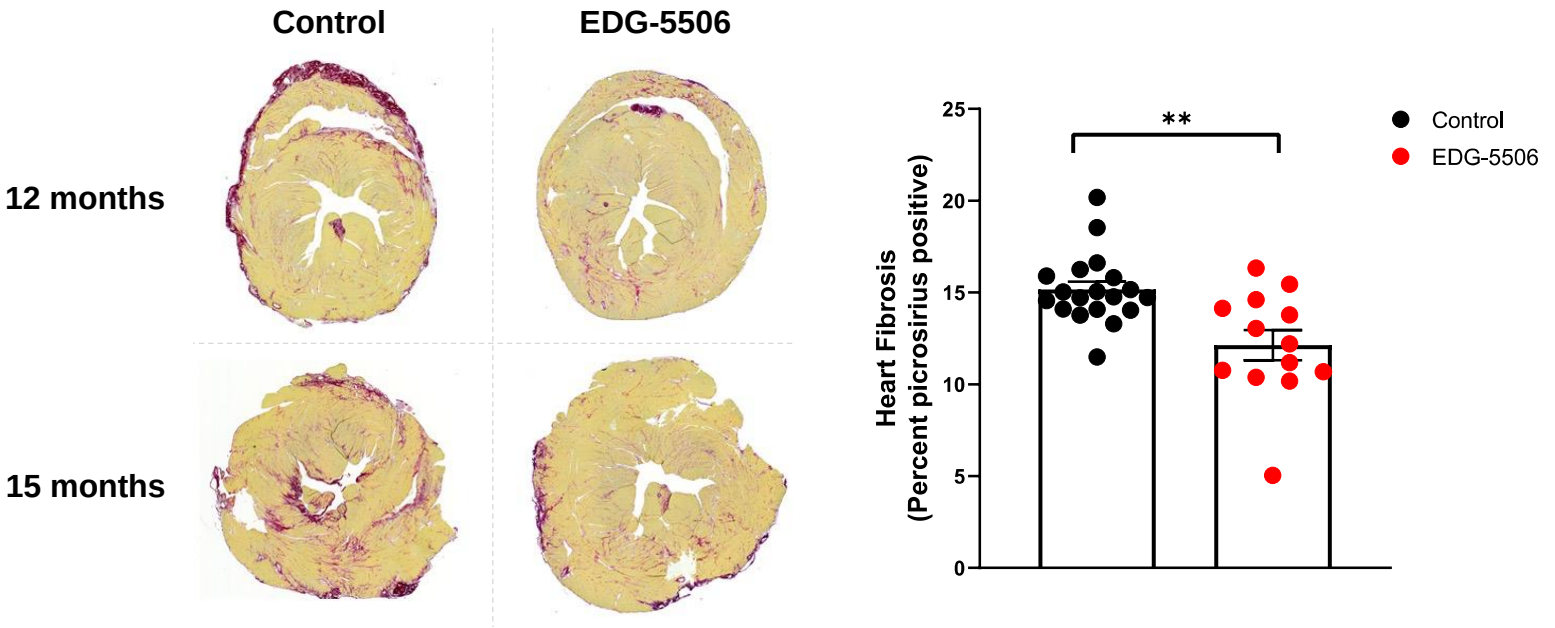
WT Control | ***mdx* Control** | ***mdx* EDG-5506 3 mg/kg**

EDG-5506 **Prevents Edema** and the Ensuing Muscle Necrosis that Result from **Muscle Membrane Disruption** in DMD

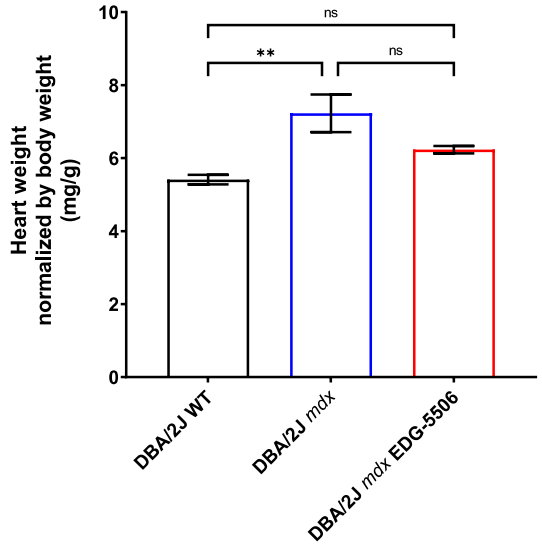
Graph shows mean +/- 1 SEM. Significance calculated by one-way ANOVA with Dunnet's multiple comparison (****0.0001)

EDG-5506's Impact on Cardiac Fibrosis is a Significant Finding Since Cardiac Myopathy is a Common Driver of Mortality in DMD and BMD

15 Months Dosing of DBA/2J *mdx* Mice Demonstrated Lower Cardiac Fibrosis Compared to Vehicle Controls*

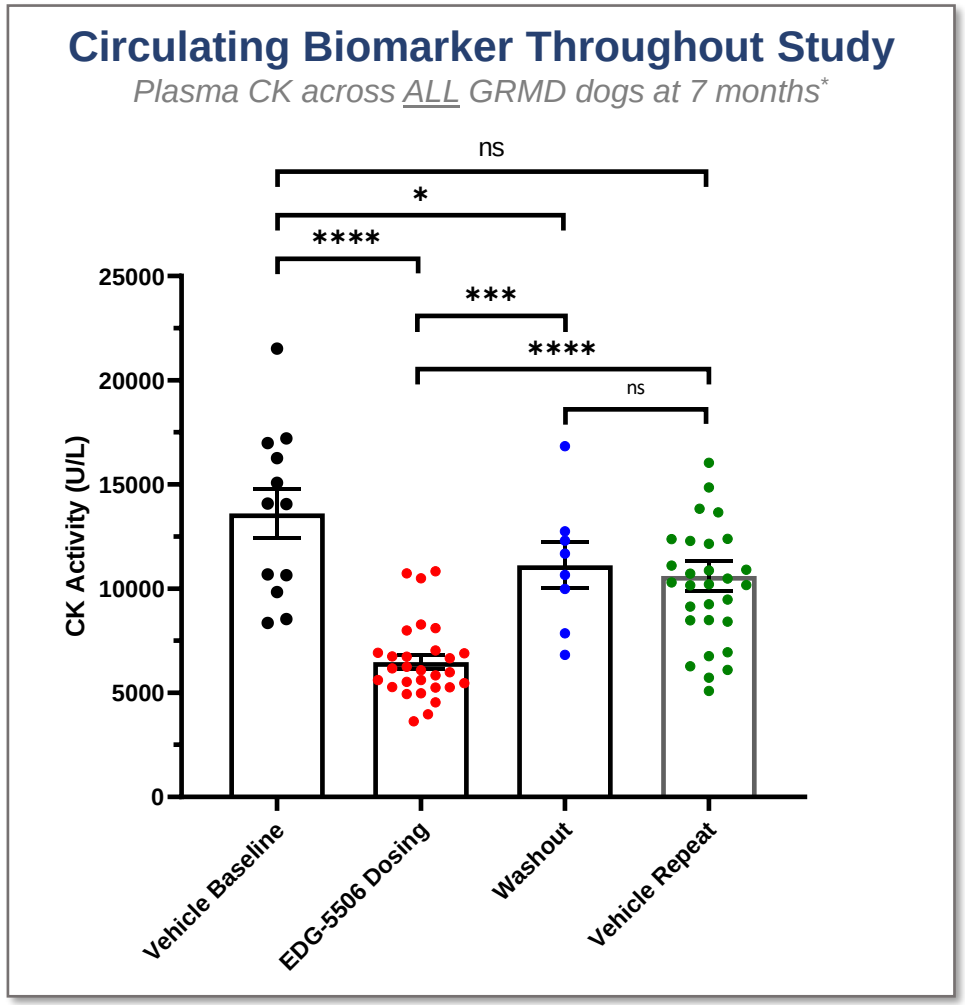


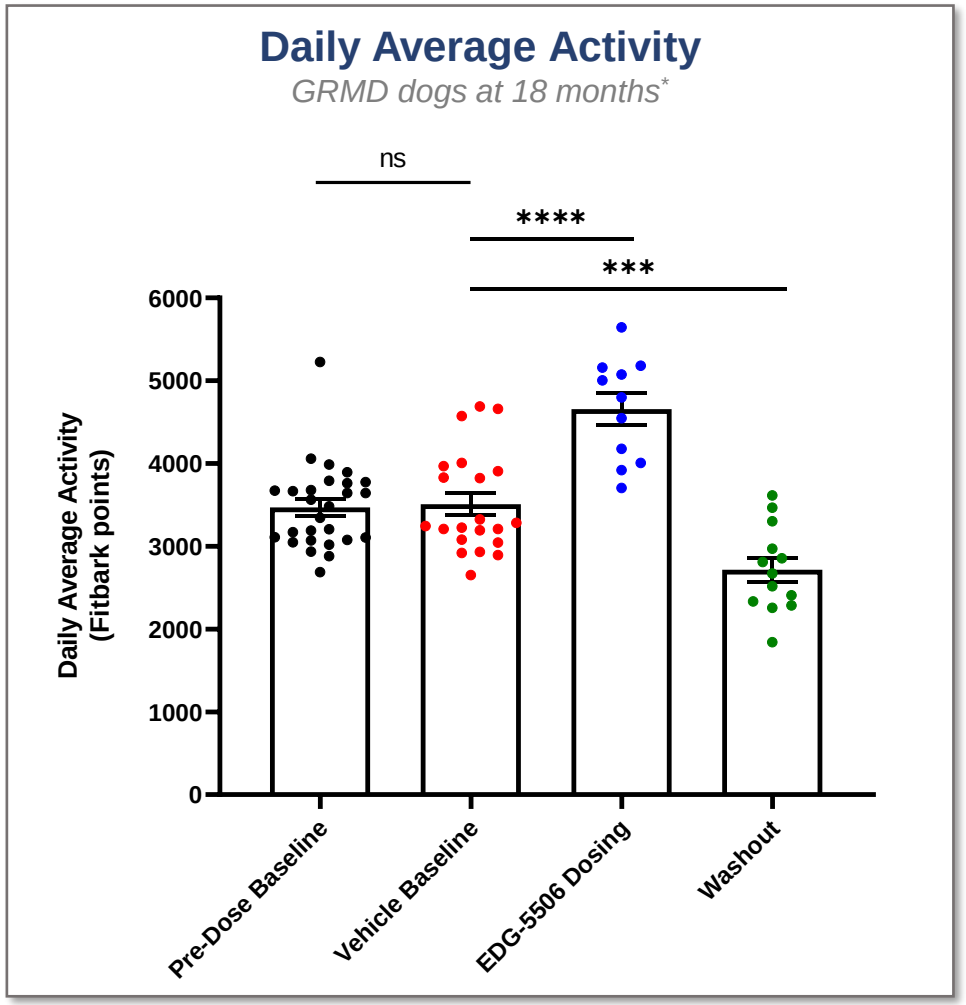
EDG-5506 Led to a Reduction in the Incidence of Cardiac Hypertrophy*



* Graph shows mean +/- SEM. Significance calculated by one-way ANOVA with Dunnet's multiple comparison (*<0.05; **<0.01; ***<.001; ****<0.0001)

EDG-5506 Decreased Creatine Kinase and Increased Habitual Activity in a GRMD Dog Model





Abbreviations: Golden retriever muscular dystrophy (GRMD)

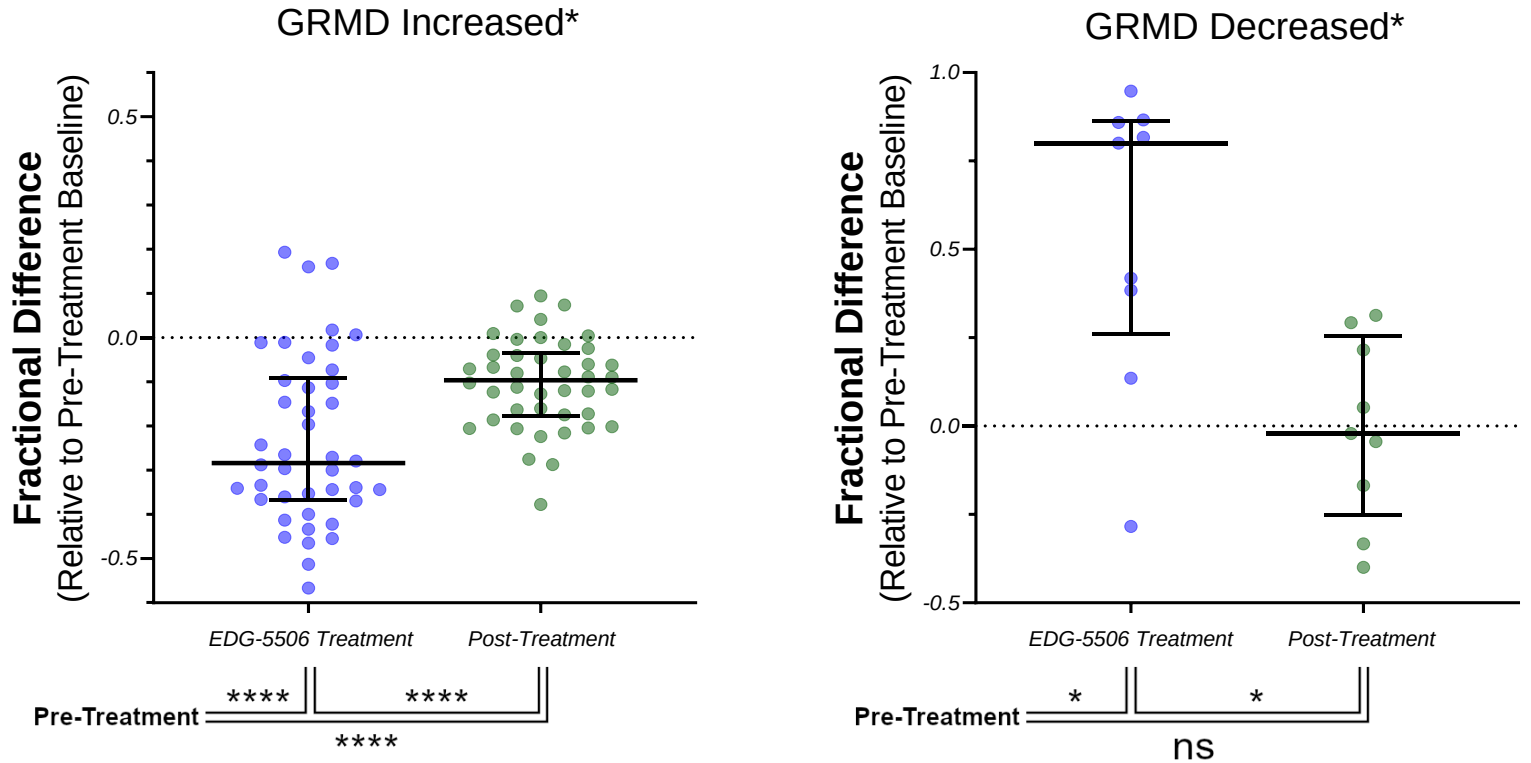
* Graph shows mean +/- SEM. Significance calculated by one-way ANOVA with Dunnet's multiple comparison (*<0.05; **<0.01; ***<.001; ****<0.0001)

In the GRMD Dog Model, EDG-5506 Positively Altered Circulating Proteins Identified as being Associated with the Dystrophic State in DMD

SOMAscan® analysis of patient plasma has previously been used to generate a common serum protein signature for DMD patients[1]

[1] Hathout Y, *et. al.*, *Sci Rep*, 2019

EDG-5506's response fingerprint in GRMD was compared to the DMD patient signature



* Proteins selected by overlap between GRMD and published DMD signature biomarkers[1]: 40 increased and 9 decreased

Significance calculated by one-way ANOVA with Tukey's multiple comparison correction. * p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Clinical Update and Plans

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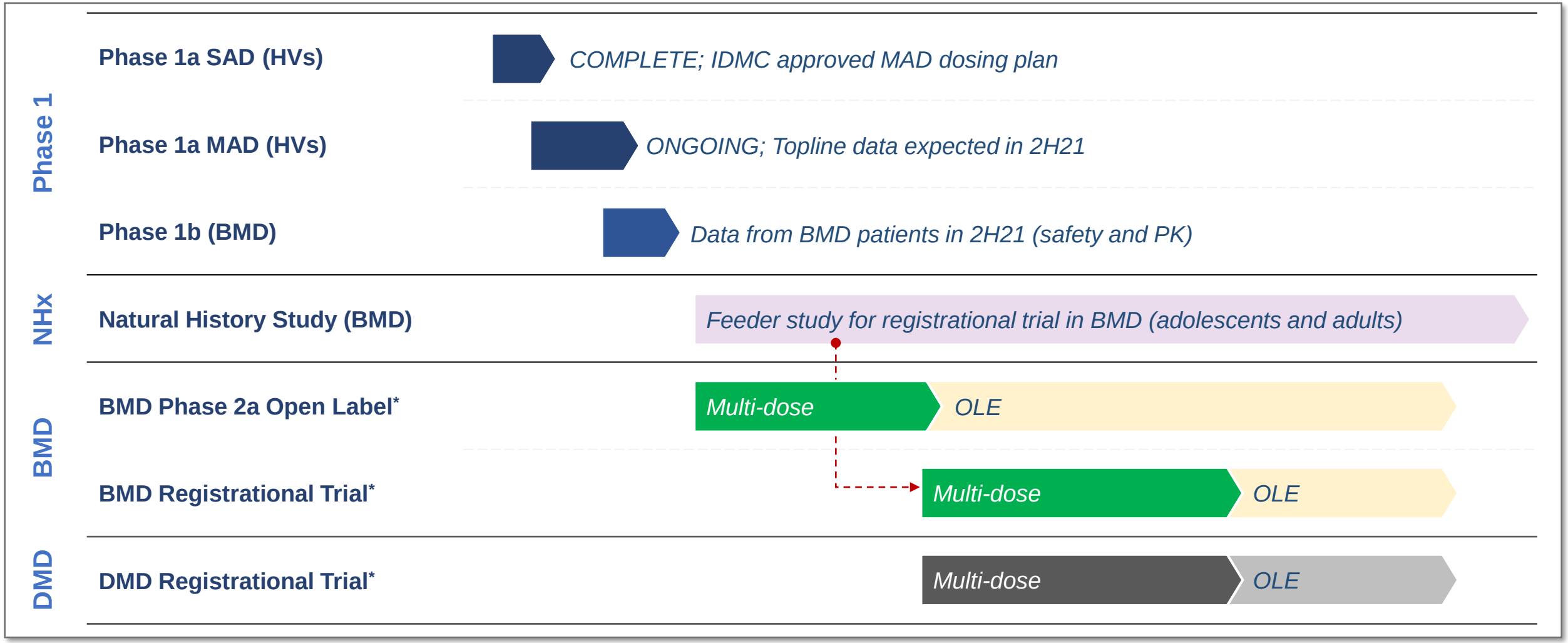
EDG-5506 Development Plan in DMD and BMD



* Pending regulatory feedback

Abbreviations: OLE, open label extension; IDMC, independent data monitoring committee

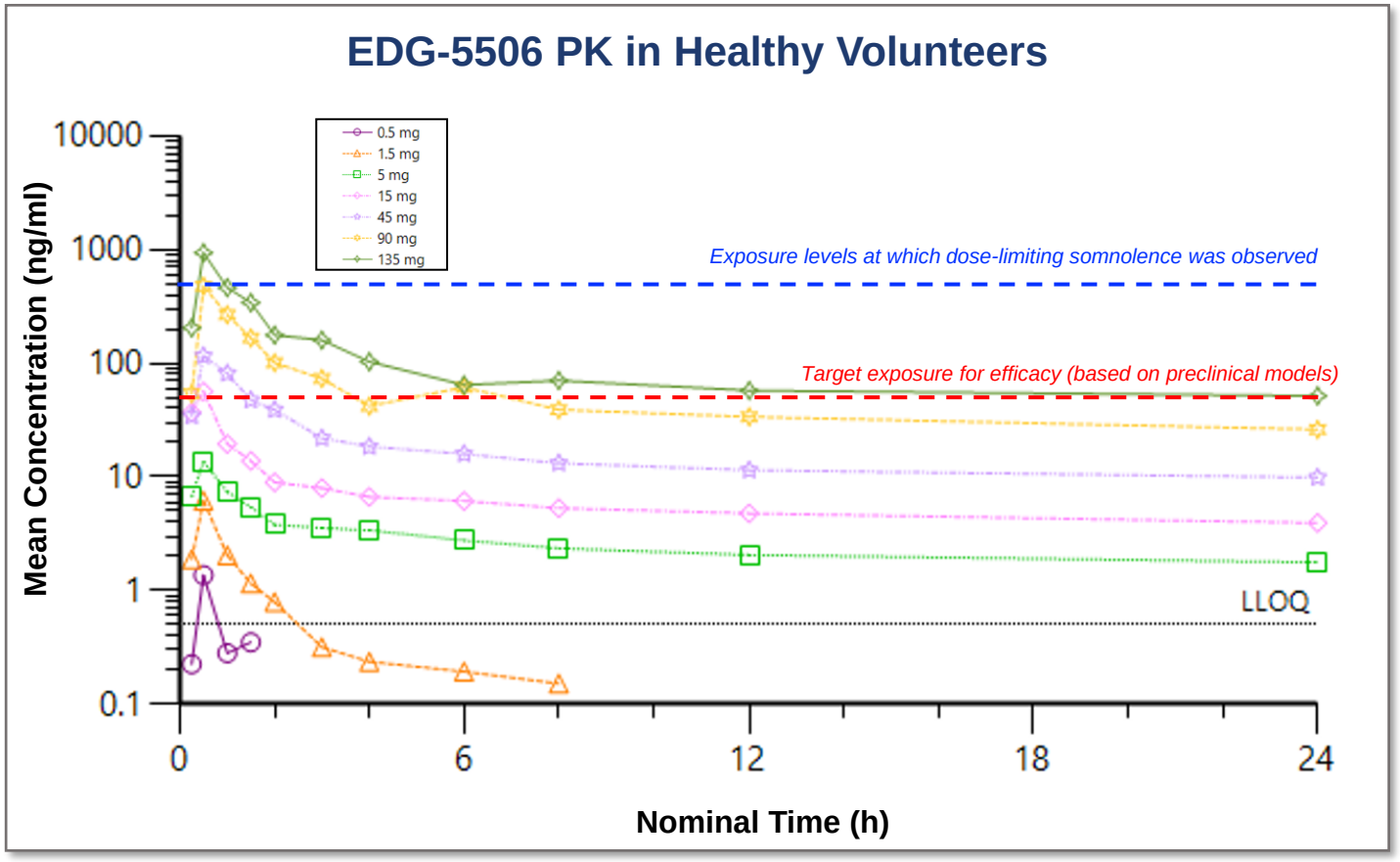
Phase 1 SAD Demonstrated EDG-5506 was Generally Safe and Well Tolerated; PK Consistent with Extensive Muscle Distribution

Pharmacokinetics

- **Favorable human pharmacokinetics (PK)**, consistent with extensive target muscle distribution
- Long half life (**~15 days**); exposure greater than dose proportional above 45 mg

Safety and Tolerability

- Generally safe and well tolerated
- 90 mg declared as MTD by IDMC; at 90 mg and 135 mg there were observations of somnolence:
  - Correlated with dose and exposure
  - **Rapid onset** pharmacology/**C_{max} driven**
  - Readily **monitorable** and **self-resolving within 4-8 hrs.**
- Physical exam findings: normal respiratory and heart rate, oxygen saturation and blood glucose



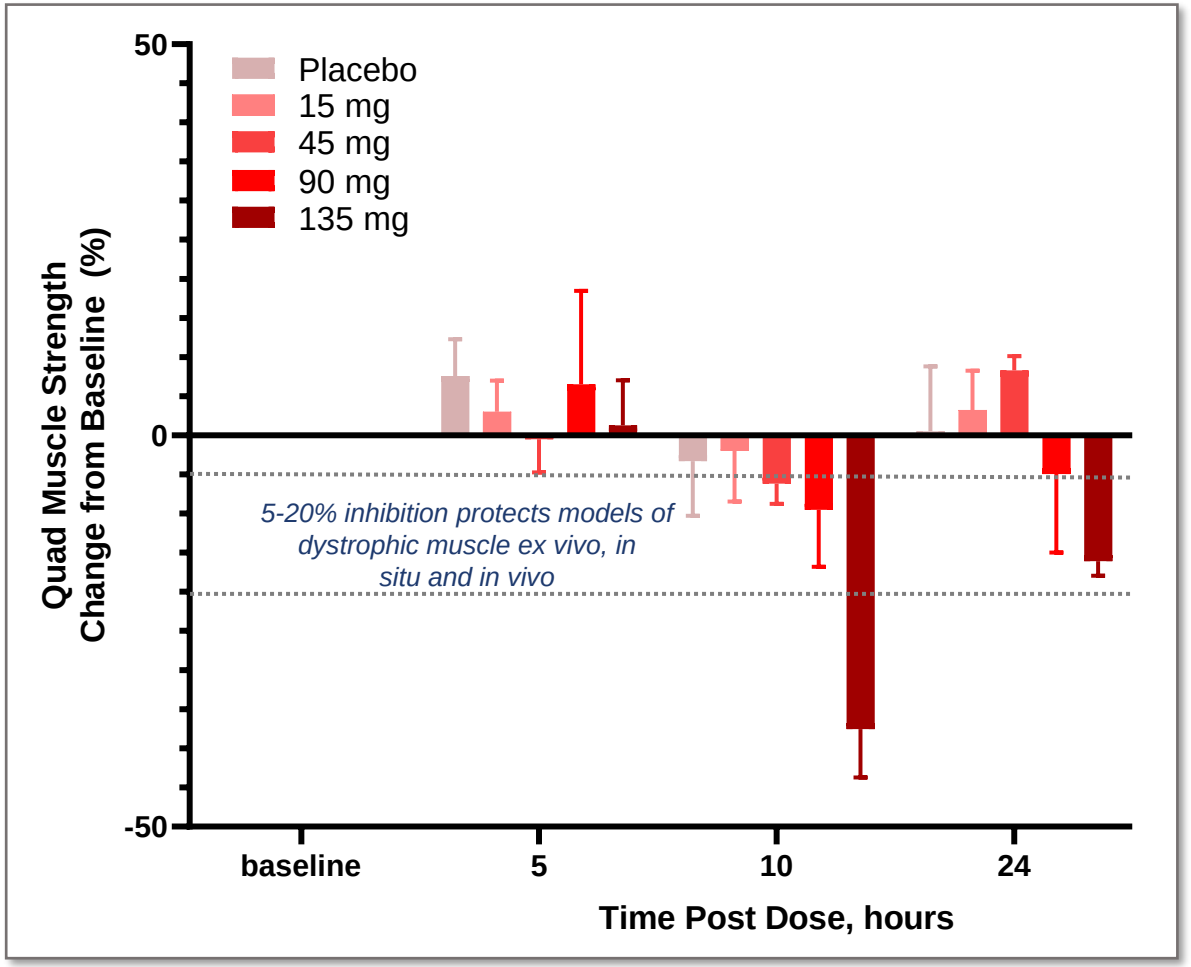
Daily doses of 10-15 mg are projected to provide **steady state exposures at or above levels observed in preclinical efficacy studies**

Abbreviations: SAD, single ascending dose; MAD, multiple ascending dose; IDMC, independent data monitoring committee; MTD, maximal tolerated dose

EDG-5506 Demonstrated Preliminary Evidence of PD Activity in Healthy Volunteers

Pharmacodynamic (PD) Activity

- Explored EDG-5506's effect on quadriceps involuntary twitch response using a trans-magnetic device
- Demonstrated **robust PD effects** at exposures similar to those observed in disease models
  - Meaningful PD activity observed starting at **45 mg**
  - Dose dependent biomarker of fast myosin inhibition consistent with single dose administration
  - Returned to baseline after single dose
  - Time course of PD separated from onset of somnolence
  - **No impact on voluntary grip strength**



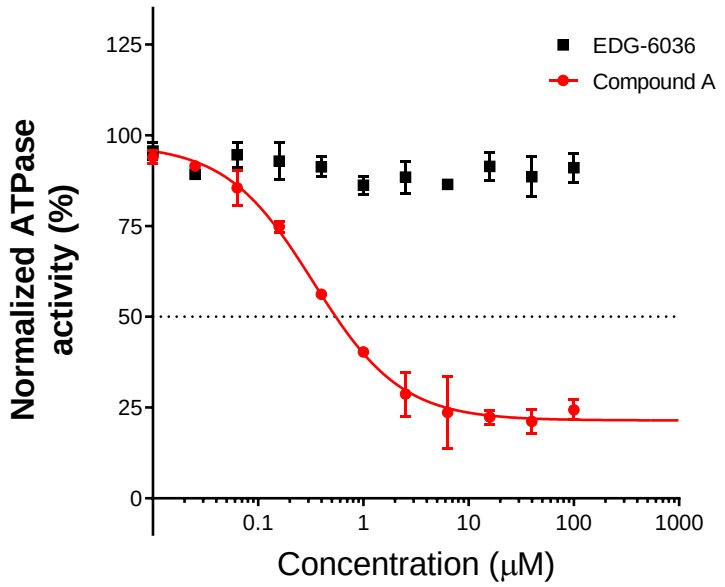
Cardiac Disorders

EDG-002 Program

EDG-6036 Targets Cardiac Contractility Through a Novel MOA from Myosin Inhibitors via Desensitization of Cardiac Muscle to Stimulation

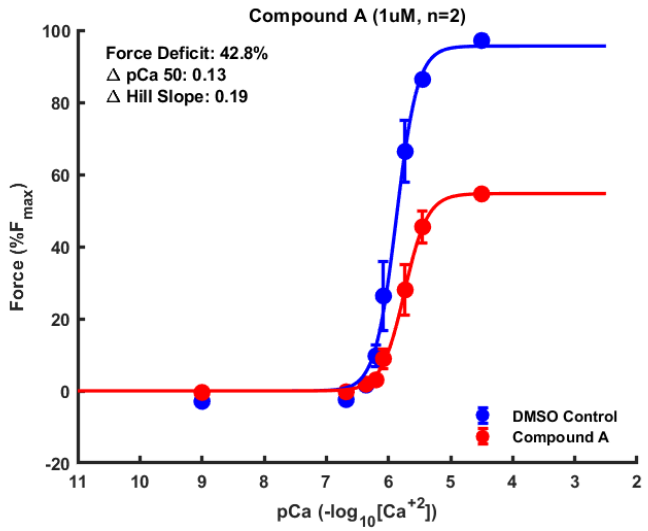
ATP Consumption by S1 Domain of Cardiac Myosin

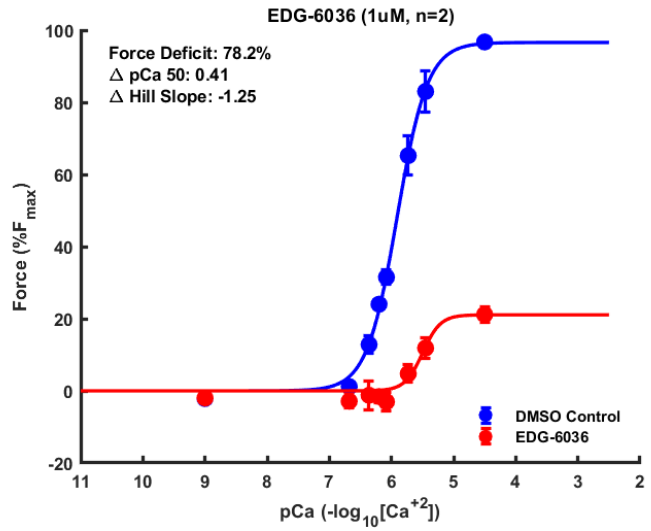
Cardiac myosin inhibitor (Compound A) decreases ATPase; EDG-6036 DOES NOT



Force Measurements in Single Fibers from Slow Skeletal Muscle

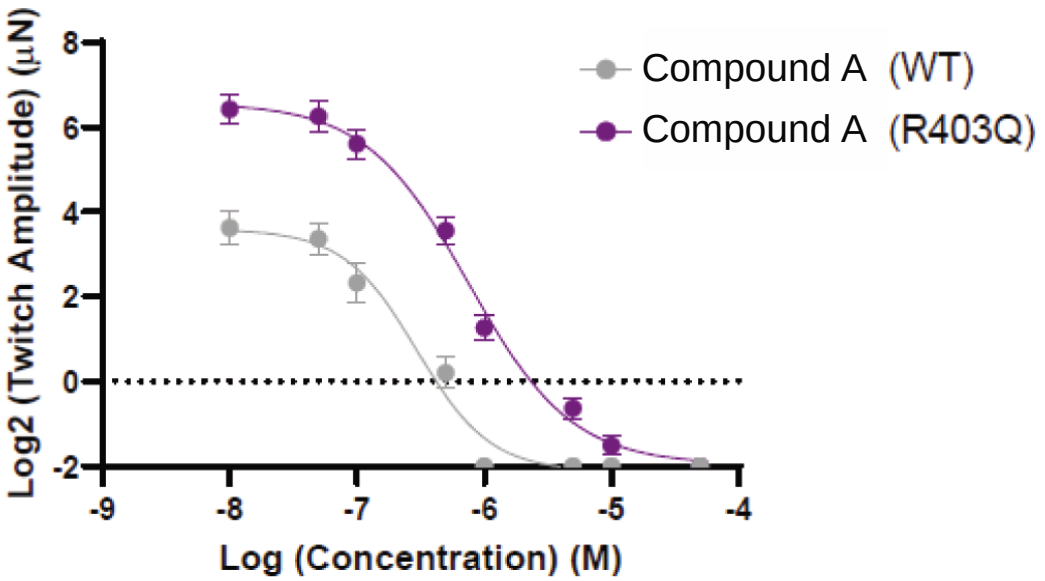
Cardiac myosin inhibitor (Compound A) AND EDG-6036 inhibit this intact system



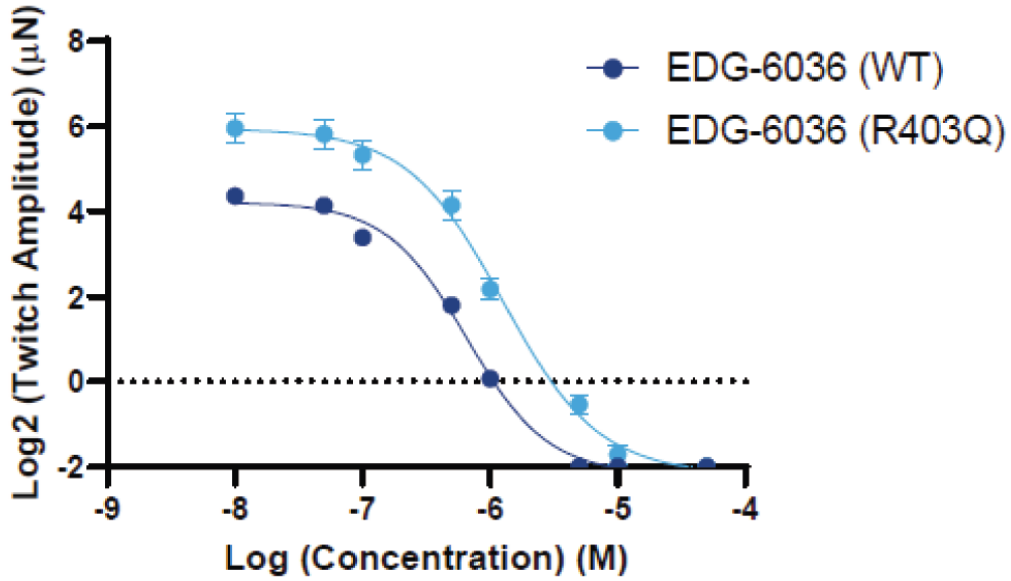


Compound A: Clinical-stage type I myosin inhibitor

EDG-6036 Decreased Contraction in Reconstituted Human Myofibers with a Hypertrophic Cardiomyopathy Mutation



Compound A	
WT	**R403Q**
0.296 µM	0.759 µM

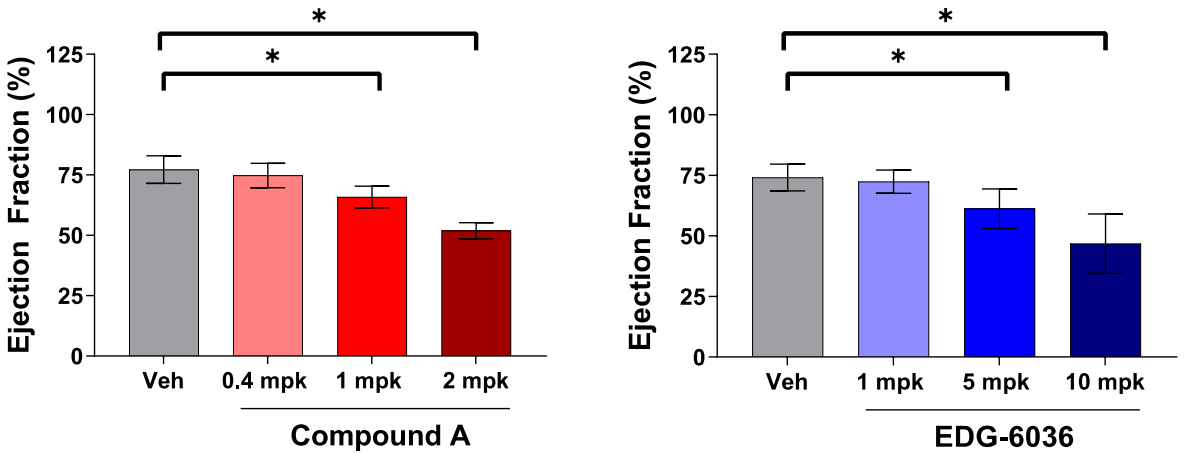


EDG-6036	
WT	**R403Q**
0.658 µM	1.262 µM

Compound A: Clinical-stage type I myosin inhibitor

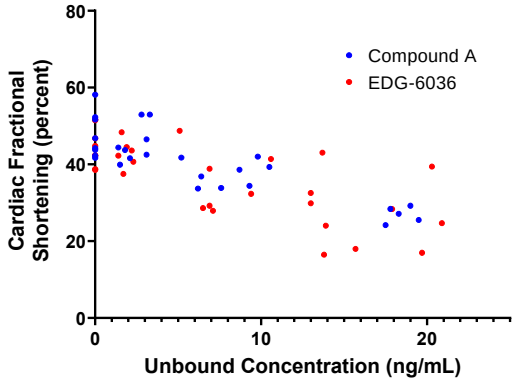
EDG-6036 Decreased Cardiac Contractility in Healthy Rats and Offered a Better Dose Titration Profile *vis-à-vis* a Compound A

EDG-6036 has an Equivalent Effect on Ejection Fraction to Compound A with Approximately 5X Dosing

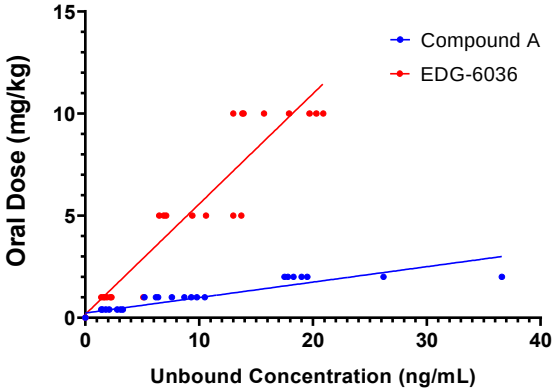


- *In vivo* cardiac inhibition with EDG-6036 also showed **enhanced relaxation** and **reversibility** versus Compound A

EDG-6036 and Compound A have a similar PK/PD relationship



Marked Difference in Dose/ Exposure Between EDG-6036 and Compound A



Compound A: Clinical-stage type I myosin inhibitor
Graphs show mean +/- 1 SEM. Significance calculated by one-way ANOVA with Dunnet's multiple comparison (*<0.05)

Edgewise Corporate Overview

Well-Capitalized to Execute Important Value-Driving Milestones Across Both EDG-5506 and Pipeline Programs

$299M
Cash & Cash Equivalents(1)

No Debt

NASDAQ: EWTX

49.3M
Common Shares Outstanding(1)

(1) As of June 30, 2021

Strategic Priorities to Drive Significant Value Recognition and Near-Term Milestones Across the Pipeline

- Complete EDG-5506 Phase 1/Phase 2 trials to enable potential **breakthrough designation** and/or **accelerated approval**
- Develop EDG-5506 to become the ***de facto* standard of care** for all dystrophinopathies
- Continue disciplined investments in **high-value early preclinical pipeline programs** driving towards IND filing
- Expand pipeline by leveraging **internal research platform** and **external business development**
- Strategically **recruit talented employees** to support and expand existing capabilities


Edgewise
THERAPEUTICS
Thank You