48-Week Results from FORWARD-53 Trial of WVE-N531 in Duchenne Muscular Dystrophy

Investor presentation

March 26, 2025

Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

Today's agenda

Opening remarks and opportunity for WVE-N531
Paul Bolno, MD, MBA
President and CEO

FORWARD-53: 48-week clinical trial results
Erik Ingelsson, MD, PhD
Chief Scientific Officer

WVE-N531 next steps and anticipated milestones
Paul Bolno, MD, MBA
President and CEO

Opening remarks and opportunity for WVE-N531

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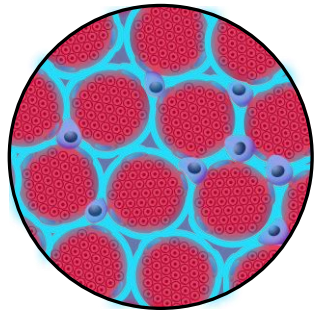
WAVE™ LIFE SCIENCES CONTINUES OUR COMMITMENT

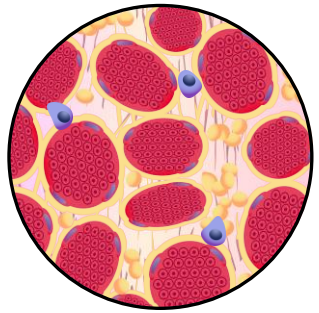
TO REIMAGINE POSSIBLE IN DMD

DMD is a fatal genetic disorder leading to progressive muscle degeneration



Healthy muscle

- Dystrophin supports stabilizing and repairing muscle fibers and stem cell replenishment & function



DMD muscle lacking dystrophin

- Muscle fibers susceptible to damage
- Stem cells and regeneration impaired
- Muscle replaced with adipose and fibrous tissue

Progressive muscle deterioration in DMD

Progressive weakness in skeletal muscle leads to decline in motor function and loss of ambulation

Increasing diaphragm weakness causes respiratory failure

Cardiac dysfunction leads to heart failure

Urgent need for improved therapeutic options

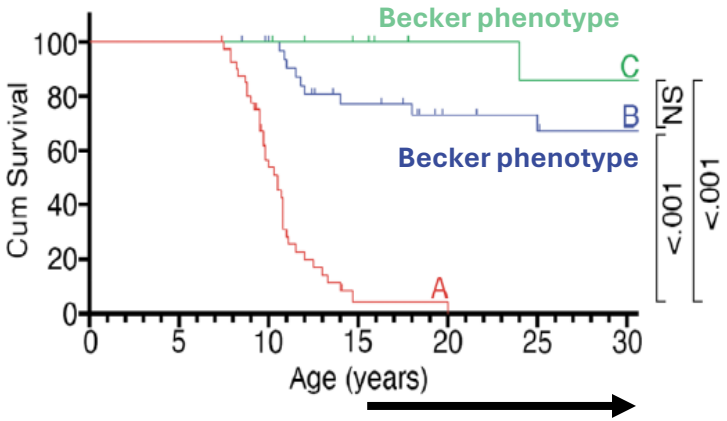
~20,000 new cases of DMD annually worldwide

Duan, D., et al. 2021 Nat Rev Dis Primers; Dumont, N.A., et al. 2015 Nat Med; Muscular Dystrophy Association

Therapeutic strategy in DMD is to achieve broad and consistent delivery of >5% endogenous functional dystrophin to reverse muscle damage

Produce endogenous functional dystrophin protein

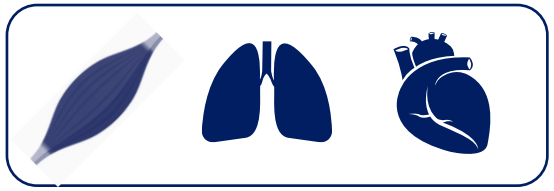
Loss of ambulation

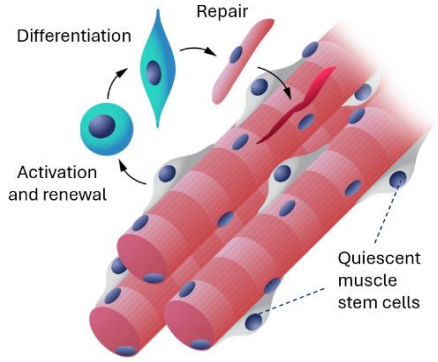


Delayed loss of ambulation

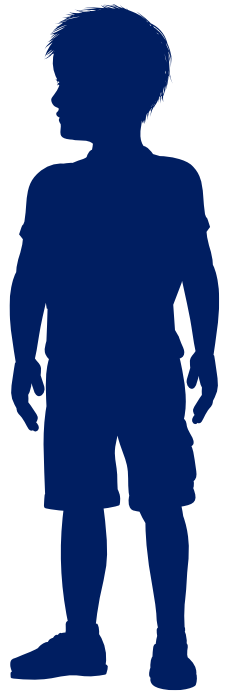
Group	%Dystrophin expression
A (DMD)	0%
B (BMD)	>0%-5%
C (BMD)	≥5%

Broad muscle distribution, including heart and diaphragm, and access stem cells



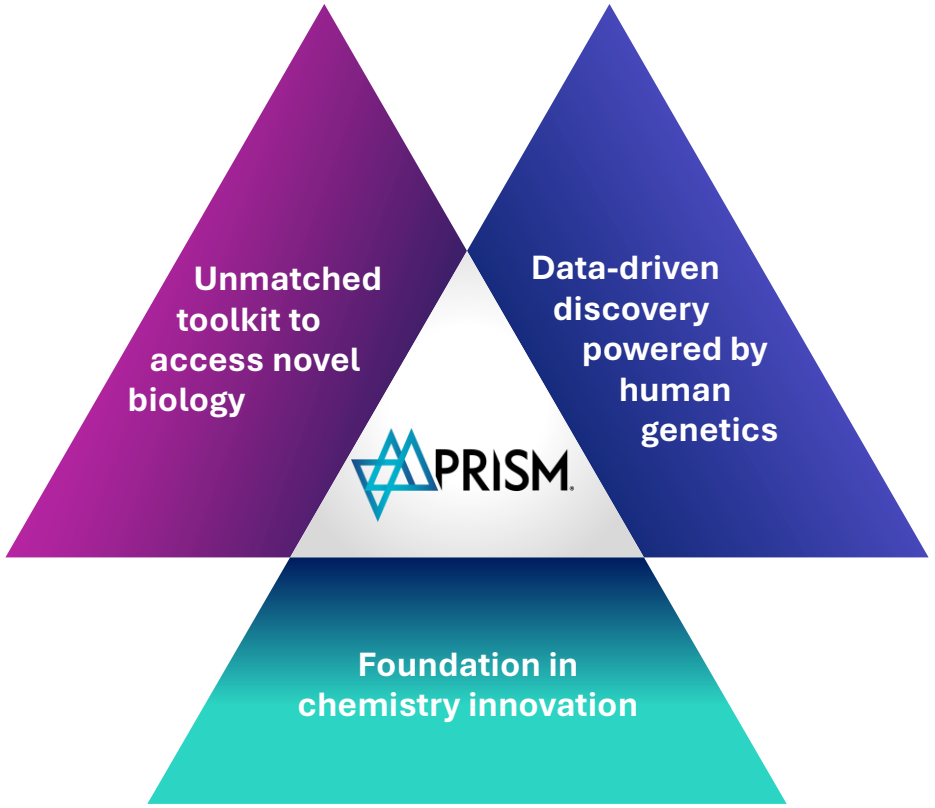


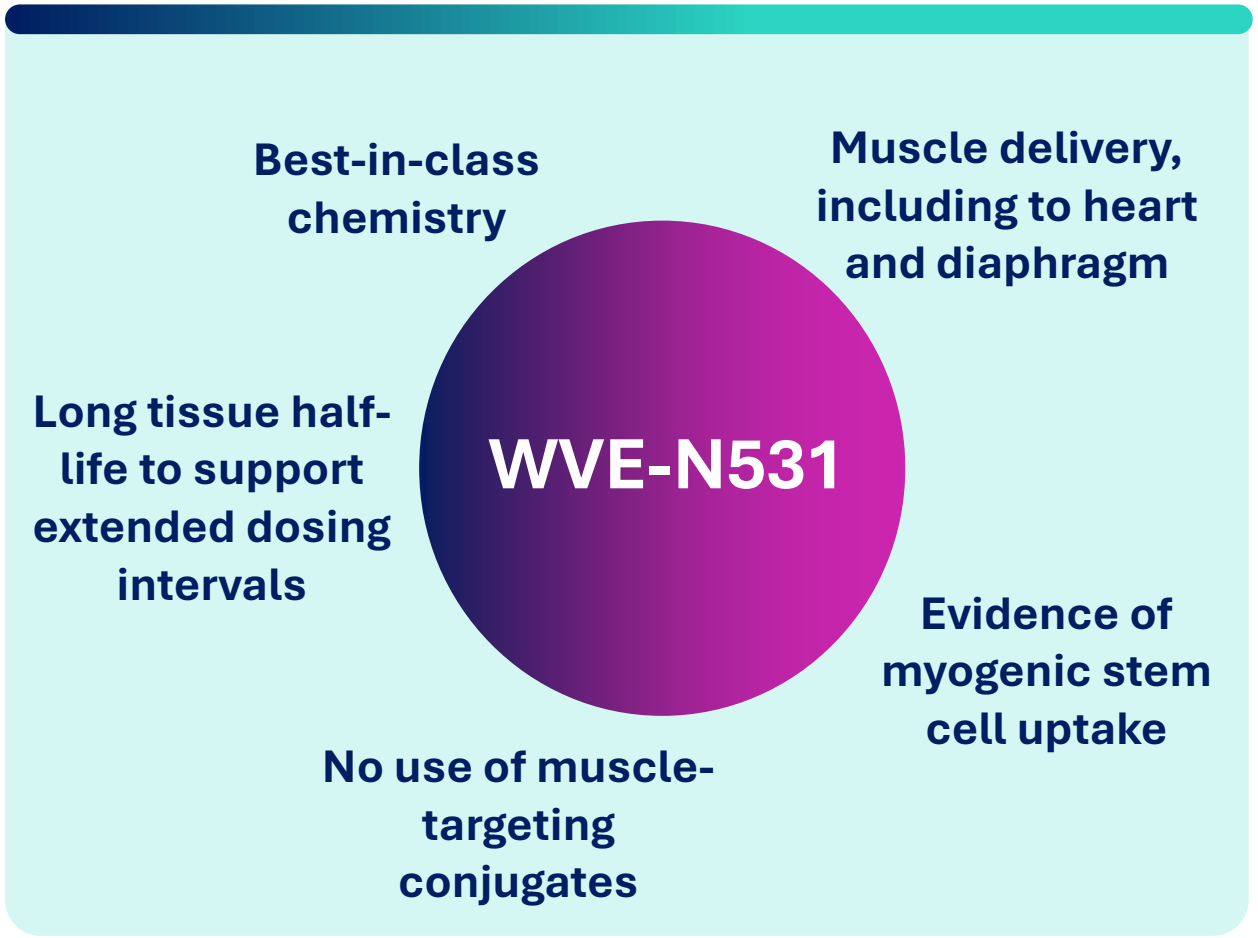
Slow, stop or reverse loss of function



Feraudy, Y., et al. 2020 Annals Neurology 89, 280

WVE-N531 for Exon 53 amenable DMD is designed from Wave's best-in-class oligonucleotide PRISM platform





Kandasamy et al., 2022 Nuc Acids Res doi: 10.1093/nar/gkac018

Phase 2 open-label FORWARD-53 trial was designed to evaluate safety, dystrophin expression, longitudinal muscle health and functional outcomes

FORWARD-53

Part A: 3 doses 10 mg/kg Q2W n=3	Part B: Biopsies after 24 and 48 weeks of dosing 10 mg/kg Q2W n=11	Extension 10 mg/kg Q4W

IV: Intravenous; Q2W: Every 2 Weeks; Q4W: Monthly

FORWARD-53 enabled longitudinal evaluation of WVE-N531 across essential elements of a disease modifying therapy for DMD

Part A
10 mg/kg Q2W x 3 doses (n=3)

- ✓ Exon skipping: 53%
- ✓ Muscle tissue concentration: 42,000 ng/g
- ✓ Distribution to myofibers and muscle stem cells
- ✓ Safe and well tolerated, no SAEs

SAE: Serious Adverse Event; Q2W: Every 2 Weeks

FORWARD-53 enabled longitudinal evaluation of WVE-N531 across essential elements of a disease modifying therapy for DMD

Delivery → Exon Skipping → Dystrophin Production → Muscle Regeneration → Functional Benefit

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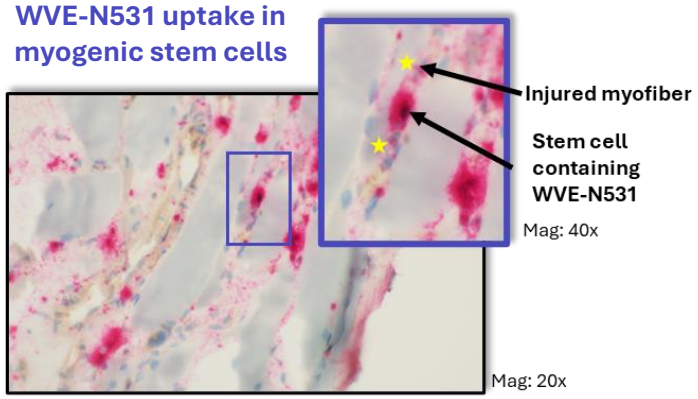
Part B: Interim at 24 Weeks
10 mg/kg Q2W (n=11)

- ✓ Dystrophin consistently above 5% with mean of 9.0%
- ✓ Safe and well tolerated, no SAEs
- ✓ Shift to myofiber regeneration
- ✓ Leading indicators: improvement in serum biomarkers, including CK
- ✓ With 61-day tissue half-life, profile supports monthly dosing

WVE-N531 uptake in myogenic stem cells



SAE: Serious Adverse Event; Q2W: Every 2 Weeks
Right: RNAScope for N531 (red) and immunohistochemistry for PAX7 (brown): a stem cell marker

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Objectives for 48 weeks
10 mg/kg Q2W (n=11)

Can we demonstrate these achievements translate to:

- ➡ **Improvements in muscle health**
- ➡ **Improvements in functional outcomes**

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SAE: Serious Adverse Event; Q2W: Every 2 Weeks

Today's update: 48-week data demonstrate WVE-N531's best-in-class profile for boys amenable to exon 53 skipping

- Statistically significant and clinically meaningful improvement (3.8s) in Time-to-Rise vs. natural history; functional benefits on other measures including NSAA
- Statistically significant reductions in muscle fibrosis and CK, driven by decreases in inflammation and necrosis; transition from regenerative to mature muscle
- Consistent dystrophin expression averaged 7.8% between 24 and 48 weeks, with 88% of boys above 5% dystrophin
- WVE-N531 remains safe and well-tolerated with no Serious Adverse Events

NDA filing for accelerated approval with monthly dosing planned for 2026

FORWARD-53: 48-week clinical trial results

Erik Ingelsson, MD, PhD
Chief Scientific Officer

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Baseline participant characteristics

Baseline DMD Participant Characteristics	FORWARD-53 population (n=11)
Age at consent (years) (mean (SD)) Age 5-7 (n (%)) Age 8-11 (n (%))	8.1 (2.3) 5 (45) 6 (55)
BMI (kg/m^2) (mean (SD))	19.1 (4.0)
Years since DMD diagnosis (mean (SD))	3.9 (2.6)
Participants on Oral Steroids (n (%)) Prednisone Deflazacort	11 (100) 4 (36.4) 7 (63.6)
Ambulatory (n (%))	10 (90.9)
Functional baselines (n=10 ambulatory) NSAA total score TTR (sec) 10MWR (sec) 4SC (sec)	 20.0 6.2 5.5 5.0

NSAA: North Star Ambulatory Assessment; TTR: Time to Rise; 10MWR 10-meter walk/run test; 4SC: 4-stair climb

WVE-N531 continues to be safe and well tolerated at 48 weeks

TEAE Category	WVE-N531 10 mg/kg Q2W n=11 Participants (%)
Any TEAE	11 (100%)
Mild	10 (90.9%)
Moderate	7 (63.6%)
Severe	1 (9.1%)
Any drug-related TEAE	4 (36.4%)
Mild	4 (36.4%)
Moderate	1 (9.1%)
Severe	0
Any serious TEAE	0
Any TEAE leading to discontinuation	0
Any TEAE leading to death	0

No Serious Adverse Events and all drug-related TEAEs were mild to moderate

TEAE: Treatment emergent adverse event; Data as of February 5, 2025; *One participant had a severe TEAE non-study drug related event of self-limiting, short-lived, viral gastroenteritis

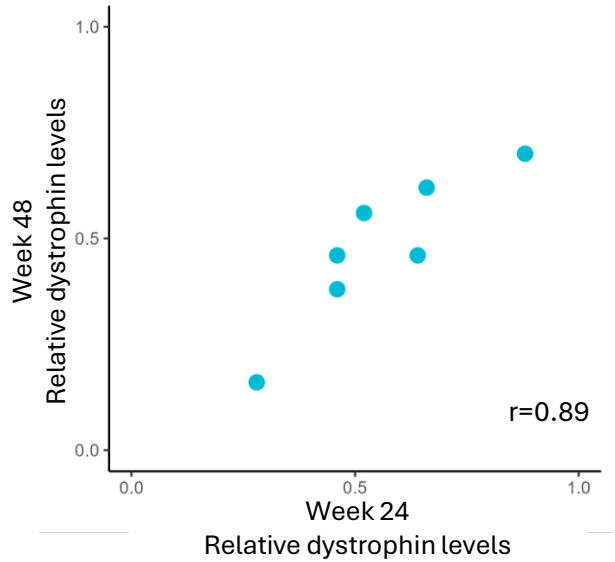
Best-in-class profile: 7.8% average dystrophin expression, consistently exceeding levels associated with milder Becker phenotype

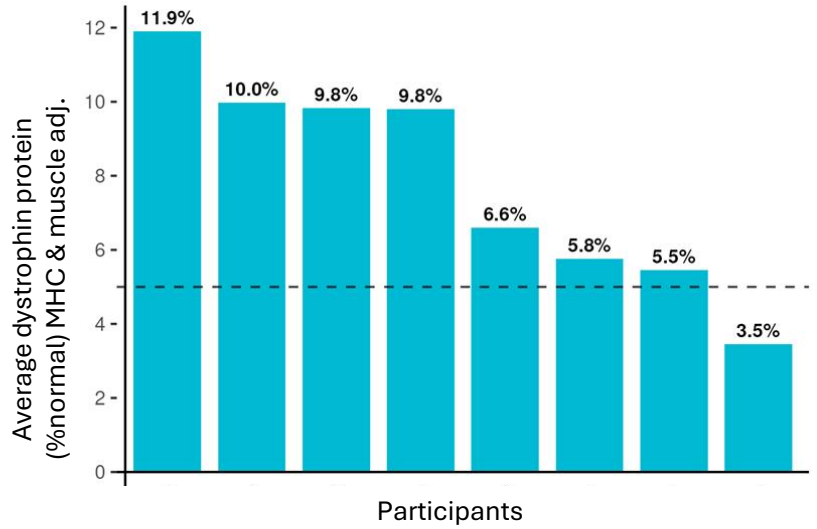
Dystrophin expression by western blot stabilized by 24 weeks

Consistency at 24 and 48 weeks confirmed with orthogonal assay

88% of boys achieving greater than 5% average dystrophin

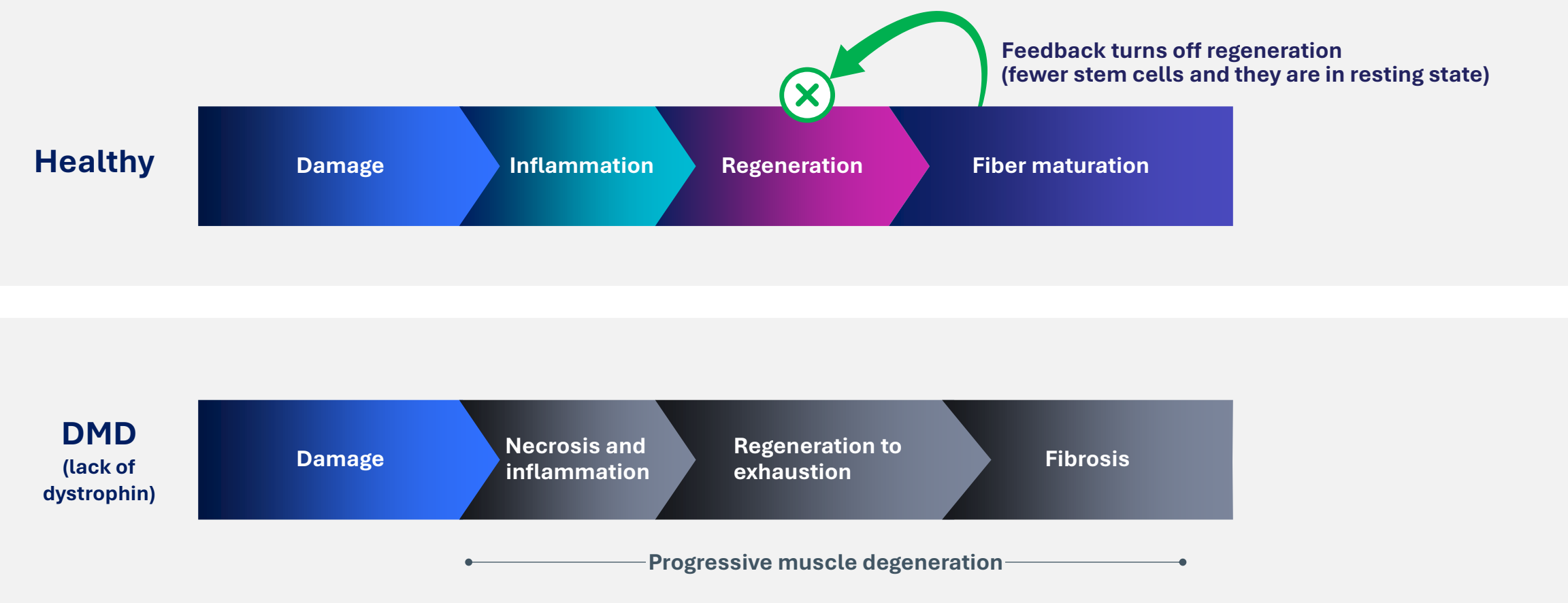
	Week		Average
	24	48	
Mean exon skipping induced	57% (95% CI: 49-65%)	54% (95% CI: 44-65%)	**54%** (95% CI: 46-63%)
Mean MCA dystrophin	9.0% (95% CI: 6.5-11.5%)	6.4% (95% CI: 3.8-9.0%)	**7.8%** (95% CI: 5.4-10.3%)





Left: week 24 (n=9), among these participants eight had muscle biopsies available for week 48 and average; Dystrophin measured by western blot (AB15277). Dystrophin expression was quantified from two isoforms; MCA: muscle content-adjusted (MHC-normalized dystrophin/(total myofiber area/total area of biopsy section)). Middle: Dystrophin levels were scaled to range between 0 and 1; Pearson correlation (r) is presented; Right: Average between 24 and 48 weeks.

DMD is characterized by a progressive decline in muscle function

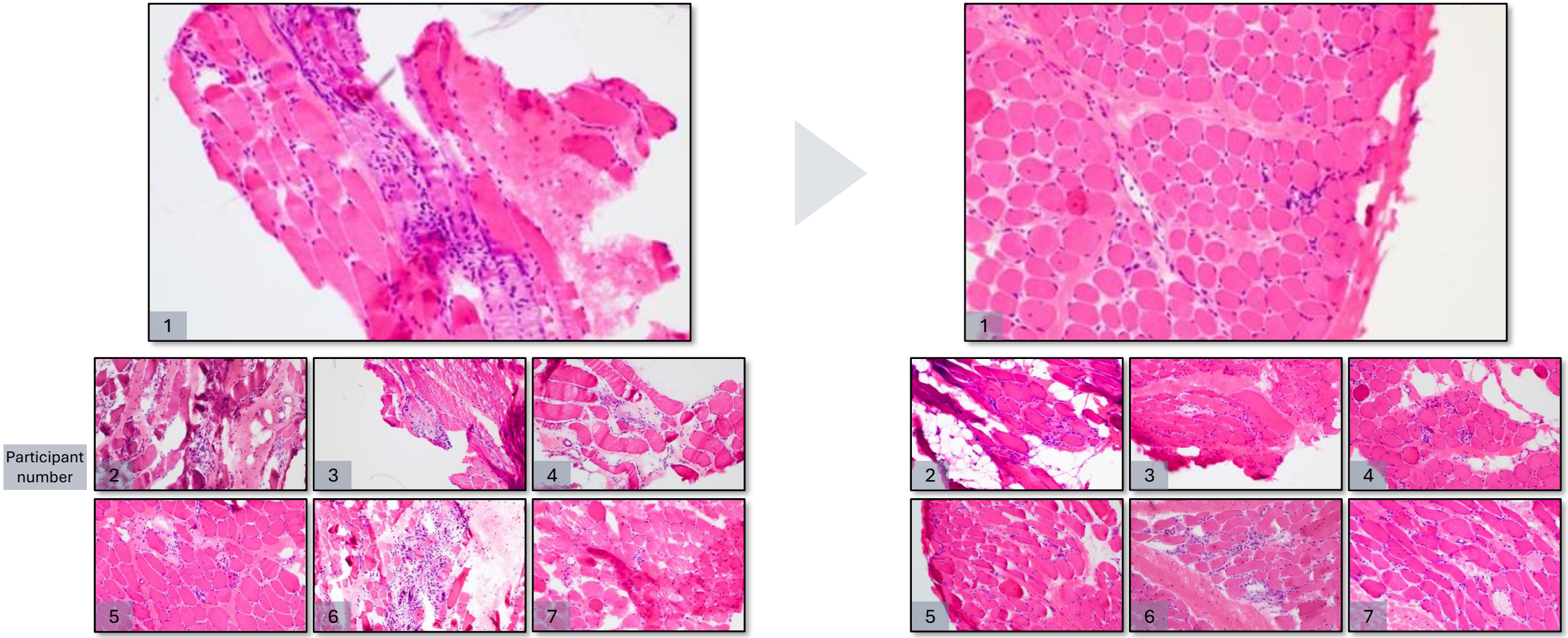


Cardone et al., 2023 Acta Neuropathol Comm

Evidence of reversal of muscle damage across majority of participants

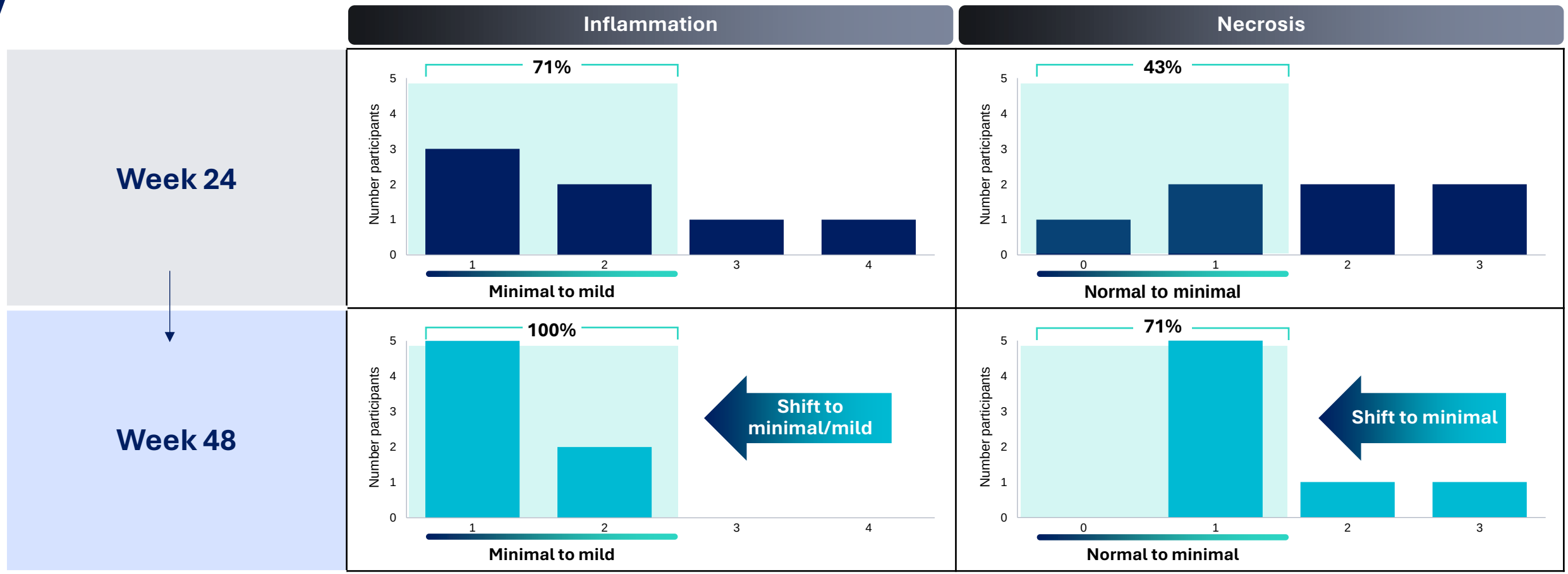
Week 24

Week 48



H&E-stained sections (20X magnification). Seven paired biopsies available from week 24 and 48 for histopathology.

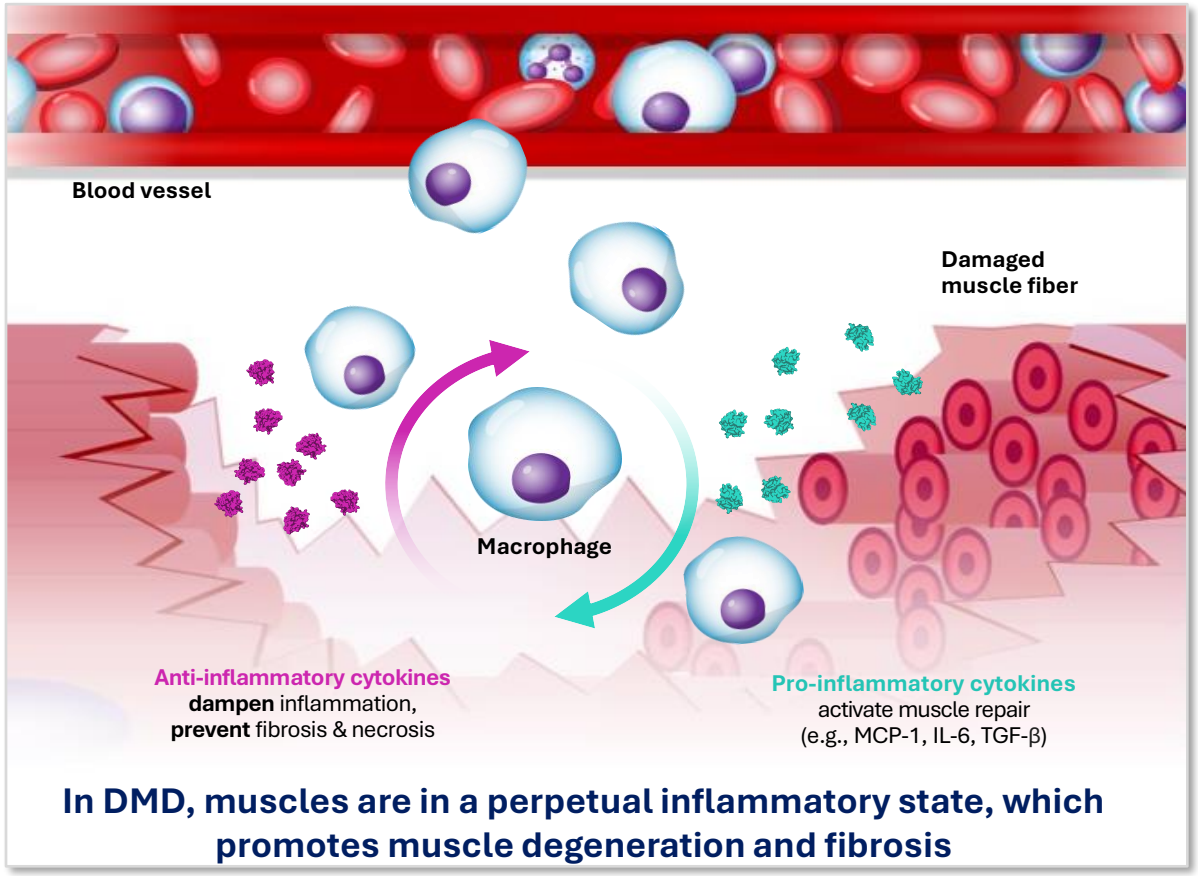
Improving muscle inflammation and necrosis to lower (minimal/mild) levels



Median muscle inflammation and necrosis scores decreased from 2 to 1 between week 24 and 48

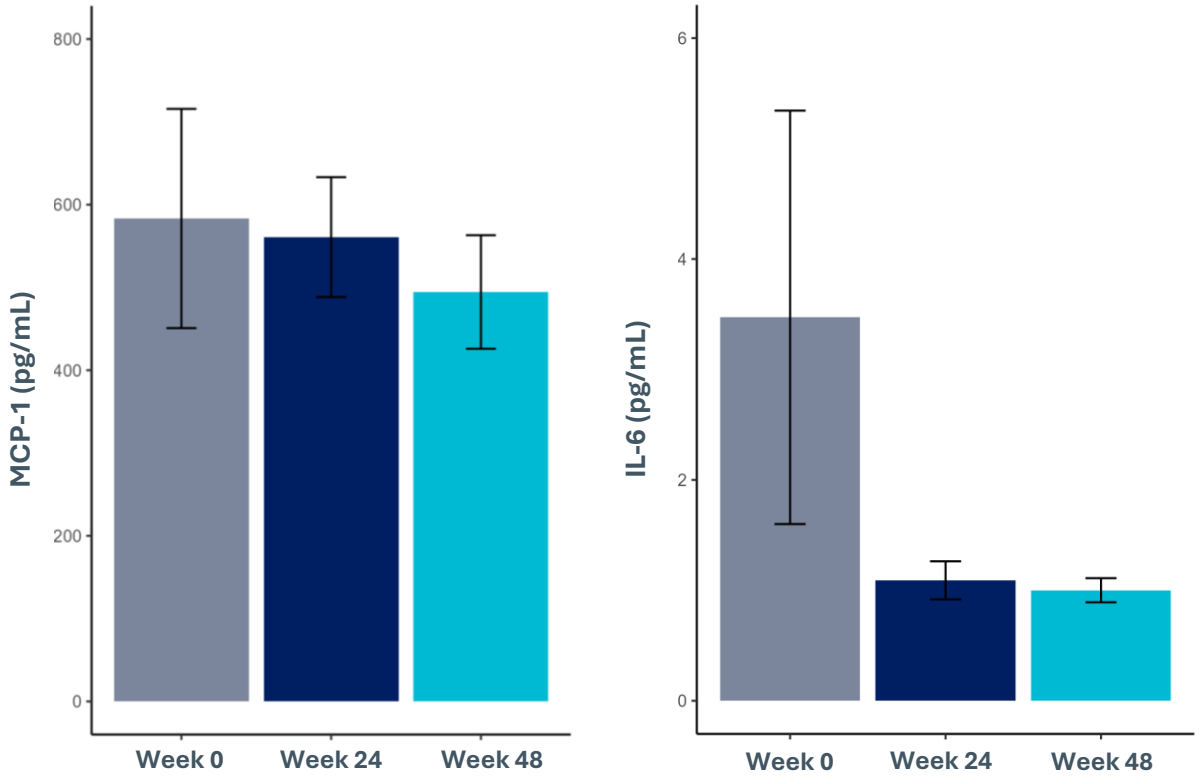
Severity scoring (x-axis) based on Schafer et al., 2018 *Toxicol Pathol.* Severity scores: 1 = minimal, 2= mild, 3 = moderate, and 4 = marked

Meaningful decreases in inflammatory cytokines with treatment



In DMD, muscles are in a perpetual inflammatory state, which promotes muscle degeneration and fibrosis

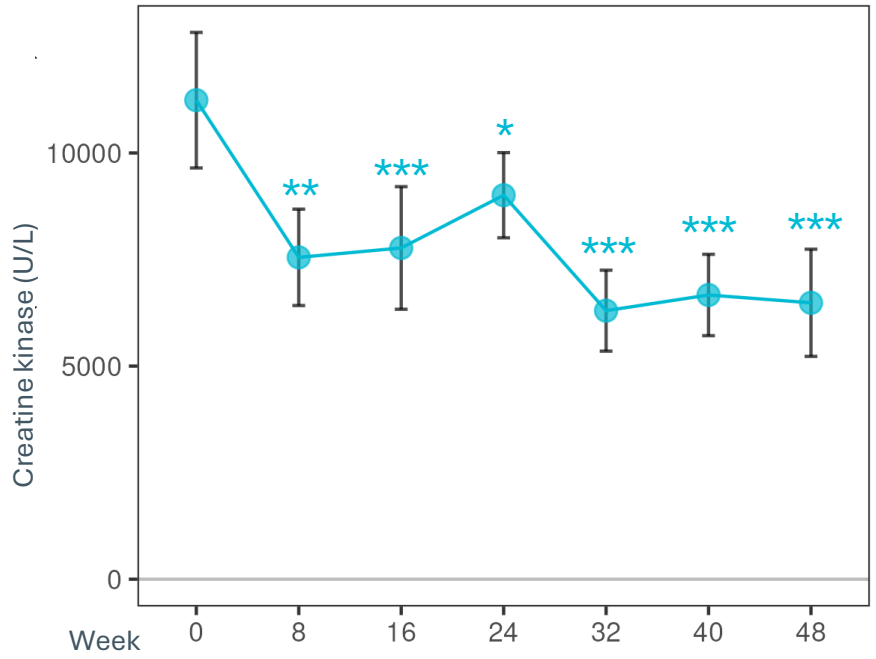
Decrease in MCP-1 and IL-6 suggests reduction in inflammation with treatment



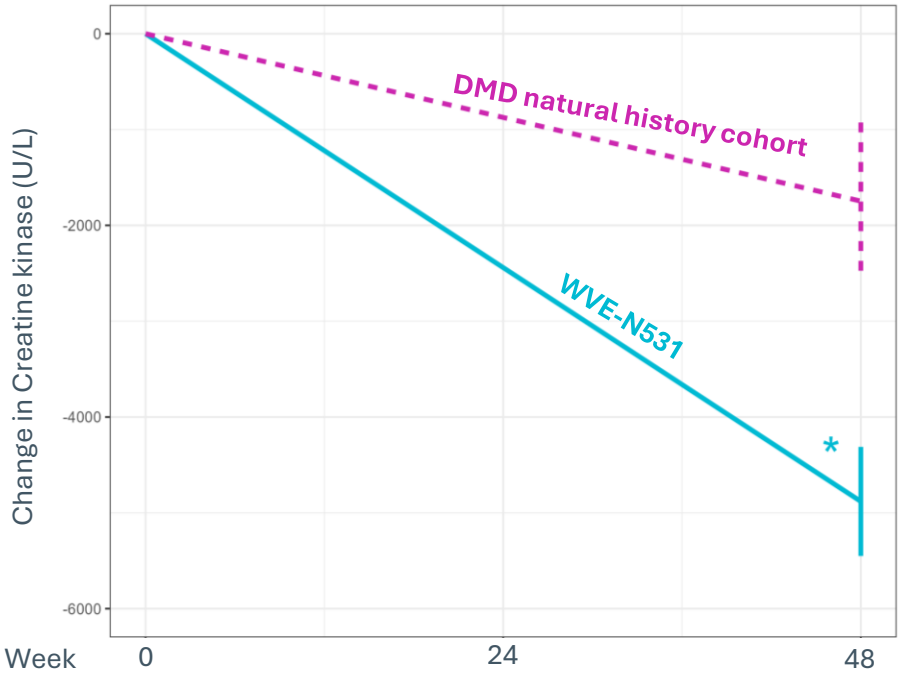
Data are means ± SE

Statistically significant reductions in creatine kinase (CK) as compared to baseline and natural history

~50% CK reduction from baseline at 48 weeks



Statistically significant reduction in CK vs. C-PATH Natural History



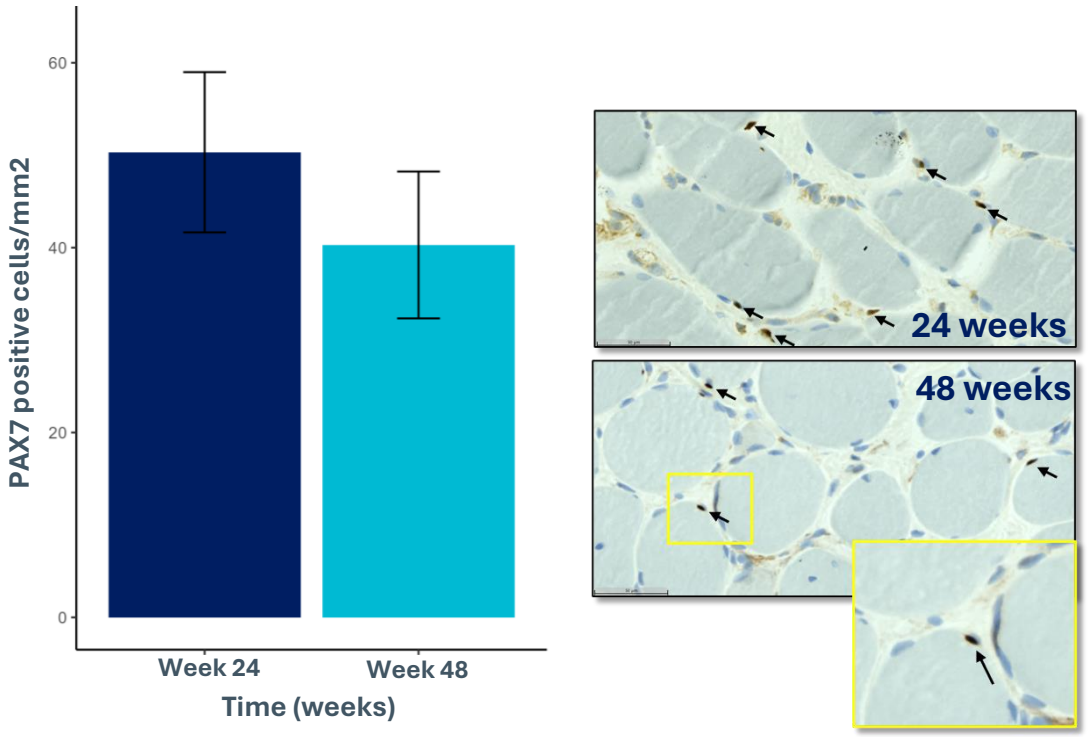
Decreased CK to levels observed in milder DMD individuals

*p<0.05, ** p<0.01, ***p<0.001; Data are mean ± SE
Left: n=11; right: n=10 (all ambulatory)

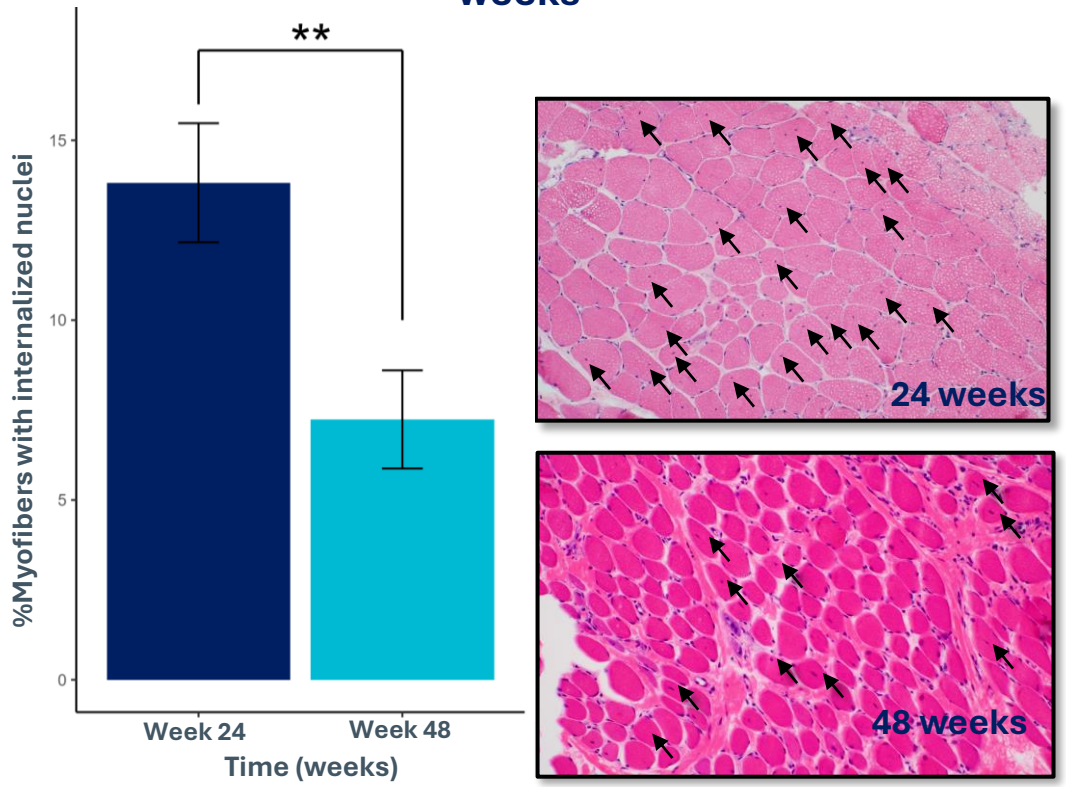
Changes to key cell populations in muscle supports muscle maturation, suggesting transition to healthier muscle

Progression of regenerative to mature state of muscle tissue

~20% change in density of myogenic stem cells at 48 weeks



Significant decrease (~48%) in internalized nuclei at 48 weeks

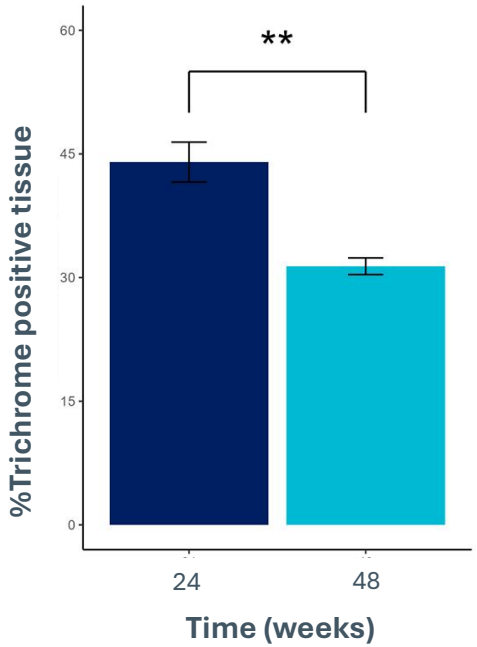


Left: NS; Data are mean ± SE (of n = 9); PAX7-positive cells/mm^2 quantified using Pax7 immunohistochemistry (IHC) with HALO.
Right: Data are mean ± SE (of n=9) (wk 24) and n=8 (wk 48);**p<0.01 (two-tailed Welch's test); Internalized nuclei quantified using 6 random fields in H&E stained sections

First evidence of reversal of muscle damage with exon skipping treatment

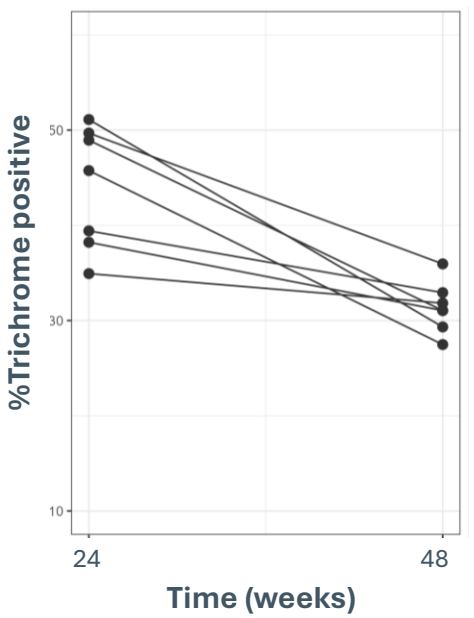
Mean fibrotic muscle declined 28.6% at 48W

(n = 7)

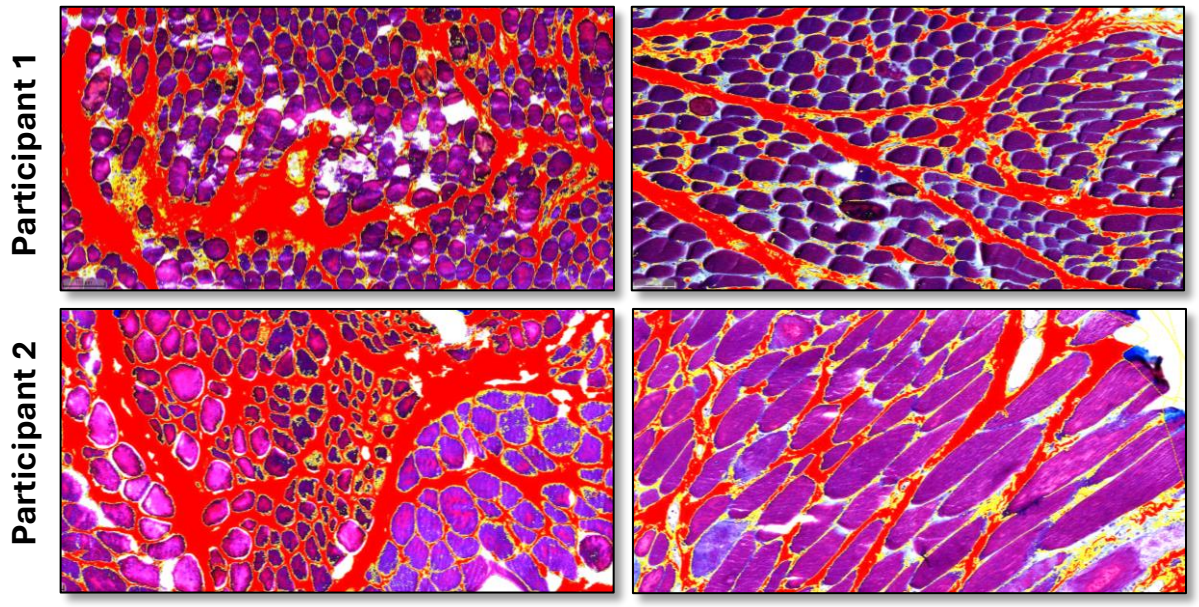


% Fibrotic muscle declined by individual

(n = 7)

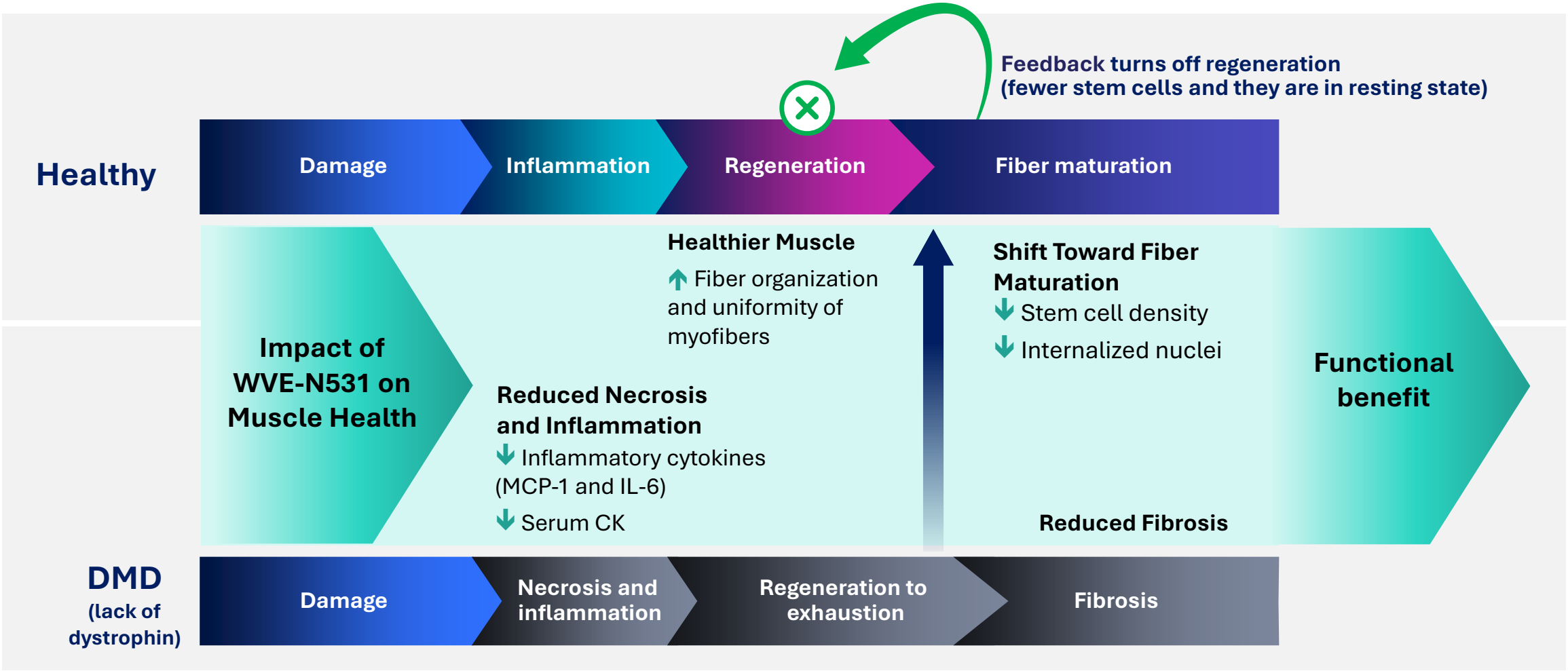


Week 48 showed improved organization and uniformity of myofibers



Right: Magnification 5X; fibrosis stained with trichrome stain and analyzed with HALO; ** p<0.01; Data are mean ± SE

WVE-N531 appears to shift dystrophic muscle towards healthy muscle



Cardone et al., 2023 Acta Neuropathol Comm

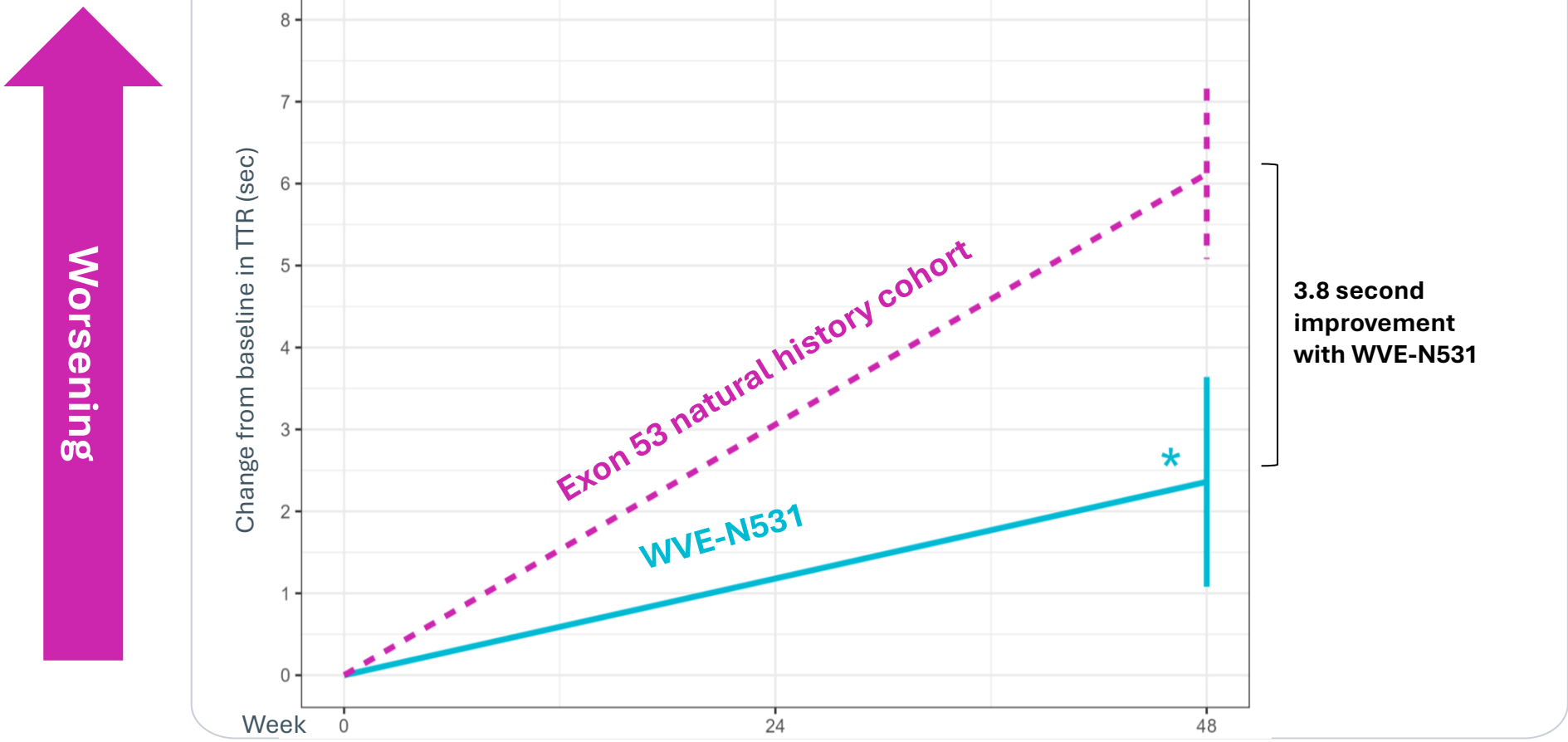
Functional assessments: Baseline FORWARD-53 population well matched to natural history cohort

	WVE-N531 FORWARD-53 (Exon 53)	**Natural History Cohort PRO-DMD-01** (Exon 53)
N	10	18
Age (years)	7.8	7.9
NSAA total score	20.0	20.4
TTR (sec)	6.2	7.4
10MWR (sec)	5.5	6.1
4SC (sec)	5.0	4.6

All boys on stable steroids; Analysis of ambulatory participants
NSAA: North Star Ambulatory Assessment; TTR: Time to Rise; 10MWR 10-meter walk/run test; 4SC: 4-stair climb

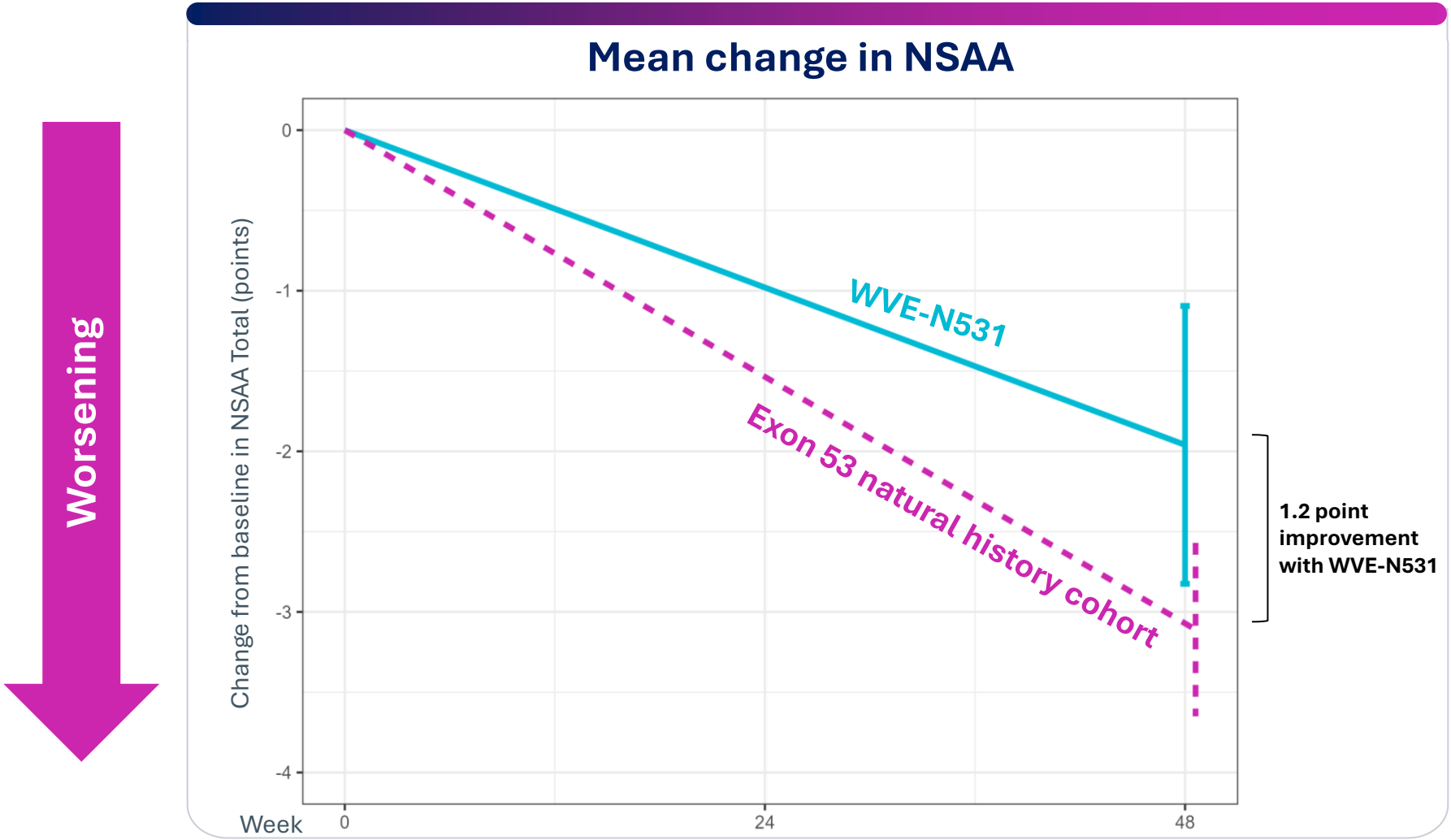
Statistically significant and clinically meaningful slowing of disease progression as measured by TTR

Mean change in time-to-rise (TTR)



Minimal Clinical Important Difference (MCID) for TTR: 1.4 sec based on method from McDonald 2013; *p<0.05; Data are mean ± SE

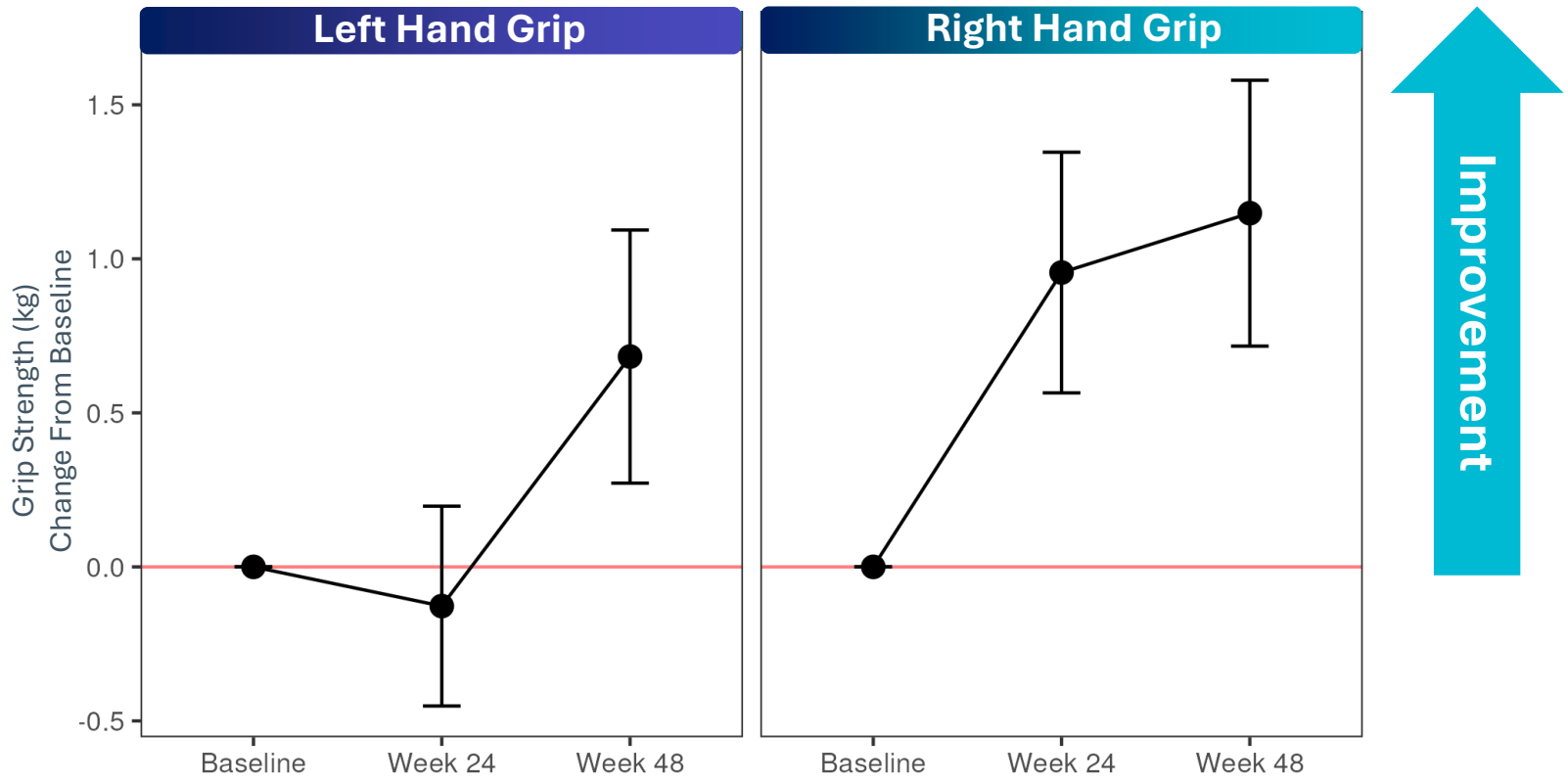
Treatment with WVE-N531 slowed progression as measured by NSAA



NSAA: North Star Ambulatory Assessment; data are mean ± SE

Positive trends on additional functional measures supporting muscle restoration

Mean change in grip strength from baseline



Data are mean ± SE; n=11

Investigator feedback supports potential clinical benefit of WVE-N531

*"…**developed the ability to run in reverse**, which is a significant improvement."*

*"…**shown remarkable progress, as they are now able to play football**, which was something they previously struggled with."*

*"…have become **more independent in their daily activities**. They are now able to jump, run, and even dress themselves without assistance, which marks a **clear improvement in their overall mobility and quality of life."***

WVE-N531 next steps and anticipated milestones

Paul Bolno, MD, MBA
President and CEO

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Regulatory update and exon skipping franchise derisked

FORWARD-53

- All participants are enrolled in the ongoing open-label FORWARD-53 extension trial receiving monthly doses of WVE-N531
- Expanding FORWARD-53 to include additional boys on monthly dosing regimen

REGULATORY

- FDA feedback confirmed that the accelerated approval pathway using dystrophin expression as a surrogate endpoint remains open
- Based on FDA feedback and the 48-week data, Wave intends to submit an NDA in 2026 to support accelerated approval of WVE-N531 with monthly dosing
- Wave will continue to engage the Agency with the new 48-week data, including functional outcomes, and its planned global confirmatory trial of WVE-N531

EXON SKIPPING FRANCHISE

- Expect to submit multiple CTAs for other exon skipping candidates in 2026
- Candidates all use Wave's best-in-class chemistry; and preclinical data suggest best-in-class exon skipping franchise

WVE-N531 is expected to offer a differentiated profile that addresses key unmet needs for boys with exon 53 amenable DMD

	Currently marketed exon 53 skipping therapies under accelerated approval	WVE-N531
Dystrophin consistency	No[1] or few[2] boys achieve levels above 5%	✓
Evidence of ability to reach myogenic stem cells	✗	✓
Favorable dosing frequency	Weekly	**Monthly**
Favorable safety profile	✓	✓
Favorable evidence of functional benefit (TTR)[3]	✗	✓
Evidence of disease reversal in muscle	✗	✓
Evidence of ability to reach heart and diaphragm	✗	✓ [4]

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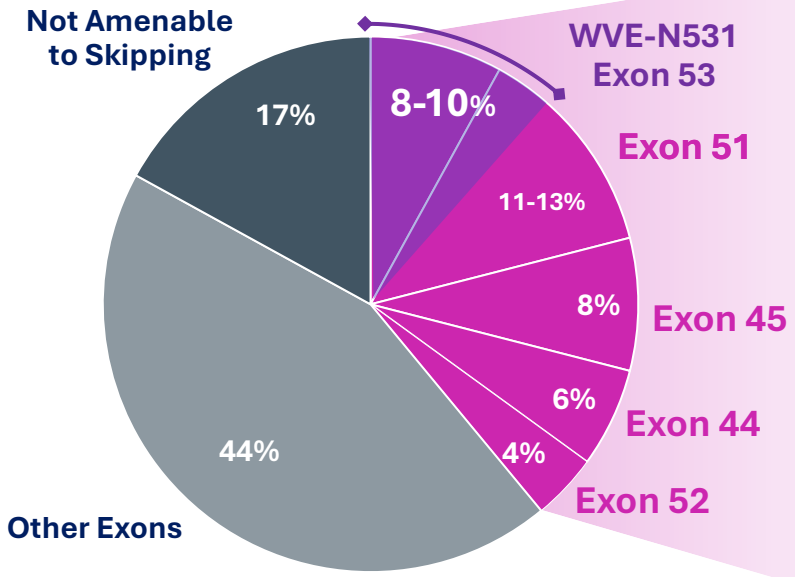
1. 48 weeks (Vyondys 53); 2. 24 weeks (Viltepso); 3. Based on 48-week data; 4. Evidence of ability to reach heart and diaphragm through preclinical studies (Kandasamy et al., 2022 Nuc Acids Res doi: 10.1093/nar/gkac018)

Wave DMD portfolio addresses >$2.4 billion opportunity in US alone with potential for expansion

Wave portfolio addresses up to 40% of the DMD population



Multiple drivers of value with Wave portfolio

Increasing exon skipping treatment rates

- ~40–50% of exon 53, 51, 45 skipping amenable boys remain untreated today
- No exon skipping therapies available for exons 44 and 52
- Advantages over gene therapy (endogenous dystrophin, favorable safety)

Switches from marketed exon skipping therapies

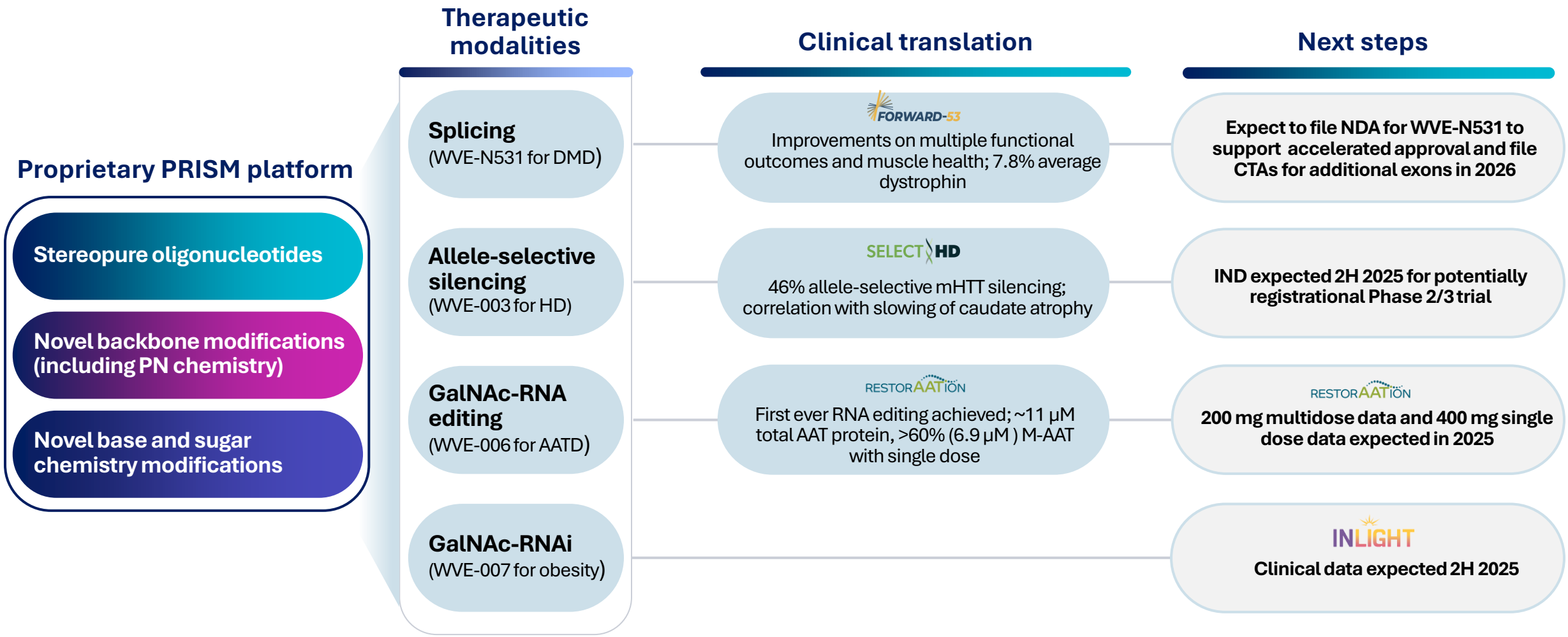
- Monthly dosing, superior dystrophin profile, and improvements in muscle health

Expansion to ex-US markets

- Best-in-class exon skipping profile where no exon skipping therapies are available

Aartsma-Rus, et al. 2009 Hum Mutat

Continued clinical translation sets foundation for multiple near-term milestones



Full list of Wave publications: https://ir.wavelifesciences.com/events-publications/publications
HD: mHTT reductions compared to placebo; DMD: Mean muscle-adjusted dystrophin









FORWARD-53

Thank you to the boys, families, clinicians and study site staff who are participating in this study

Q&A

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