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

Investor Presentation

September 24, 2024

Forward-looking statements

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Today’s agenda

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

FORWARD-53 interim analysis clinical results
Anne-Marie Li-Kwai-Cheung, MChem, MTOPRA, RAPS
Chief Development Officer

Anticipated upcoming milestones
Paul Bolno, MD, MBA
President and CEO

Opening remarks and opportunity for WVE-N531

Paul Bolno, MD, MBA

President and CEO

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WAVE LIFE SCIENCES HAS BEEN DEDICATED TO DMD FOR MORE THAN A DECADE



Urgent need for improved therapeutic options for the treatment of DMD

Duchenne is a devastating and fatal disease

- Genetic mutation in dystrophin gene prevents the production of dystrophin protein, a critical component of healthy muscle function
- Impacts ~1 / 5,000 newborn boys annually; ~20,000 new cases annually worldwide
  - ~8–10% are amenable to exon 53 skipping
  - Potential for Wave to address up to 40% of DMD with additional exon skipping therapeutics

Multiple urgent unmet needs

- Need for therapies delivering **more consistent dystrophin expression,** as few patients today achieve dystrophin >5% of normal
- **Opportunity to extend dosing intervals** beyond weekly standard of care to alleviate burden for patients and caregivers
- **Need to reach stem cells and distribute broadly to muscle tissues** to potentially enable muscle regeneration and impact respiratory and cardiac function

Boy living with DMD

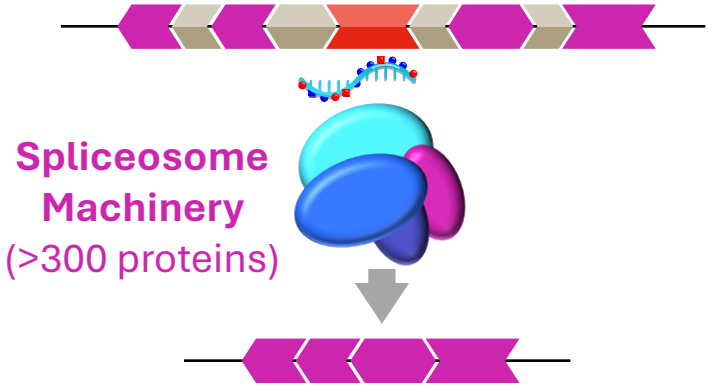
Duan, D. et al. 2021 Nat Rev Dis Primers 7, 13; Muscular Dystrophy Association; Aartsma-Rus, et al. 2009 Hum Mutat 30, 293.

Wave's best-in-class multi-modal platform

Clinically-validated oligonucleotide chemistry (PN, stereochemistry)

Splicing

Restore RNA transcripts and **turn on** protein production

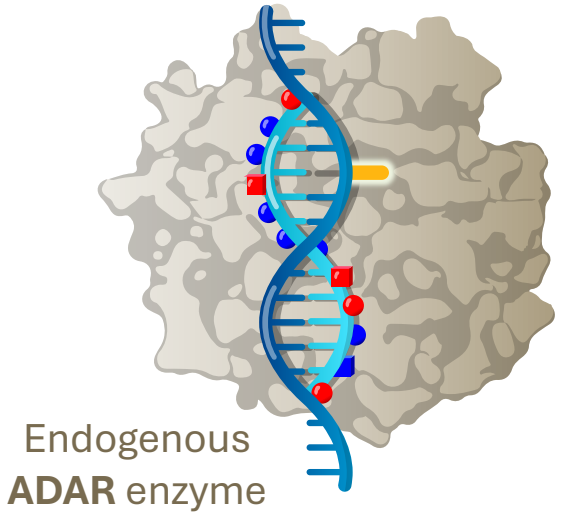


Restored **Reading Frame** for **Functional Protein**

WVE-N531 (DMD)

Editing

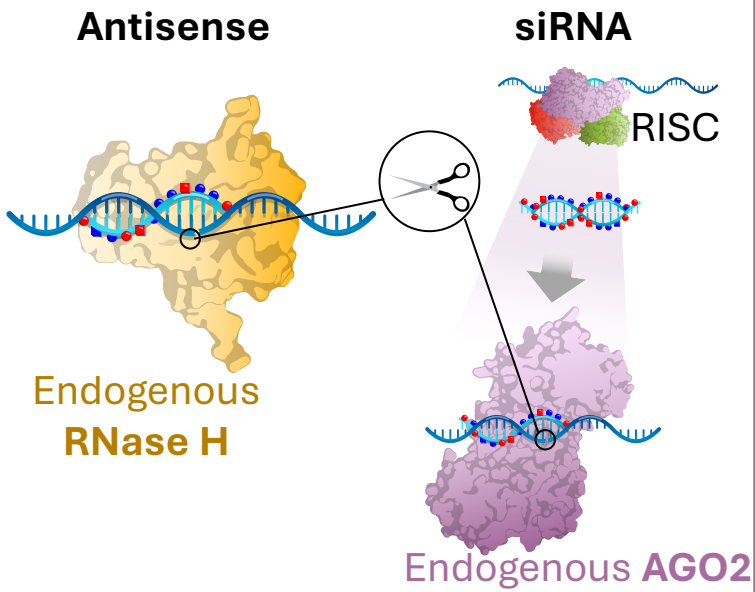
Efficient editing of RNA bases to **restore** or **modulate** protein production



WVE-006 (AATD)
Additional wholly owned editing programs

Silencing

Degradation of RNA transcripts to **turn off** protein production

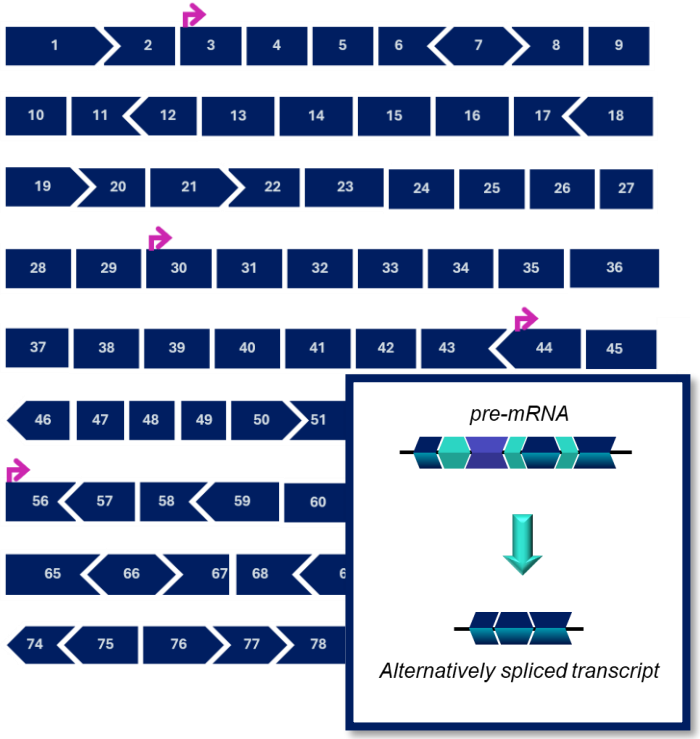


WVE-003 (HD)

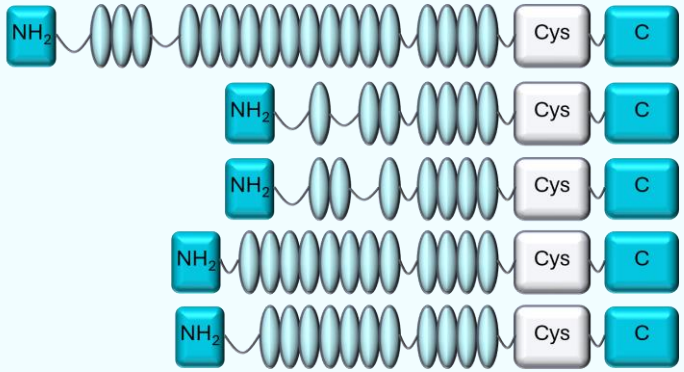
WVE-007 (obesity)

The therapeutic strategy in DMD is to consistently produce ≥5% dystrophin

Exon skipping aims to restore the reading frame…



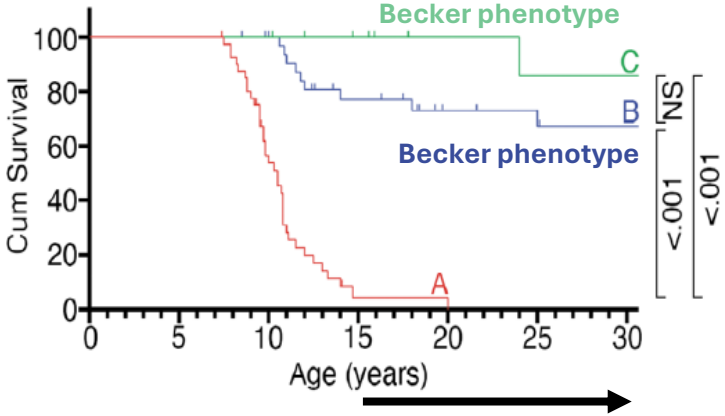
…producing dystrophin isoforms…



Many more functional isoforms observed

…that delay loss of function

Loss of ambulation



Delayed loss of ambulation

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

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

Today's update: Positive interim data from FORWARD-53

- Highly consistent, 9.0% mean muscle content-adjusted dystrophin (5.5% unadjusted); dystrophin comprised of two isoforms consistent with Becker
- Evidence of improvement in muscle health, accessing stem cells
- Best-in-class muscle delivery, tissue half-life to support extended dosing intervals
- Safe and well tolerated; no SAEs, no oligonucleotide-class effects

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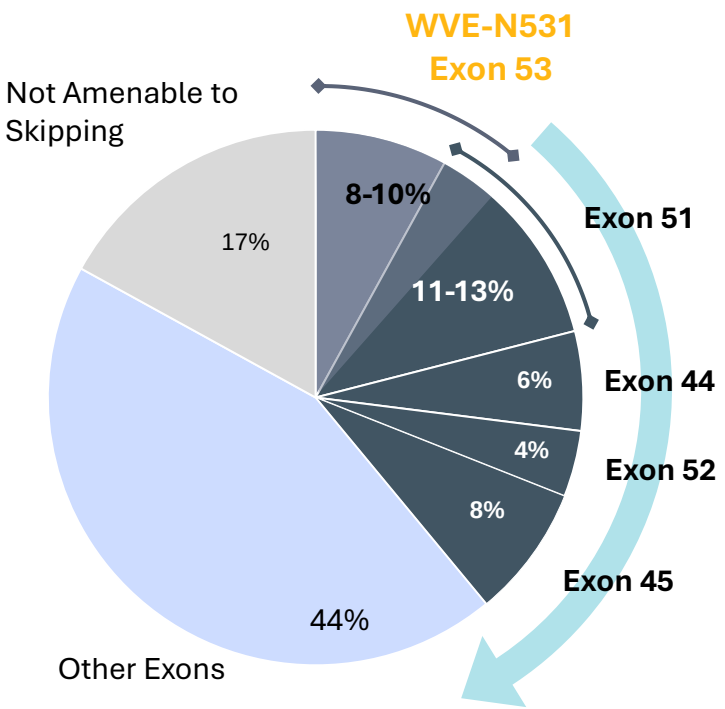
Dystrophin measured in a prespecified analysis of ambulatory patients; SAEs: Serious adverse events;

Unlocking Wave's best-in-class exon skipping portfolio

DMD Population



- Data for exons 51, 44, 52, 45 demonstrate potential for even greater dystrophin expression
- Opportunity to address up to 40% of population
- Expect to engage regulators on a platform trial design that incorporates multiple exons

Aartsma-Rus, et al. 2009 Hum Mut 30, 293

FORWARD-53
interim analysis clinical results

Anne-Marie Li-Kwai-Cheung, MChem, MTOPRA, RAPS

Chief Development Officer

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WVE-N531 has potential to be the best-in-class therapeutic for exon 53 DMD

Highly consistent dystrophin expression across patients

- 9.0% muscle-content adjusted dystrophin (5.5% unadjusted), quantified from two isoforms that are consistent with Becker patients who display milder disease
- 89% of patients over 5% of normal (muscle-content adjusted)

Muscle delivery and extended dosing intervals

- Skeletal muscle tissue concentrations of WVE-N531: ~41,000 ng/g
- WVE-N531 tissue half-life of 61 days supports monthly dosing
- Preclinical data suggests WVE-N531 is translating in heart and diaphragm

Evidence supporting improved muscle health

- Improvement in serum biomarkers for muscle health
- Localization of WVE-N531 in myogenic stem cells
- Improvement in myofiber regeneration

Safe and well tolerated

- No SAEs
- No discontinuations
- No oligonucleotide class effects

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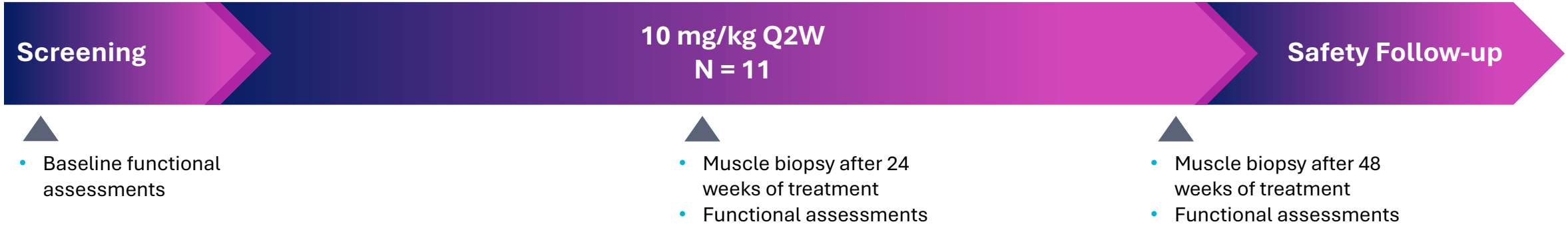
Dystrophin data from prespecified analysis of ambulatory boys; Muscle content adjustment was done using the formula: MHC-normalized dystrophin/(total myofiber area/total area of biopsy section).

FORWARD-53: An ongoing potentially registrational open-label Phase 2 clinical trial of WVE-N531 in boys with DMD amenable to exon 53 skipping



Key Assessments:

- Safety and tolerability
- Muscle biopsies after 24 and 48 weeks of treatment
  - PK: Drug tissue concentrations
  - PD: Exon-skipping, Dystrophin level (% of normal) as assessed by Western Blot
- Functional outcome measures
- 11 participants enrolled, including two from prior Part A clinical trial
  - Pre-specified analyses in ambulatory patients

IV: Intravenous; Q2W: Every 2 Weeks; PK: Pharmacokinetics; PD: Pharmacodynamics

Baseline patient characteristics

Baseline DMD Patient Characteristics	FORWARD-53 population (n=11)
Age (years) (mean (SD))	8.2 (2.1)
Age 5-7 (n (%))	5 (45)
Age 8-11 (n (%))	6 (55)
BMI (kg/m2) (mean (SD))	19.1 (4.0)
Years since DMD diagnosis (mean (SD))	4.0 (2.5)
Patients on Oral Steroids (n (%))	11 (100)
Prednisone	4 (36.4)
Deflazacort	7 (63.6)
Ambulatory (n (%))	10 (90.9)
Exon Deletion (n (%))	
45-52	6 (54.5)
52-52	2 (18.2)
Others*	3 (27.3)

*Other deletions include 48-52, 49-52 and 50-52

WVE-N531 was safe and well tolerated

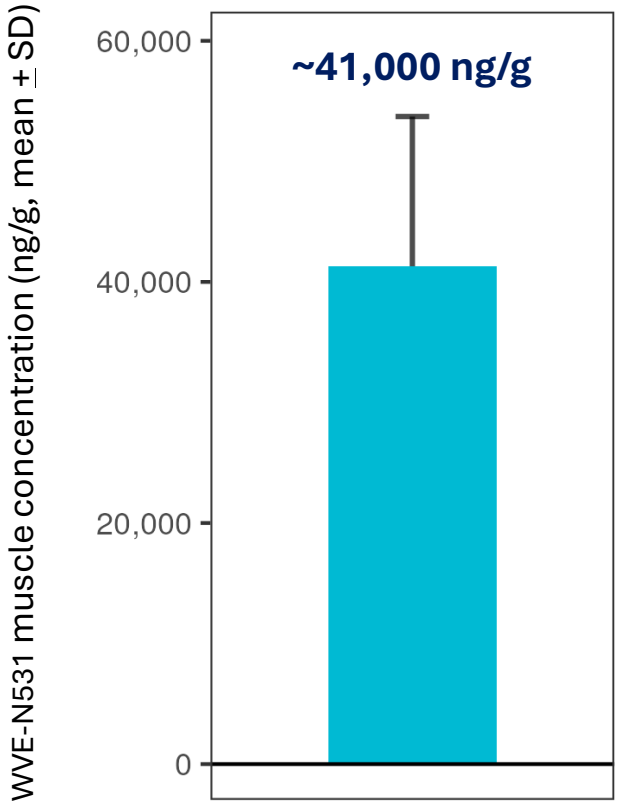
TEAE Category	WVE-N531 10 mg/kg n=11 Patients (%)
Any TEAE	10 (90.9)
Any drug-related TEAE Mild Moderate Severe	3 (27.3) 3 (27.3) 0 0
Any serious TEAE	0
Any severe TEAE	0
Any TEAE leading to discontinuation	0
Any TEAE leading to death	0

No Serious Adverse Events and no oligonucleotide class-related events

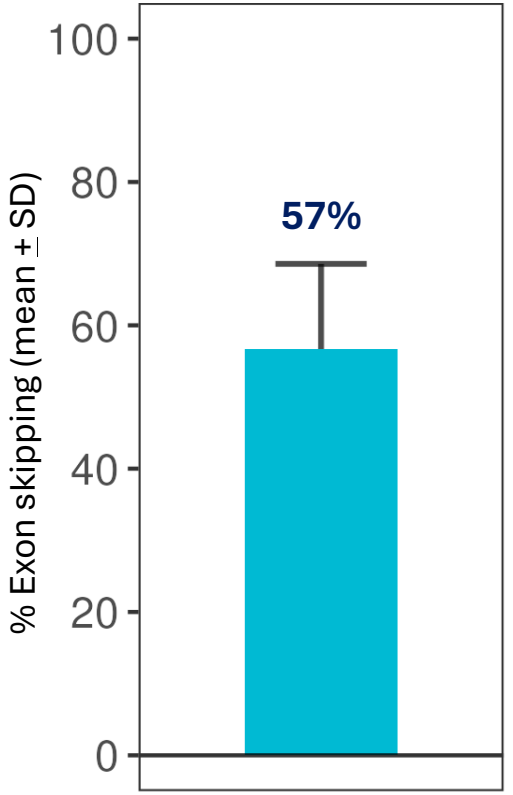
TEAE: Treatment emergent adverse event; Data as of August 19, 2024

Industry-leading muscle tissue concentrations and exon skipping

Muscle tissue concentrations



Exon skipping

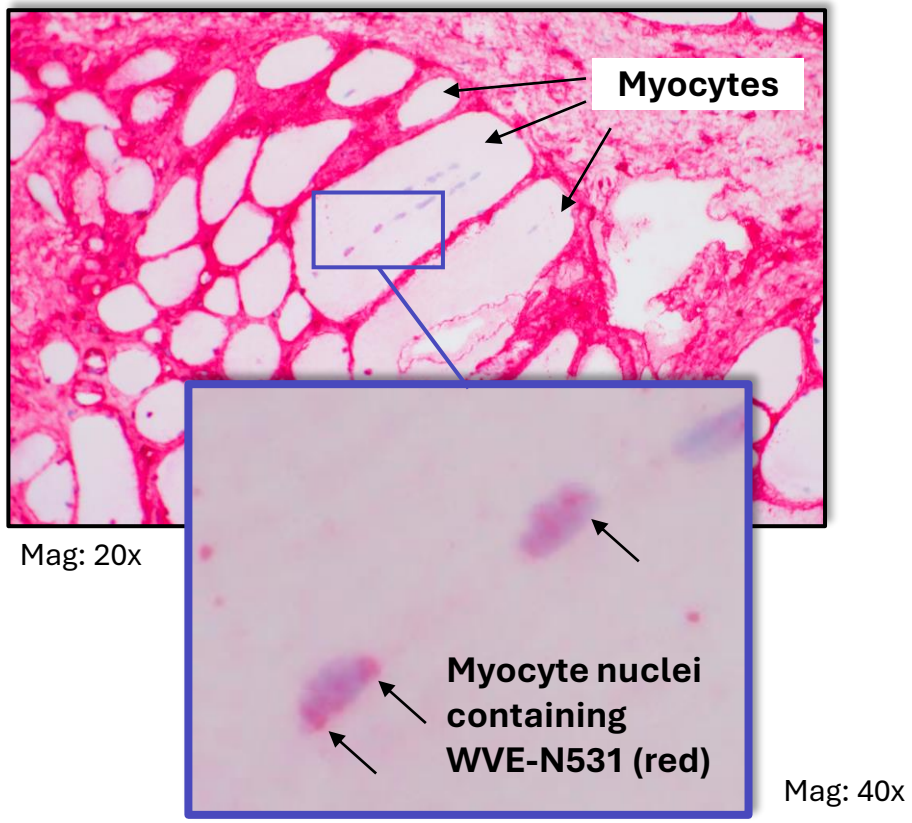


Tissue half-life of 61 days supports monthly dosing

Muscle tissue concentrations and exon skipping n=11; ~41,000 ng/g = ~5,900 nM

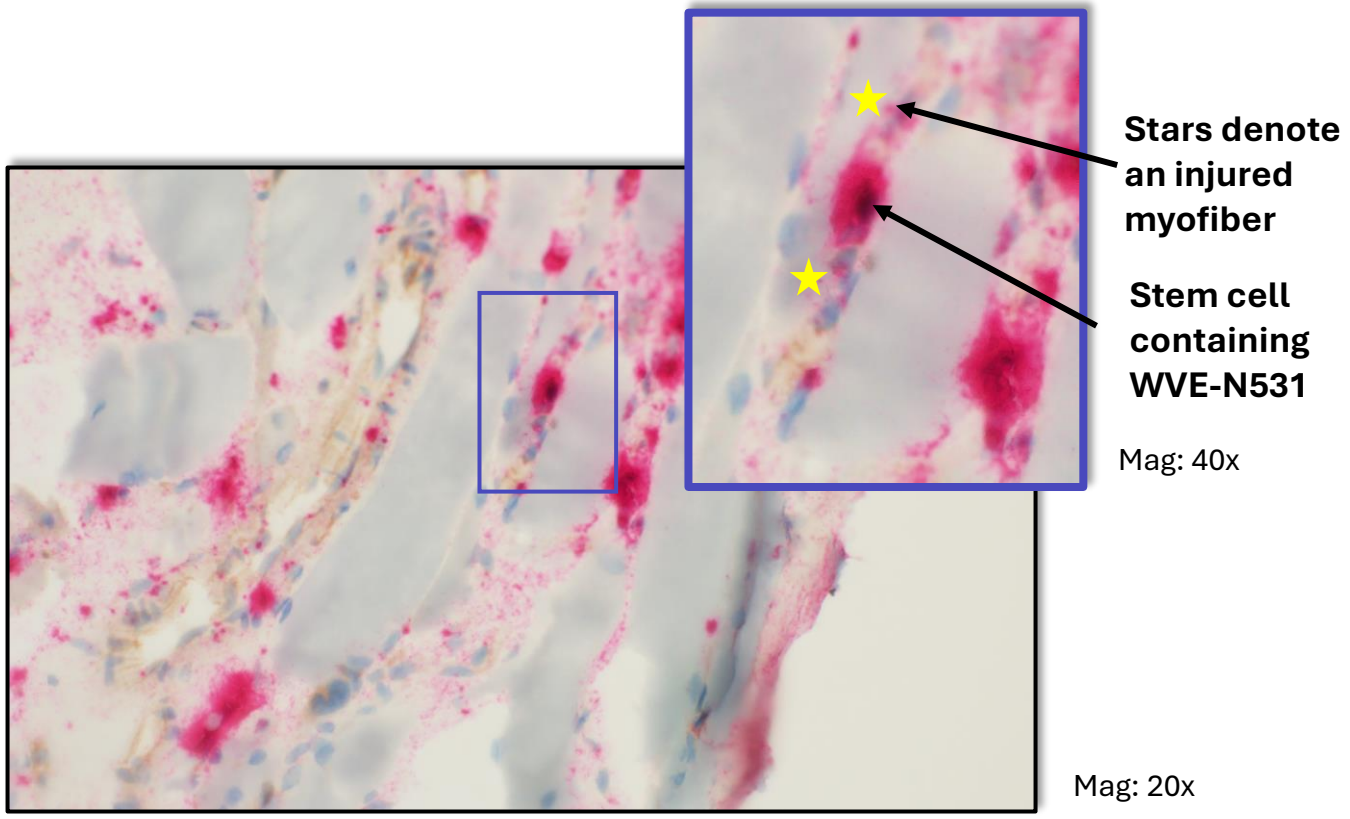
WVE-N531 was localized in myofiber nuclei and myogenic stem cells

WVE-N531 uptake in myofiber nuclei



In-situ hybridization for WVE-N531

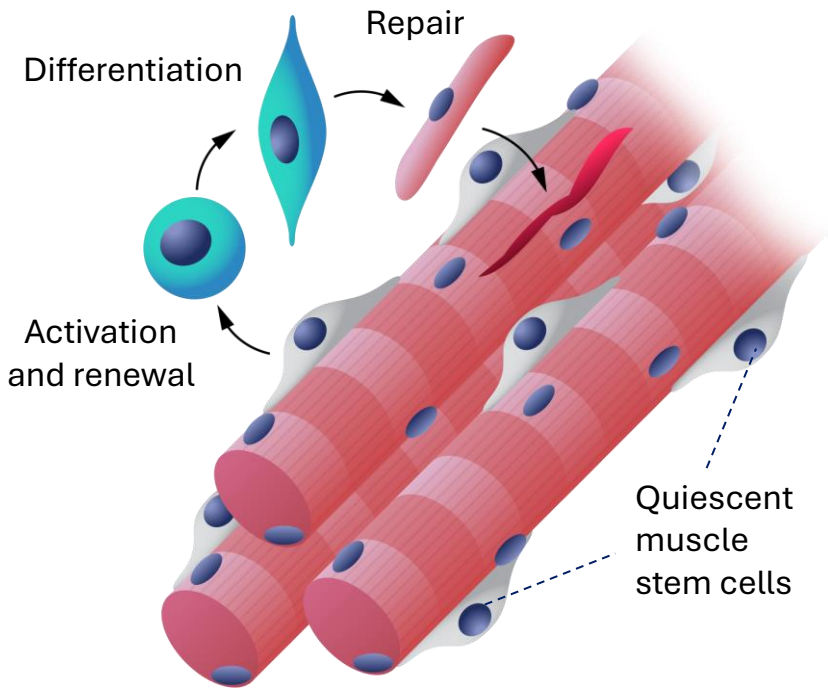
WVE-N531 uptake in myogenic stem cells



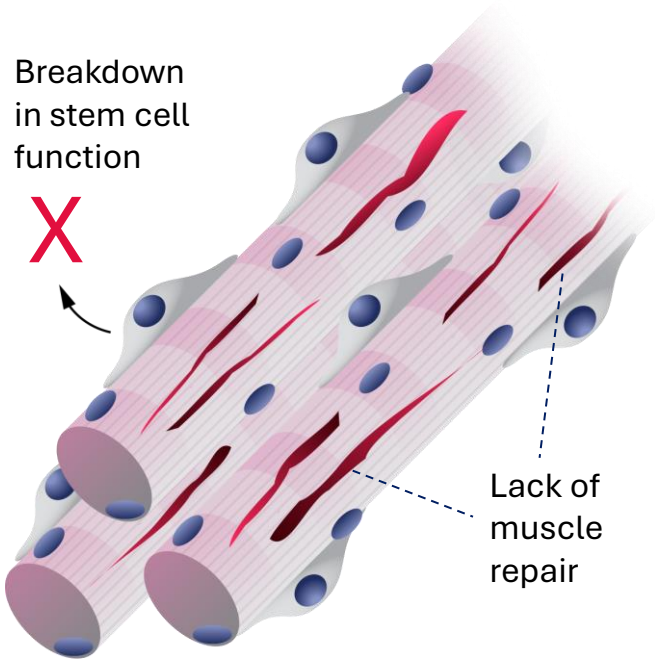
Dual staining utilizing in-situ hybridization for WVE-N531 and PAX7 immunohistochemistry for stem cells

Restoring dystrophin in muscle stem cells enables repair of muscle fibers

- Absence of dystrophin in **muscle stem cells** impairs cell division and myogenesis, and inhibits self-renewal, leading to a **reduction of viable stem pools** and halting of subsequent muscle repair.
- **Restoring dystrophin in muscle stem cells** enables them to function properly, allowing quiescent cells to "wake up," differentiate, and **initiate repair** of muscle fibers.



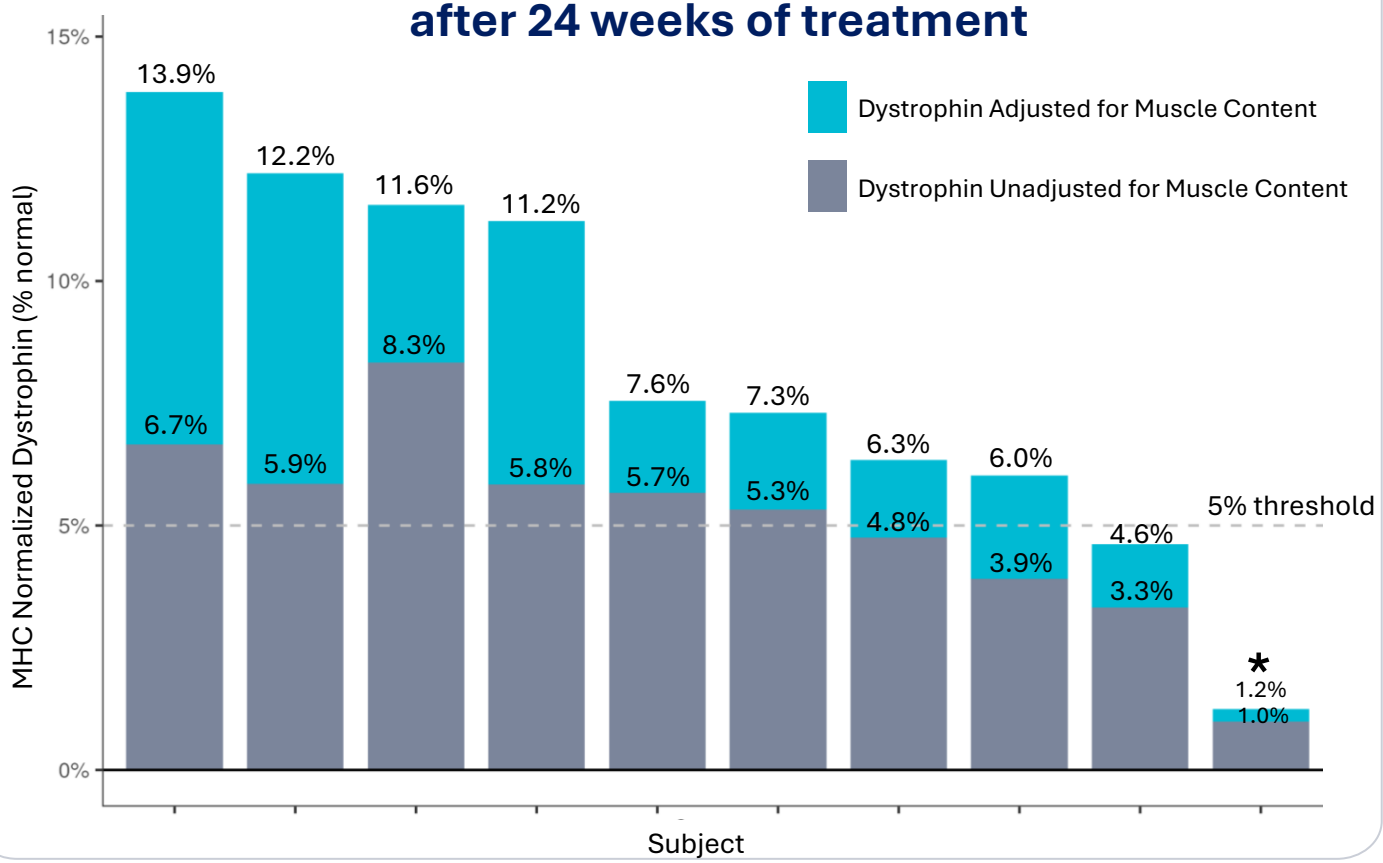
Normal Muscle



Dystrophic Muscle

Dystrophin expression of up to 14% with high consistency across participants

Percentage dystrophin expression across each patient after 24 weeks of treatment



- Mean 9.0% absolute muscle content adjusted dystrophin
- Mean 5.5% absolute unadjusted dystrophin
- Dystrophin expression was quantified from two isoforms consistent with those observed in Becker patients who display milder disease

89% of ambulatory participants achieve muscle content-adjusted dystrophin levels of at least 5%

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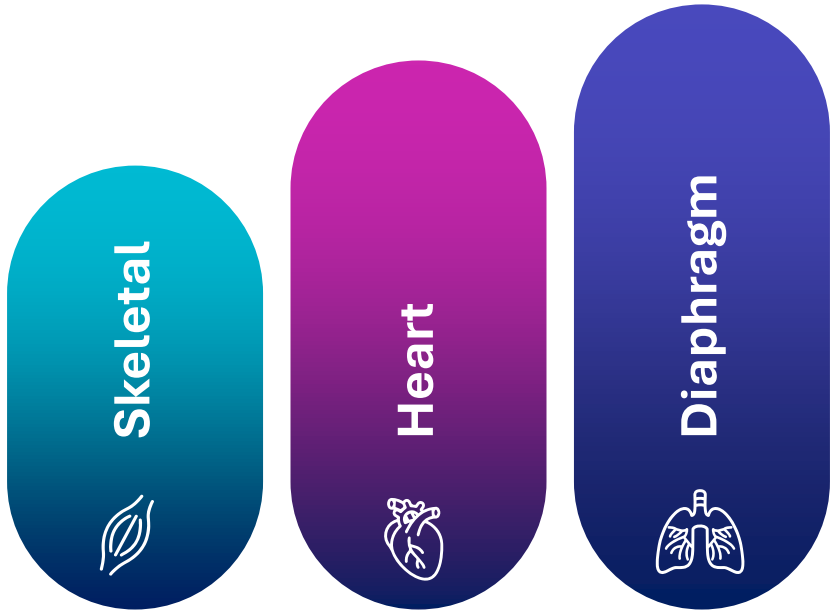
*Excluded from prespecified mean analysis of ambulatory patients; Muscle content adjustment was done using the formula: MHC-normalized dystrophin/(total myofiber area/total area of biopsy section); Graph shows all patients (including non-ambulatory) with appropriate biopsy sample; dystrophin measured by Western Blot (AB15277)

WVE-N531 in skeletal muscle likely to underrepresent activity in heart and diaphragm



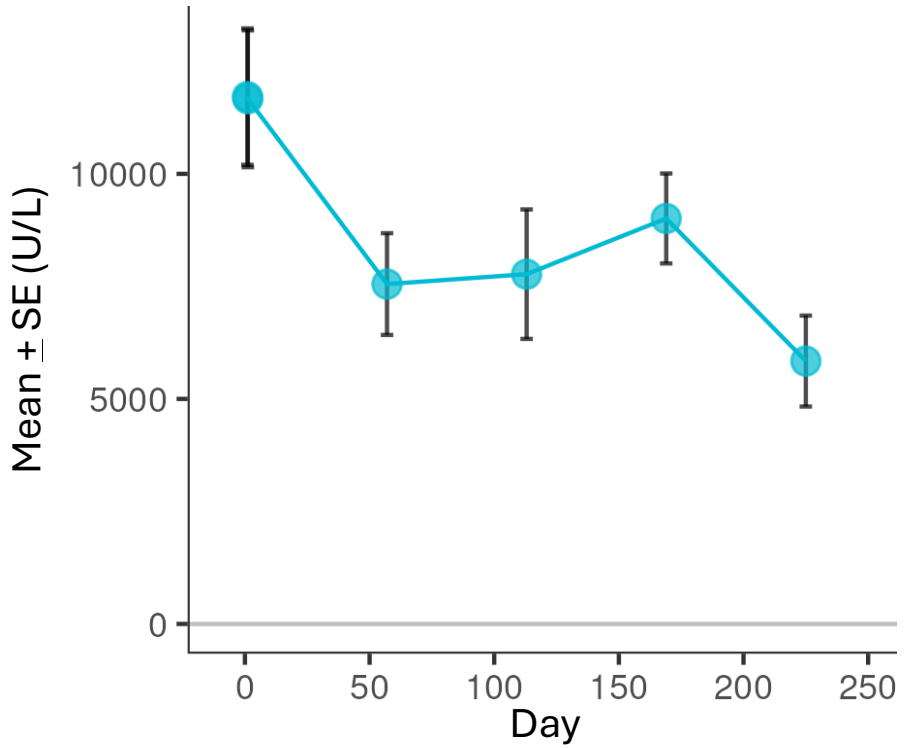
Preclinical data:

dKO:	**Dystrophin restoration**		**~9%**	**~12%**	**~17%**	**→ Higher dystrophin in heart and diaphragm, survival benefit**
				cardiac and respiratory functional improvements		
NHP:	**WVE-N531 muscle tissue concentration (µg/g)**		**2.17**	**57.2**	**10.8**	**→ Greater exposure in heart and diaphragm**

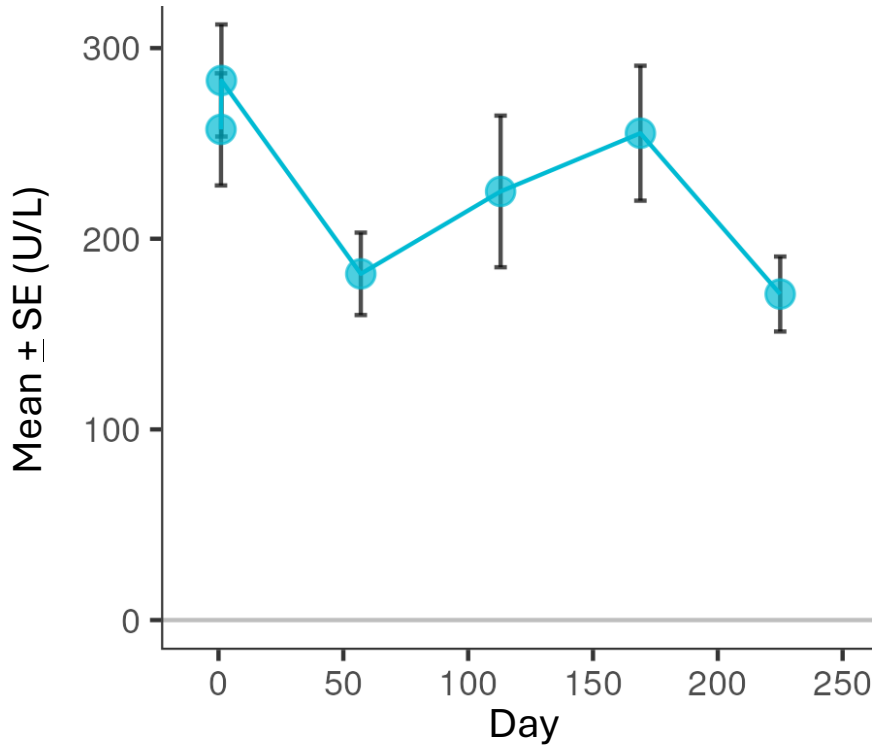
Kandasamy et al., 2022 Nuc Acids Res doi: 10.1093/nar/gkac018

WVE-N531 treatment led to substantial decreases in muscle-related biomarkers

CK



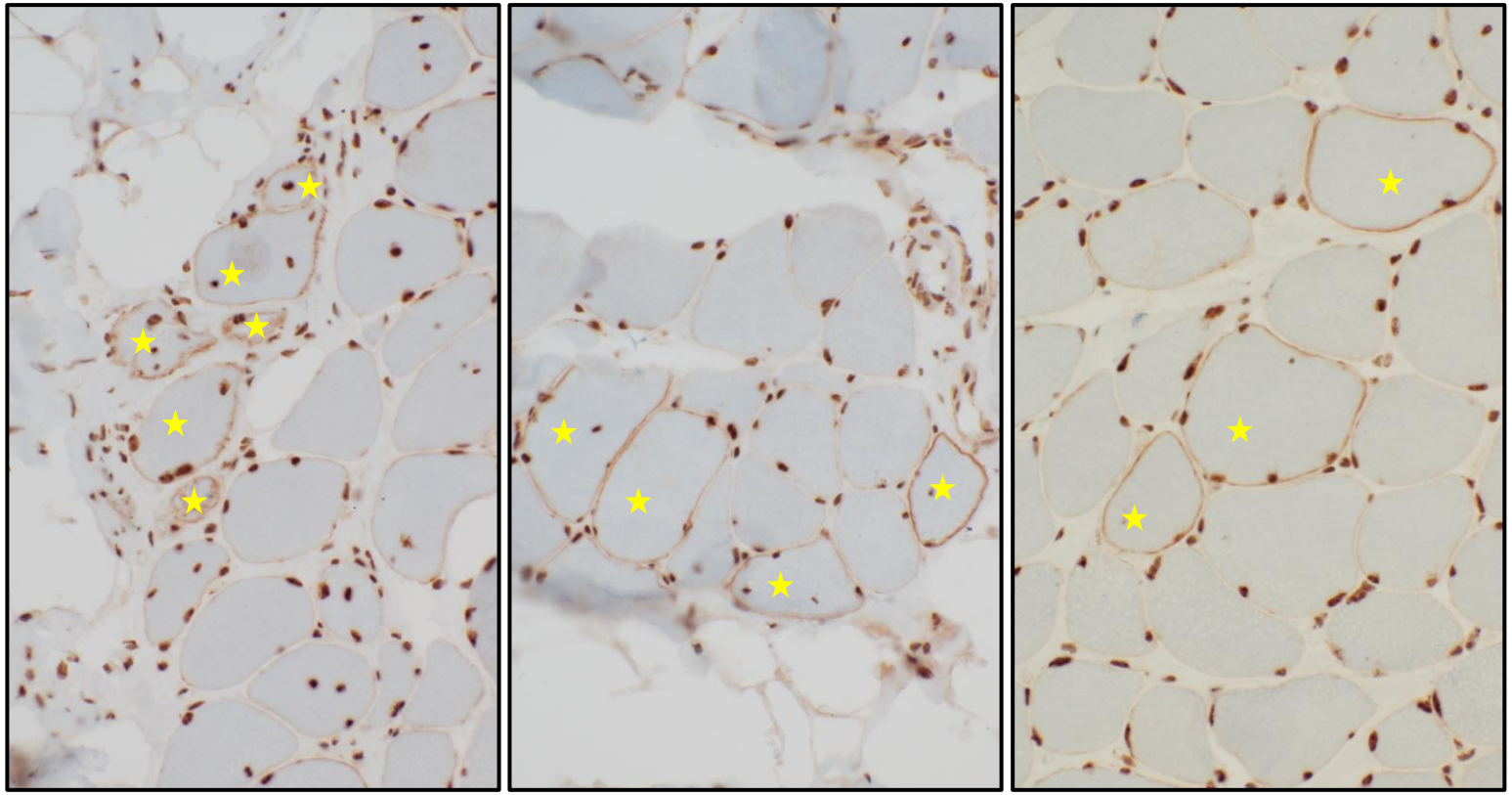
AST



CK: Creatine Kinase; AST: Aspartate Aminotransferase

Dystrophin is localized to the sarcolemma membrane

Immunohistochemistry for dystrophin



Mag 40x

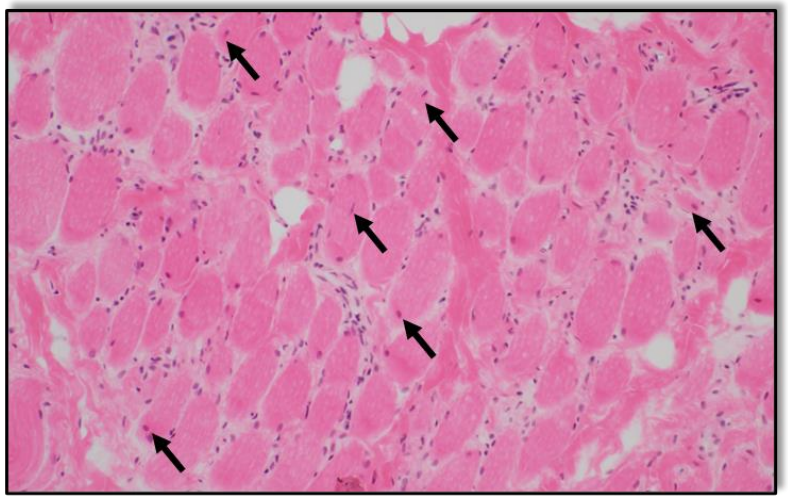
Immunohistochemistry stains dystrophin brown (★)

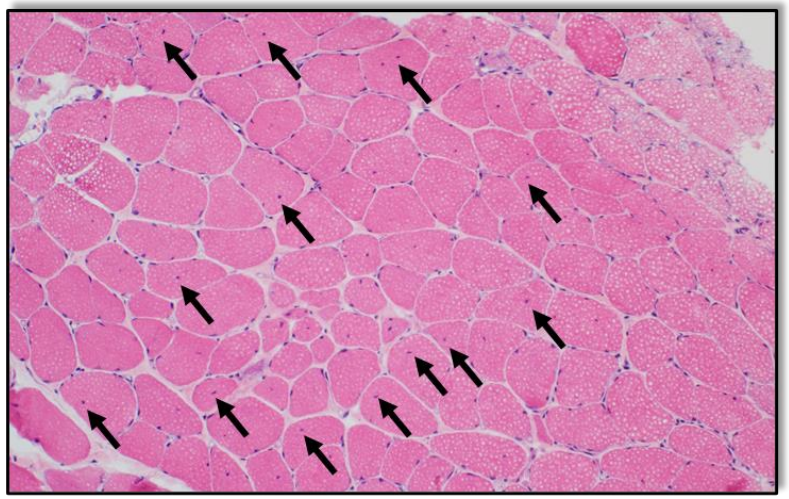
Evidence of myocyte regeneration and improvement in muscle health

Patient 1 – Part A
(After 6 weeks of WVE-N531, Q2W)

Patient 1 – FORWARD-53
(After 24 weeks of WVE-N531, Q2W)

Histological Staining

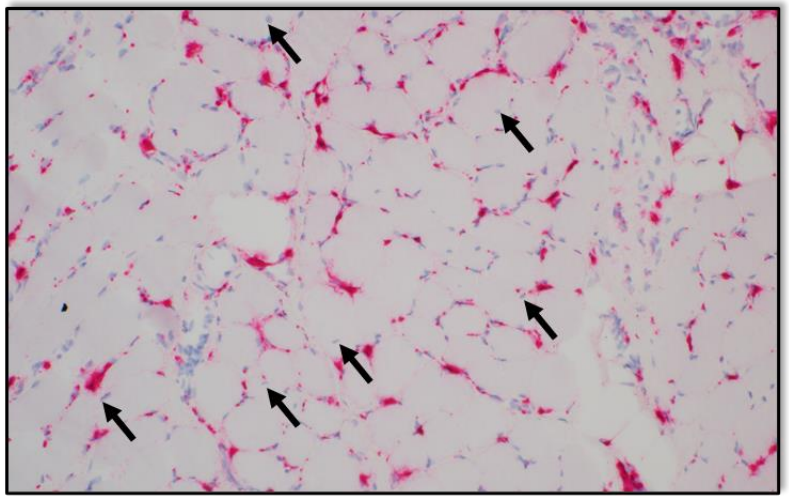


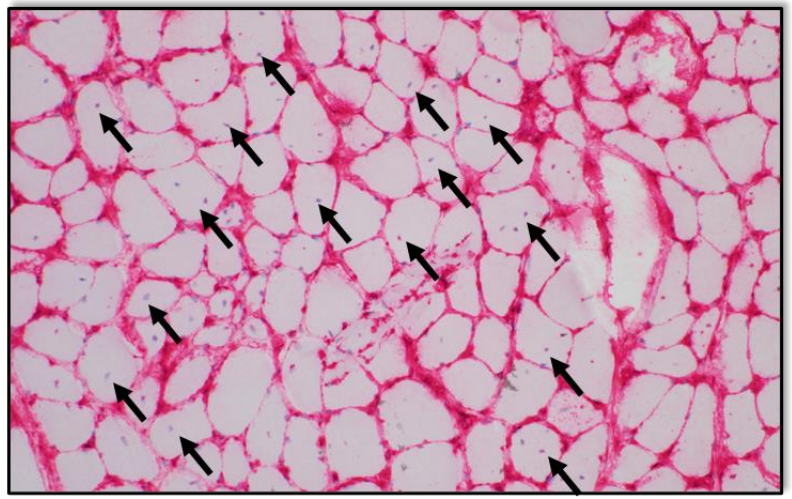


↖ **Denotes internalized nuclei**

Mag. 20x

Staining for WVE-N531 (red)
RNA Scope
(in situ hybridization)





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Q2W: Every other week dosing

Next steps for WVE-N531

- FORWARD-53 is ongoing; patients are being transitioned to a monthly dosing regimen
- Wave expects to deliver 48-week FORWARD-53 data in 1Q 2025
- Wave will engage regulators and expects feedback on a pathway to accelerated approval in 1Q 2025

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

Anticipated upcoming milestones

Paul Bolno, MD, MBA

President and CEO

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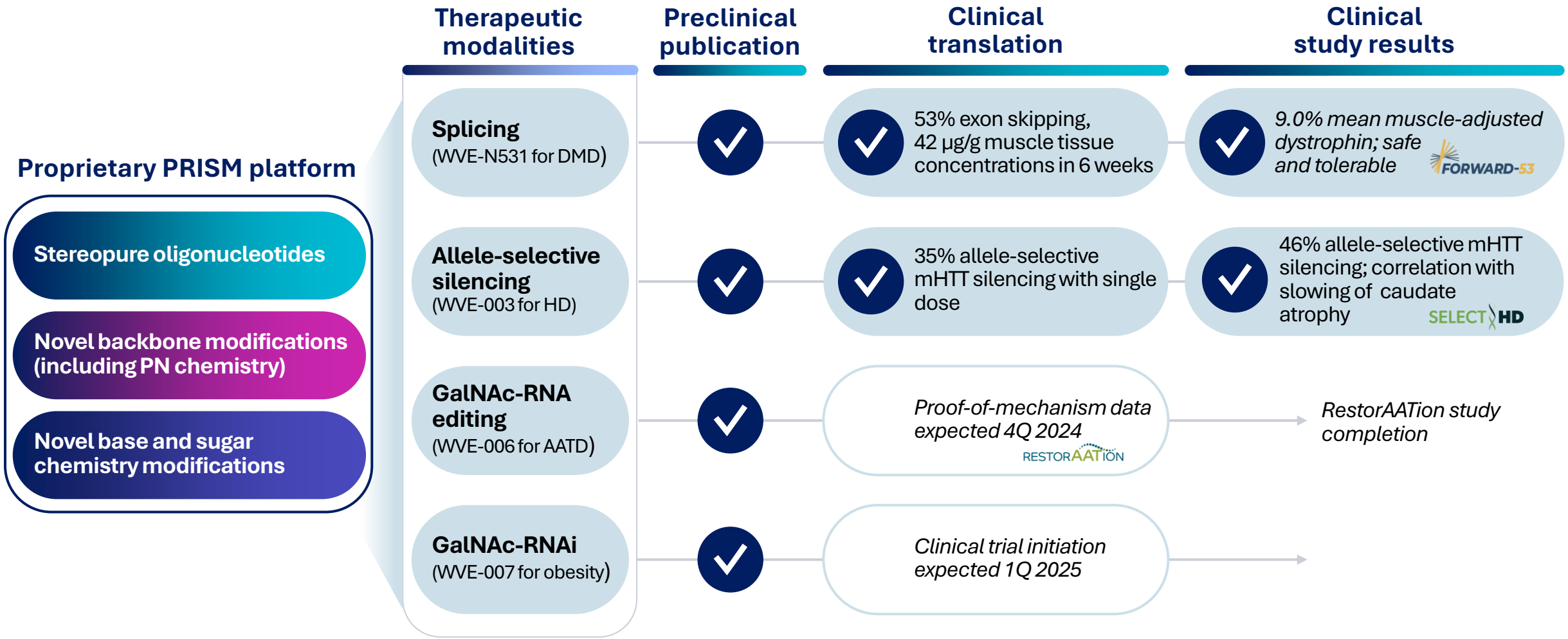
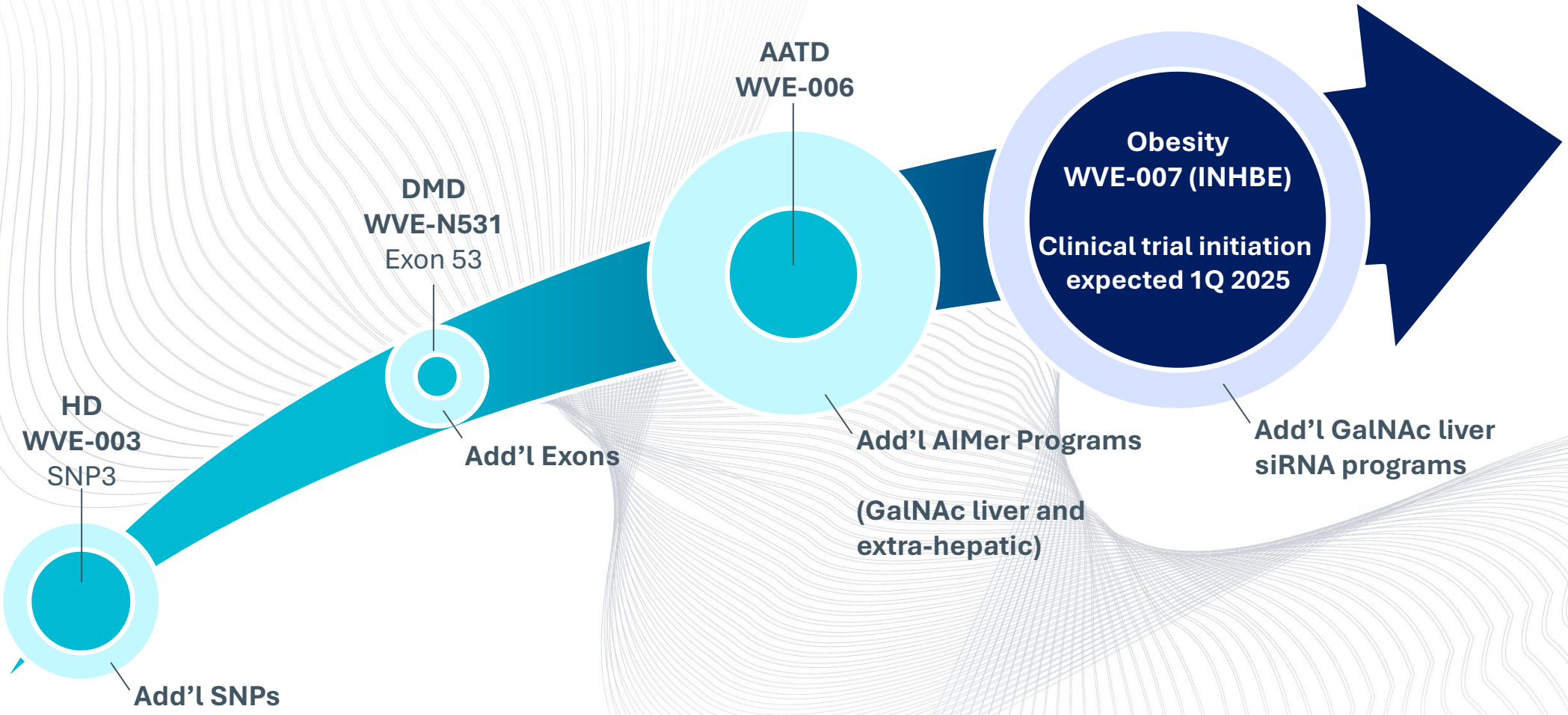
Proprietary chemistry continues to translate in clinic across modalities, enabling first-in-class and best-in-class therapies



Full list of Wave publications: https://ir.wavelifesciences.com/events-publications/publications
*mHTT reductions compared to placebo

Wave is poised for significant and sustained growth



Wave's platform is translating in the clinic and has potential to treat >50M patients in the US and Europe

Note: Bubble size illustrative of size of total addressable US market (assuming 100% share of addressable patients)

Q&A

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Reimagine possible.