Initial results from an open-label phase 1/2 study of nivudirsen (BMN 351), an antisense oligonucleotide for exon 51 skip–amenable Duchenne muscular dystrophy

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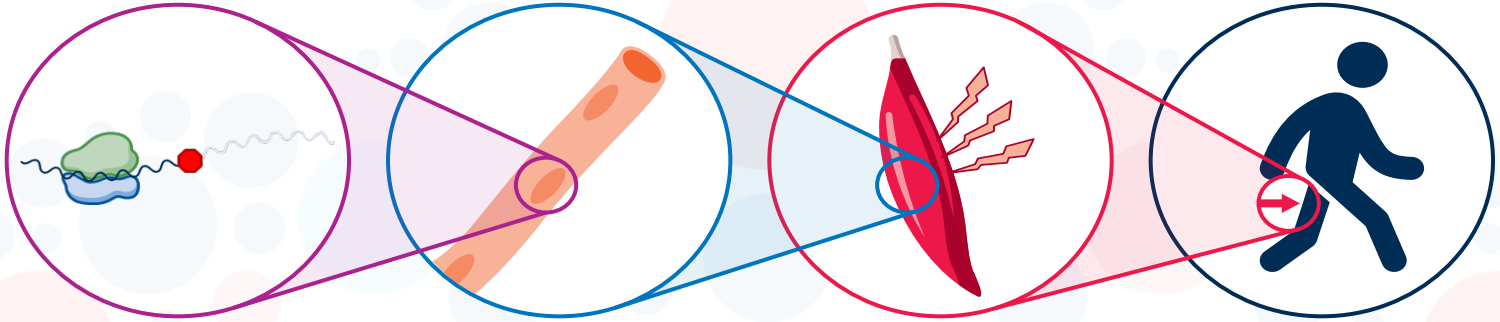
Disclosures for Giovanni Baranello

Commercial interest	Relationship(s)
Principal investigator of clinical trials	BioMarin Pharmaceutical Inc., Novartis, NS Pharma, Percheron, Pfizer, ReveraGen BioPharma, Roche, Sarepta Therapeutics, and Scholar Rock
Speaker and/or consulting fees	Biogen, Entrada Therapeutics, Novartis Gene Therapies (formerly AveXis), Pfizer, PTC Therapeutics, Roche, and Sarepta Therapeutics
Grants	Novartis Gene Therapies, Roche, and Sarepta Therapeutics

Duchenne muscular dystrophy is caused by a severe deficiency in the level of dystrophin protein

Without sufficient dystrophin, progressive muscle wasting leads to functional impairments

Genetic	Protein/cell	Tissue	Function
Variants alter the open reading frame, causing premature truncation of translation[1,2]	Nonsense-mediated decay reduces transcript abundance,[3] and any produced protein is truncated, nonfunctional, and unstable[4]	Dystrophin deficiency causes muscle damage, necrosis, inflammation, and fibrosis[2]	Speed, endurance, and quality of movement are negatively impacted[5]



1. Bladen CL, et al. *Hum Mutat*. 2015;36(4):395–402. 2. Duan D, et al. *Nat Rev Dis Primers*. 2021;7(1):13. 3. Rossi R, et al. *Neuromuscul Disord*. 2026;59:106306. 4. Wattin M, et al. *Int J Mol Sci*. 2018;19(1):178.
5. Ryder S, et al. *Orphanet J Rare Dis*. 2017;12(1):79.

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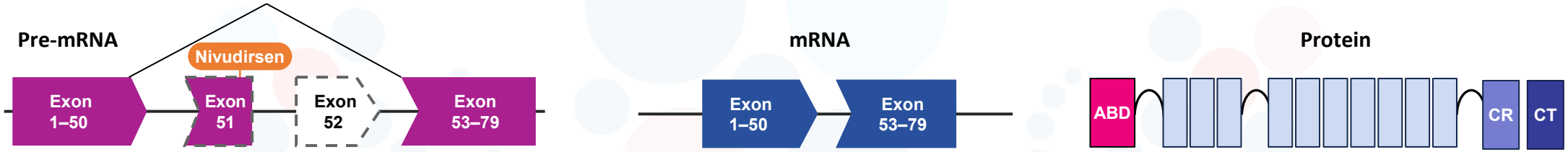
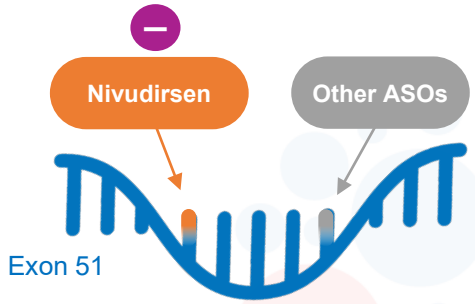
Nivudirsen (BMN 351) is an ASO designed to restore the open reading frame by inducing skipping of exon 51



By masking the splicing enhancer site, the target exon flanking the deletion is removed with the introns

Reading frame restored

Near full-length, functional dystrophin protein



- Nivudirsen targets a novel and **highly active splicing enhancer site** within exon 51[1–3]
- Nivudirsen includes a negatively charged 2'OMePS backbone to facilitate cellular uptake[4]
- Nivudirsen contains additional structural modifications[1–3] to
  - **Reduce immunogenicity**
  - **Increase binding affinity and half-life**

1. Oppeneer T, et al. *Nucleic Acid Ther*. 2025;35(2):68–80. 2. Oppeneer T, et al. *Nucleic Acid Ther*. 2025;35(2):81–92. 3. van Deutekom J, et al. *Nucleic Acid Ther*. 2023;33(3):193–208. 4. DeVos S, et al. *Neurotherapeutics*. 2013;10(3):486–97.

ABD, actin-binding domain; ASO, antisense oligonucleotide; CR, cysteine-rich domain; CT, C-terminal domain; mRNA, messenger RNA; OMePS, *O*-methyl-phosphorothioate.

351-201 study objectives

1

Primary objective:
To assess the safety and tolerability of nivudirsen at different dose levels in boys with DMD amenable to exon 51 skipping

2

Secondary objectives:

- Plasma and urine pharmacokinetics
- Muscle concentration of nivudirsen

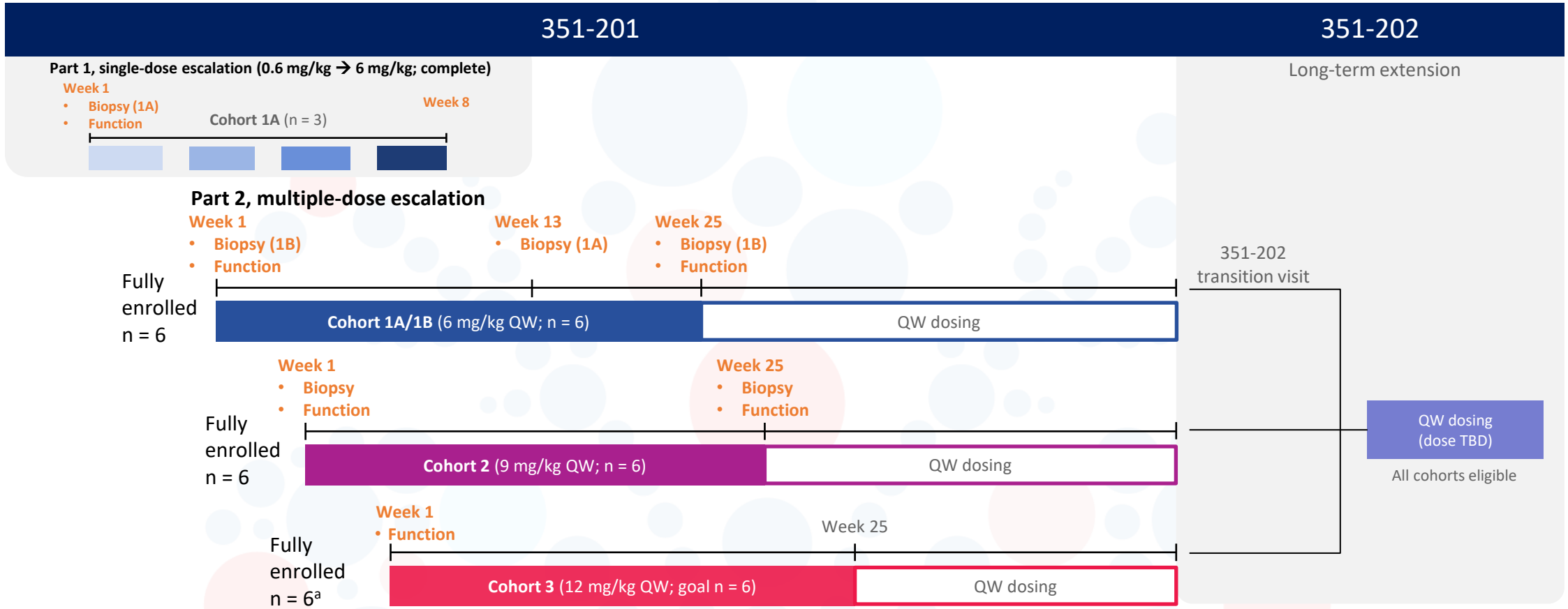
3

Other objectives:

- Exon skipping and near full-length dystrophin expression
- Functional assessments

351-201 (EUCT#2023-506737-30-00; NCT06280209) is a phase 1/2, open-label, dose-escalation study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of nivudirsen in boys with DMD.
DMD, Duchenne muscular dystrophy.

351-201 study design and enrollment as of 23 March 2026



[a]The sixth and final participant enrolled in the 12 mg/kg cohort after the data cutoff of 23 March 2026.
QW, once weekly; TBD, to be determined.

Demographics and baseline characteristics as of 23 March 2026

Today's presentation: Safety, N = 17; biopsy (PD), n = 12; functional outcomes, n = 12

Mean (SD)	6 mg/kg QW (n = 6)	9 mg/kg QW (n = 6)	12 mg/kg QW (n = 5)	Overall (N = 17)
Age at enrollment, years	7.2 (1.3)	7.3 (1.2)	6.4 (2.1)	7.0 (1.5)
Weight, kg	21.8 (4.0)	23.6 (1.5)	21.7 (4.7)	22.4 (3.5)
Height, cm	114.2 (6.9)	121.4 (3.6)	113.3 (12.0)	116.5 (8.3)
BMI, kg/m^2	16.7 (2.2)	16.0 (0.6)	16.8 (0.8)	16.5 (1.4)
NSAA total score, points	19.0 (7.2)	22.3 (3.2)	20.8 (5.7)[a]	20.7 (5.4)[b]
6-minute walk distance, m	373.1 (79.7)	371.6 (79.5)	270.8 (201.1)[a]	346.9 (119.9)[b]

Study sites and participant enrollment


Türkiye (n = 7)


United Kingdom (n = 4)


Spain (n = 3)


Italy (n = 2)


Netherlands (n = 1)

Data cutoff: 23 March 2026. All enrolled participants were male.
[a]n = 4. [b]n = 16.
BMI, body mass index; NSAA, NorthStar Ambulatory Assessment; PD, pharmacodynamic; QW, once weekly; SD, standard deviation.

Manageable safety profile with dosing ongoing up to 12 mg/kg

Summary of AEs

AE category, n (%)	6 mg/kg QW (n = 6)	9 mg/kg QW (n = 6)	12 mg/kg QW (n = 5)	Overall (N = 17)
Participants with any AE	6 (100.0)	6 (100.0)	3 (60.0)	15 (88.2)
Leading to dose interruption[a]	5 (83.3)	5 (83.3)	1 (20.0)	11 (64.7)
Leading to dose reduction	0	0	0	0
Participants with any treatment-related AE	6 (100.0)	5 (83.3)	3 (60.0)	14 (82.4)
Participants with any SAE	2 (33.3)	1 (16.7)	0	3 (17.6)
Participants with any treatment-related SAE	0	0	0	0
Any AEs leading to death	0	0	0	0
Mean treatment duration, wk	86.3	61.1	13.5	56.0

[a]Temporary dose interruptions were due to protocol-specified criteria for treatment interruption based on laboratory abnormalities. Participants have been able to restart treatment after improvement of the laboratory abnormality. All events resolved without clinical sequelae.

All treatment-related AEs were grade 1 or 2

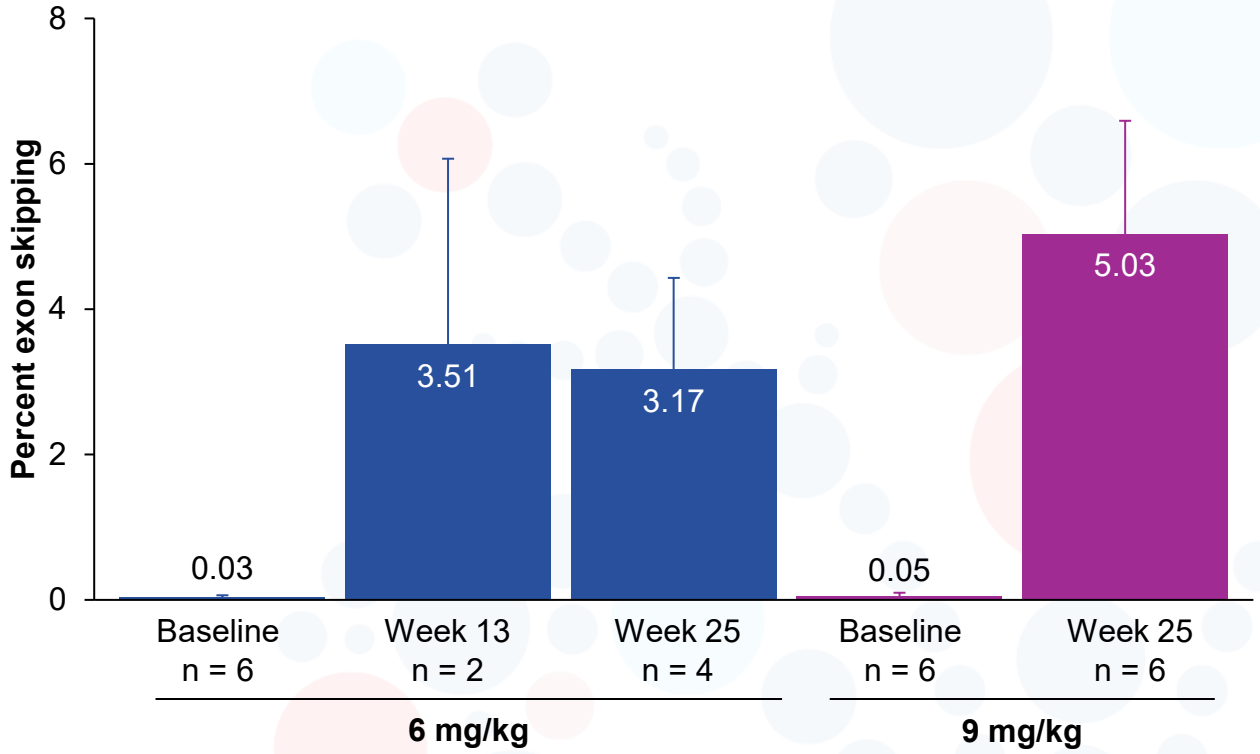
- There were 3 unrelated SAEs (grade 3 influenza, appendicitis, and viral gastroenteritis)
- No AEs caused permanent dose discontinuation

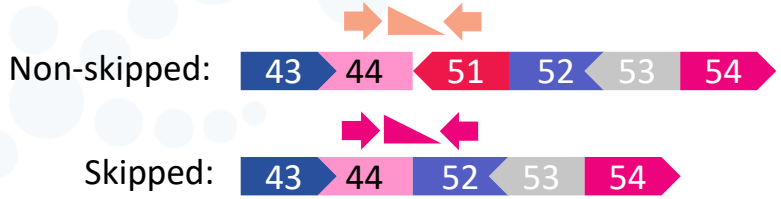
Most frequent AEs (≥25%) by preferred term

- Laboratory abnormalities
  - Cystatin C increased, 59%
  - GLDH increased, 29%
- Vomiting, 47%
- Cough, 41%
- Rhinorrhea, 35%
- Diarrhea, 35%
- Pyrexia, 29%

Data cutoff: 23 March 2026. After the data cutoff, 1 participant withdrew consent. AEs with onset during the SAD portion of the study were included for the 6 mg/kg QW cohort.
AE, adverse event; GLDH, glutamate dehydrogenase; QW, once weekly; SAD, single ascending dose; SAE, serious AE.

Nivudirsen demonstrated dose-dependent exon skipping in all participants

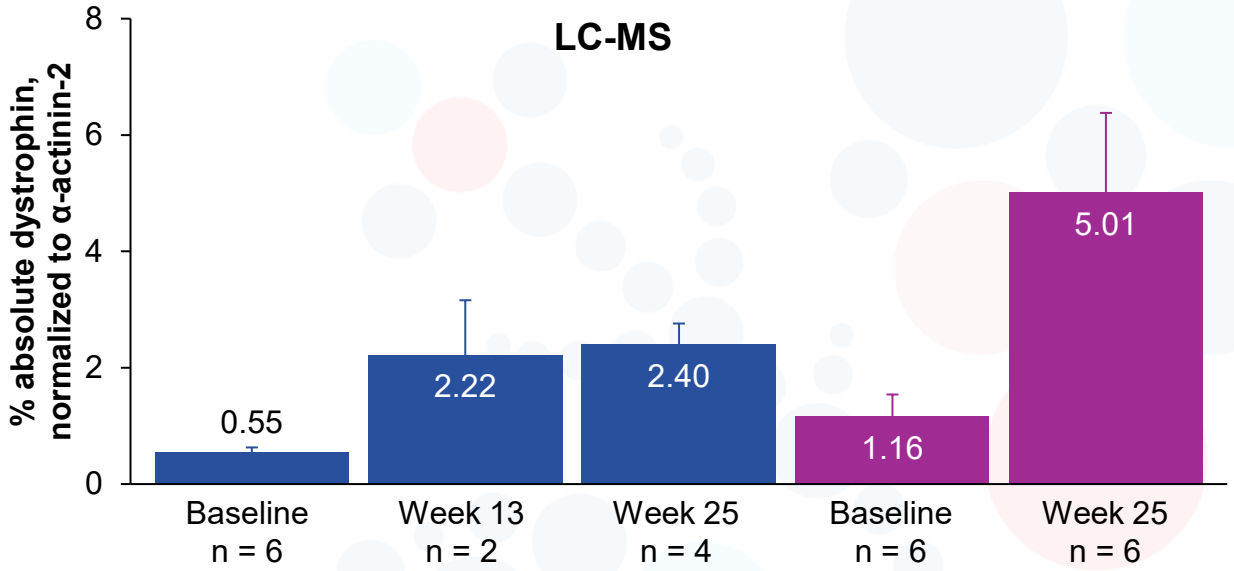


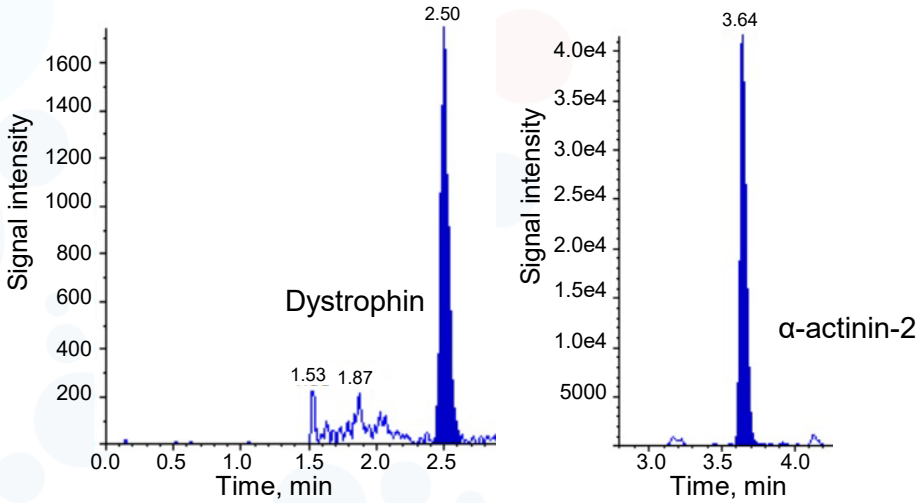


A skipped ddPCR product is only produced when exon 51 is skipped
(Exon sequence representative of a Del45–50 genotype)

Data cutoff: 8 December 2025. Results are presented as the mean ± SEM.
ddPCR, droplet digital PCR; Del, deletion; SEM, standard error of the mean.

Nivudirsen increased dystrophin expression in a dose-dependent manner as assessed by LC-MS



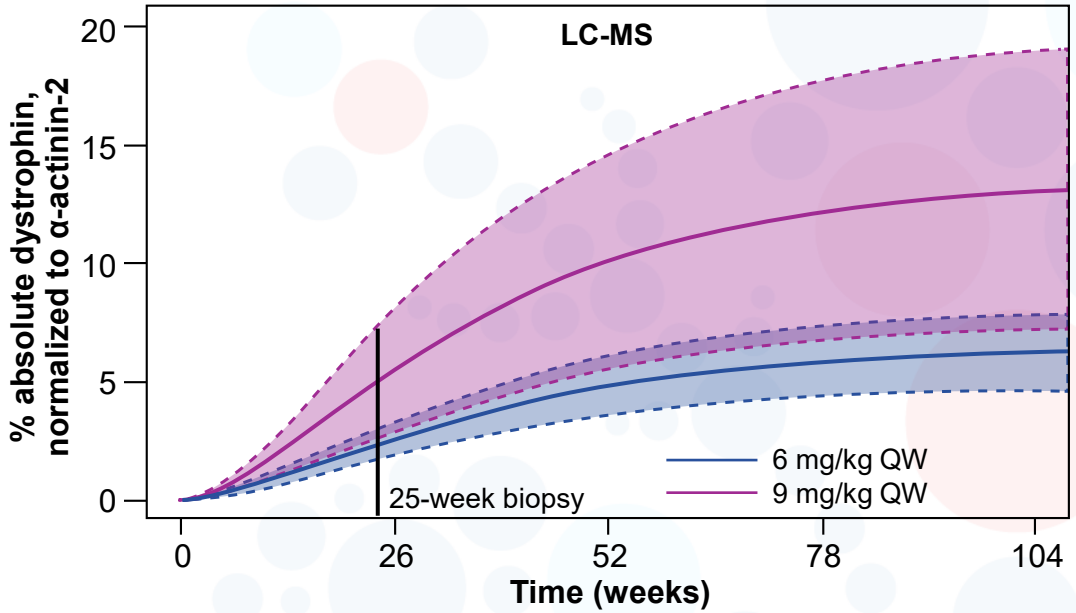


Example of an LC-MS chromatogram—a method offering absolute quantitation, sensitivity, precision, and reproducibility

Data cutoff: 8 December 2025. Results are presented as the mean ± SEM. [a]Western blot results reported as absolute dystrophin level (% normal muscle, myosin heavy chain normalized).
LC-MS, immunoaffinity ultra-performance liquid chromatography coupled with tandem mass spectrometry; SEM, standard error of the mean.

Nivudirsen PD models predict dose-dependent increases in dystrophin with accumulation toward steady state

PS-based ASOs will continue to accumulate in muscle tissue over time[1]

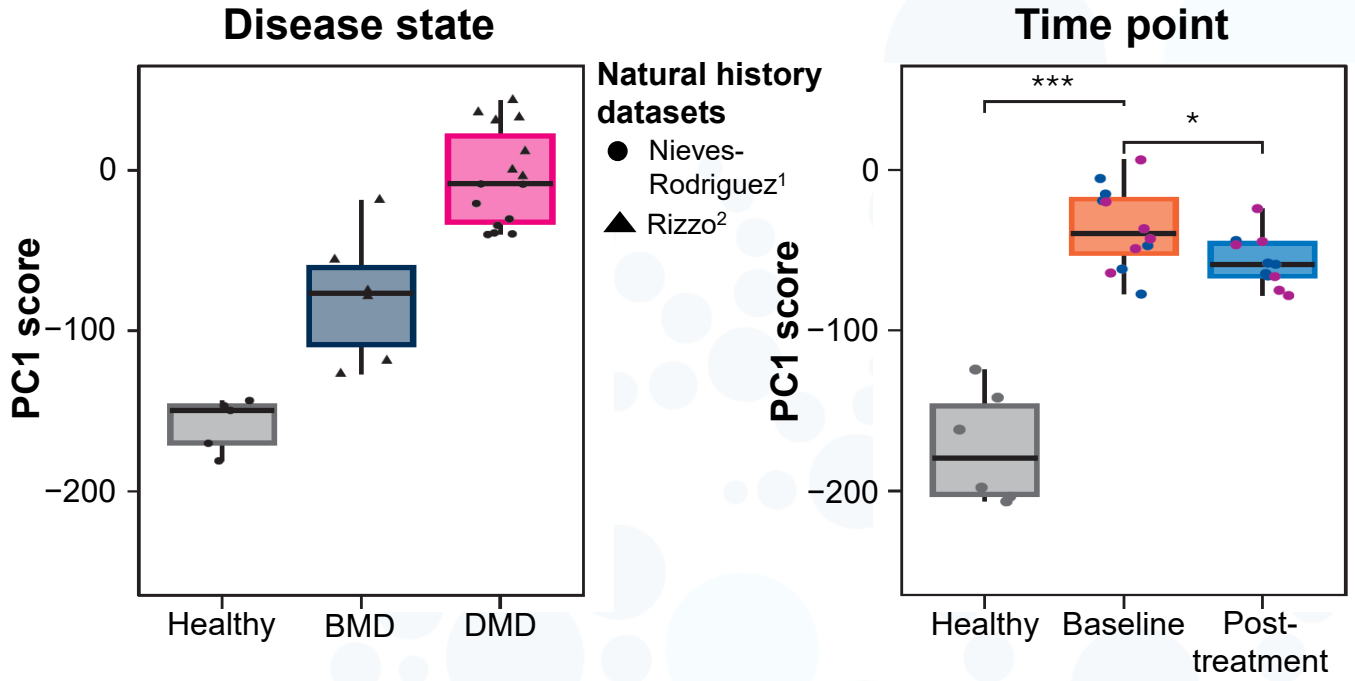


- The projected time course is governed by
  - PS-based ASO tissue half-life
  - Dystrophin protein turnover
- Projected dystrophin levels are within a range considered potentially therapeutically beneficial based on associations with milder Becker muscular dystrophy phenotypes[2]

Data cutoff: 8 December 2025. Solid lines represent mean dystrophin (% of normal) and dashed lines represent 90% CI. Simulations are informed by observed dystrophin data from the 6 and 9 mg/kg QW cohorts and rely on model-based assumptions that include structural PK parameters (apparent volume [V] and elimination rate constant [Ke]) and PD modeled using an indirect response with production rate (Kin), degradation rate (Kout), and half-maximal effective concentration; residual variability is incorporated via a proportional error model. The simulations are based on the best available data but do not account for all potential biological variables and should not be interpreted as a guarantee of clinical efficacy, safety, or actual patient outcomes.

1. Goemans N, et al. *Neuromuscul Disord*. 2018;28(1):4–15. 2. Beekman C, et al. *PLoS One*. 2018;13(4):e0195850. ASO, antisense oligonucleotide; CI, confidence interval; LC-MS, immunoaffinity ultra-performance liquid chromatography coupled with tandem mass spectrometry; PD, pharmacodynamic; PK, pharmacokinetic; PS, phosphorothioate; QW, once weekly.

Nivudirsen treatment shifted the muscle transcriptomic profile toward a healthier tissue profile



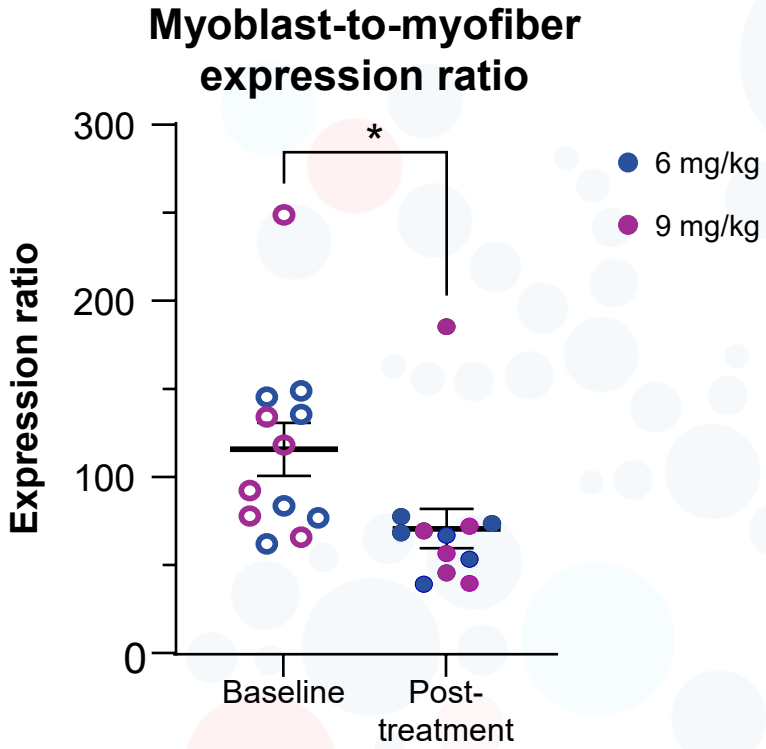
- RNAseq data from muscle biopsy samples were analyzed for genome-wide gene expression changes
- The PC1 score captures the most variance in the data and scales with severity of the muscular dystrophy phenotype
- Reduction in PC1 score suggests improvement in quality and composition

The time points of post-treatment biopsies were 13 or 25 weeks. Healthy denotes commercially sourced muscle samples. Differential gene expression analysis was performed with DESeq2, PCs were calculated with stats::prcomp() within the Rizzo 2025 dataset,[2] and the other datasets[1] were projected onto the PC analysis with stats::predict(). Boxplots comparing PC1 from each group were constructed with ggplot2, and 2-tailed Wilcoxon *P*-values were calculated with ggpubr; *** and * represent $P < 0.001$ and $P < 0.05$, respectively.

1. Nieves-Rodriguez S, et al. *Front Genet.* 2023;14:1216066. 2. Rizzo B, et al. *Int J Mol Sci.* 2025;26(14):6594.

BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; PC, principal component.

Muscle composition gene expression metric shifts toward healthy following treatment with nivudirsen

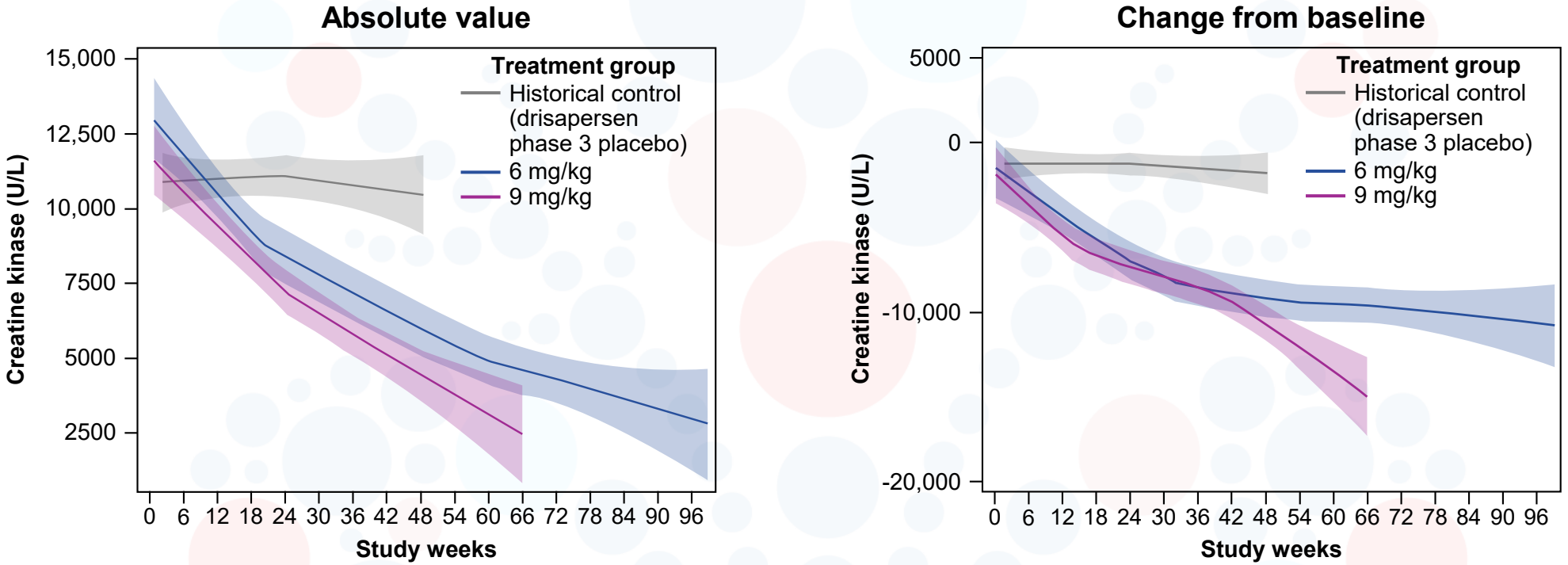


- Expression ratio is composed of multiple genes expressed primarily in
  - Myoblasts (immature, regenerating muscle cells)
  - Myofibers (mature, functional muscle cells)
- In DMD tissue, there is elevated expression from myoblasts and reduced expression from myofibers that contribute to an increase in this composite ratio relative to healthy muscle
- A decrease in the myoblast-to-myofiber expression ratio represents improved muscle cell repair and maturation during tissue remodeling

The time points of post-treatment biopsies were 13 or 25 weeks. Expression ratio is calculated with reference to healthy individual samples. Expression ratio statistical differences were determined using a paired t-test (*P <0.05). Error bars represent the standard error.
DMD, Duchenne muscular dystrophy.

Clinical biomarkers suggest there is decreased muscle damage following nivudirsen treatment compared to historical matched placebo

Similar trends were observed for lactate dehydrogenase

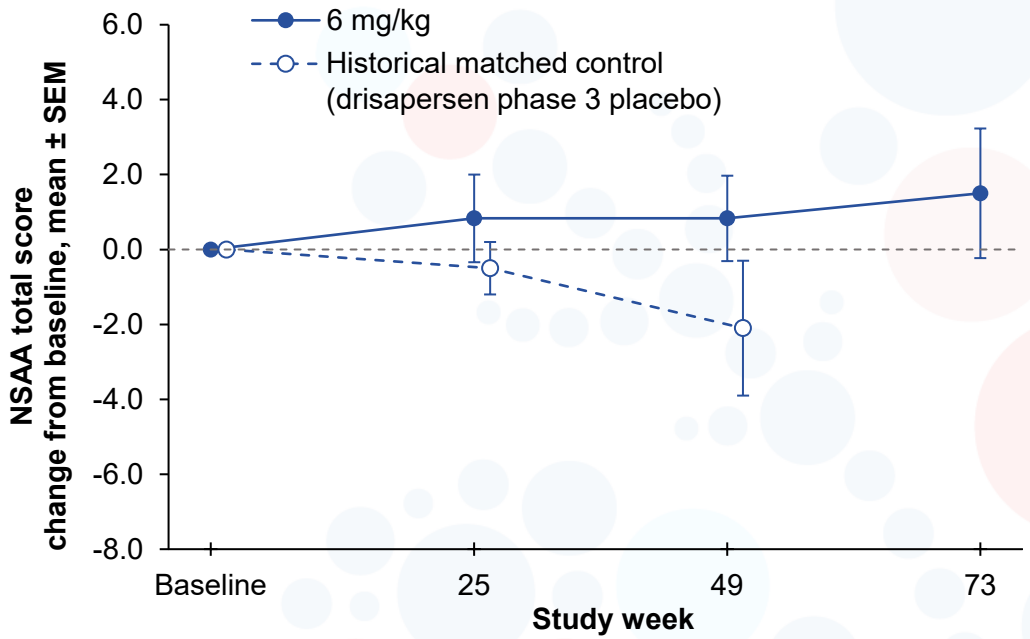


Historical controls plotted from participants in the placebo arm of the drisapersen phase 3 trial (NCT01254019; n = 61 participants; age range, 5–16 years).

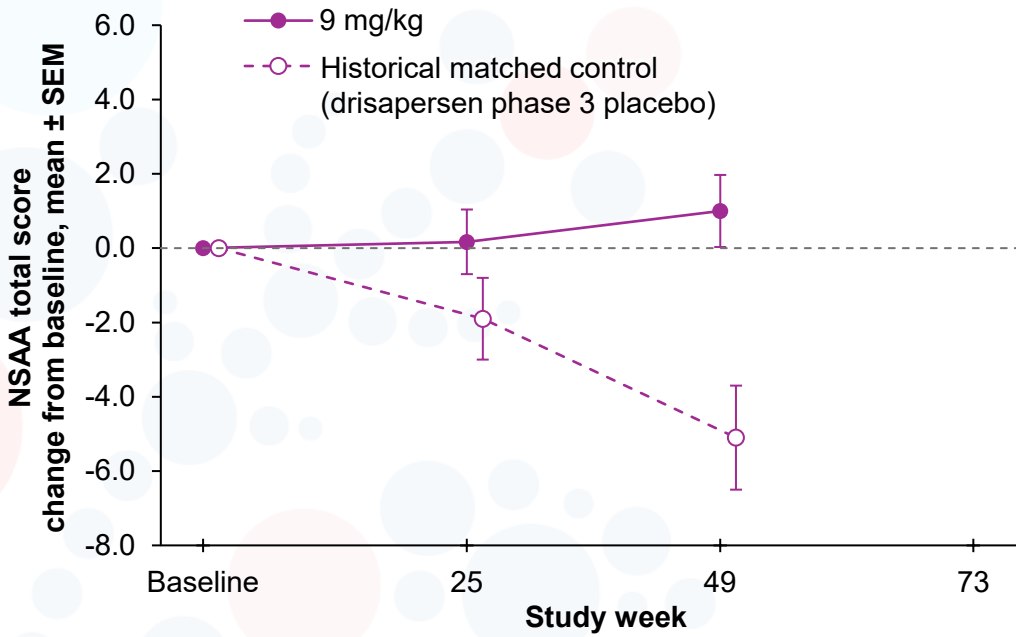
Data cutoff: 23 March 2026. Lines represent locally estimated scatterplot smoothing (LOESS) estimates, and shaded areas represent 95% point-wise confidence intervals.

Nivudirsen demonstrated potential benefits in functional domains compared to historical matched placebo

Nivudirsen 6 mg/kg prevented functional deterioration during 1.5 years of follow-up



Treated, n = 6	6	6	3
Matched control, n = 11	10	10	0



Treated, n = 6	6	5	
Matched control, n = 14	14	14	

Historical controls were participants in the placebo arm of the drisapersen phase 3 trial, and the placebo control data were matched based on participant age and baseline function.

Data cutoff: 23 March 2026. SV95C functional assessments will be presented at a later date.

NSAA, NorthStar Ambulatory Assessment; SEM, standard error of the mean; SV95C, Stride Velocity 95th Centile.

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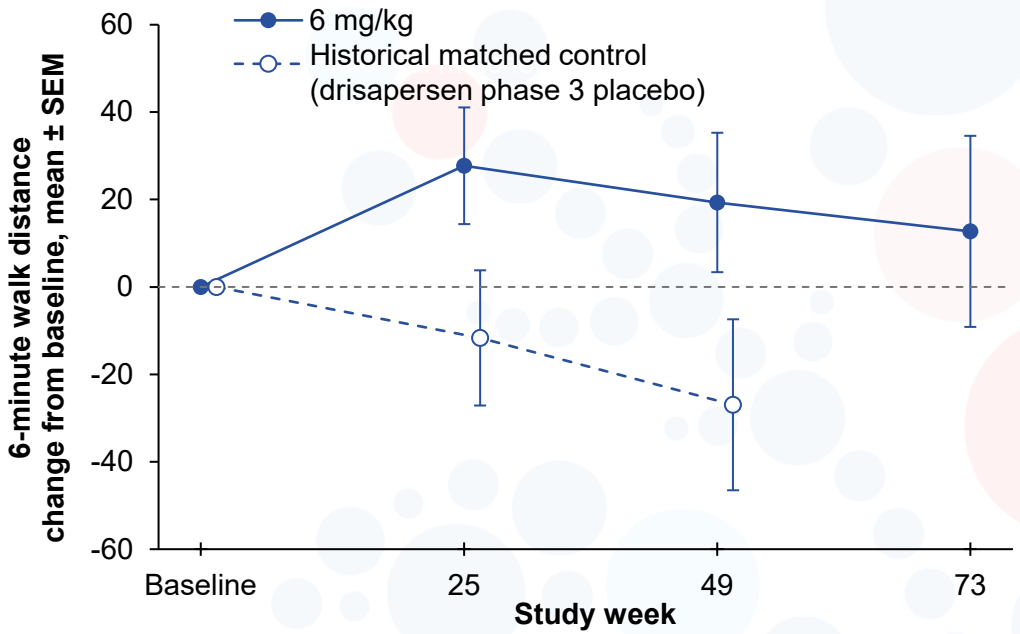
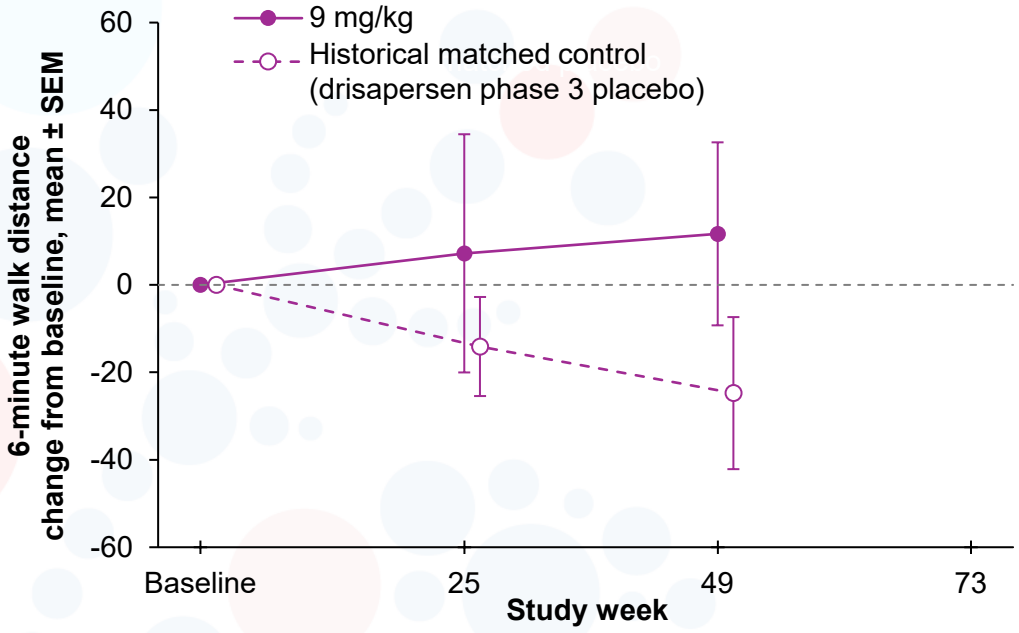


Treated, n =	6	6	6	6
Matched control, n =	14	14	14	0



Treated, n =	6	6	6
Matched control, n =	15	15	15

Historical controls were participants in the placebo arm of the drisapersen phase 3 trial, and the placebo control data were matched based on participant age and baseline function.

Data cutoff: 23 March 2026. SV95C functional assessments will be presented at a later date.

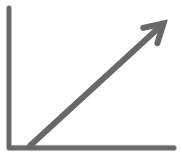
SEM, standard error of the mean; SV95C, Stride Velocity 95th Centile.

Summary

Most AEs with nivudirsen were generally mild, and no dose-limiting toxicities were observed, thereby enabling dose escalation to the 12-mg/kg dose

Interim analyses up to 25 weeks demonstrated positive dystrophin changes in boys with DMD receiving nivudirsen ≤9 mg/kg

Clinical biomarkers and transcriptomic profiles suggest improvement in overall muscle health, and exploratory outcomes across multiple functional endpoints suggest benefit that continues to accrue over time



PD modeling of 2'OMePS-based ASOs predict that dystrophin levels will continue to rise over time

AE, adverse event; ASO, antisense oligonucleotide; DMD, Duchenne muscular dystrophy; OMePS, *O*-methyl-phosphorothioate; PD, pharmacodynamic.

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Additional posters presented at ICNMD 2026

A transcriptomics-based biomarker for muscle quality measures nivudirsen (BMN 351) treatment response in DMD patient biopsies

Orthogonal methods demonstrate pharmacodynamic responses in Duchenne muscular dystrophy patients treated with nivudirsen (BMN 351)

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DMD, Duchenne muscular dystrophy.