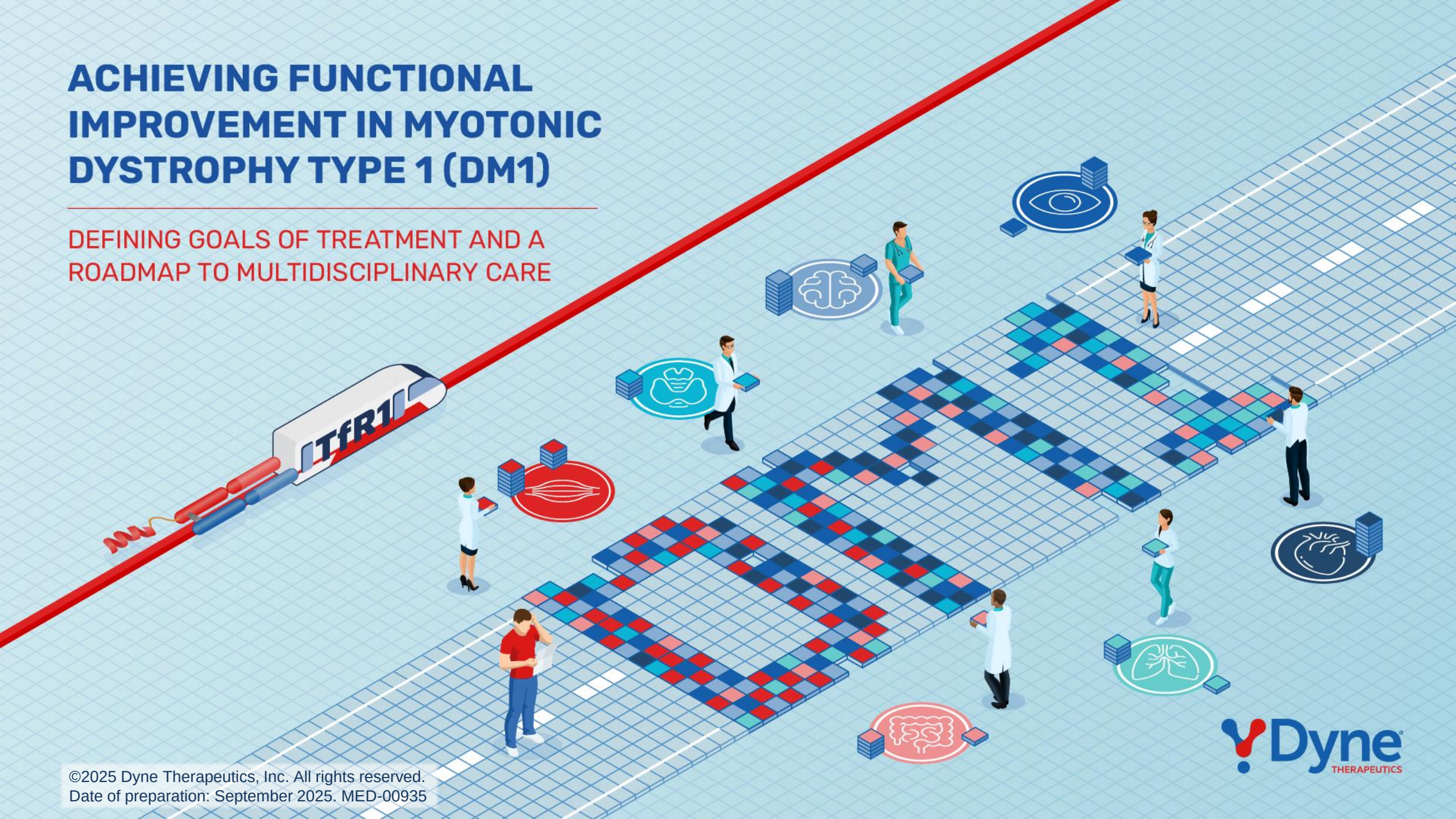
ACHIEVING FUNCTIONAL IMPROVEMENT IN MYOTONIC DYSTROPHY TYPE 1 (DM1)

DEFINING GOALS OF TREATMENT AND A ROADMAP TO MULTIDISCIPLINARY CARE



Date of preparation: September 2025. MED-00935

Forward-looking statements and disclaimer

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- The FORCE™ platform and zeleciment basivarsen (z-basivarsen, formerly known as DYNE-101) are investigational or otherwise in development and have not been approved as safe or effective by the US FDA, EMA, or any other regulatory authority
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Disclosures

Nicholas Johnson

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Monica Visone

- Nothing to declare

Lori Planco

- Participation in meetings for Alnylam Pharmaceuticals, Avidity Biosciences, and Dyne Therapeutics

Valeria Sansone

- Consultancy and participation in advisory boards for ARTHEx Biotech, Avidity Biosciences, Biogen, Dyne Therapeutics, Italfarmaco, Novartis, Roche, Sanofi, Scholar Rock, Solid Biosciences, and Vertex Pharmaceuticals

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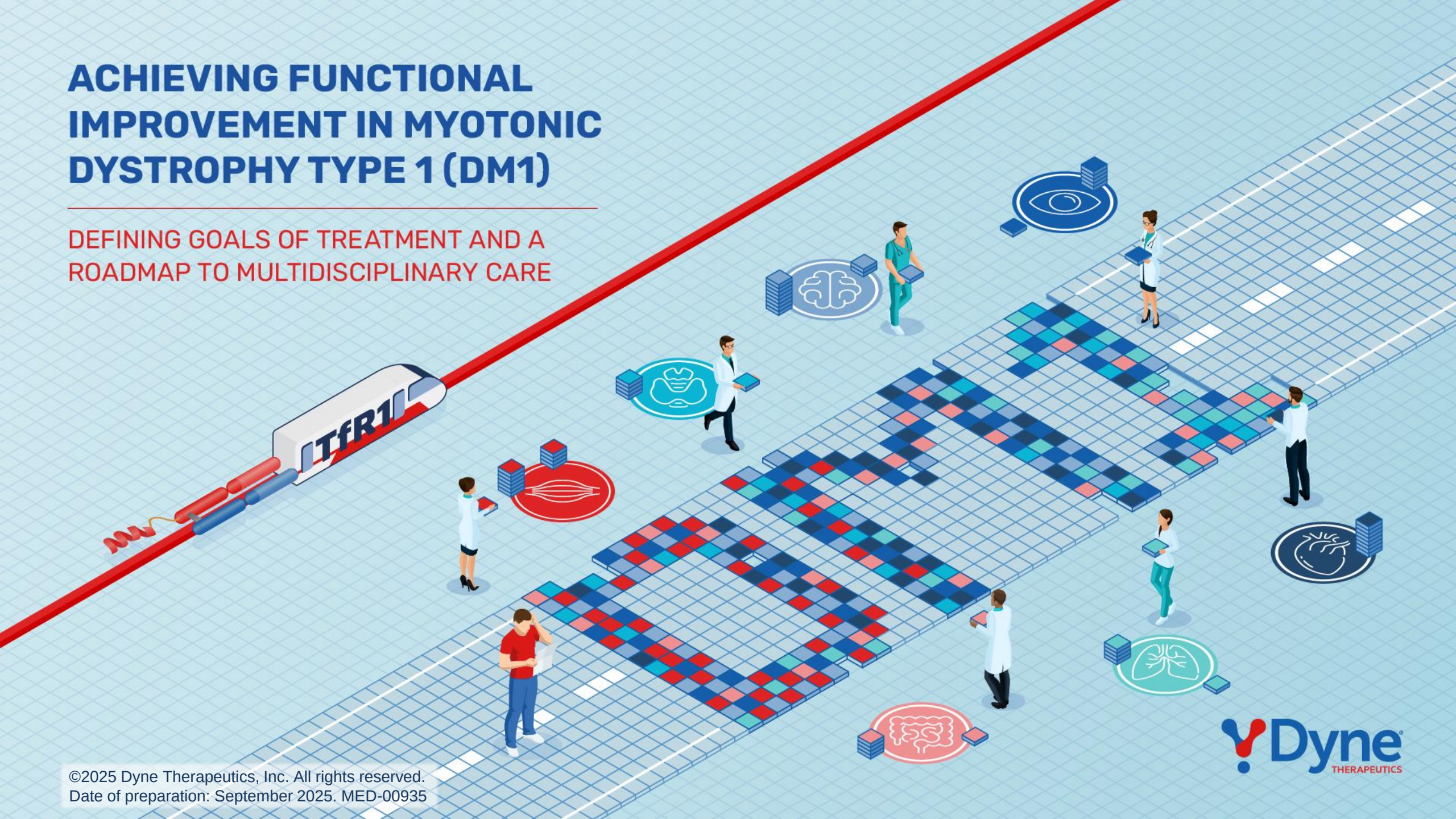


Date of preparation: September 2025. MED-00935

Today's faculty

Nicholas Johnson, MD, MSCI, FAAN (Chair)

Professor and Vice Chair of Research,
Director, Center for Inherited Myology Research (CIMR),
George Bliley Research Chair,
Virginia Commonwealth University

Lori Planco

DM1 community member,
Research Support Specialist,
The RNA Institute

Monica Visone

DM1 community member,
Attorney

Valeria Sansone, PhD, MD

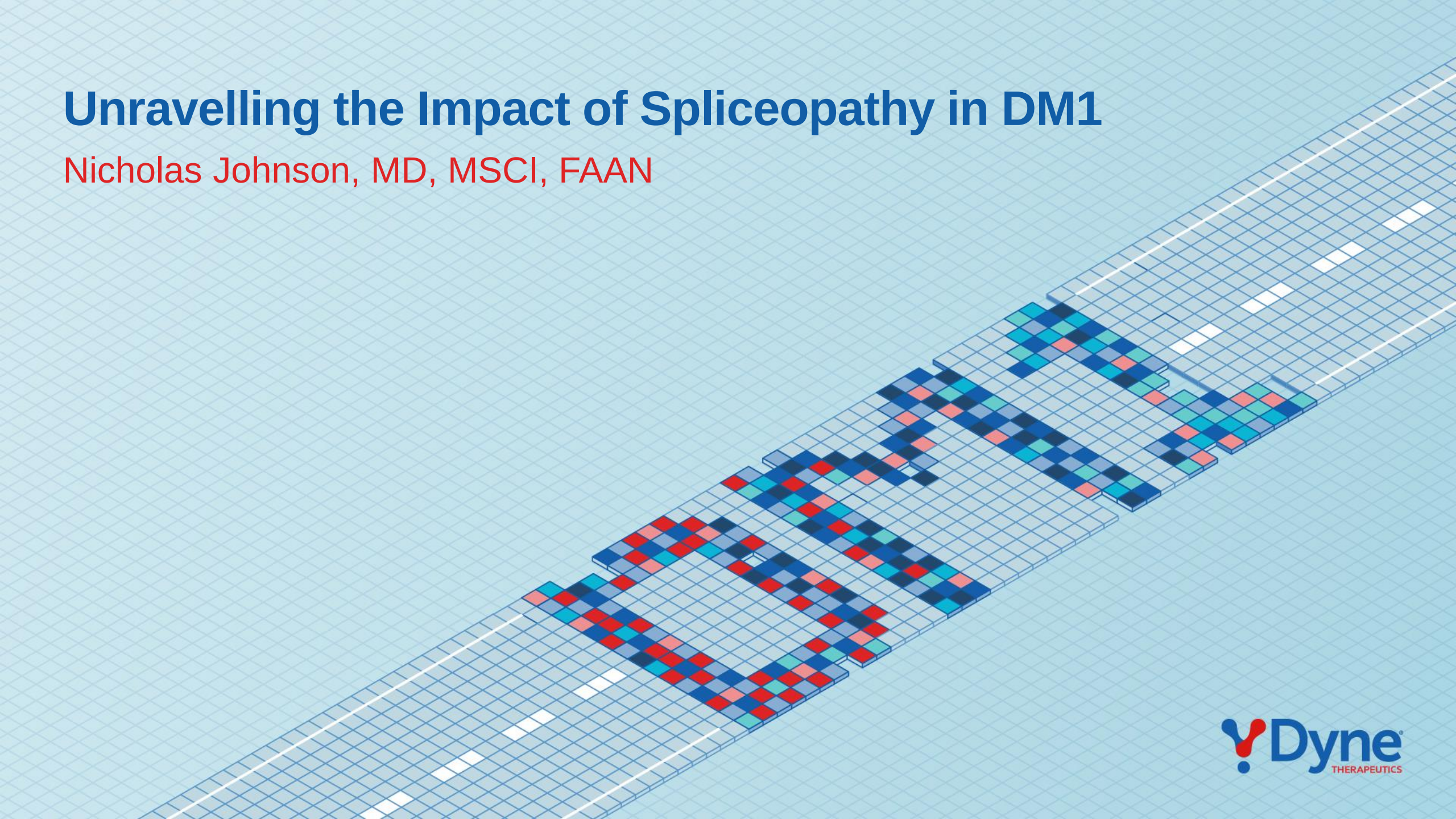
Full Professor of Neurology,
Neurorehabilitation Unit,
University of Milan,
Clinical & Scientific Director,
The NeMO Clinical Centre in Milan

Agenda

Session	Speaker
Unravelling the impact of spliceopathy in DM1	Nicholas Johnson
Fireside chat: What's the real impact of DM1?	All
Multidisciplinary management of DM1: are we getting it right?	Valeria Sansone
Addressing the multisystem manifestations of DM1 with DYNE-101 to deliver functional improvement	Valeria Sansone
Q&A and close	Nicholas Johnson

Unravelling the Impact of Spliceopathy in DM1

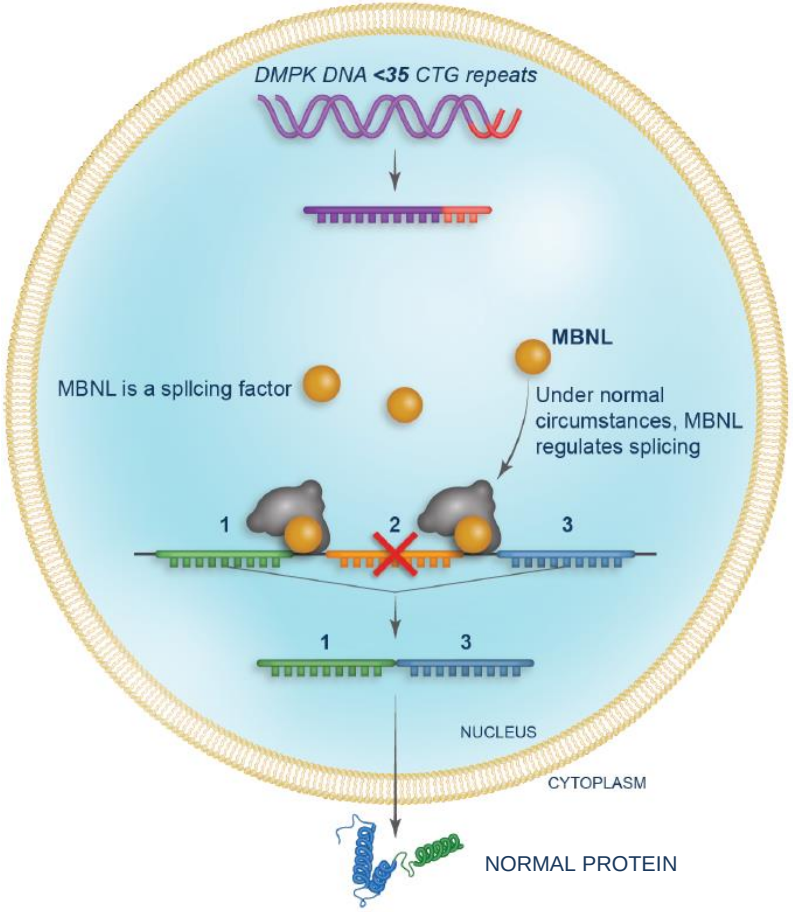
Nicholas Johnson, MD, MSCI, FAAN



Dyne THERAPEUTICS

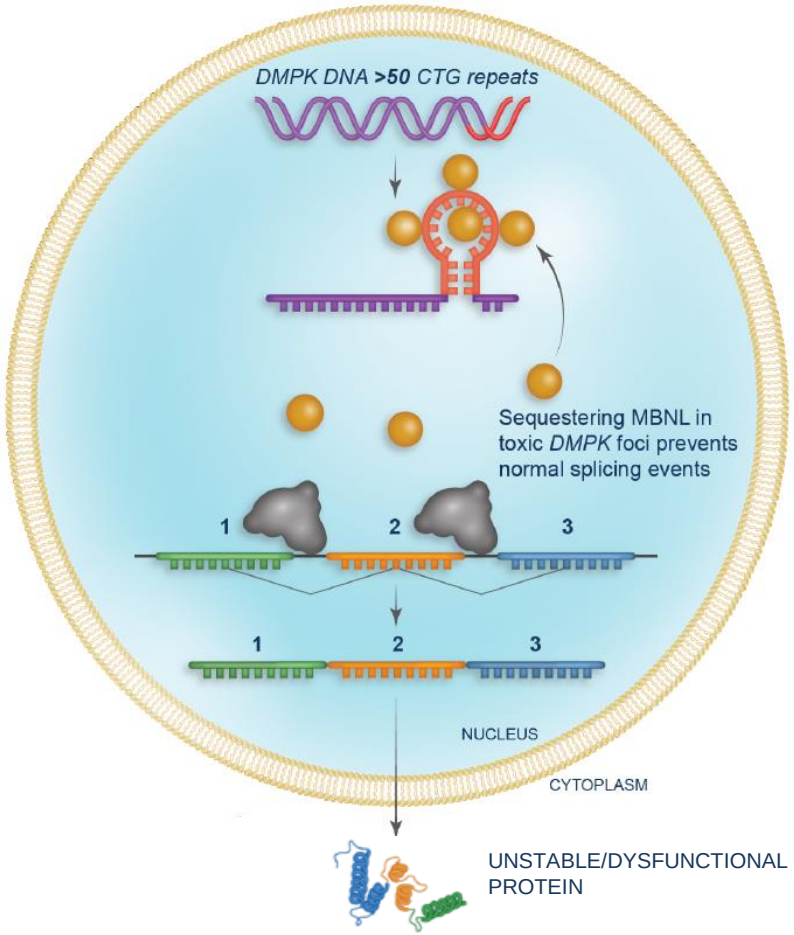
Myotonic Dystrophy Type 1 (DM1) is a Spliceopathy

Normal Splicing



Normal splicing leads to **appropriate protein synthesis**

DM1 Spliceopathy



Disrupted splicing **impairs** normal **protein synthesis**

CTG, cytosine, thymine, and guanine; *DMPK*, dystrophia myotonica protein kinase; MBNL, muscleblind-like.
Berglund JA, et al. *J Neuromuscul Dis.* 2025:22143602251365101.

Abnormal Splicing in Multiple Tissues Drives Multisystem Disease Manifestations

CNS[1–4]

- Fatigue
- Excessive daytime sleepiness
- Difficulty concentrating
- Behavioral/personality changes

Ocular[1–4]

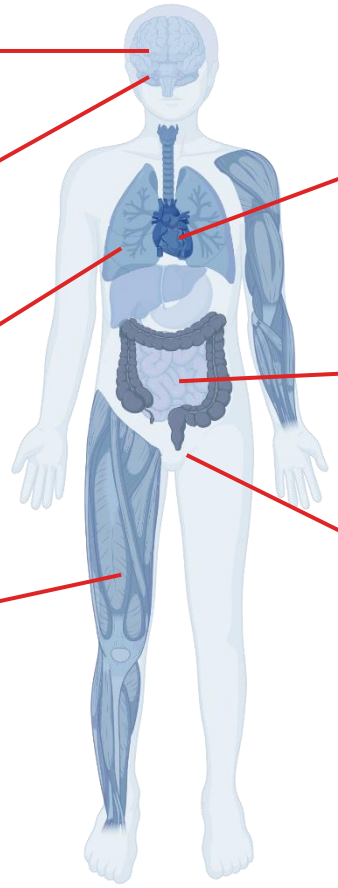
- Cataracts
- Ptosis

Skeletal muscle (respiratory)[1–4]

- Restrictive ventilatory pattern
- Shortness of breath

Skeletal muscle[1–4]

- Muscle weakness
- Myotonia
- Balance issues
- Muscle pain
- Atrophy



Cardiac[1–4]

- Conduction disturbances
- Arrythmia
- Cardiomyopathy
- Sudden cardiac death

Smooth muscle[1–4]

- Dysphagia
- Constipation
- Heartburn
- Regurgitation

Endocrine[1–4]

- Thyroid disorders
- Diabetes
- Male hypogonadism
- Vitamin D deficiency

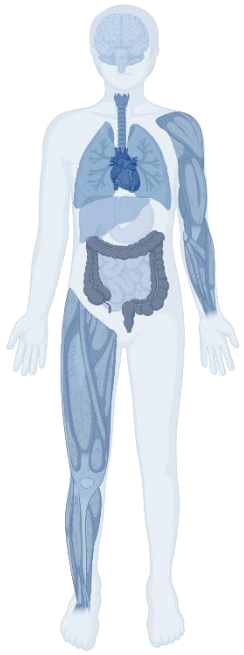
Slide does not represent an exhaustive list of symptoms.
CNS, central nervous system.
Image from BioRender.

1. Thornton CA. *Neurol Clin.* 2014;32(3):705–19; 2. Ho G, et al. *World J Clin Pediatr.* 2015;4(4):66–80; 3. Hagerman KA, et al. *Muscle Nerve.* 2019;59(4):457–64; 4. Gutierrez Gutierrez G, et al. *Neurologia (Engl Ed).* 2020;35(3):185–206.

Muscle Weakness, Fatigue, and Daytime Sleepiness Are the Most Prevalent and Impactful Symptoms Reported by Individuals With DM1

Top 10 Most Commonly Reported DM1 Symptoms and Their Impact*

Prevalence, %		Prevalence, %	
94	Muscle weakness (dystrophy)	Muscle aches (cramps)	79
93†	Fatigue	Difficulty swallowing (dysphagia)	73
93	Daytime sleepiness	Muscle pain	72
88†	Myotonia (difficulty relaxing muscles)	Constipation	68†
79	Balance issues	Droopy eyelids (ptosis)	66



Maximum impact — Minimum impact

Symptom Impact Scale

DM1, myotonic dystrophy type 1.
Image from BioRender.
*Respondents were from the United States and Canada. Statistics were controlled for age differences, and a Bonferroni correction for multiple comparisons was applied. Prevalence calculations were based on n=457. Impact score ranged from 0 to 4. †Significantly higher prevalence or impact of symptoms in females ($p<0.05$).
Hagerman KA, et al. *Muscle Nerve.* 2019;59(4):457–64.

Mis-splicing Has Been Directly Linked to Symptoms in DM1[1,2]

Splicing Correction	Symptom
↑ *CLCN1*[1–3]	↓ Myotonia[1–3]
↑ *BIN1, DMD* and others[3]	↓ Muscle weakness[3]
↑ *NMDAR1,* and others[3]	↓ CNS symptoms[3]
↑ *SCN5a*, and others[3]	↓ Cardiac arrhythmia[3]
↑ *INSR*, and others[3]	↓ Insulin resistance[3]
↑ ???[5]	↓ Gastrointestinal symptoms[5]

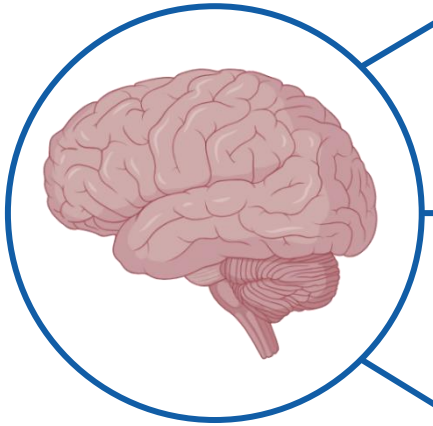
Splicing correction linked to myotonia improvement*[4]

*Myotonia improvement in HSA^{LR} mouse model.
HSA^{LR}, human skeletal actin long repeat.

1. Hartman JM, et al. *Ann Clin Transl Neurol.* 2024;11:3175–91; 2. Mankodi A, et al. *Mol Cell.* 2002;10(1):35–44;
3. López-Martínez A, et al. *Genes (Basel)*. 2020;11(9):1109; 4. Wheeler TM, et al. J Clin Invest. 2007;117(12):3952–7;
5. Peterson JAM, Cooper TA. *Int J Mol Sci.* 2022;23(23):14779.

Mis-splicing in the Brain Contributes to Cognitive and Neurodegenerative Pathology in DM1[1]

Mis-splicing in transcripts in brain tissue of individuals with DM1 has implications for disease pathology:[1,2]



- ***MAPT***[1,2] — Tautopathy-like degeneration of brain tissue
- ***NMDAR1***[1,2] — Memory impairment
- ***GRIP1***[2] — Implicated in synaptic trafficking

Congenital or childhood-onset DM1

Generally associated with prominent CNS symptoms, including:[3,4]

- Intellectual impairment
- Fatigue
- Learning difficulties
- Excessive daytime sleepiness

Adult-onset DM1

Associated with multiple CNS manifestations, including:[3,5]

- Excessive daytime sleepiness
- Fatigue
- Cognitive impairment

CNS, central nervous system; DM1, myotonic dystrophy type 1.
Image from BioRender.

1. López-Martínez A, et al. *Genes (Basel).* 2020;11(9):1109; 2. Berglund AJ, et al. J Neuromuscul Dis. 2025:22143602251365101; 3. Hagerman KA, et al. *Muscle Nerve*. 2019;59(4):457–64; 4. Ho G, et al. *World J Clin Pediatr*. 2015;4(4):66–80; 5. De Antonio M, et al. *Rev Neurol (Paris)*. 2016;172(10):572–80.

DM1 Presents With Varying Disease Phenotypes Based on Age at Symptom Onset

Congenital[1–3]
(<1 month)

- Hypotonia
- Respiratory distress
- Cognitive defects
- Motor and developmental delays
- Feeding difficulties

Childhood-onset[1–3]
(1 month–18 years)

- Facial weakness
- Cognitive defects
- Psychosocial issues
- Incontinence
- Muscle weakness

Adult-onset[1–3]
(18–40 years)

- Myotonia
- Muscle weakness
- Cognitive defects
- Cataracts
- Conduction defects
- Insulin resistance
- Respiratory failure

Late-onset adult[1–3]
(40+ years)

- Mild myotonia
- Cataracts
- Cardiac defects

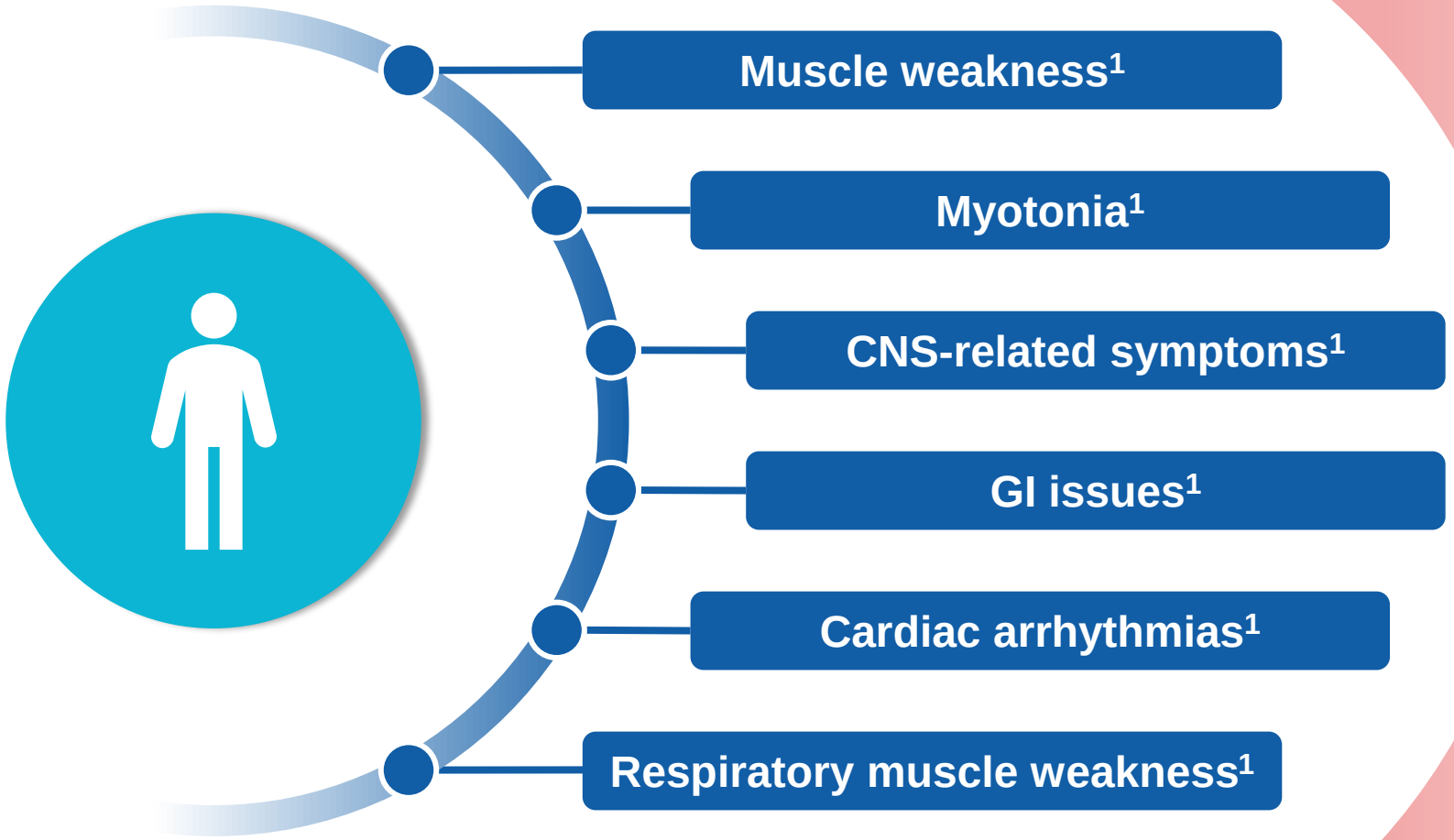
DM1, myotonic dystrophy type 1.
There is currently no standard on the classifications of DM1. Slide does not represent an exhaustive list of symptoms.
1. De Antonio M, et al. *Rev Neurol (Paris)*. 2016;172(10):572–80; 2. Ho G, et al. *World J Clin Pediatr*. 2015;4(4):66–80; 3. Professor Johnson; Personal communication.

Multidisciplinary Management of DM1: Are We Getting It Right?

Valeria Sansone, PhD, MD

Dyne THERAPEUTICS

Management of DM1 Should Address the Range of Symptoms That Impact the Daily Lives of Individuals Living with the Disease



Management goals[2,3]

Management by a **multidisciplinary team** to support multisystem involvement and reduce the risk of complications

Therapeutic approaches that address the totality of symptoms

Slide does not represent an exhaustive list of symptoms.
CNS, central nervous system; DM1, myotonic dystrophy type 1; GI, gastrointestinal.
1. Hagerman KA, et al. *Muscle Nerve.* 2019;59(4):457–64; 2. Gutierrez Gutierrez G, et al. *Neurologia (Engl Ed)*. 2020;35:185–206;
3. Ho G, et al. *World J Clin Pediatr*. 2015;4(4):66–80.

The NeMO Model: Multidisciplinary, Holistic Care That Addresses the Needs and Priorities of Individuals with DM1

CENTRO CLINICO Nemo

A reference network for the diagnosis, treatment, and research of NMD

Structured outpatient clinics

- Mobility/ independence
- Nutrition/ swallowing
- Orthosis/ independence

Cross-specialty assessments

- Cardiac
- Blood
- Psychologic and neuropsychologic

DM1, myotonic dystrophy type 1; NMD, neuromuscular disease.
Professor Sansone; Personal communication.

The NeMO Model in Practice: Meet the Patient

Gender: Female

Age: 45 years

Occupation: School teacher

History:

- Diagnosed with DM1 at 20 years of age
  - 530 CTG repeats
  - Paternally transmitted
  - First symptom: hand myotonia
- Lost her job because of the disease
- Using a wheelchair due to foot fracture after a fall

Present day:

- Very depressed
- Feeling more fatigued
- Weight constantly increasing, despite episodes of choking

DM1, myotonic dystrophy type 1; CTG, cytosine, thymine, guanine.
Professor Sansone; Personal communication.

The NeMO Model in Practice: The Patient's Care Needs Are Assessed in the Mobility/Independence Outpatient Clinic

Gender: Female

Age: 45 years

Occupation: School teacher

Care needs:

- **Neurologist + PT:** due to loss of ability to stand and walk unaided
- **Pulmonologist + respiratory PT:** for assessment of pulmonary function and potential need for a ventilator
- **Psychologist:** as additional mental health support is required
- **Nutritionist:** to investigate the disconnect between choking and increased weight

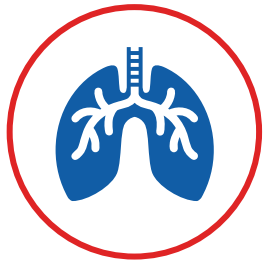
INPATIENT STAY PLANNED

PT, physical therapist.
Professor Sansone; Personal communication.

The NeMO Model in Practice: The Multidisciplinary Care Team Manages The Patient's Symptoms During Her Inpatient Stay

Neurologists, physiatrist, and PTs

- Motor rehabilitation program to regain walking ability initiated



Pulmonologists and respiratory PTs

- Ventilatory parameters assessed to see if patient meets criteria for NIV
  - Improvement of nocturnal saturimetry and reduced clusters observed
  - Ventilatory parameters were not quite right
- CT scan of thorax showed food in the esophagus
- Qualitative sleep assessment undertaken, using PROs

Psychology team and neuropsychologists

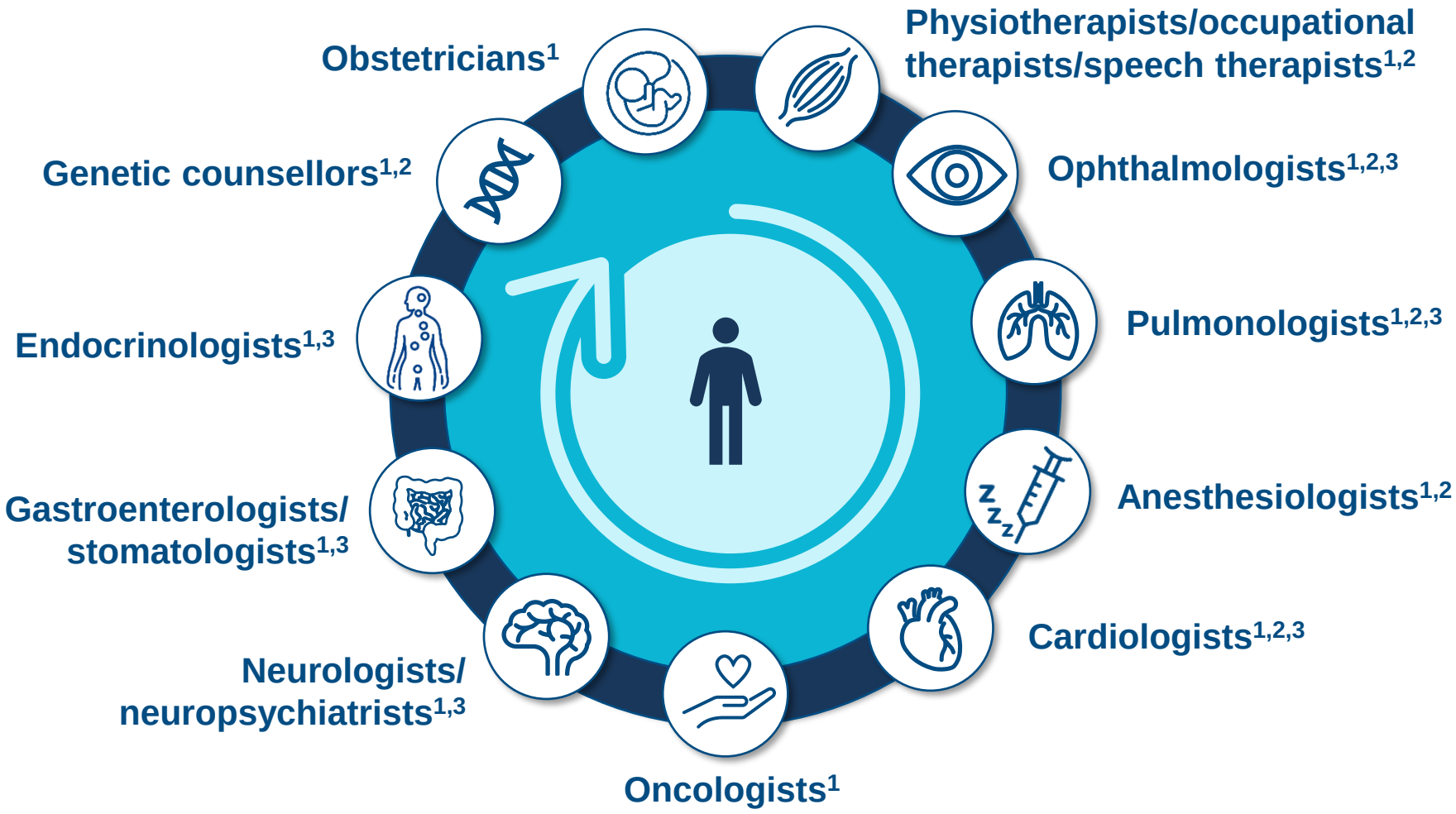
- Interviews to address depression
- Medication discussed with neurologists
- Battery of NPS tests completed
- Brain MRI showed multiple white matter hyperintense lesions, but NPS tests were within normal range

Nutritionist, speech therapist, and ENT

- FEES showed achalasia
- Overweight: diet consistencies and postural modifications

CT, computed tomography; ENT, ear, nose, and throat; FEES, fiberoptic endoscopic evaluation of swallowing; MRI, magnetic resonance imaging; NIV, non-invasive ventilation; NPS, neuropsychologic; PRO, patient-reported outcome; PT, physical therapist. Professor Sansone; Personal communication.

The Goal of Current DM1 Management is Symptom Relief But There is a Need for Treatment That Addresses the Totality of Symptoms



DM1, myotonic dystrophy type 1.

1. Gutiérrez Gutiérrez G, et al. *Med Clin (Barc).* 2020;153(2):82.e1-82.e17; 2. Ashizawa T, et al. *Neurol Clin Pract*. 2018;8:507–20; 3. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022.

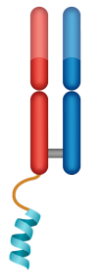
Addressing the Multisystem Manifestations of DM1 with DYNE-101 to Deliver Functional Improvement

Valeria Sansone, PhD, MD

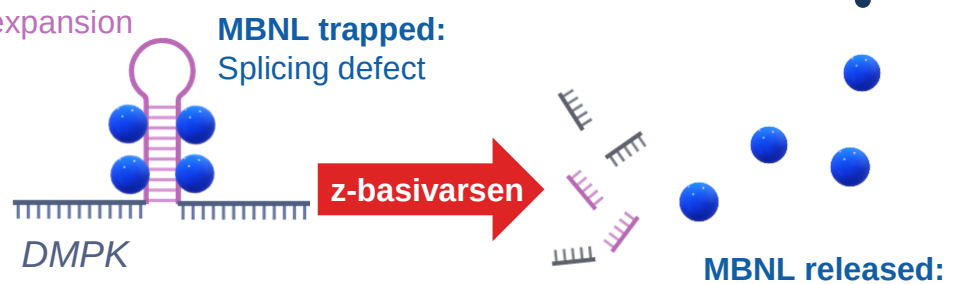
Dyne THERAPEUTICS

zeleciment basivarsen (z-basivarsen, Formerly Known as DYNE-101) Addresses the Central Pathobiology of DM1 to Enable Broad Functional Improvement

Robust and widespread delivery → ***DMPK* degradation in the nucleus** → **MBNL release and splicing correction** → **Early clinical effect** → **Broad functional improvement**



z-basivarsen
ASO conjugated to Fab targeting TfR1



Differentiated MOA

Myotonia:
Video Hand Opening Time (vHOT)

Muscle strength:
Quantitative Muscle Testing

Functional assessments:
10-Meter Walk/Run;
5 Times Sit-to-Stand

Patient-reported outcomes:
Myotonic Dystrophy Health Index (MDHI)

z-basivarsen is an investigational medicine being evaluated in the ongoing ACHIEVE trial and has not received approval by the FDA, EMA, or any other regulatory authorities.
Image depicts the intended z-basivarsen mechanism of action.
ASO, antisense oligonucleotide; DM1, myotonic dystrophy type 1; *DMPK*, dystrophia myotonica protein kinase; Fab, antigen-binding fragment; MBNL, muscleblind-like; MOA, mechanism of action; TfR1, transferrin receptor 1.
1. Lilleker J, et al. Oral presentation at the MDA Clinical and Scientific Conference, Dallas, TX, USA, March 16–19, 2025. Oral O44; 2. Sansone V, et al. Poster presentation at the Annual International Congress of the WMS, Vienna, Austria, October 7–11, 2025. Poster 380P.

The Safety and Efficacy of z-basivarsen are Being Investigated in the Phase 1/2 ACHIEVE Trial: MAD Portion Overview

ACHIEVE

Population[1,2]

- Adult patients living with DM1
- Ages 18 to 49 years

Primary Endpoints[1,2]

- Safety and tolerability

Key Secondary Endpoints[1,2]

- Pharmacokinetics
- Change from baseline of:
  - Splicing
  - *DMPK* RNA expression
  - Multiple assessments of muscle strength and function
  - Patient-reported outcomes, including MDHI

Stages of ACHIEVE[1,2]

- ✓ Multiple ascending dose (MAD): 24 weeks
- Open-label extension (OLE): 24 weeks
- Long-term extension (LTE): 96 weeks

Data from the MAD portion of the study used to select the registrational dose and dose regimen[1,2]

z-basivarsen is an investigational medicine being evaluated in the ongoing ACHIEVE trial and has not received approval by the FDA, EMA, or any other regulatory authorities.

DM1, myotonic dystrophy type 1; *DMPK*, dystrophia myotonica protein kinase; MDHI, myotonic dystrophy health index.

Additional endpoints include select secondary and exploratory endpoints.

1. Lilleker J, et al. Oral presentation at the MDA Clinical and Scientific Conference, Dallas, TX, USA, March 16–19, 2025. Oral O44; 2. Sansone V, et al. Poster presentation at the Annual International Congress of the WMS, Vienna, Austria, October 7–11, 2025. Poster 380P.

z-basivarsen Showed a Favorable Safety Profile[a] with No Serious Related TEAEs

Summary of Treatment Emergent Adverse Events (TEAEs)[a]

TEAE Category	Participants with ≥1 TEAE – n (%)					
	1.8 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q8W N=8	5.4 mg/kg Q8W N=8	6.8 mg/kg Q8W N=8	Overall (N=56)
Any TEAE	16 (100)	16 (100)	8 (100)	8 (100)	8 (100)	56 (100)
Any related TEAE	9 (56)	10 (63)	3 (38)	6 (75)	6 (75)	34 (61)
Any serious TEAE	4 (25)	0	1 (13)	0	0	5 (9)
Any serious related TEAE	0	0	0	0	0	0
Any TEAE leading to withdrawal from study	0	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0

Most TEAEs Were Mild or Moderate in Intensity[a]

- 6 serious TEAEs unrelated to study drug
  - Atrioventricular block first degree (1)[b]
  - Pneumonia (2 events in same participant)
  - Pulmonary embolism (1)[c]
  - Hyponatremia (1)
  - Influenza (1)
- Most common TEAEs (≥20% participant incidence)[d]
  - Nasopharyngitis (41%)
  - Procedural pain (34%)
  - Influenza (30%)
  - Infusion-related reaction (29%)
  - Headache (27%)
  - Diarrhea (23%)

Additional Safety Data

- Liver enzyme elevations have been observed in a minority of participants
  - No impact on liver function (bilirubin or coagulation)
  - Interpretation is complicated by underlying disease and elevated baseline values up to ~2.5x greater than the upper limit of normal
- No participants have demonstrated persistent related anemia or thrombocytopenia

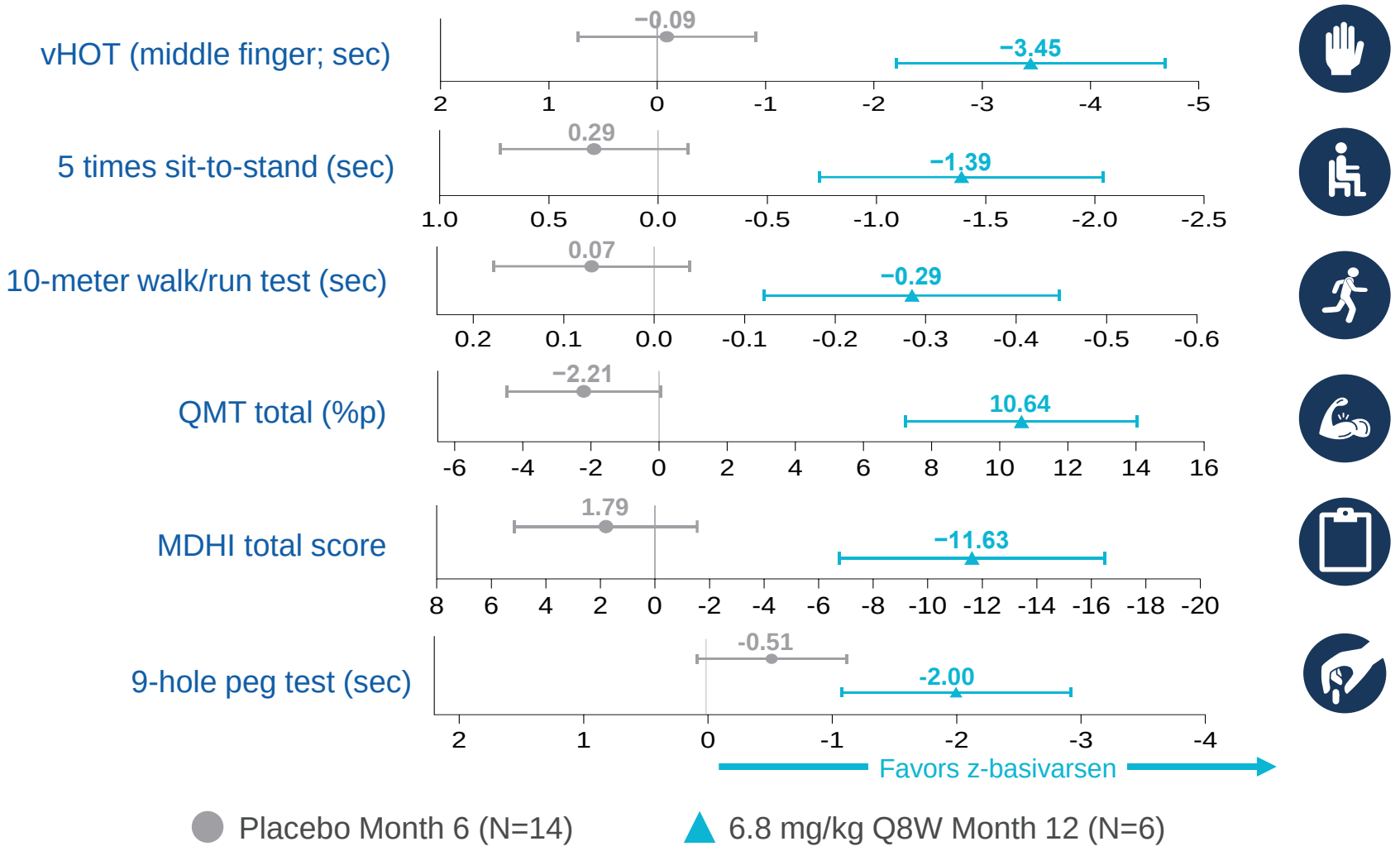
~1000 doses of study drug administered to date representing 93 patient-years of follow-up[1]

z-basivarsen is an investigational medicine being evaluated in the ongoing ACHIEVE trial and has not received approval by the FDA, EMA, or any other regulatory authorities.

TEAE, treatment-emergent adverse event; Q4W, every 4 weeks dosing; Q8W, every 8 weeks dosing; Rec, recovery. [a]Data as of April 23, 2025; [b]Transient worsening of atrioventricular (AV) block in a participant with ongoing medical history of first-degree AV block; [c]Attributed to risk factors for pulmonary embolism; [d]All cohorts combined; preferred terms are reported.

Sansone V, et al. Poster presentation at the Annual International Congress of the WMS, Vienna, Austria, October 7–11, 2025. Poster 380P.

z-basivarsen Led to Functional Improvement Across Several Clinical Measures



z-basivarsen is an investigational medicine being evaluated in the ongoing ACHIEVE trial and has not received approval by the FDA, EMA, or any other regulatory authorities.

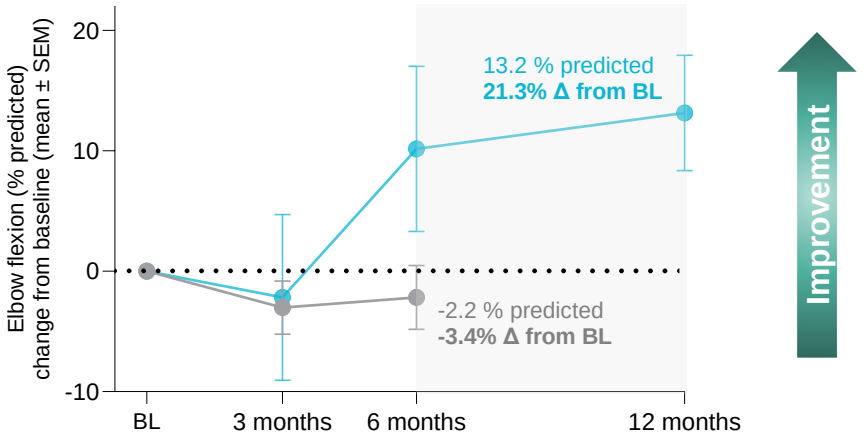
MDHI, myotonic dystrophy health index; Q8W, every 8 weeks dosing; QMT quantitative muscle testing; SEM, standard error of the mean; vHOT, video hand opening time.

Mixed model for repeated measures (MMRM) fixed effects: dose, visit, baseline, dose by visit interaction, baseline by visit interaction. All dose groups except recovery group; excluding placebo data after 6 months; Data presented are least squares (LS) mean change from baseline ± SEM; 6 months = 169 days, 12 months = 337 days.

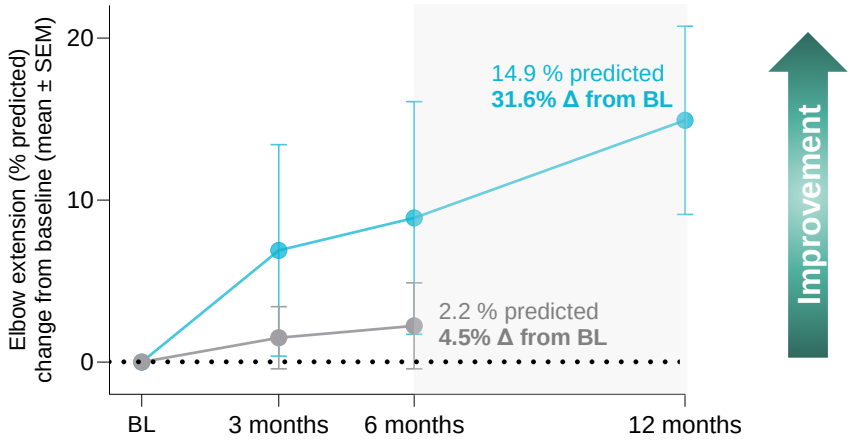
Sansone V, et al. Poster presentation at the Annual International Congress of the WMS, Vienna, Austria, October 7–11, 2025. Poster 380P.

Improvement in Strength in Proximal and Distal Muscles of the Upper Body Were Supported by Patient-Reported Improvement in Upper Extremity Function

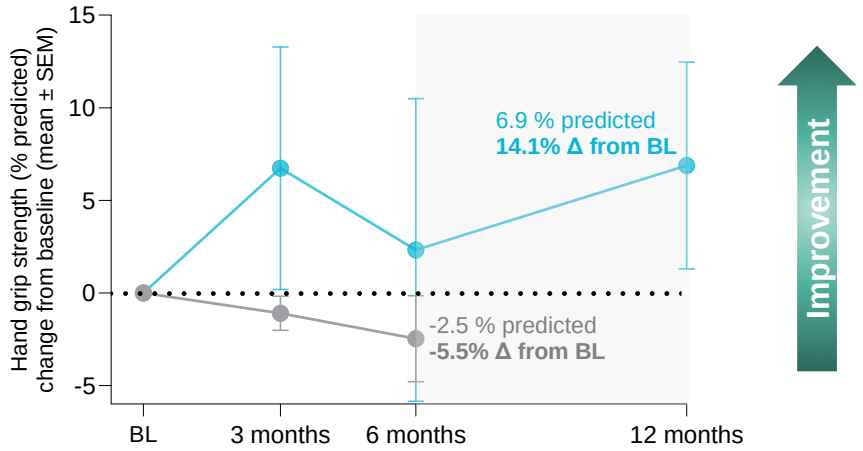
QMT Elbow Flexion



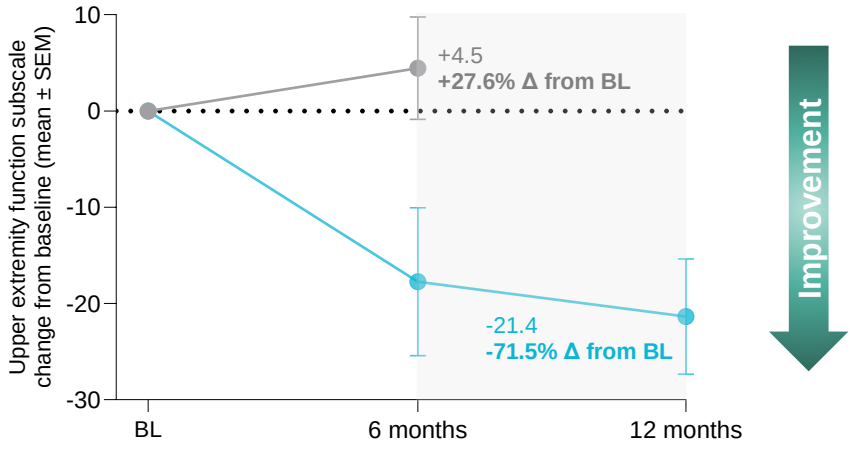
QMT Elbow Extension



QMT Hand Grip Strength



MDHI Upper Extremity Function Subscale



Placebo (N=14) 6.8 mg/kg Q8W (N=6)

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BL, baseline; MDHI, myotonic dystrophy health index; Q8W, every 8 weeks dosing; QMT, quantitative muscle testing; SEM, standard error of the mean. 3 months = 85 days; 6 months = 169 days; 12 months = 337 days.

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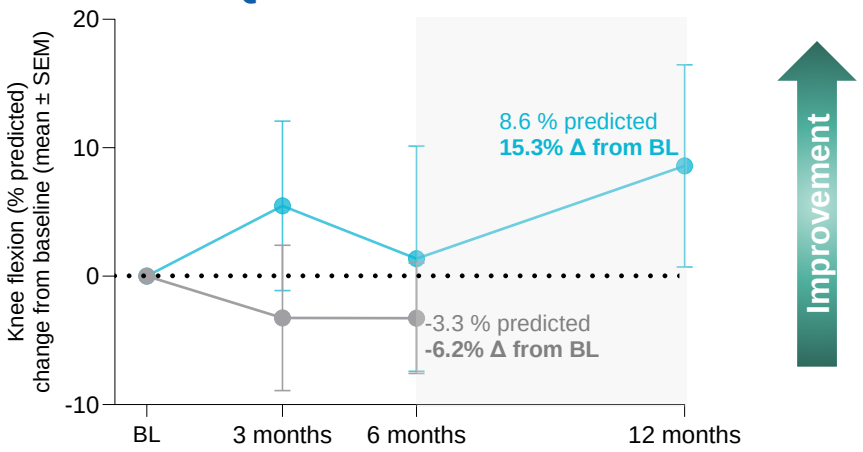
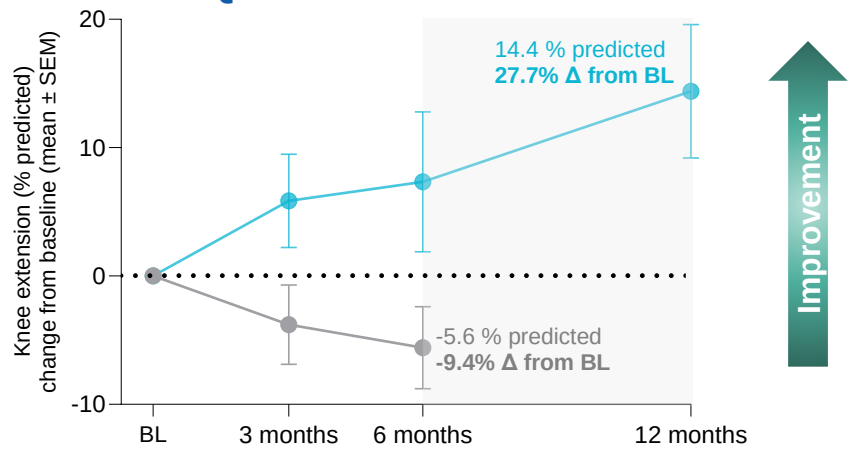
Strength Improvement Was Also Noted In Proximal and Distal Muscles of the Lower Body Through 12 Months

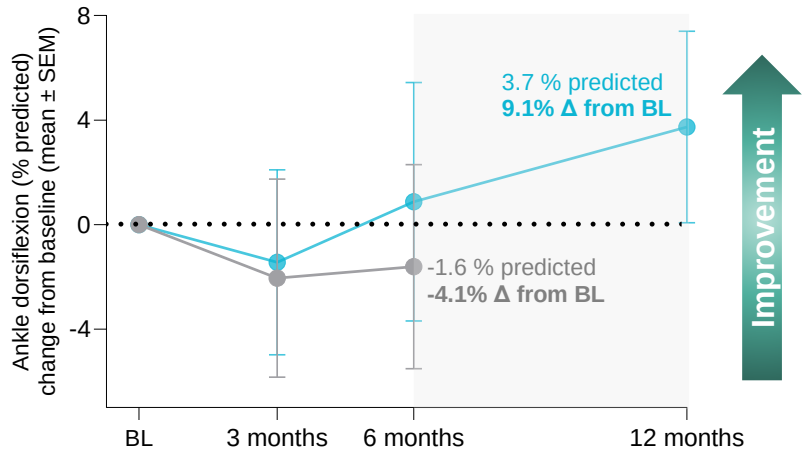
QMT Knee Flexion



QMT Knee Extension



QMT Ankle Dorsiflexion



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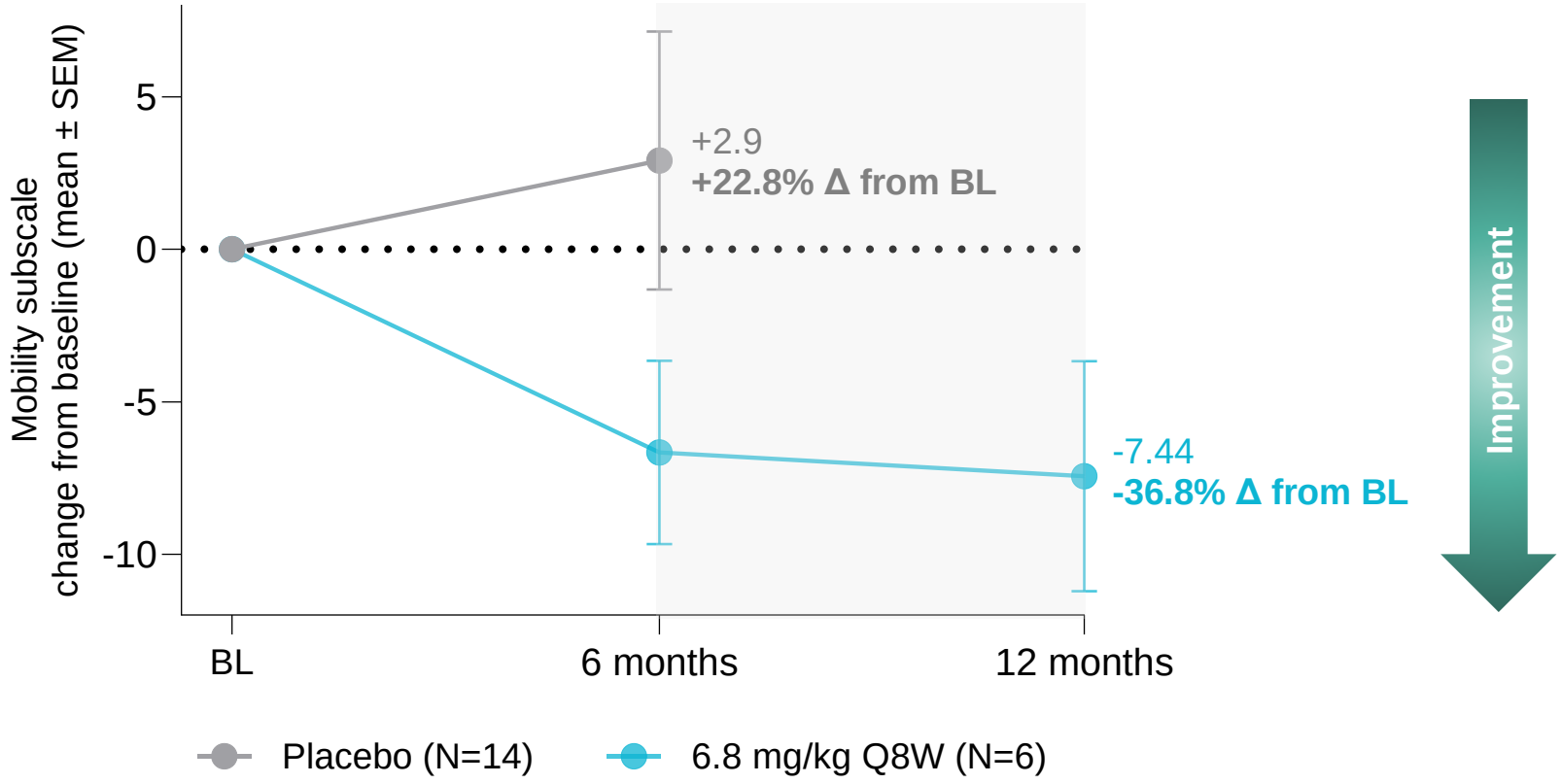
Lower Extremity Strength and Ambulation Improvement Was Supported By Patient-Reported Improvement in Mobility

MDHI Mobility Subscale



Improvement

Baseline score, mean (SEM)	**12.8 (4.3)**	**20.2 (8.7)**

MDHI Mobility Subscale

How much do the following impact your life now?

1) Difficulty staying in a standing position
2) Difficulty walking long distances
3) Difficulty with stairs
4) Inability to walk fast
5) Difficulty with balance
6) Impaired walking
7) Difficulty rising from a seated position
8) Inability to run
9) Ankle weakness
10) Tripping
11) Falls
12) Difficulty getting up from a lying position
13) Limitations with your mobility or walking

Response options
It affects my life severely
It affects my life very much
It affects my life moderately
It affects my life a little
I experience this but it does not affect my life
I don't experience this

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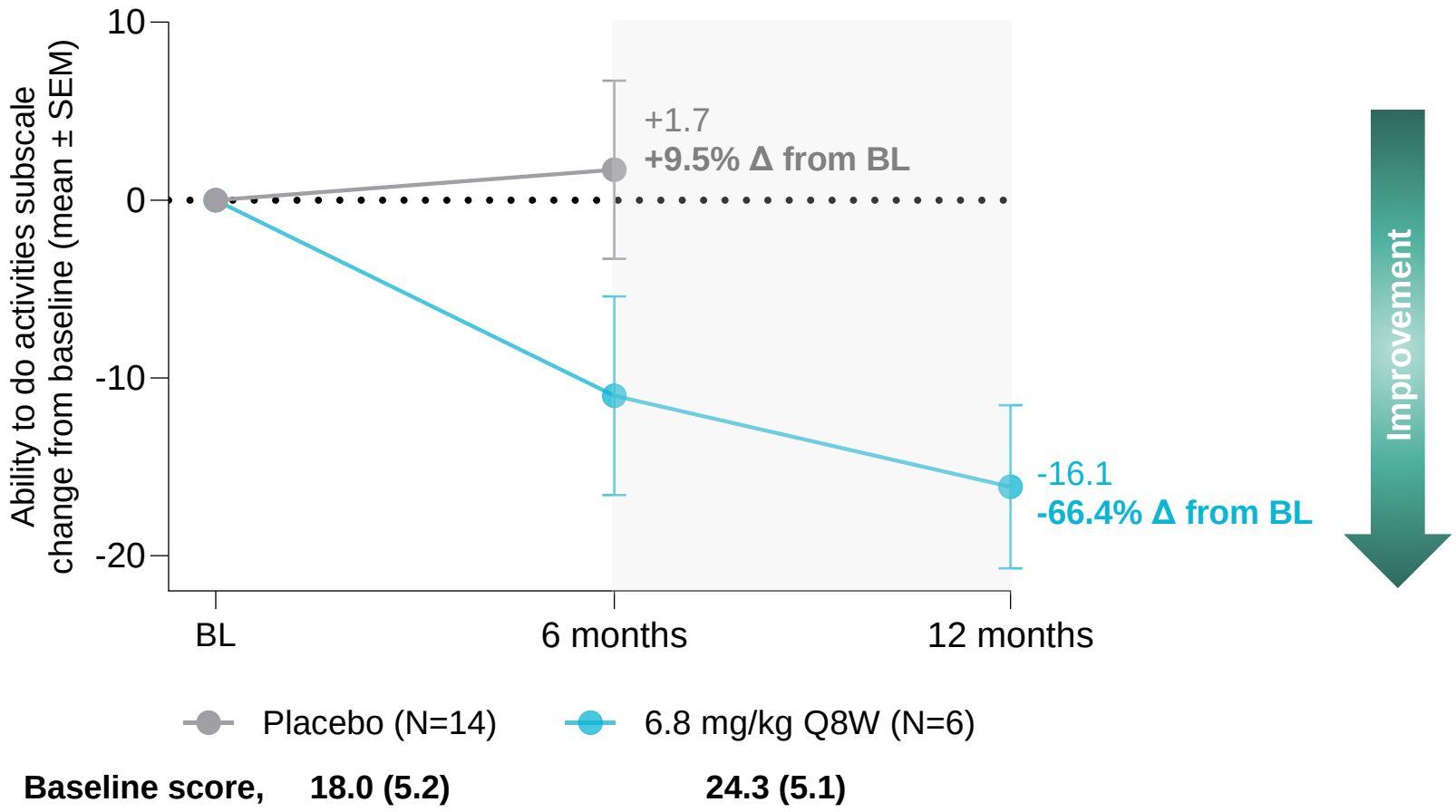
Strength and Function Improvement Was Associated With Patient-Reported Improvement in Ability to Perform Activities

MDHI Ability to Do Activities Subscale



Baseline score, mean (SEM)	**18.0 (5.2)**	**24.3 (5.1)**

MDHI Ability to Do Activities Subscale

How much do the following impact your life now?

1) Inability to do activities
2) Difficulty opening jars or bottles
3) Difficulty playing sports
4) Trouble going up step ladders
5) Inability to keep pace with friends while walking
6) Impaired dancing
7) Impaired ability to exercise
8) Difficulty using a hammer or other tool
9) Taking longer to do household chores
10) Impaired sexual function
11) Problems using buttons or zippers
12) Difficulty scrubbing surfaces
13) Difficulty cleaning a home
14) A change in your activities because of gastrointestinal symptoms

Response options
It affects my life severely
It affects my life very much
It affects my life moderately
It affects my life a little
I experience this but it does not affect my life
I don't experience this

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BL, baseline; MDHI, myotonic dystrophy health index; Q8W, every 8 weeks dosing; SEM, standard error of the mean. 6 months = 169 days; 12 months = 337 days.

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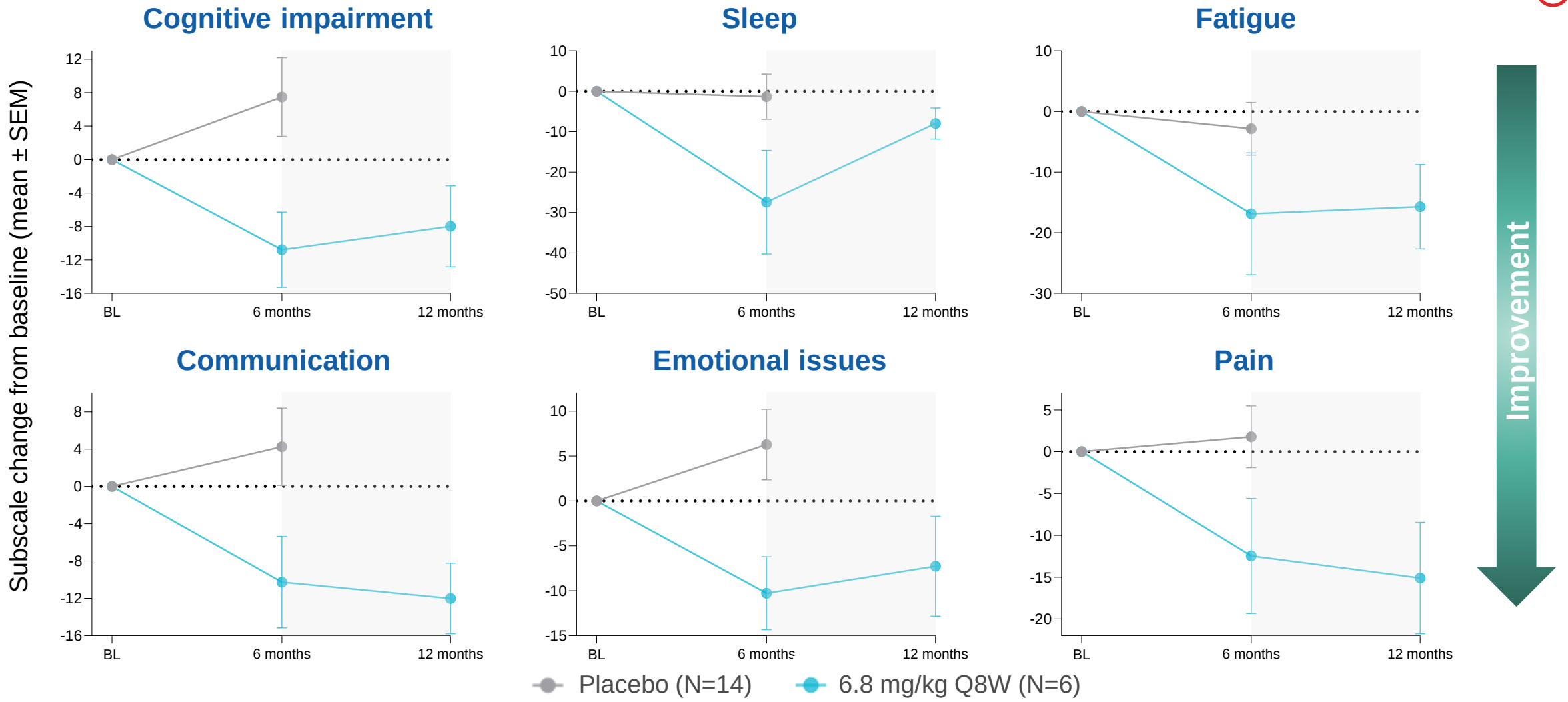
Sustained Improvement in CNS-related MDHI Subscales Was Seen Over Time



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BL, baseline; CNS, central nervous system; MDHI, myotonic dystrophy health index; Q8W, every 8 weeks dosing; SEM, standard error of the mean.

Patient-reported outcomes (PROs) including MDHI collected at baseline, 6 months (169 days), and 12 months (337 days).

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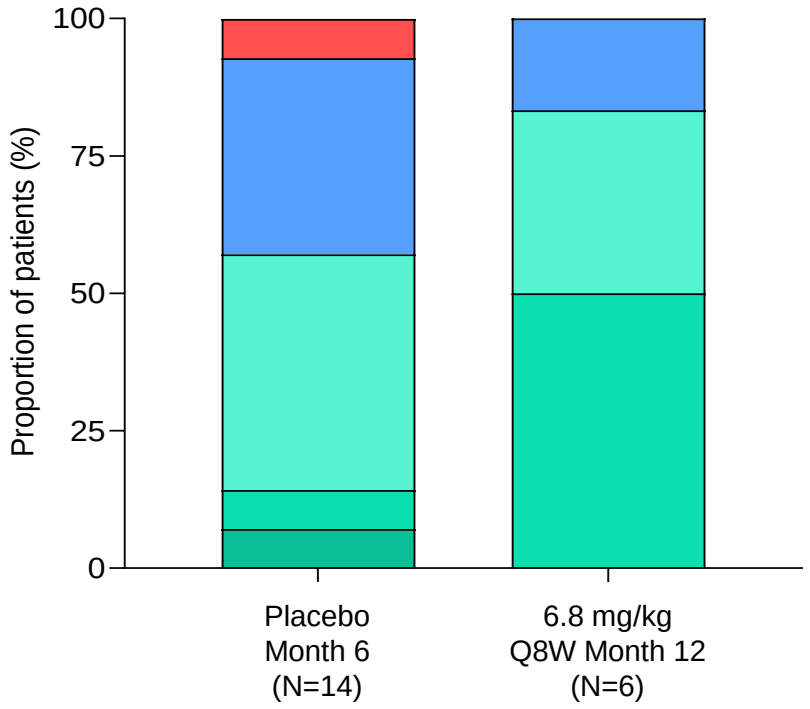
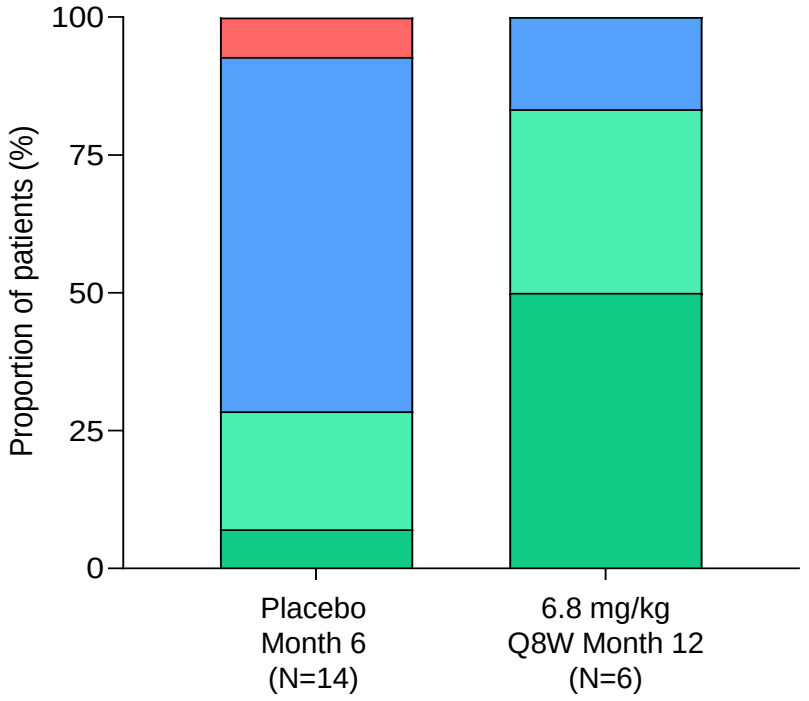
Questionnaires Showed Improvements in Patient and Clinician Impressions of Global Functioning From Baseline

Patient Global Impression of Change



Clinician Global Impression of Change



Very much improved | Much improved | Minimally improved | No change | Minimally worse | Much worse | Very much worse

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Summary

- z-basivarsen showed a continued favorable safety profile, with no serious related TEAEs[a]
- Multisystem improvement in function and strength in upper and lower extremities was observed with z-basivarsen
  - This was supported by patient-reported outcomes, including CNS-related MDHI subscales
- The functional improvements seen with z-basivarsen translate into meaningful impact, as described by clinicians and their patients

Poster Session 3: Hall X1 (Friday, October 10 at 14.15–15.15)

380P – DYNE-101 Targets the Underlying Cause of DM1 to Enable Multisystem Functional Improvement in the ACHIEVE Trial

[a]Data as of April 23, 2025.
CNS, central nervous system; DM1, myotonic dystrophy type 1; MDHI, myotonic dystrophy health index; TEAE, treatment-emergent adverse event.
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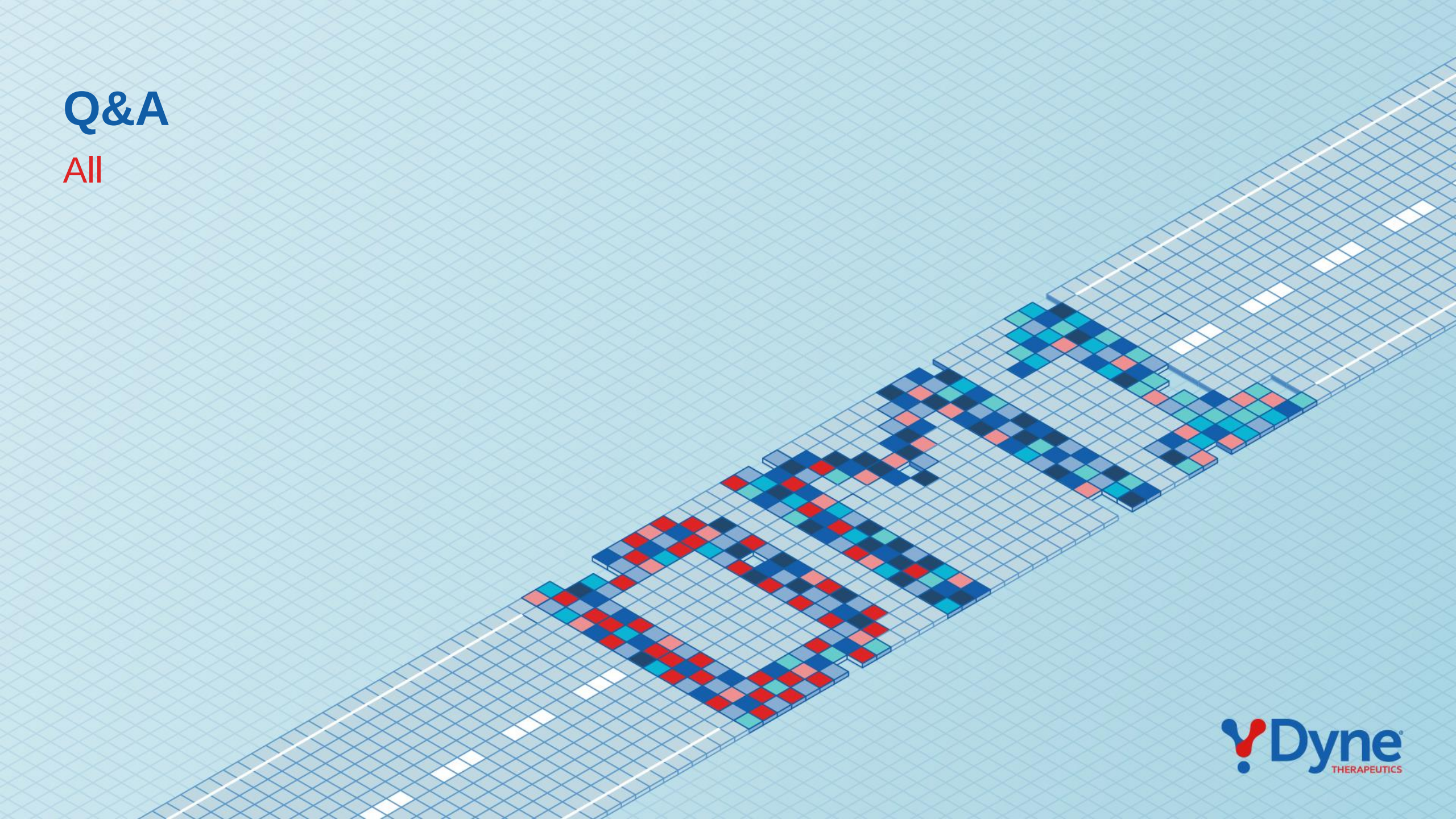
Q&A

All



Thank you

Dyne THERAPEUTICS