Zeleciment Basivarsen Targets the Underlying Cause of DM1 to Enable Functional Improvement in the Phase 1/2 ACHIEVE Trial

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Disclosures

- I am an employee of Dyne Therapeutics, Inc. and may hold stock in the company
- Zeleciment basivarsen (z-basivarsen, also known as DYNE-101) is an investigational medicine or otherwise in development and has not been approved as safe or effective by the US FDA, EMA, or any other regulatory authority

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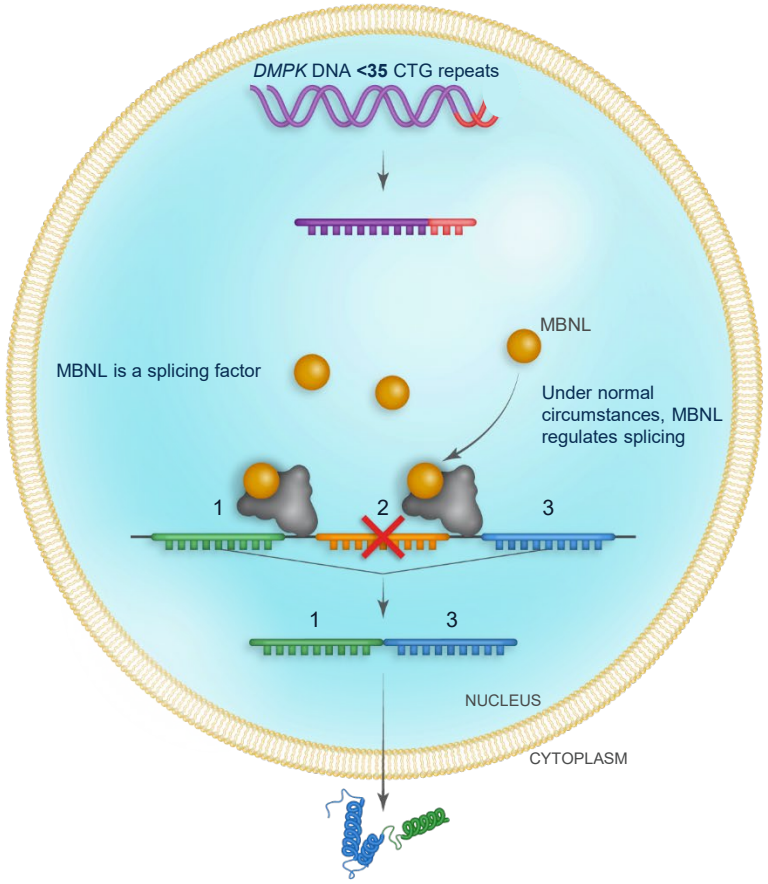
EMA, European Medicines Agency; FDA, Food and Drug Administration.

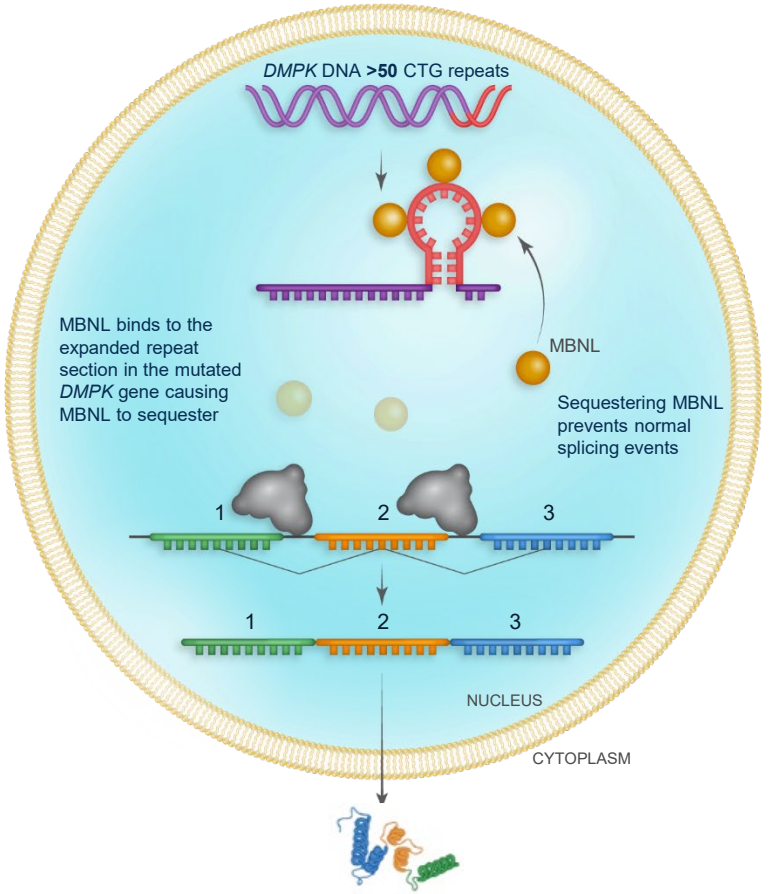
Spliceopathy in DM1 drives multisystem disease manifestations

Normal splicing



Normal splicing leads to **appropriate protein synthesis**

DM1 spliceopathy



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

Consequences of spliceopathy

- **Myotonia and muscle weakness**
- **Cognitive impairment, fatigue, EDS**
- **Cardiac conduction complications**
- **Pulmonary abnormalities**

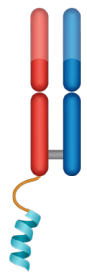
Abnormal splicing in **multiple tissues** causes symptoms of DM1

Goal of treatment: address the genetic cause of DM1 to correct splicing and improve function

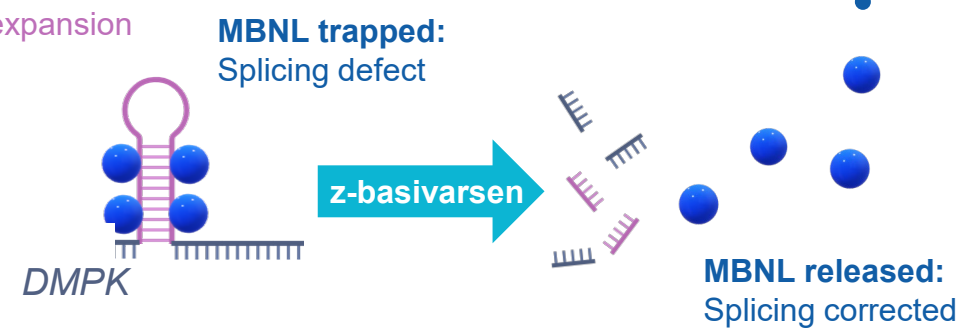
CTG, cytosine, thymine and guanine; DM1, myotonic dystrophy type 1; DMPK dystrophia myotonica protein kinase; EDS, excessive daytime sleepiness; MBNL, muscleblind-like.

Zeleciment basivarsen addresses the central pathobiology of DM1 with the goal of enabling broad functional improvement

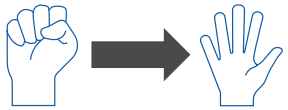
Robust and widespread delivery → ***DMPK* degradation in the nucleus** → **MBNL release and splicing correction** → **Early clinical effect** → **Broad functional improvement**



z-basivarsen
ASO conjugated to Fab targeting TfR1



Differentiated MOA



Myotonia:
Video Hand Opening Time (vHOT)

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

Muscle strength:
Quantitative Muscle Testing

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

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.

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ACHIEVE trial of z-basivarsen in adults with DM1: MAD portion

Placebo-controlled period (MAD cohorts)

- **6.8 mg/kg** N=8 (3:1) Q8W with Booster, Placebo
- **5.4 mg/kg** N=8 (3:1) Q8W with Booster, Placebo
- **3.4 mg/kg** N=8 (3:1) Q8W with Booster, Placebo
- **3.4 mg/kg** N=16 (3:3:2) Q4W, Recovery, Placebo
- **1.8 mg/kg** N=16 (3:3:2) Q4W, Recovery, Placebo

Fully enrolled

Muscle biopsies at baseline, 12, and 24 weeks

Transition to 6.8 mg/kg[1]

Open-label extension (OLE)

Long-term extension (LTE)

Population

- Ages 18–49 years

Primary endpoints

- Safety and tolerability

Additional endpoints

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

Registrational dose and dose regimen selected at 6.8 mg/kg Q8W

Doses provided refer to antisense oligonucleotide component of DYNE-101. Recovery cohort Q4W x 2 doses then placebo for the remainder of the 24W placebo-controlled period. Q8W with booster includes Q4W x 3 doses then Q8W dosing. Additional endpoints include select secondary and exploratory endpoints.

1. Transition to 6.8 mg/kg dose occurs at non-uniform times during OLE or LTE.

DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase; MAD, multiple ascending dose; MDHI, Myotonic Dystrophy Health Index; Q4W, every 4 weeks; Q8W, every 8 weeks.

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Baseline participant characteristics in 6.8 mg/kg Q8W cohort

Mean (SD) or n (%)	Placebo (N=14)	6.8 mg/kg Q8W (N=6)
Age (years)	32.6 (9.6)	37.2 (9.7)
BMI (kg/m^2)	24.4 (4.7)	23.4 (5.6)
CASI-22	0.68 (0.20)	0.74 (0.25)
CTG repeats	597 (246)	542 (191)
vHOT (middle finger) (sec)	7.5 (3.0)	7.8 (3.8)
QMT total (% predicted)	51.5 (14.3)	51.3 (10.4)
10-meter walk/run (sec)	3.34 (0.48)	3.94 (1.56)
5 times sit-to-stand (sec)	9.24 (2.03)	9.98 (3.33)
MDHI total	18.7 (13.8)	26.5 (13.7)

BMI, body mass index; CASI, composite alternative splicing index; CTG, cytosine, thymine and guanine; MDHI, Myotonic Dystrophy Health Index; Q8W, every 8 weeks; QMT, quantitative muscle testing; SD, standard deviation; sec, seconds; vHOT, video hand opening time.

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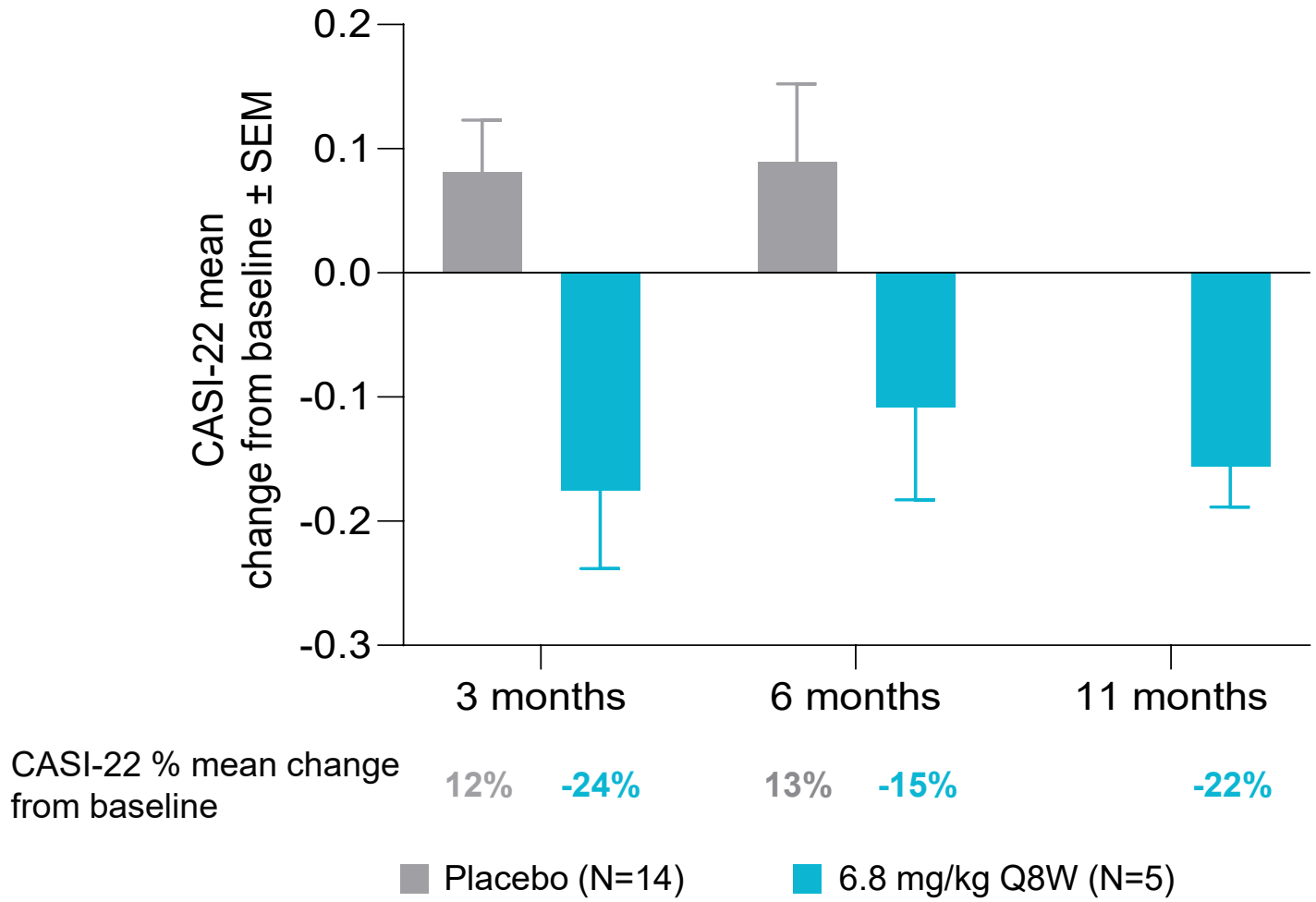
Z-basivarsen at 6.8 mg/kg Q8W led to consistent splicing correction



CASI, composite alternative splicing index; QC, quality control; Q8W, every 8 weeks dosing.
All patients transitioned to treatment at Month 6. Multiple aliquot approach, all aliquots are tested and median taken across those with valid results, up to 4. One baseline sample in 6.8 mg/kg treatment groups not included within splicing assay as the sample did not meet QC criteria. Percent mean change, calculated as mean change from baseline divided by baseline mean. 3 months = 85 days; 6 months = 169 days; 11 months = 309 days.

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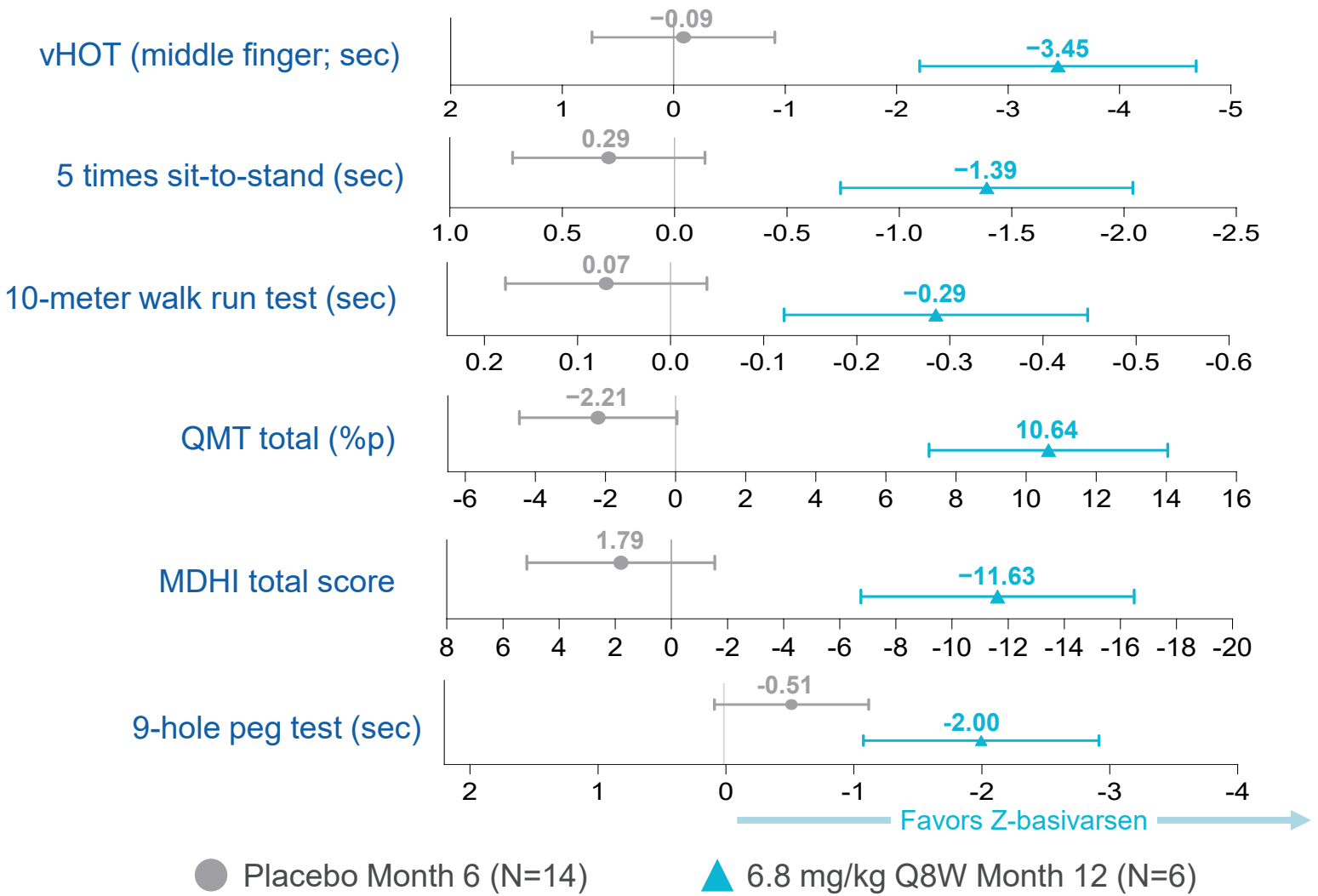
Z-basivarsen led to functional improvement across several clinical measures



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.

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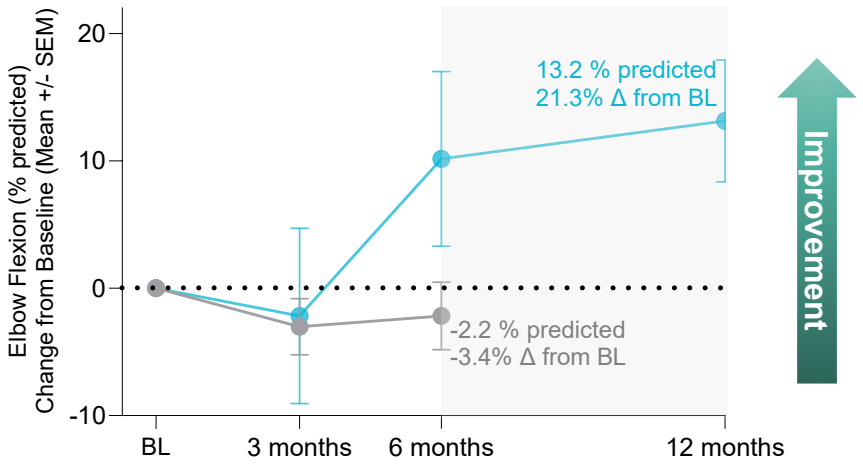
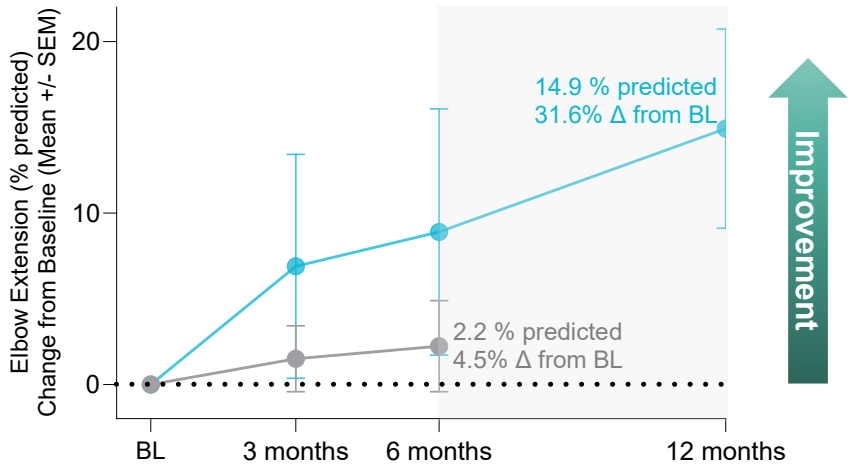
Improvement in strength in both proximal and distal muscles of upper body were supported by patient reported improvement in upper extremity function

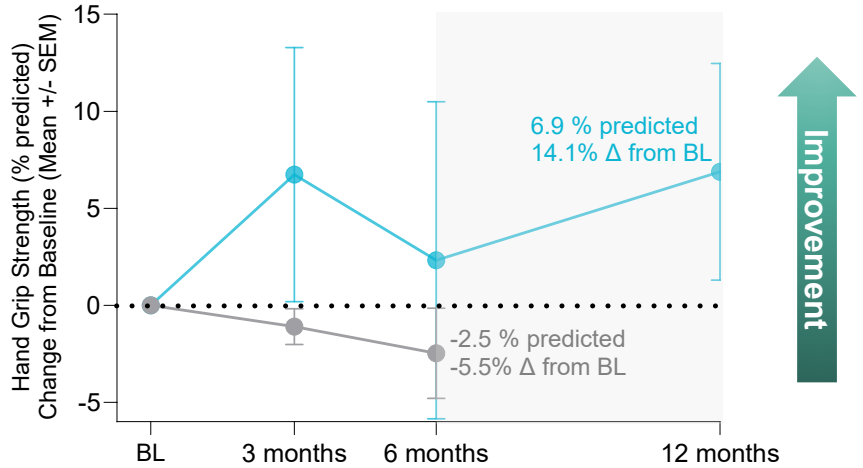
QMT Elbow Flexion



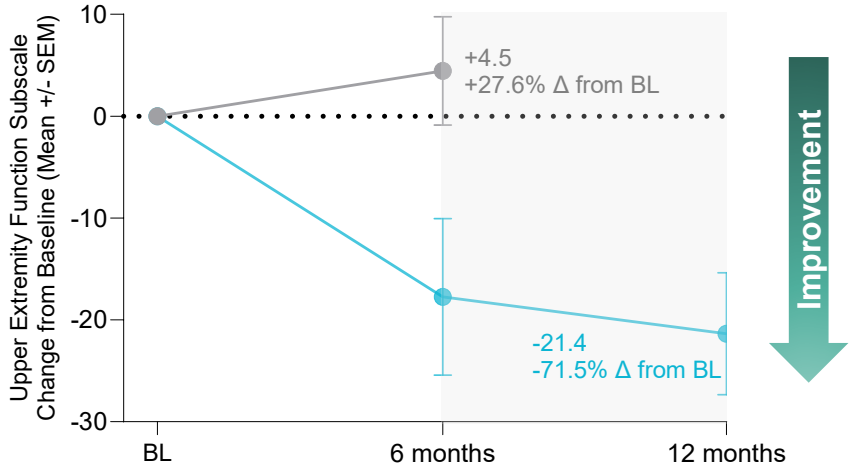
QMT Elbow Extension



QMT Hand Grip Strength



MDHI Upper Extremity Function Subscale



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

BL, baseline; Q8W, every 8 weeks dosing; SEM, standard error of the mean.
3 months = 85 days; 6 months = 169 days; 12 months = 337 days.

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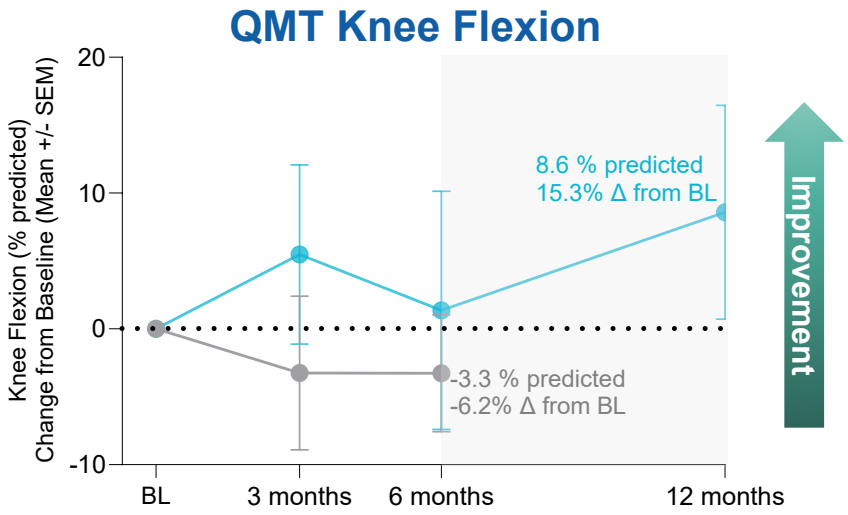
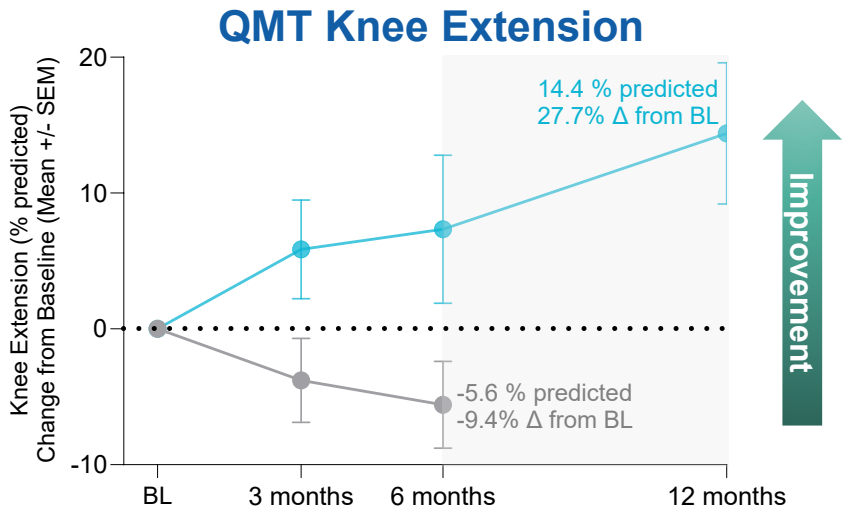
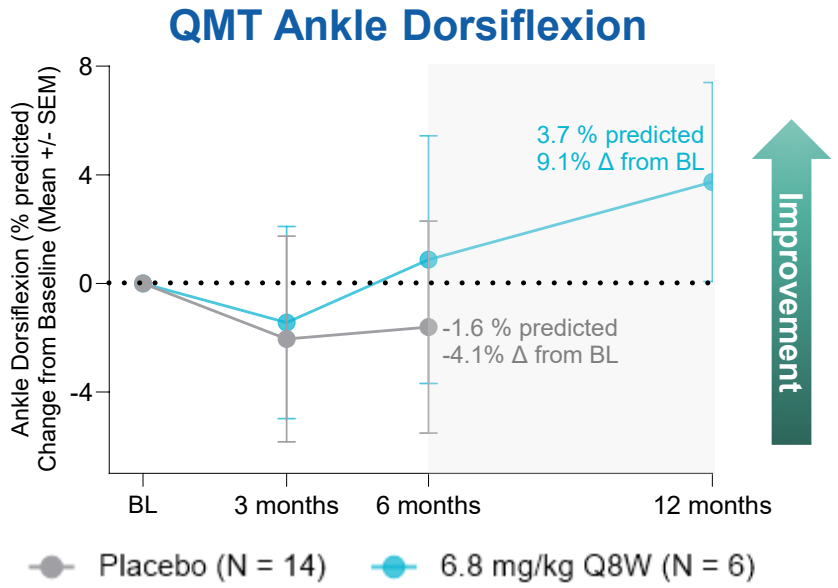
Strength improvement also noted in lower body through 12 months







BL, baseline; Q8W, every 8 weeks dosing; SEM, standard error of the mean.
3 months = 85 days; 6 months = 169 days; 12 months = 337 days.

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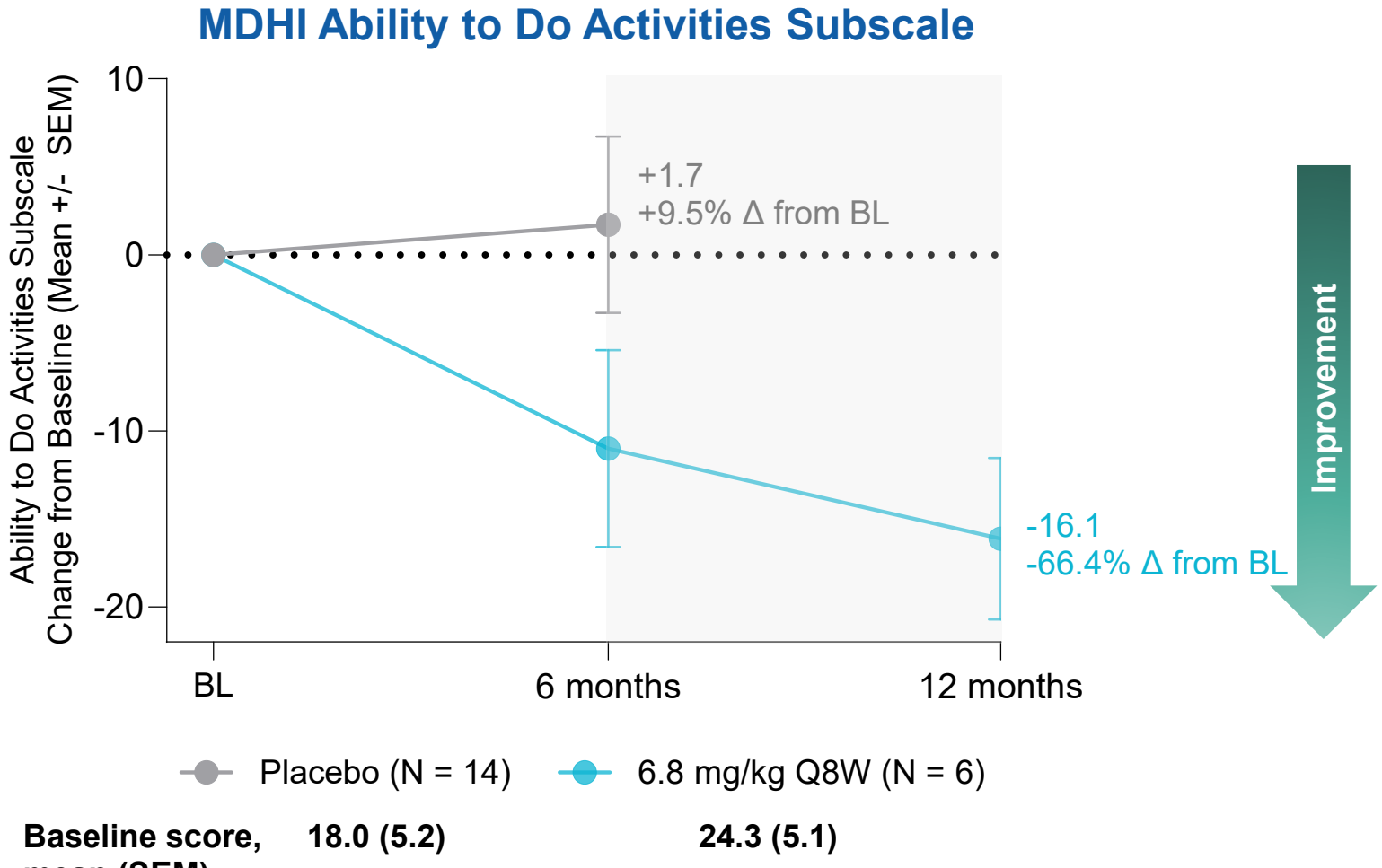
Strength and function improvement associated with patient-reported improvement in ability to perform activities



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

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

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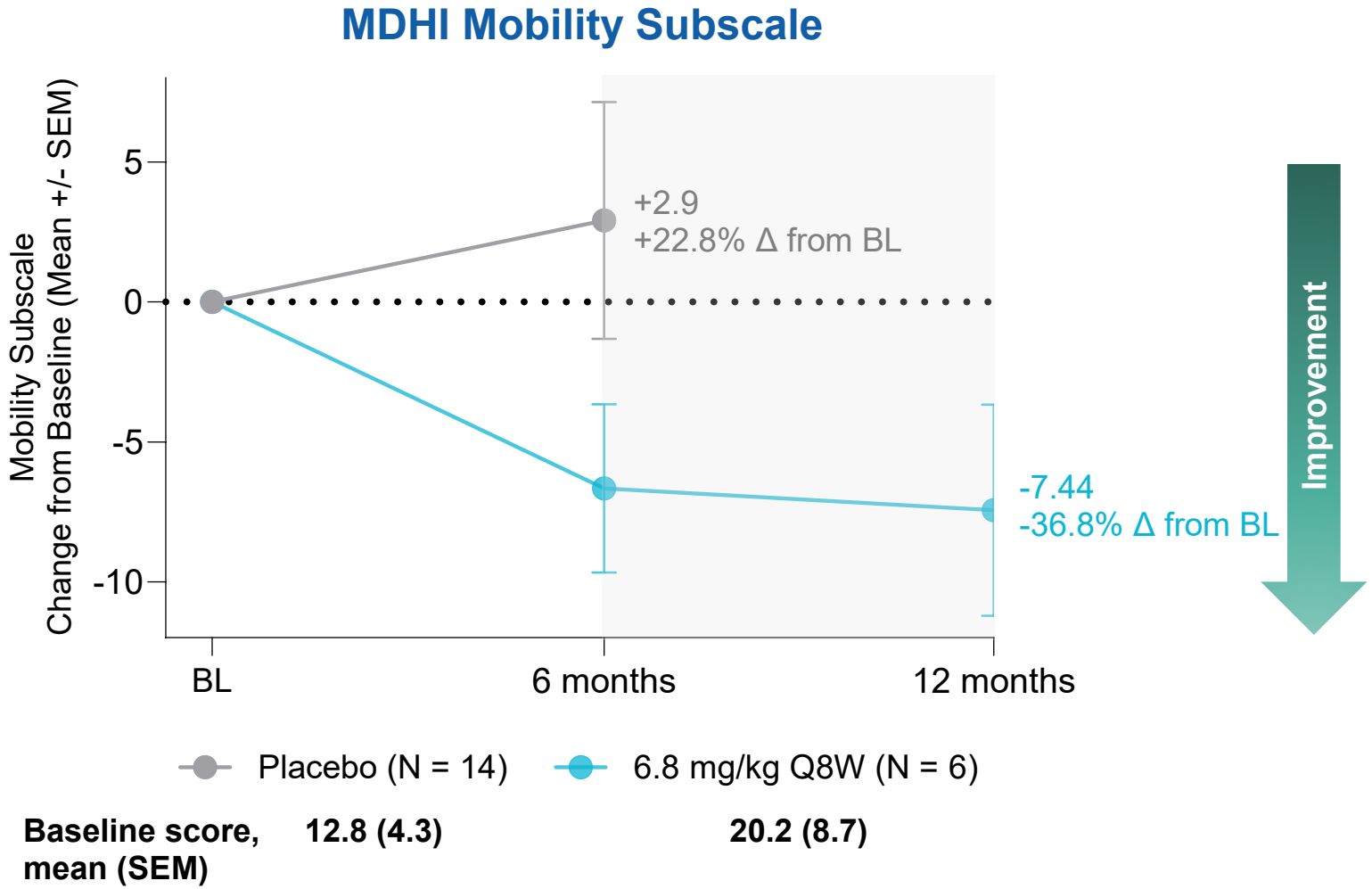
Lower extremity strength and ambulation improvement associated with patient-reported improvement in mobility



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

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

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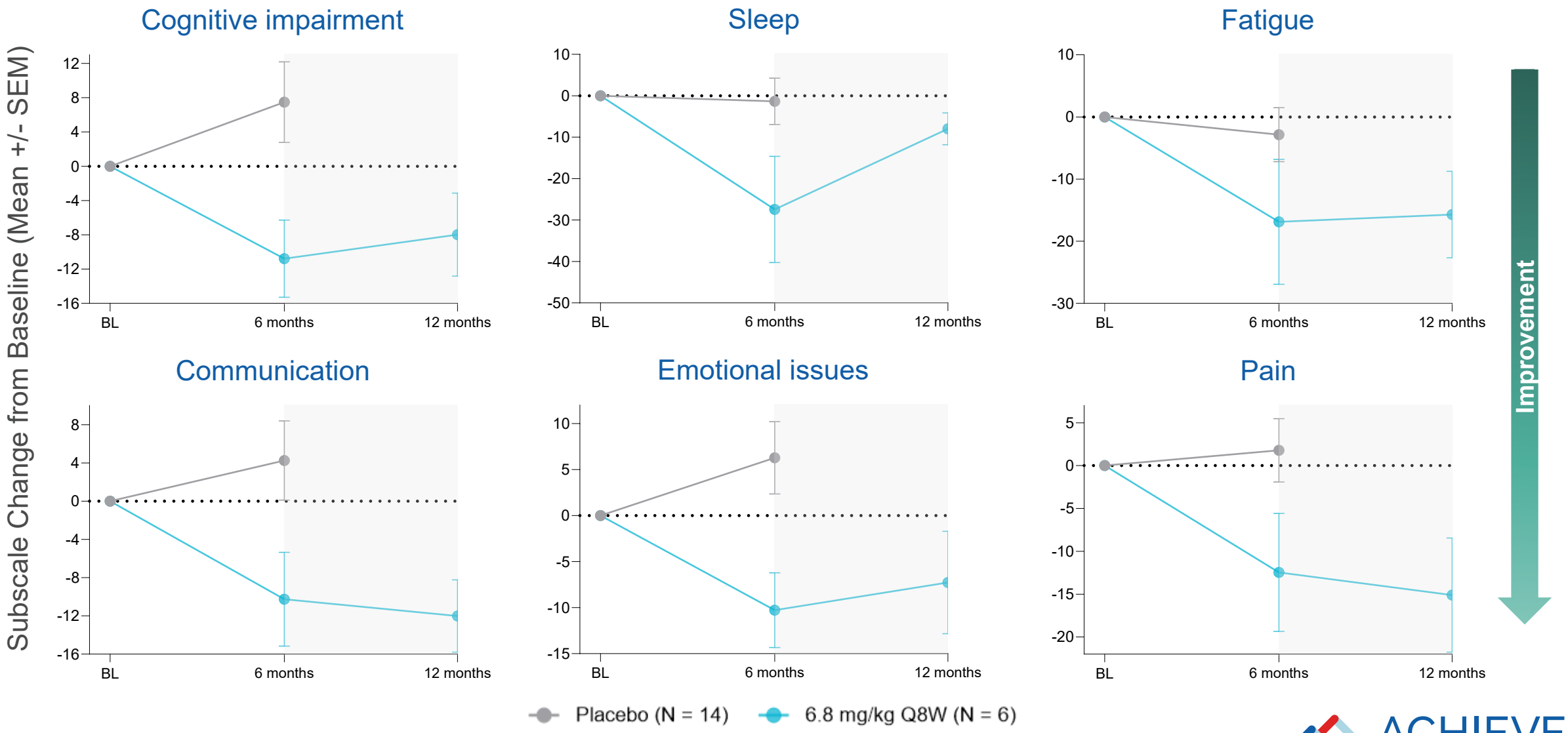
Improvement in CNS-related MDHI subscales over time



BL, baseline; Q8W, every 8 weeks dosing; SEM, standard error of the mean.
Patient-reported outcomes (PRO) including Myotonic Dystrophy Health Index (MDHI) collected at baseline, 6 months (169 days), and 12 months (337 days).

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Favorable safety profile with no serious related TEAEs[1]

Summary of Treatment Emergent Adverse Events (TEAEs)[1]

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[1]

- 6 serious TEAEs unrelated to study drug
  - Atrioventricular block first degree (1)[2]
  - Pneumonia (2 events in same participant)
  - Pulmonary embolism (1)[3]
  - Hyponatremia (1)
  - Influenza (1)
- Most common TEAEs (≥20% participant incidence)[4]
  - 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]

1. Data as of April 23, 2025; 2. Transient worsening of atrioventricular (AV) block in a participant with ongoing medical history of first-degree AV block; 3. Attributed to risk factors for pulmonary embolism; 4. All cohorts combined; preferred terms are reported.

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Summary

- Z-basivarsen targets the underlying cause of DM1 to enable functional improvement in multi-systems in the ACHIEVE trial, including improvement in measures of myotonia, muscle strength and function, and PROs
- Key clinical outcomes are supported by patient-reported improvement in muscle strength, function and ability to do activities
- Z-basivarsen showed a continued favorable safety profile[a] with no serious related TEAEs

*Data as of April 23, 2025.
PRO, patient reported outcome; TEAE, treatment-related adverse event

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Acknowledgements

ACHIEVE participants and their families

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