Impact of baseline characteristics on apitegromab efficacy in patients with spinal muscular atrophy

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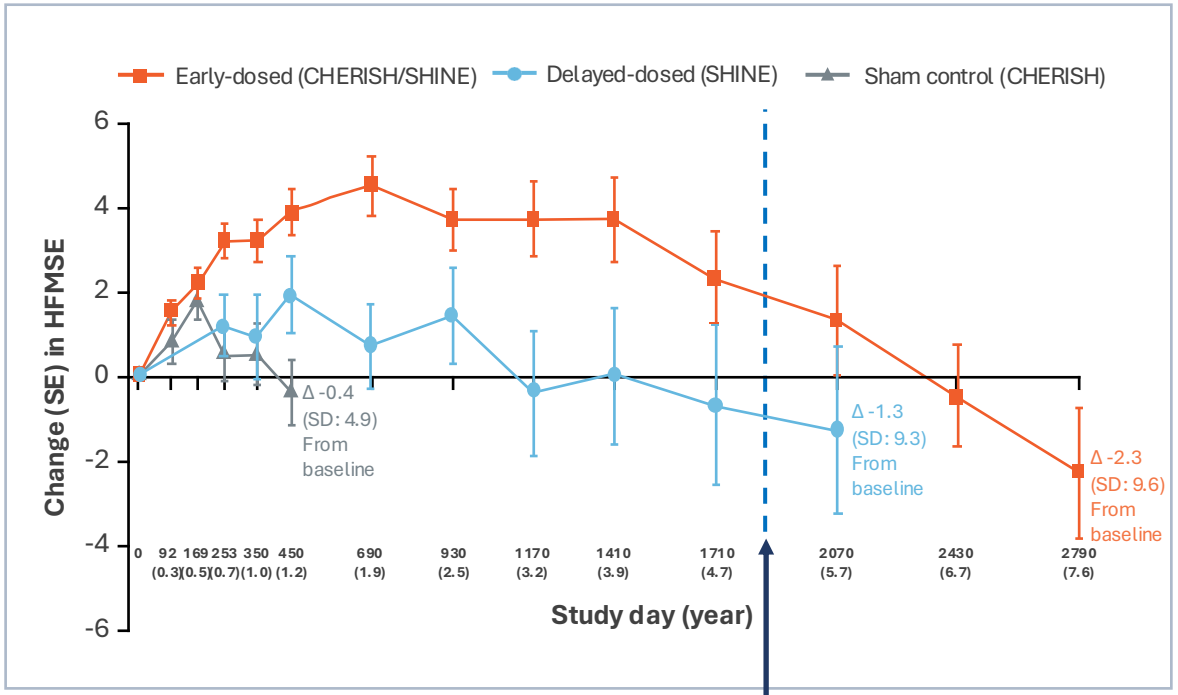
Declaration of interests

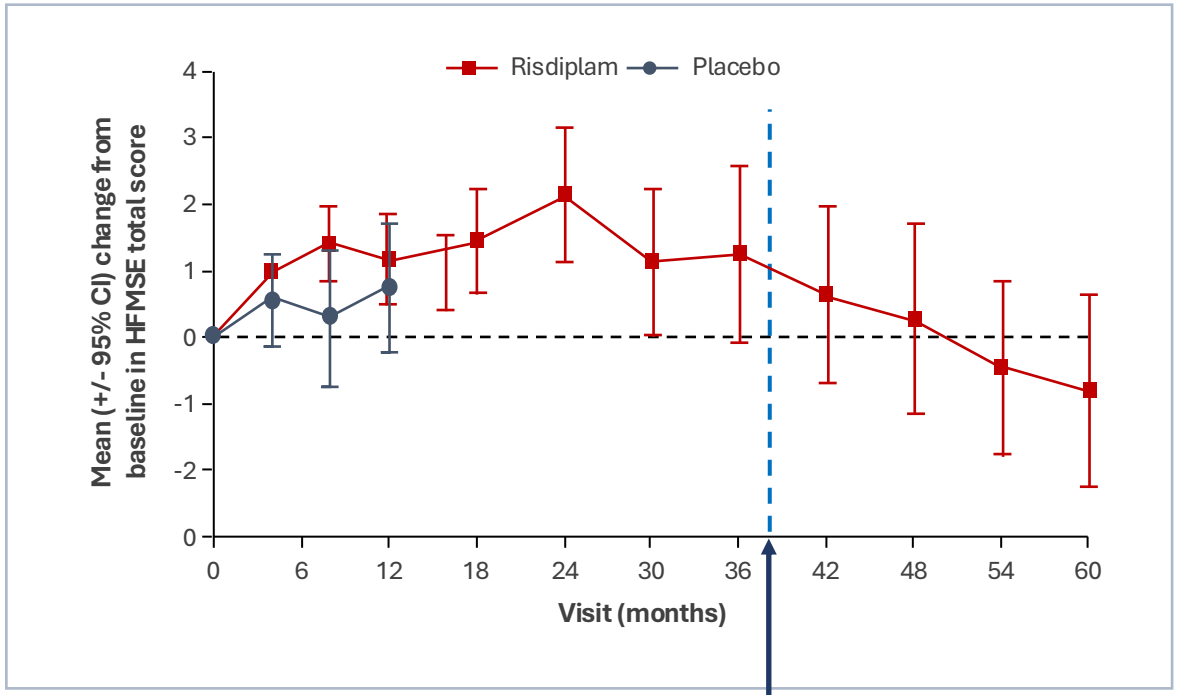
Dr. Jing L. Marantz is an employee of Scholar Rock

Outcomes after long-term treatment with SMN-targeted treatments

Nusinersen (2-9 years old)[1]



Risdiplam (2-25 years old)[2]



Mean duration of nusinersen or risdiplam treatment before randomization in SAPPHIRE was 5.2 and 3.2 years
Patients in the SAPPHIRE Phase 3 study therefore expected to decline without further intervention

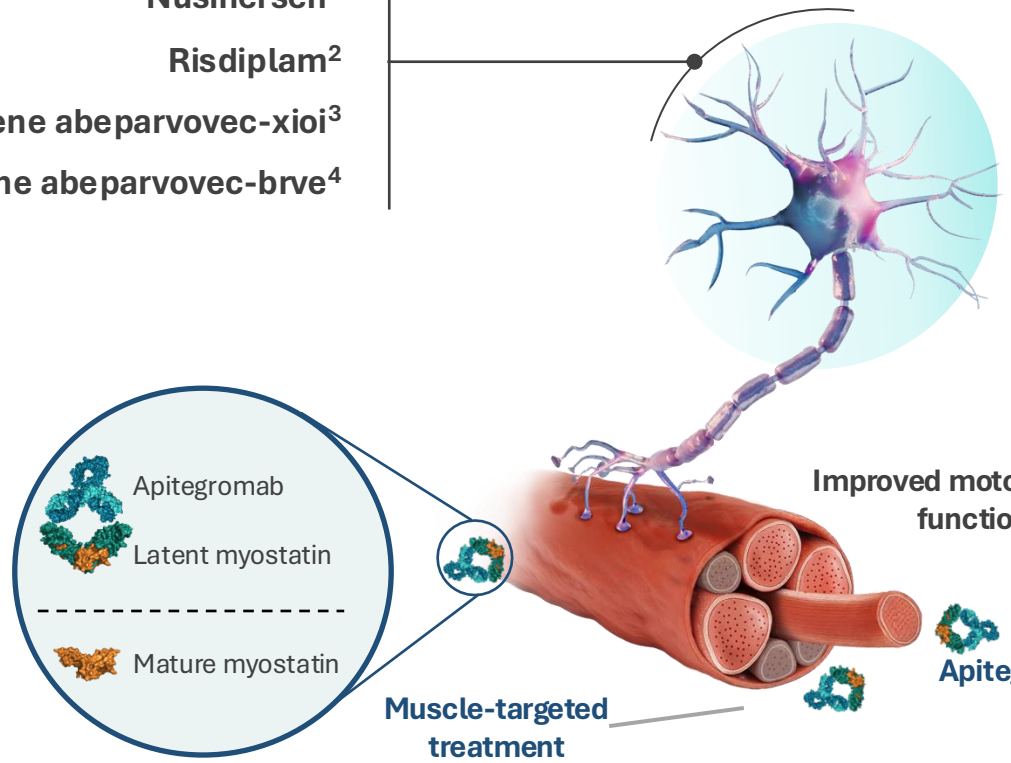
CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale–Expanded; SD, standard deviation; SE, standard error; SMN, survival motor neuron.
1. Finkel RS, et al. Poster presented at: Annual SMA Research & Clinical Care Meeting; Jun 5-7, 2024; Austin, TX. P95. 2. Servais L, et al. Poster presented at: the Muscular Dystrophy Association Clinical and Scientific Congress; Mar 16-19, 2025; Dallas, TX. P94.

Spinal muscular atrophy

Motor neuron degeneration and muscle atrophy

SMN-targeted treatments address motor neuron survival and motor function

Nusinersen[1]
Risdiplam[2]
Onasemnogene abeparvovec-xioi[3]
Onasemnogene abeparvovec-brve[4]



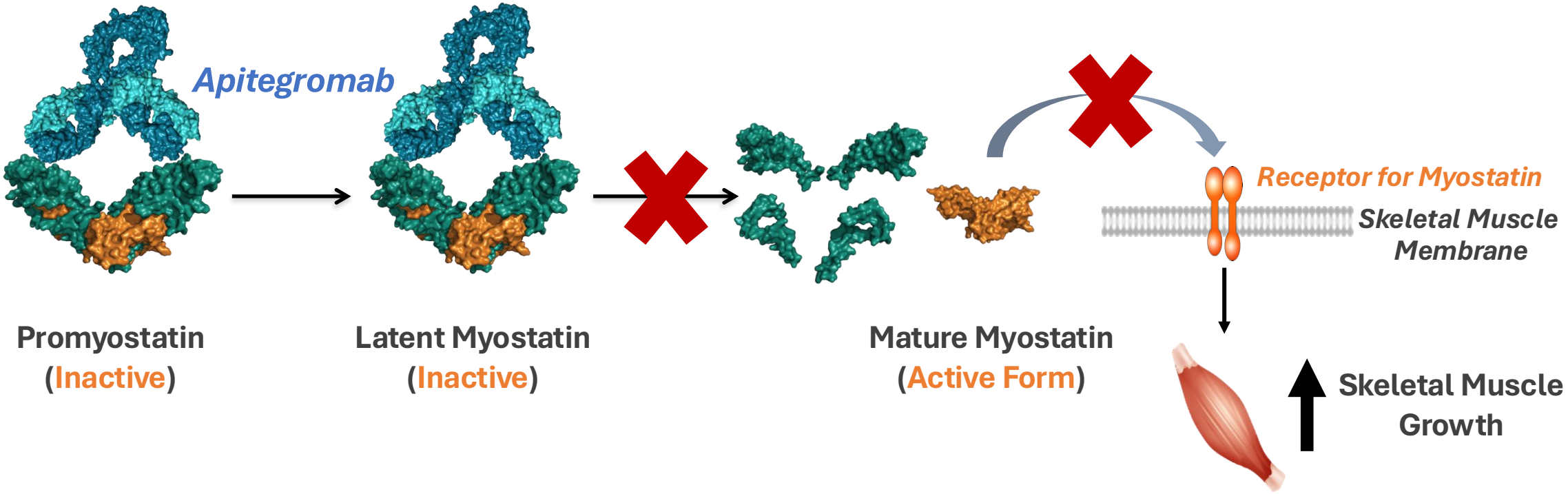
...but do not directly address muscle atrophy

Therapeutic hypothesis

Apitegromab selectively inhibits myostatin, thus improving motor function by addressing muscle atrophy directly

Figure adapted from: SMA Foundation Overview. Accessed Jun 4, 2026. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf.
SMA, spinal muscular atrophy; SMN, survival motor neuron.
1. SPINRAZA (nusinersen). Prescribing information. Biogen; 2024. 2. EVRYSDI (risdiplam). Prescribing information. Genetech, Inc; 2026. 3. ZOLGENSMA (onasemnogene abeparvovec-xioi). Prescribing information. Novartis Gene Therapies, Inc.; 2025. 4. ITVISMA (onasemnogene abeparvovec-brve). Prescribing information. Novartis Gene Therapies, Inc.; 2025.

Apitegromab mechanism of action[1-3,a]

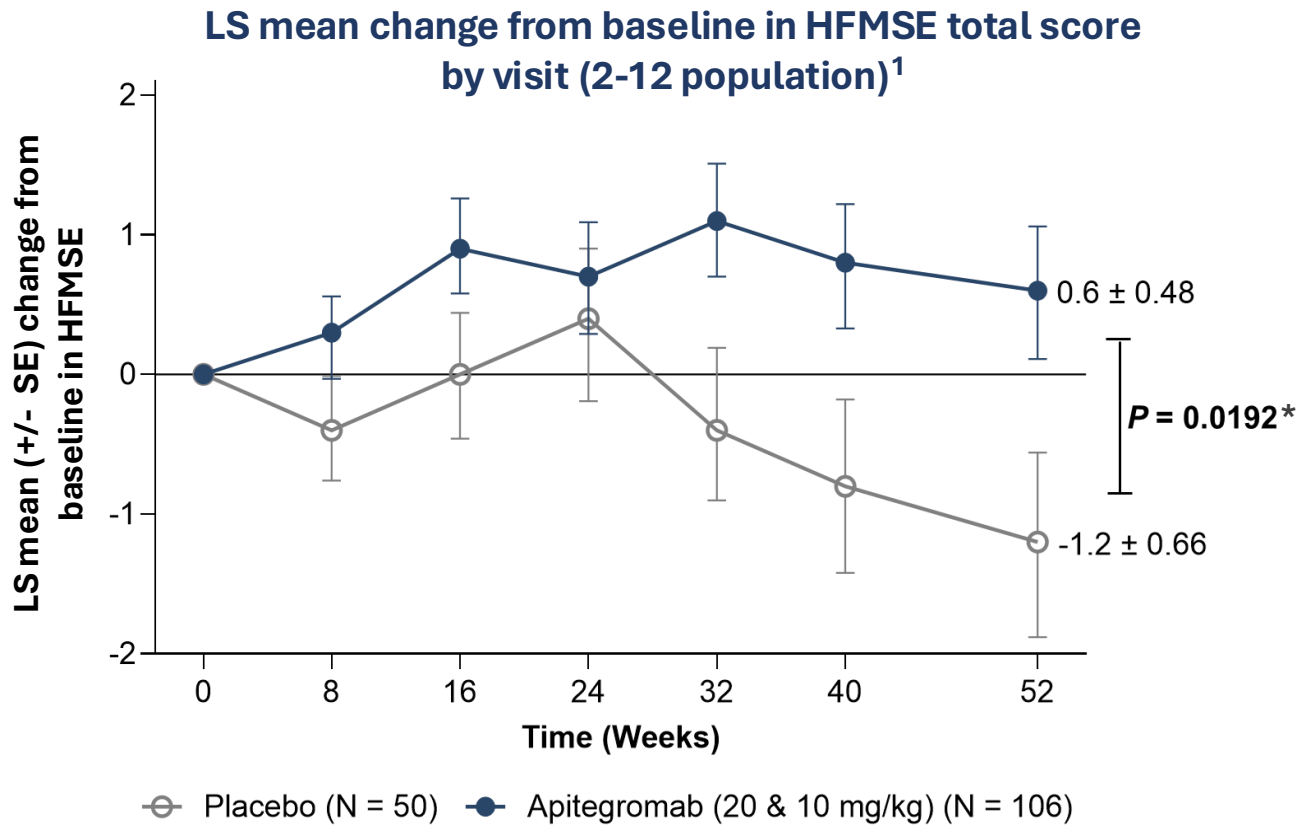


Myostatin is known to regulate muscle size and strength throughout life, across healthy individuals and in diseases, including SMA

[a]Mechanism of action is based on preclinical data.
SMA, spinal muscular atrophy.

1. Long KK, et al. *Hum Mol Genet*. 2019;28(7):1076-1089. 2. Pirruccello-Straub M, et al. *Sci Rep*. 2018;8(1):2292. 3. Nielsen TL, et al. *Cells*. 2021;10(3):533.

SAPPHIRE: significantly improved motor function on apitegromab

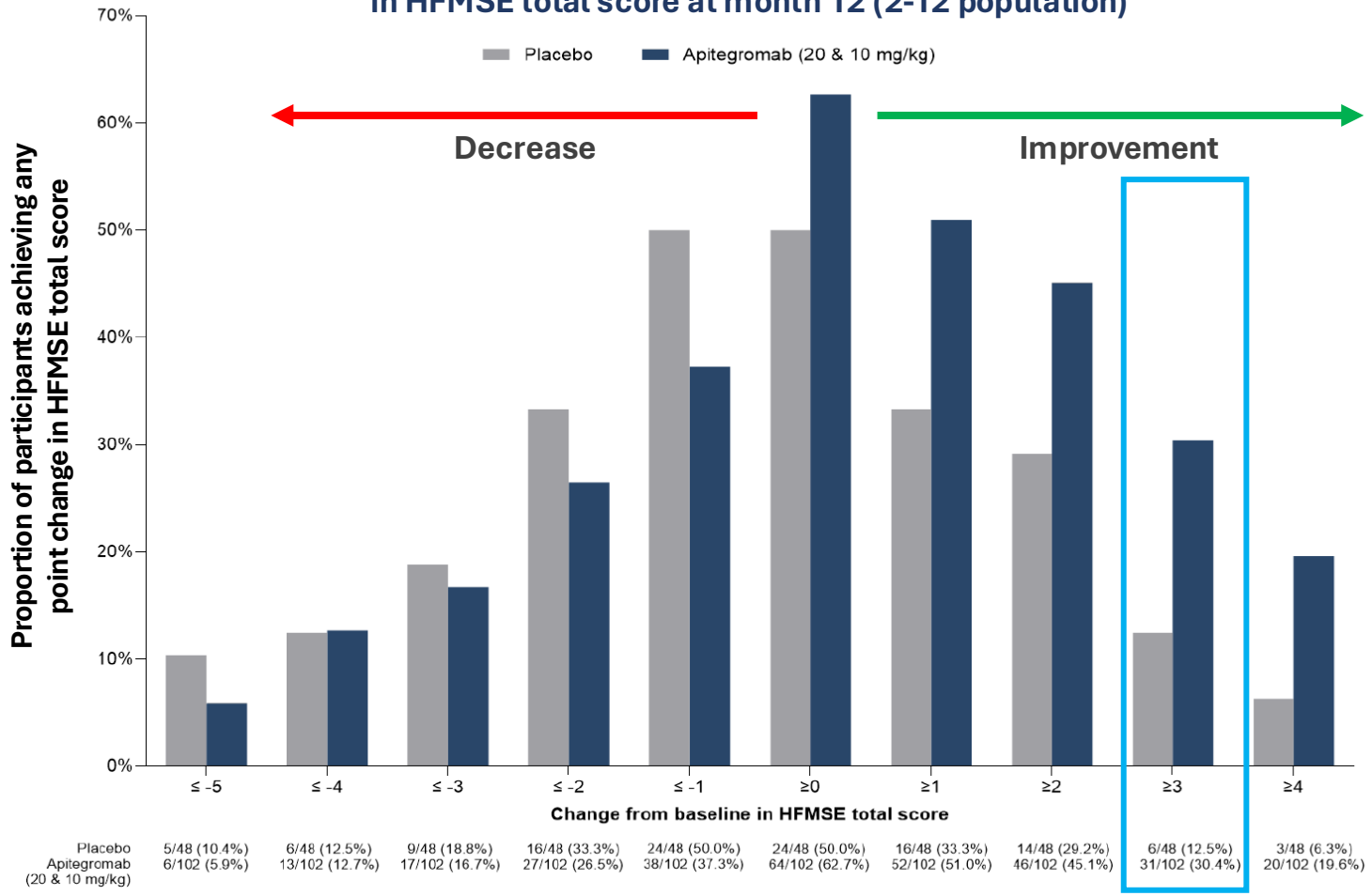


- Patients on apitegromab demonstrated improved motor function while those on SMN-targeted treatment alone lost function over time
- Motor function outcomes were consistent across 2–12 and 13–21 age groups, favoring apitegromab
- Apitegromab had a favorable and well-characterized safety profile (with >700 patient-years of exposure to date[2])

**P* value from primary analysis by Hochberg method prespecified for multiplicity adjustment
2-12, population aged 2 to 12 years; HFMSE, Hammersmith Functional Motor Scale–Expanded; LS, least squares; SE, standard error.
1. Crawford TO, et al. *Lancet Neurol.* 2025;24(9):727-739. 2. Scholar Rock. Data on file.

SAPPHIRE: apitegromab improved motor function across HFMSE thresholds

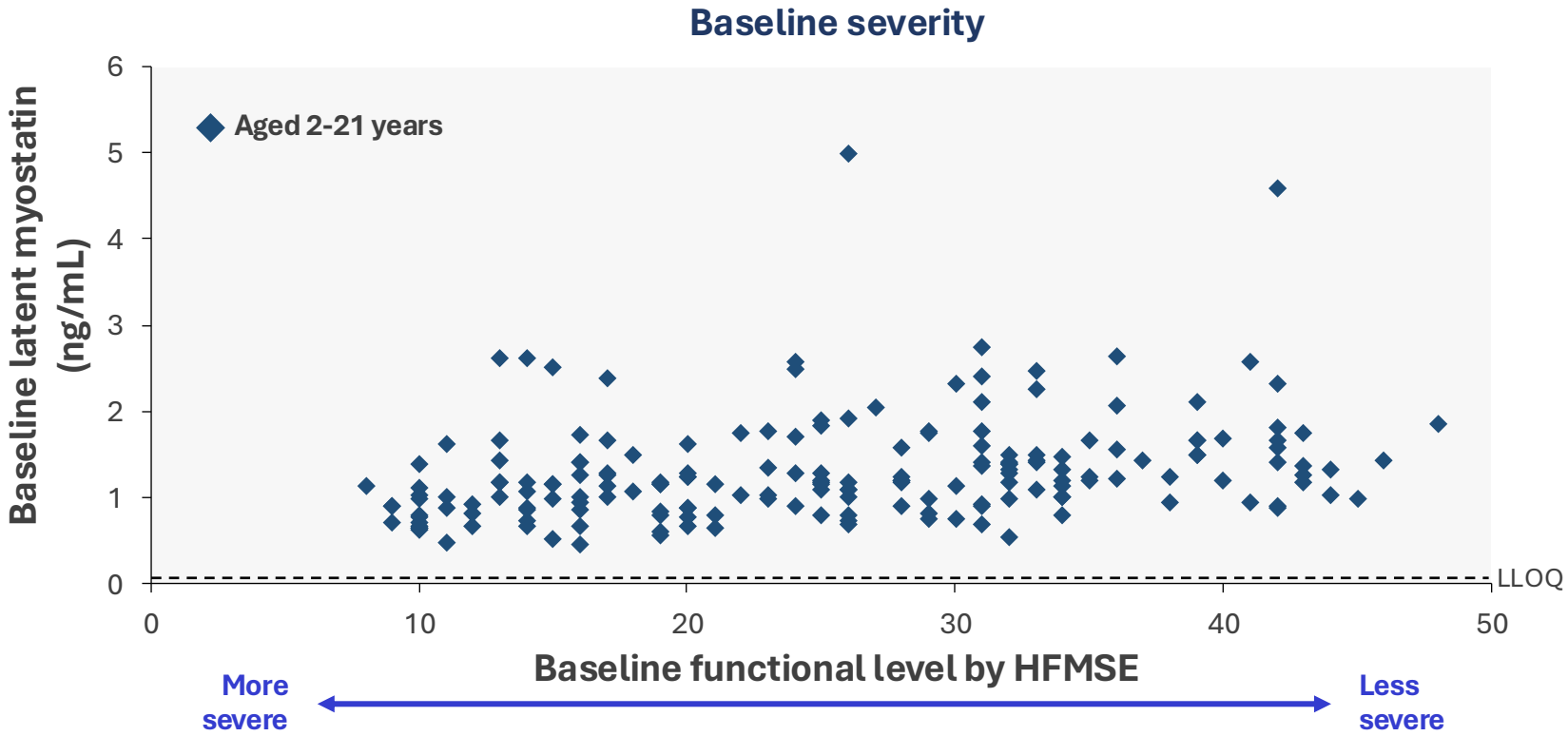
Proportion of participants achieving any point change from baseline in HFMSE total score at month 12 (2-12 population)



- Apitegromab benefit on motor function observed across thresholds, with proportion achieving ≥3-point gain favoring apitegromab (odds ratio 3.0, *P*=0.0256)
- Improvement observed across HFMSE domains, with individual domains representing activities highly relevant to daily lives, such as lifting the head (neck strength), kneeling, or rolling over, represent increased freedom for children and adults living with SMA

2-12, population aged 2 to 12 years; HFMSE, Hammersmith Functional Motor Scale–Expanded; SMA, spinal muscular atrophy.
Crawford TO, et al. *Lancet Neurol.* 2025;24(9):727-739.

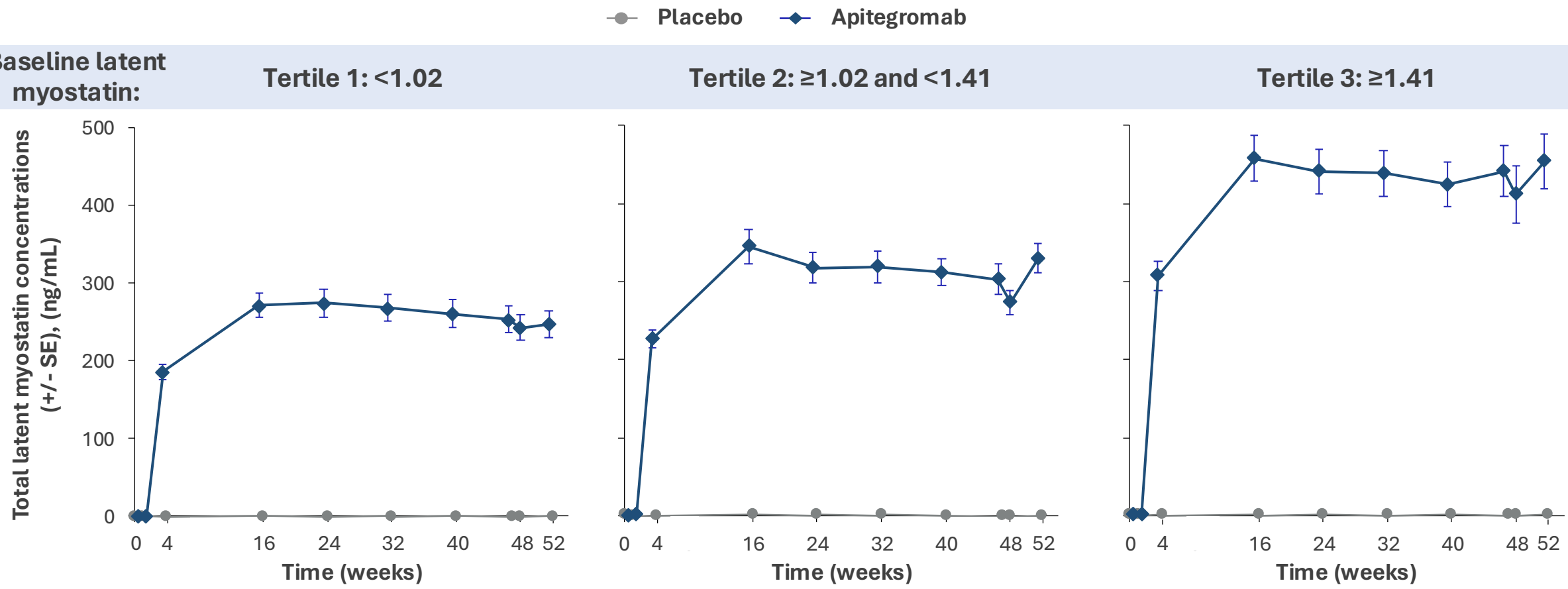
SAPPHIRE: measurable latent myostatin across disease severity



- SAPPHIRE study population is broadly representative with a wide range of baseline HFMSE (8-48)
- Latent myostatin measurable regardless of baseline function, including in ambulatory patients (TOPAZ data, not shown here)
- Apitegromab is therefore expected to enhance muscle growth and function across SMA disease spectrum

HFMSE, Hammersmith Functional Motor Scale–Expanded; LLOQ, lower limit of quantification for total latent myostatin (0.15 ng/mL); SMA, spinal muscular atrophy.
Scholar Rock. Data on file.

SAPPHIRE: target engagement across tertiles of baseline latent myostatin

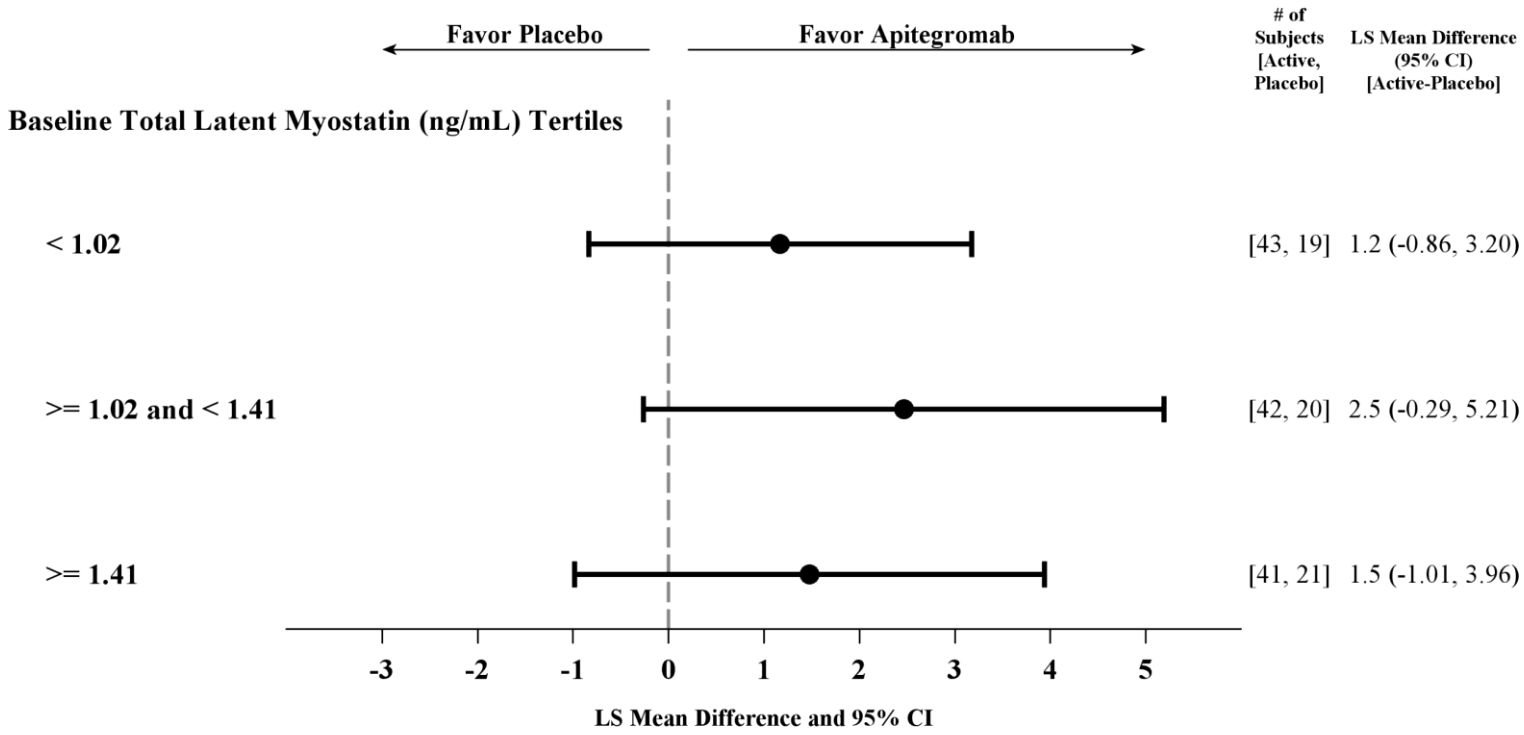


- Total latent myostatin, a reliable marker for target engagement, increased following treatment across baseline latent myostatin levels
- By contrast, no apparent change in total latent myostatin was observed in patients randomized to placebo

Lower limit of quantification for total latent myostatin concentration is 0.15 ng/mL.
SE, standard error.
Scholar Rock. Data on file.

SAPPHIRE: motor function by HFMSE across tertiles of baseline myostatin

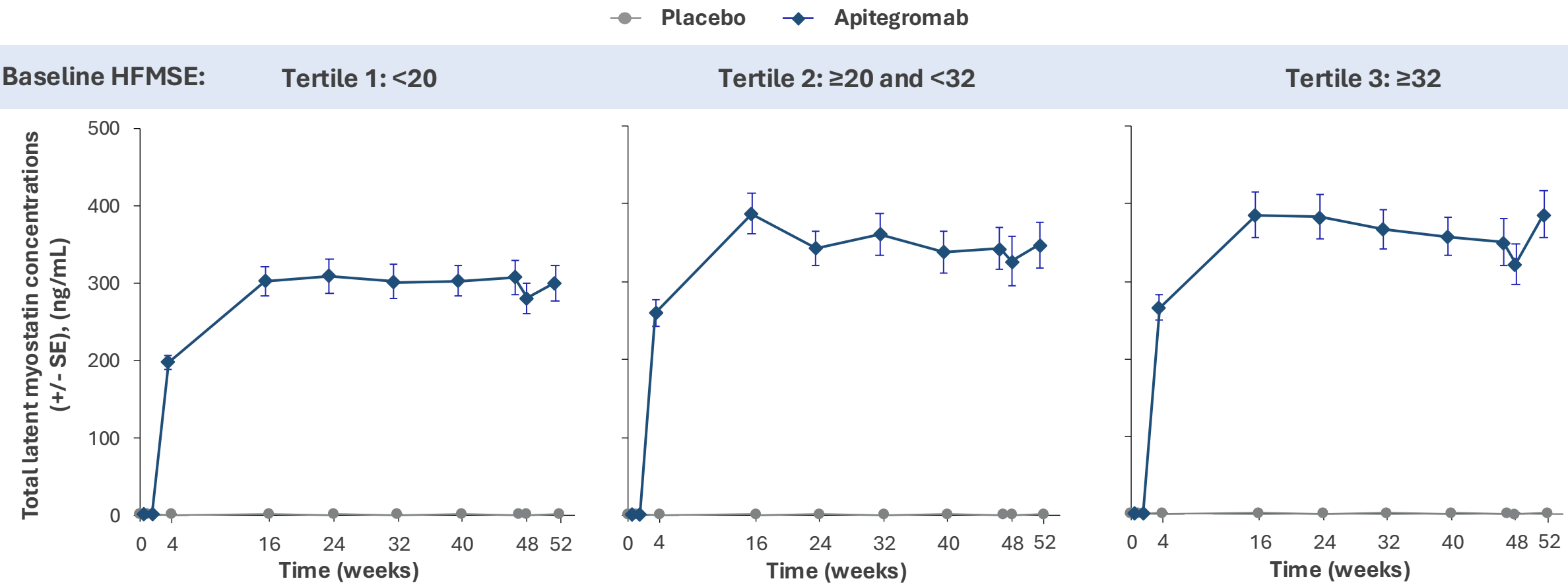
Change from baseline in HFMSE at 12 months across baseline myostatin



- Motor function by HFMSE improved following apitegromab vs placebo regardless of baseline latent myostatin levels
- Point estimates may not accurately reflect effect size given the small sample size of subgroups

CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale–Expanded; LS, least squares.
Scholar Rock. Data on file.

SAPPHIRE: target engagement across tertiles of baseline HFMSE

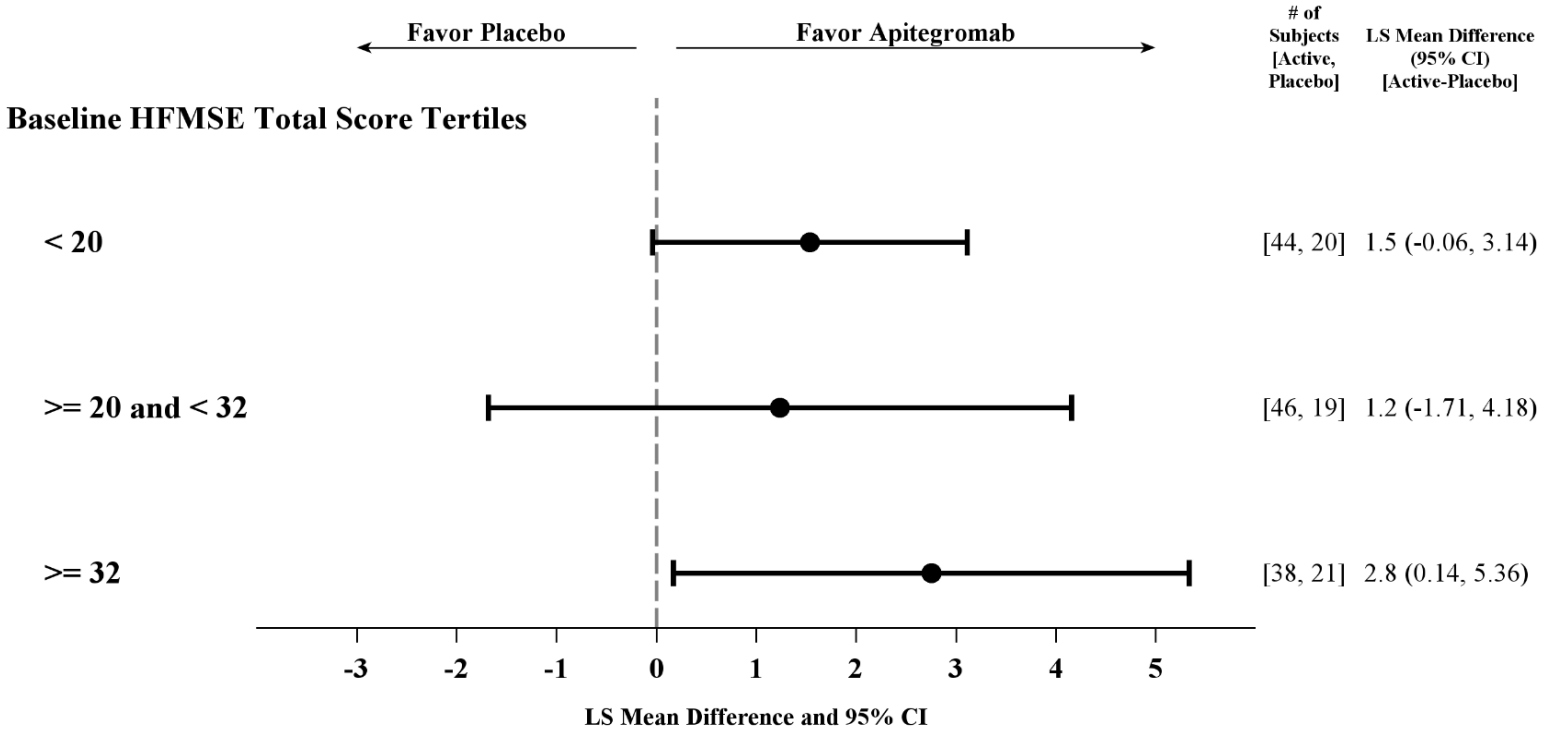


- Total latent myostatin, a reliable marker for target engagement, increased following treatment across baseline functional levels
- By contrast, no apparent change in total latent myostatin was observed in patients randomized to placebo

Lower limit of quantification for total latent myostatin concentration is 0.15 ng/mL.
HFMSE, Hammersmith Functional Motor Scale–Expanded; SE, standard error.
Scholar Rock. Data on file.

SAPPHIRE: motor function by HFMSE across tertiles of baseline function

Change from baseline in HFMSE at 12 months across baseline function

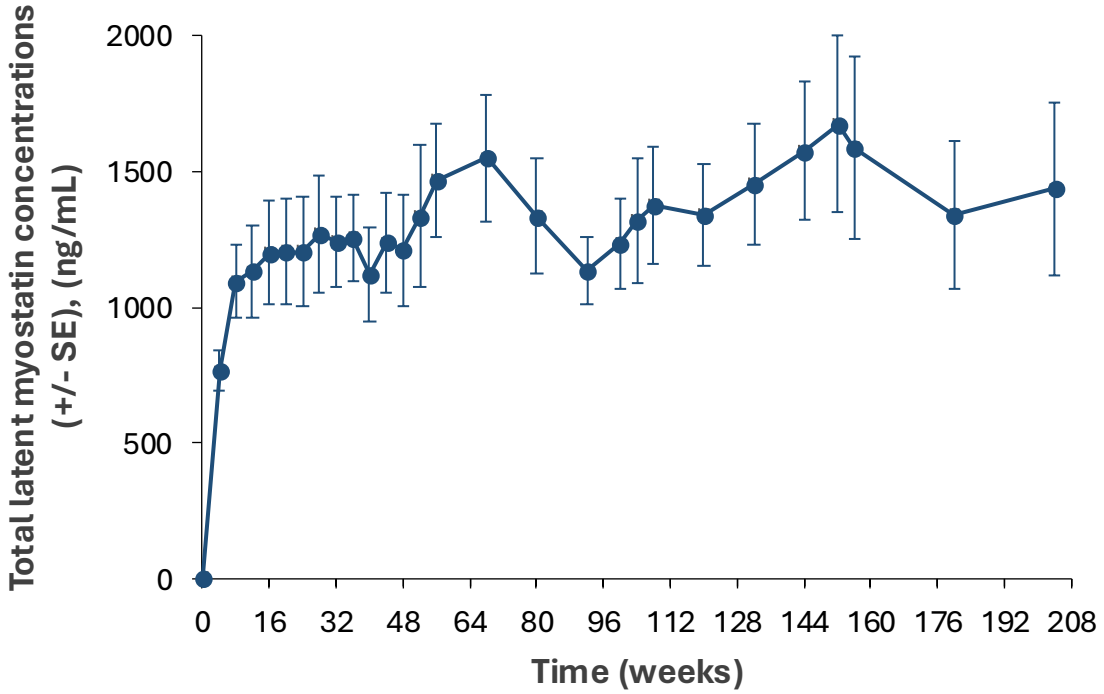


- Motor function by HFMSE improved following apitegromab vs placebo regardless of baseline functional levels
- Point estimates may not accurately reflect effect size given the small sample size of subgroups

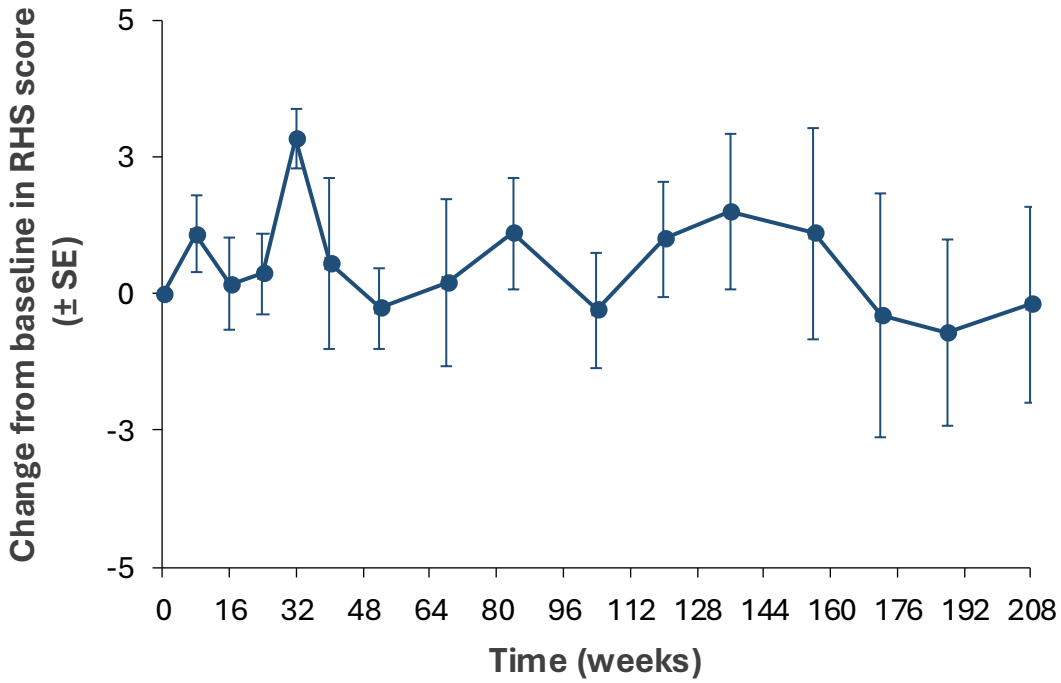
CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale–Expanded; LS, least squares.
Scholar Rock. Data on file.

TOPAZ: target engagement and motor function by RHS in ambulatory patients

PD in ambulatory patients receiving apitegromab + nusinersen (TOPAZ)



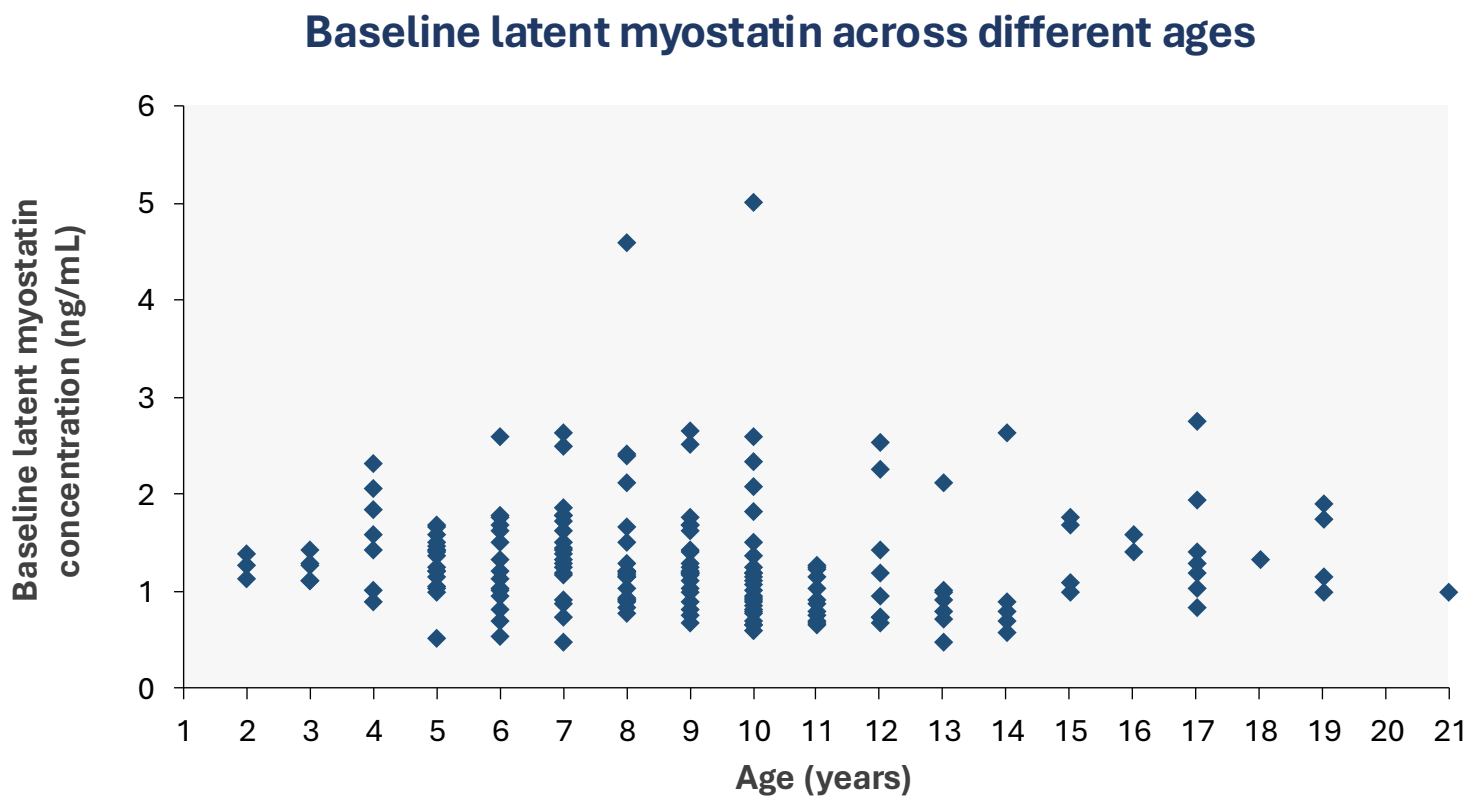
Motor function by RHS in ambulatory patients (TOPAZ)



- Robust and sustained target engagement following apitegromab treatment in 12 ambulatory patients receiving nusinersen
- Motor function by RHS, a scale developed for a broad range of physical abilities, was stable over 4 years

Lower limit of quantification for total latent myostatin concentration is 0.15 ng/mL.
PD, pharmacodynamics; RHS, Revised Hammersmith Scale; SE, standard error.
Scholar Rock. Data on file.

SAPPHIRE: measurable latent myostatin across age groups

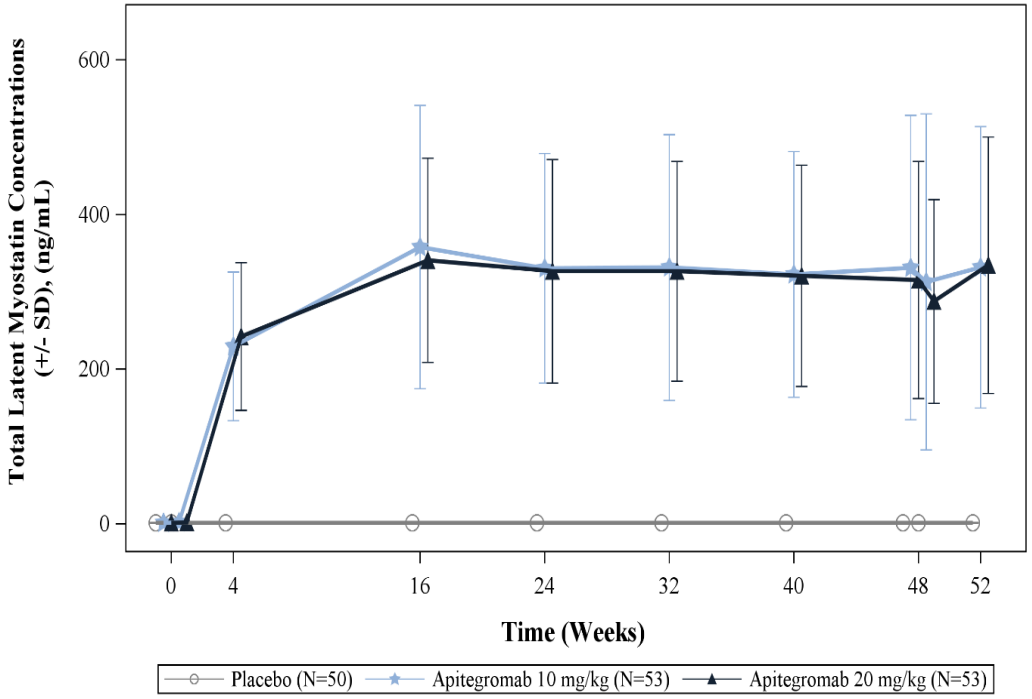


- Study population for both SAPPHIRE and TOPAZ enrolled patients aged 2-21 years
- Latent myostatin measurable and generally similar across age groups
- Apitegromab is therefore expected to enhance muscle growth and function across age groups

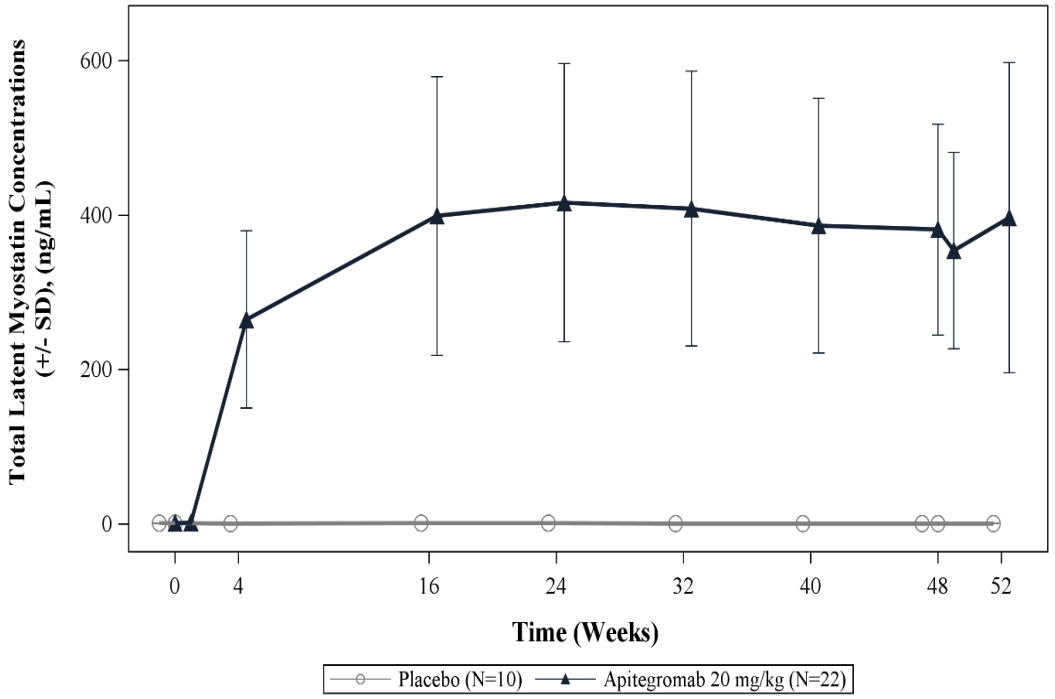
Lower limit of quantification for total latent myostatin concentration is 0.15 ng/mL.
Scholar Rock. Data on file.

SAPPHIRE: target engagement across age groups

Aged 2-12 years



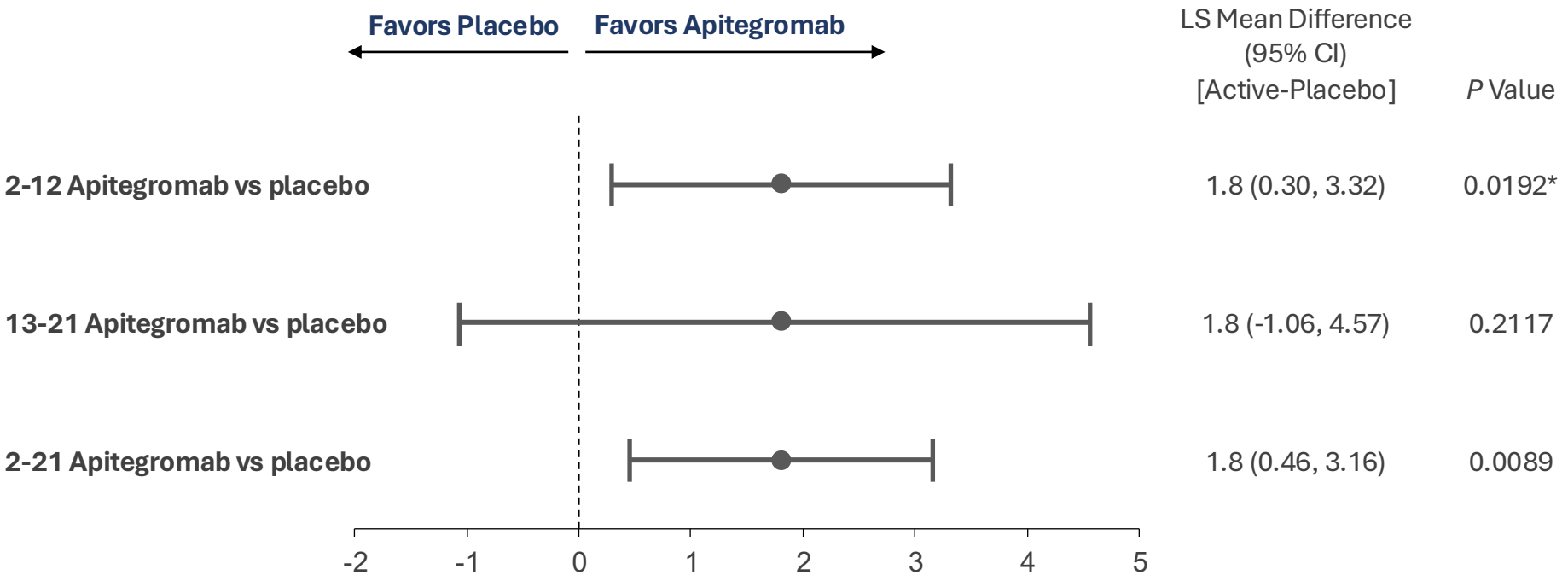
Aged 13-21 years



- Robust and sustained target engagement following treatment across age groups
- Target engagement is similar across both age groups

Pharmacodynamics data are shown as mean (±SD) ng/mL. Lower limit of quantification for total latent myostatin concentration is 0.15 ng/mL.
SD, standard deviation.
Scholar Rock. Data on file.

SAPPHIRE: motor function by HFMSE across age groups



- Motor function improved following apitegromab treatment across 2-12 and 13-21 years (SAPPHIRE)
- Effect size was the same across 2-12 and 13-21 years

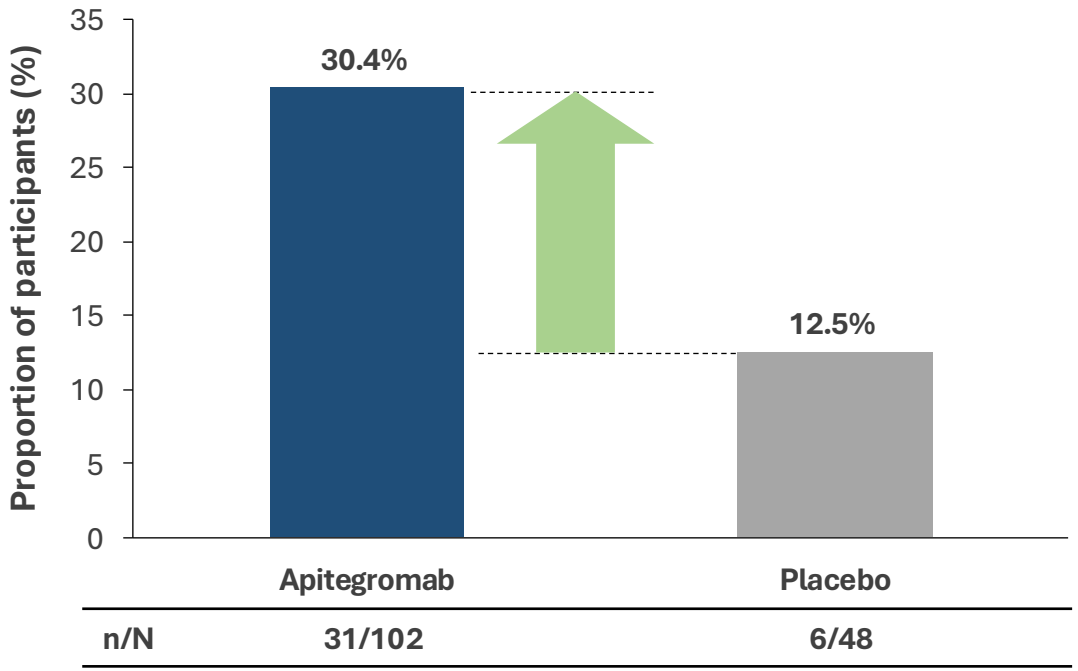
*Hochberg method was prespecified in Primary analysis for multiplicity control

2-12, population aged 2 to 12 years; 13-21, population aged 13 to 21 years; 2-21, pooled population aged 2 to 21 years; CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale–Expanded; LS, least squares.

Scholar Rock. Data on file.

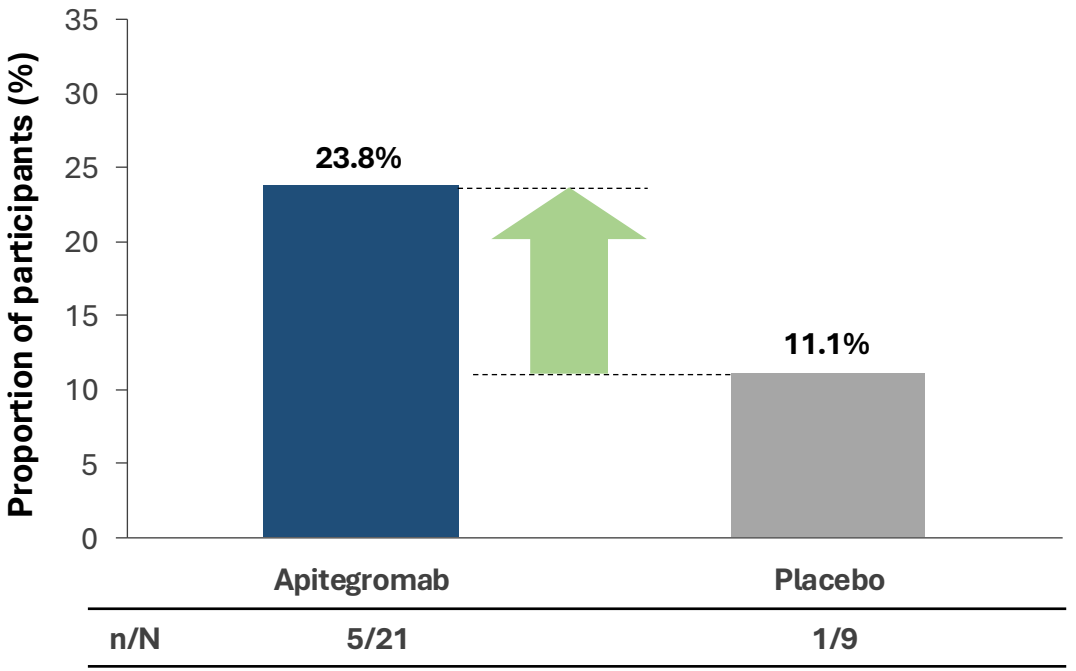
SAPPHIRE: motor function by ≥3-point HFMSE gain across age groups

Aged 2-12 years[a]



Odds ratio[b] of **3.0** favoring apitegromab (*P*=0.0256)

Aged 13-21 years[a]



Odds ratio[b] of **4.0** favoring apitegromab (*P*=0.2838)

- The proportion of patients achieving a ≥3-point gain in HFMSE was similar between patients aged 2-12 and 13-21 years

[a]Statistics are based on observed cases. [b]Statistics are based on 100 imputed datasets. Logistic regression model includes covariates of baseline HFMSE total score and type of SMN-targeted treament (ie, nusinersen or risdiplam). For the 2-12 population, age at initiation of SMN-targeted treatment (≥5 and <5 years) is also included in the logistic regression as covariate.
HFMSE, Hammersmith Functional Motor Scale–Expanded; SMN, survival motor neuron.
Scholar Rock. Data on file.

Conclusions

- **SMA is a single disease with common disease biology and shared clinical characteristics**
  - Myostatin regulates muscle throughout life, across healthy individuals and diseases, including SMA
  - The therapeutic hypothesis of apitegromab, based on this well-established physiological mechanism, is therefore applicable across disease severity and age groups
- **Clinical evidence provides strong support that apitegromab efficacy is broadly applicable**
  - Latent myostatin, the therapeutic target for apitegromab, was consistently measurable across disease severity and age groups (2-12 vs 13-21 years)
  - Robust target engagement and motor function benefit were consistent across disease severity and age groups

Acknowledgments

- We are grateful to all the patients who participated in the study and to their families, caregivers, clinicians, and patientadvocacy groups for their dedication and support.
- Funding for this trial is provided by Scholar Rock.
- Editorial support was provided by Dena McWain of Helios Global Group and funded by Scholar Rock. Project management support was provided by Ilia Antonino of Scholar Rock.

SMA, spinal muscular atrophy.