Efficacy and safety of apitegromab in individuals with type 2 and type 3 spinal muscular atrophy evaluated in the phase 3 SAPPHIRE trial

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Declaration of interests

Dr. Thomas Crawford is the lead principal investigator of the SAPPHIRE trial

Consulting/advisory boards:

- AveXis/Novartis
- Biogen
- Pfizer
- Roche/Genentech
- Scholar Rock

Study site investigator:

- AveXis/Novartis
- Biogen
- Catalyst
- Cytokinetics
- Parexel
- Scholar Rock

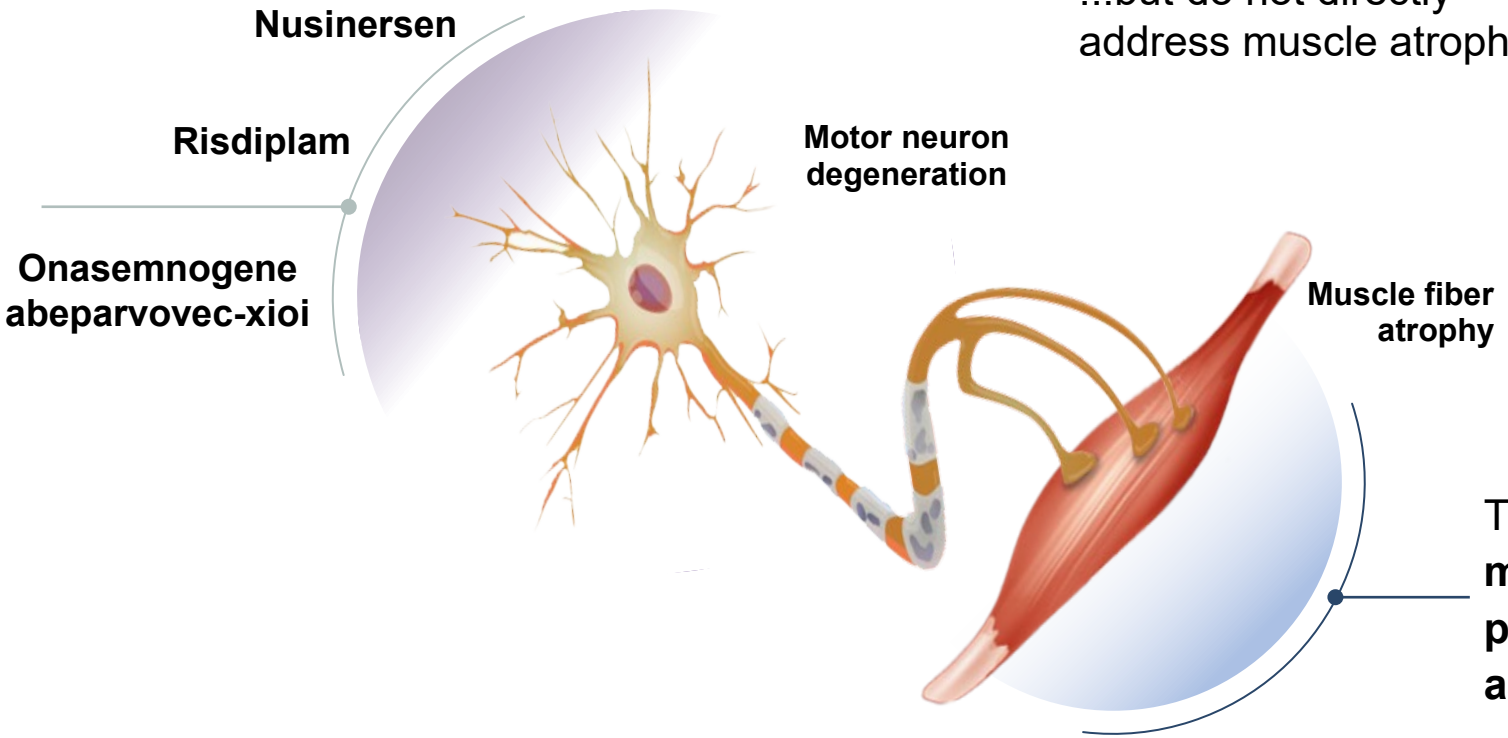
Patient organizations:

- A-T Children's Project
- Cure SMA
- MDA
- SMA Foundation

A-T, ataxia telangiectasia; MDA, Muscular Dystrophy Association; SMA, spinal muscular atrophy.

SMA disease pathology: motor neuron degeneration and muscle atrophy

SMN-targeted therapies
slow further degeneration of motor neurons[1]

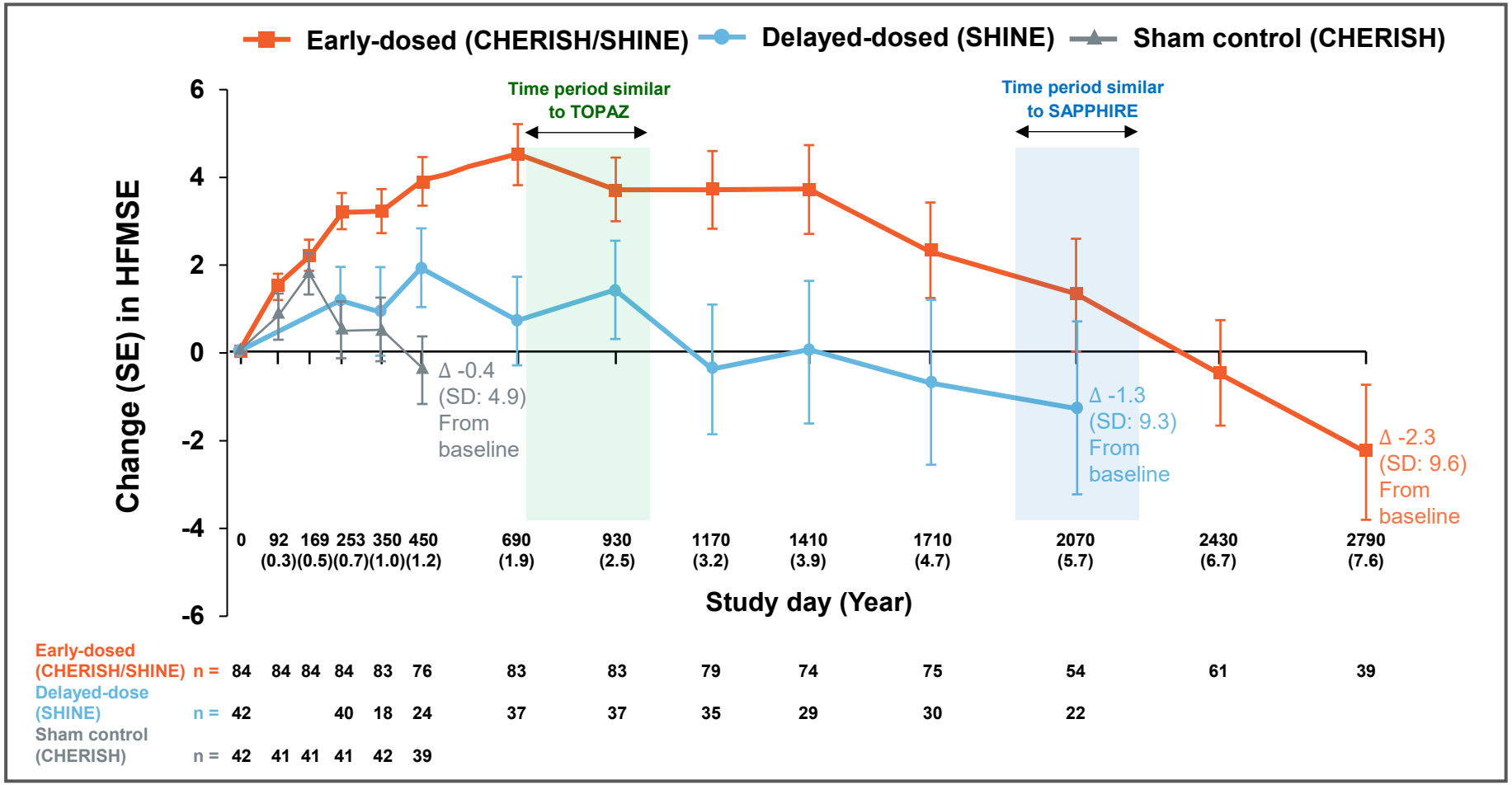


...but do not directly address muscle atrophy

There is further potential to **regain vital muscle function** by addressing the **progressive muscle atrophy and associated weakness** of SMA

Figure adapted from: SMA Foundation Overview. Accessed February 11, 2025. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf
SMA, spinal muscular atrophy; SMN, survival motor neuron.
1. Hua Y, et al. *Nature*. 2011;478(7367):123-6.

Patients with SMA continue to lose function over time despite treatment



- On average, the TOPAZ study population is on the plateau phase of nusinersen treatment, and the SAPPHIRE study population is on the declining phase of nusinersen treatment

Patient age based on those who received active treatment (mean or median).
HFMSE, Hammersmith Functional Motor Scale Expanded; SD, standard deviation; SE, standard error.

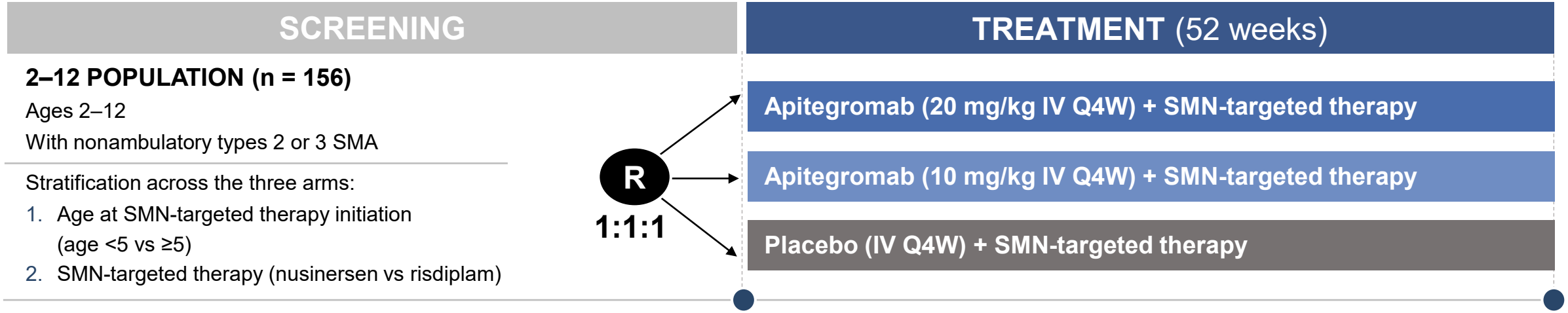
1. Finkel RS, et al. Poster at Annual SMA Research and Clinical Care Meeting; June 5-7, 2024. P95.

Phase 3 SAPPHIRE trial design

Randomized, double-blind, placebo-controlled, parallel-arm design (n = 188)

Key Eligibility Criteria

- Patients with nonambulatory type 2 or 3 SMA, receiving an approved SMN-targeted therapy, ages 2–21
- Motor function score by HFMSE ≥10 and ≤45 at the screening visit



Primary efficacy population, ages 2–12 (n = 156)

Primary efficacy endpoint
Mean HFMSE change from baseline at 12 months

Additional efficacy: RULM, WHO, other outcome measures

Safety, PK/PD, ADA

Older subpopulation, ages 13–21 (n = 32)

Exploratory endpoints
Efficacy: mean HFMSE change from baseline at 12 months

Additional efficacy: RULM, WHO, other outcome measures

Safety, PK/PD, ADA

ClinicalTrials.gov Identifier: NCT05156320. The older subpopulation was stratified by SMN-targeted therapy, randomized 2:1 between apitegromab 20 mg/kg vs placebo.
2–12, population aged 2 to 12 years; ADA, antidrug antibody; HFMSE, Hammersmith Functional Motor Scale Expanded; IV, intravenous; PD, pharmacodynamics; PK pharmacokinetics; Q4W, every 4 weeks; R, randomization; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO, World Health Organization.

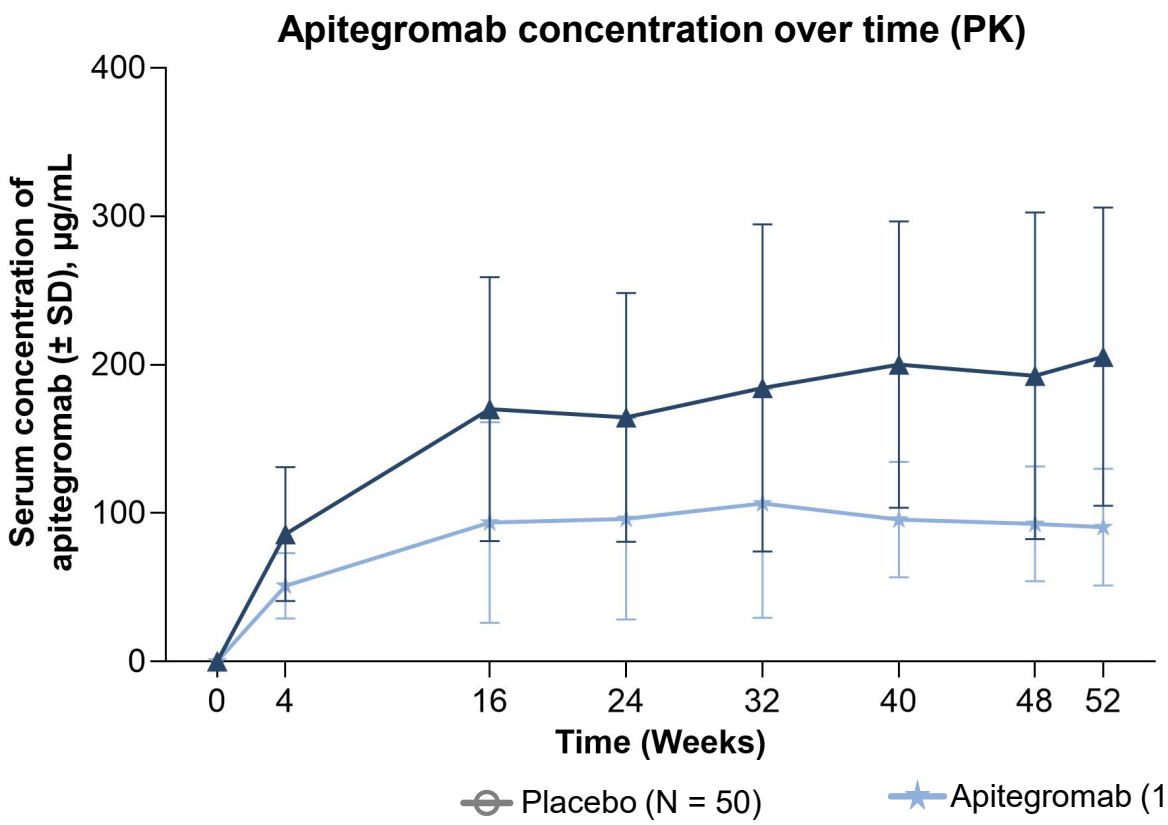
SAPPHIRE participant demographics and disease characteristics were well-balanced

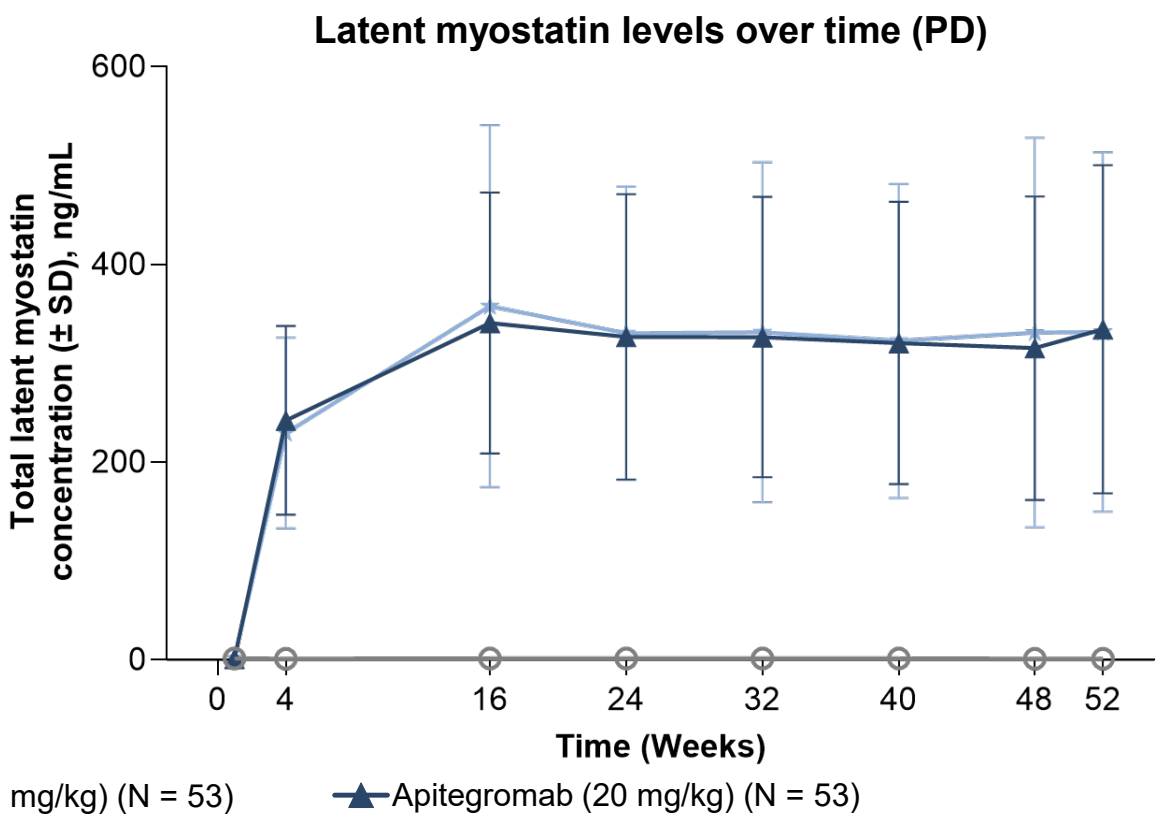
	2–12 population				13–21 population	
	Placebo + SOC (N = 50)	Apitegromab 20 mg/kg + SOC (N = 53)	Apitegromab 10 mg/kg + SOC (N = 53)	Apitegromab 20 & 10 mg/kg + SOC (N = 106)	Placebo + SOC (N = 10)	Apitegromab 20 mg/kg + SOC (N = 22)
Female sex, n (%)	25 (50.0)	26 (49.1)	23 (43.4)	49 (46.2)	5 (50.0)	15 (68.2)
Mean age at screening, years (min, max)	8.1 (3, 12)	7.9 (2, 12)	7.4 (2, 12)	7.6 (2, 12)	15.2 (13, 18)	16.1 (13, 21)
SMN-targeted therapy at randomization						
Nusinersen/risdiplam, %	80/20	77.4/22.6	75.5/24.5	76.4/23.6	60/40	54.5/45.5
Mean duration of nusinersen/risdiplam, years	5.5/2.7	5.3/3.5	4.4/3.0	4.8/3.2	6.7/3.3	5.9/3.8
SMN-targeted therapy initiation age, <5/≥5 years, %	88/12	84.9/15.1	86.8/13.2	85.8/14.2	N/A	N/A
Number of SMN-targeted therapies, 1/2, %	86/14	84.9/15.1	86.8/13.2	85.8/14.2	80/20	90.9/9.1
SMA type, type 2/3, %	94/6	90.6/9.4	83/17	86.8/13.2	60/40	40.9/59.1
SMN2 copy number, 2/3/4, %	4/90/2	7.5/86.8/5.7	11.3/77.4/7.5	9.4/82.1/6.6	0/80/10	4.5/59.1/18.2
Mean baseline HFMSE score (min, max)	27.8 (9, 46)	25.5 (10, 43)	25.5 (9, 48)	25.5 (9, 48)	22.8 (10, 45)	20.6 (8, 43)
History of scoliosis, %	70	71.7	71.7	71.7	90	86.4

- Study population was broadly representative of SMA population
- Baseline demographics and disease characteristics were well balanced across arms
- Patients were in the advanced phase of their SMN-targeted therapy journey

Baseline demographics and clinical characteristics are presented for all randomized participants. Baseline HFMSE total score was defined as the last nonmissing measurement prior to or on the day of the first dosing.
"SOC" represents treatment with either nusinersen or risdiplam.
2–12, population aged 2 to 12 years; 13–21, population aged 13 to 21 years; HFMSE, Hammersmith Functional Motor Scale Expanded; max, maximum; min, minimum; N/A, not applicable; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival motor neuron; SOC, standard of care.

SAPPHIRE PK and PD vs time



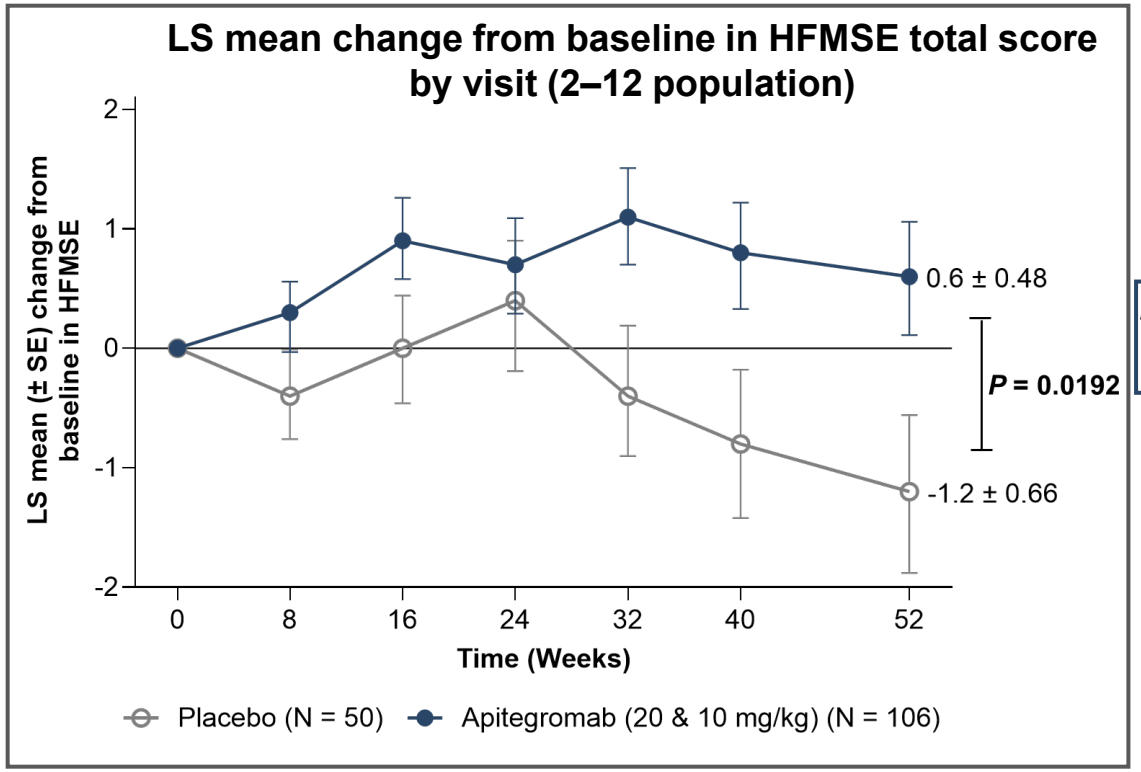


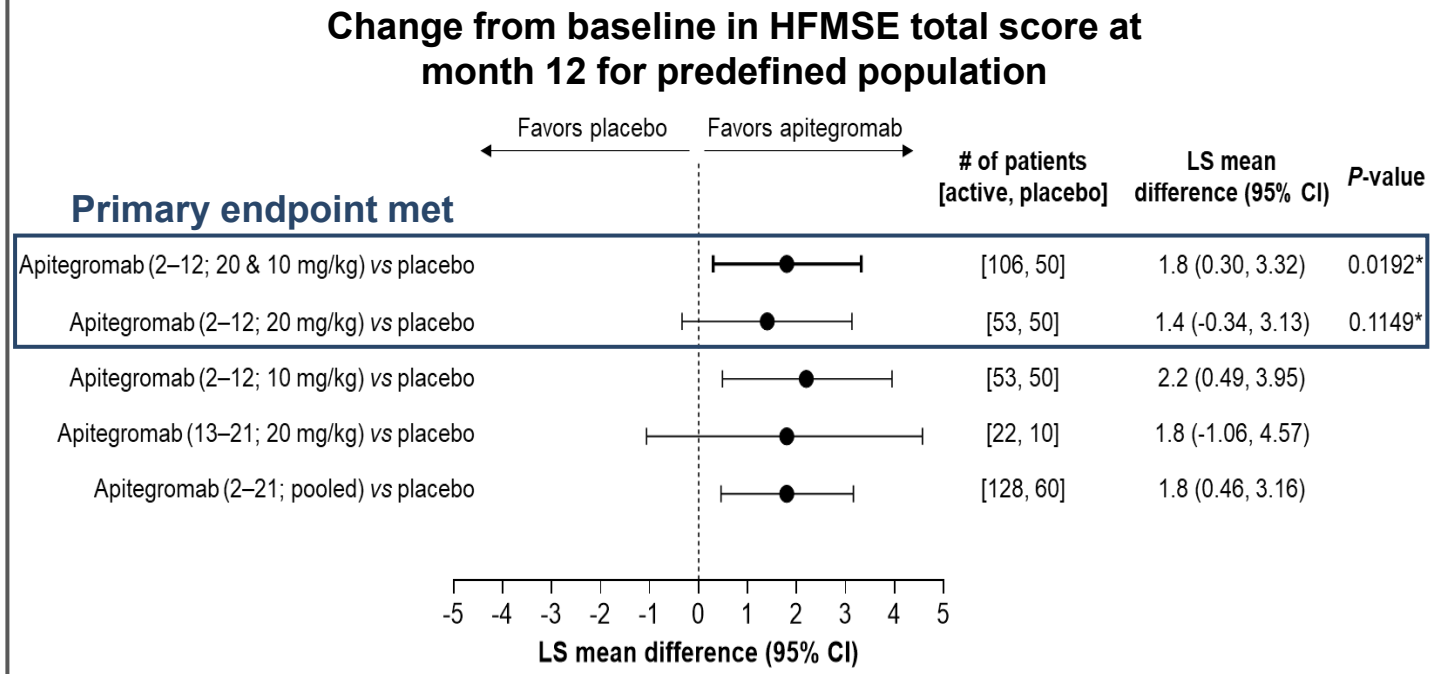
Placebo (N = 50)
Apitegromab (10 mg/kg) (N = 53)
Apitegromab (20 mg/kg) (N = 53)

- Increase in exposure of apitegromab (PK) was generally dose-proportional
- Robust and sustained target engagement (PD) was observed following apitegromab dosing
- Similar levels of target engagement were observed for 10 mg/kg and 20 mg/kg

PK data are shown as geometric mean (± SD) µg/mL, and PD data are shown as mean (± SD) ng/mL. PK samples from patients receiving placebo were not tested and therefore not included in PK assessments.
2–12, population aged 2 to 12 years; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation.

Primary endpoint met with consistency across doses and age groups



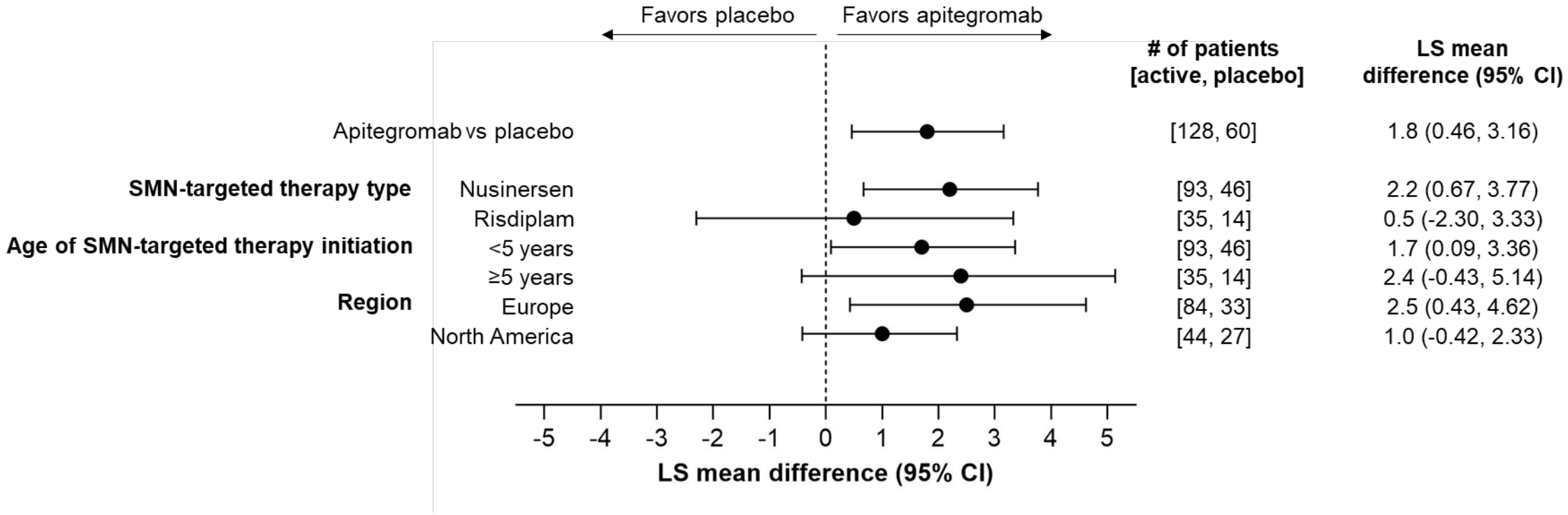


- Primary endpoint met based on the comparison of apitegromab (20 and 10 mg/kg) vs placebo with $P \leq 0.025$
- Motor function outcomes were consistent across 2–12 and 13–21 SAPPHIRE populations, favoring apitegromab vs placebo
- Patients treated with apitegromab demonstrated improved motor function while those on placebo lost function over time

*P-values controlled for multiplicity.
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.

Efficacy was consistent across subgroups in pooled 2–21 population

Change from baseline in HFMSE total score at month 12 – subgroup analyses for pooled population

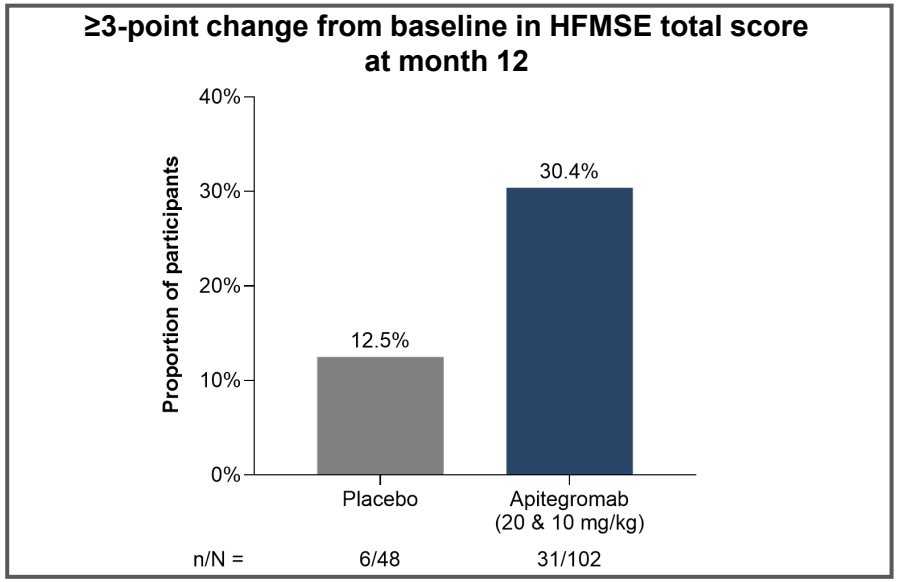


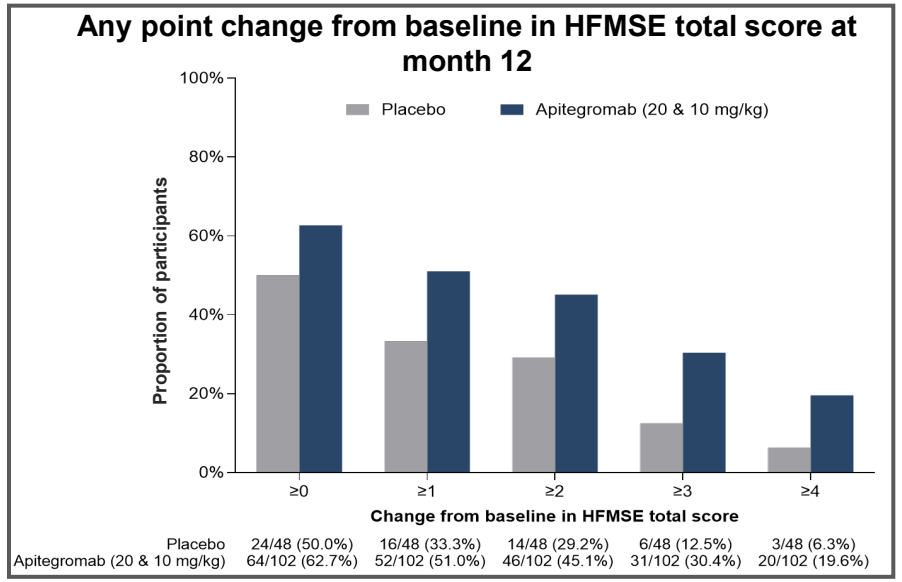
- Efficacy was consistent across prespecified subgroups (type of SMN-targeted therapy, age of SMN-targeted therapy initiation) and region

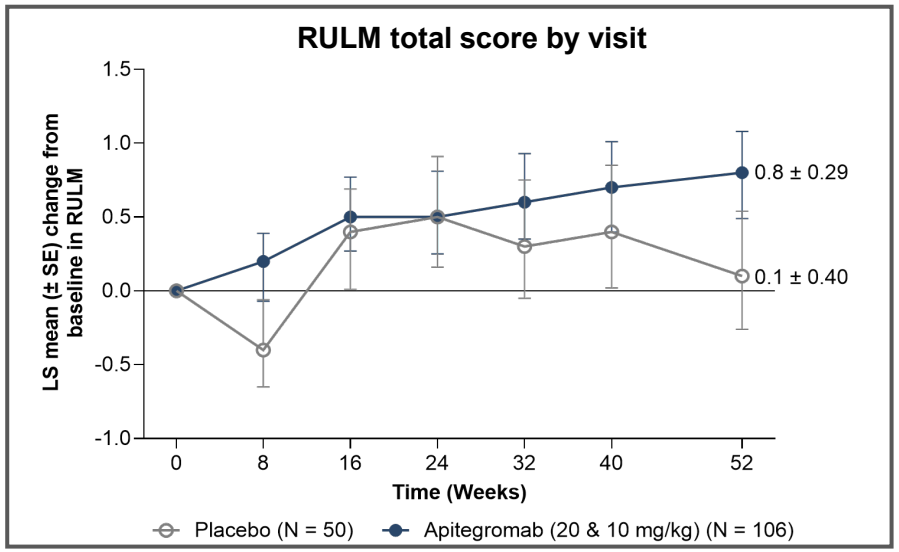
SMN-targeted therapy type was a randomization stratification factor for both the 2–12 population and 13–21 population. Age at initiation of SMN-targeted therapy (<5 years or ≥5 years) is derived from the age the participant received the first dose of SMN-targeted therapy in months.

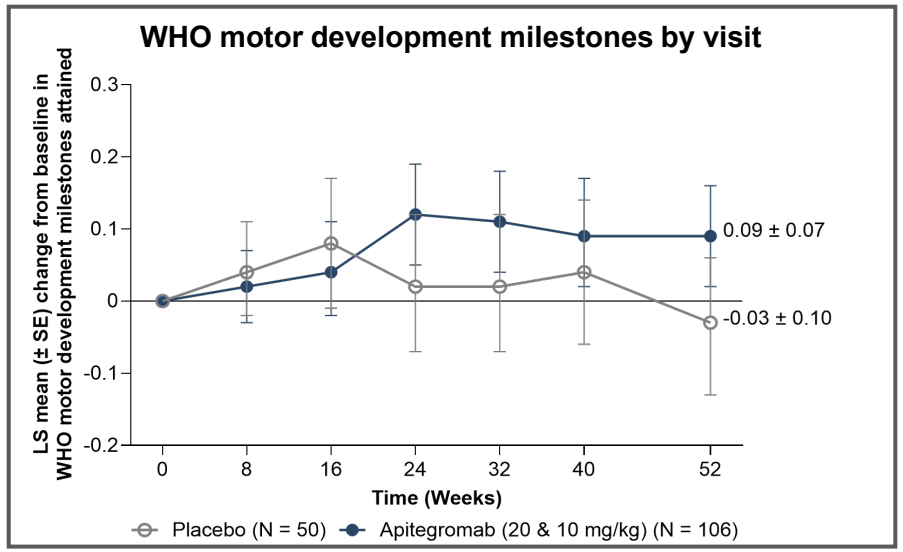
2–21, population aged 2 to 21 years; CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; LS, least squares; SMN, survival motor neuron.

Secondary endpoint outcomes for the 2–12 population









- Patients treated with apitegromab demonstrated improved motor function vs placebo
- Efficacy was consistent across outcome measures, including HFMSE, RULM, and WHO motor developmental milestones
- A greater proportion of participants treated with apitegromab had ≥3-point improvements in their HFMSE scores vs placebo (odds ratio 3.0, nominal $P = 0.0256$)
- Higher proportions of patients on apitegromab achieved HFMSE improvements vs placebo across all point thresholds

Proportionality data are based on the observed data for the placebo and apitegromab treatment groups. One participant from the apitegromab 10 mg/kg dose group was too young at baseline to conduct the RULM and therefore was not included in RULM analyses.
2–12, population aged 2 to 12 years; HFMSE, Hammersmith Functional Motor Scale Expanded; LS, least squares; RULM, Revised Upper Limb Module; SE, standard error; WHO, World Health Organization.

Well-tolerated safety consistent with established profile

Summary of AEs n (%)	2–12 population				13–21 population	
	Placebo + SOC (N = 50)	Apitegromab 20 mg/kg + SOC (N = 53)	Apitegromab 10 mg/kg + SOC (N = 53)	Apitegromab 20 & 10 mg/kg + SOC (N = 106)	Placebo + SOC (N = 10)	Apitegromab 20 mg/kg + SOC (N = 22)
AE	43 (86.0)	46 (86.8)	51 (96.2)	97 (91.5)	9 (90.0)	19 (86.4)
SAE	5 (10.0)	12 (22.6)	9 (17.0)	21 (19.8)	1 (10.0)	0
AE grade ≥3	5 (10.0)	11 (20.8)	9 (17.0)	20 (18.9)	1 (10.0)	1 (4.5)
AE leading to treatment discontinuation	0	0	0	0	0	0
AE leading to study withdrawal	0	0	0	0	0	0
AE with highest incidence						
Pyrexia	16 (32.0)	13 (24.5)	18 (34.0)	31 (29.2)	1 (10.0)	2 (9.1)
Nasopharyngitis	10 (20.0)	11 (20.8)	15 (28.3)	26 (24.5)	4 (40.0)	6 (27.3)
Cough	11 (22.0)	11 (20.8)	15 (28.3)	26 (24.5)	1 (10.0)	4 (18.2)
SAE with highest incidence						
Pneumonia	0	4 (7.5)	3 (5.7)	7 (6.6)	0	0
Dehydration	0	1 (1.9)	2 (3.8)	3 (2.8)	0	0

- Treatment with apitegromab was well-tolerated across all age groups, consistent with established safety profile[1,2]
- There were no clinically relevant differences in the AE profile by dose (10 mg/kg vs 20 mg/kg)
- SAEs were consistent with underlying disease and SMN-targeted therapy[3,4]; no SAEs were assessed as related to apitegromab
- There were no deaths or study-drug discontinuations due to AEs
- One patient tested positive for ADA; the samples were further assessed and determined to be below the sensitivity cutoff point

All AEs were coded using the MedDRA version 26.1.
2–12, population aged 2 to 12 years; 13–21, population aged 13 to 21 years; ADA, antidrug antibody; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities Terminology; SAE, serious AE; SOC, standard of care.

1. Crawford TO, et al. *Neurology*. 2024;102:e209151. **2.** Crawford TO, et al. *Front Neurol.* 2024;15:1419791. **3.** Spinraza. Package insert. Biogen; 2024. **4.** Evrysdi. Package insert. Genentech; 2024.

Conclusions

- Apitegromab treatment resulted in statistically significant and clinically meaningful[1-3] improvements in motor function
  - Efficacy results were consistent across outcomes measures (HFMSE, RULM, and WHO)
  - Efficacy results were consistent across age, background SMN-targeted therapy, age of SMN-targeted therapy initiation, and region
  - Based on similar PD, efficacy, and safety, the benefit-risk profile was optimized at the apitegromab 10 mg/kg dose
- Safety profile was consistent with the underlying SMA patient population and background SMN-targeted therapy[4-7]
- SAPPHIRE results represent the first time a myostatin-targeting agent has demonstrated improved function in any disease in a placebo-controlled clinical setting

Acknowledgments

- We are grateful to all the patients who participated in the study and to their families, caregivers, health care professionals, and patient advocacy groups for their dedication and support.
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HFMSE, Hammersmith Functional Motor Scale Expanded; PD, pharmacodynamics; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO, World Health Organization.

1. Pera MC, et al. *BMN Neurol.* 2017;17:39. **2.** Stolte B, et al. *Eur J Neurol.* 2020;27:2586-94. **3.** Wu JW, et al. *Am J Phys Med Rehabil.* 2022;101:590-608. **4**. Crawford TO, et al. *Neurology.* 2024;102:e209151. **5.** Crawford TO, et al. *Front Neurol.* 2024;15:1419791. **6.** Spinraza. Package insert. Biogen; 2024. **7.** Evrysdi. Package insert. Genentech; 2024.