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Pharmacokinetics (PK) and pharmacodynamics (PD) of apitegromab in spinal muscular atrophy

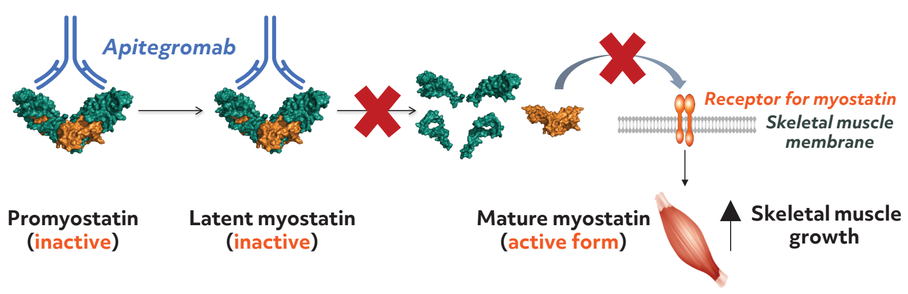
Giridhar S. Tirucherai,[1] Yang Xu,[1] Amanda Singh,[2] Sanela Bilic,[2] Nathalie H. Gosselin,[3] Kathleen Koeck,[3] Shaun M. Cote,[1] Bert Yao,[1] Jing L. Marantz[1]

[1]Scholar Rock, Inc., Cambridge, MA, USA; [2]Vanadro Drug Development Consulting, West Des Moines, IA, USA; [3]Certara Drug Development Solutions, Radnor, PA, USA

INTRODUCTION

- Spinal muscular atrophy (SMA) is a genetic neuromuscular disease characterized by motor neuron degeneration and progressive skeletal muscle atrophy and weakness[1]
- Myostatin, a negative regulator of muscle mass, requires 2 distinct proteolytic events to generate the active mature growth factor[2]
- Apitegromab is a fully human monoclonal antibody that selectively binds with high affinity to promyostatin and latent myostatin, preventing cleavage and release of mature myostatin (**Figure 1**)[2-4]
- The apitegromab clinical development program includes completed Phase 2 (TOPAZ, NCT03921528) and Phase 3 (SAPPHIRE, NCT05156320) trials, which evaluated the efficacy and safety of apitegromab in participants aged 2-21 years with Type 2/3 SMA receiving survival motor neuron (SMN)-targeted treatment[4,5]

Figure 1. Apitegromab mechanism of action[2,6]



OBJECTIVE

- To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) at various doses of apitegromab in participants with SMA using population PK and PK/PD modeling

METHODS

- Apitegromab was administered to participants aged 2-21 years with Type 2/3 SMA by intravenous (IV) infusion every 4 weeks (Q4W) at 2 or 20 mg/kg (TOPAZ) or 10 or 20 mg/kg (SAPPHIRE)
  - Baseline demographics and characteristics are listed in **Table 1** for TOPAZ and **Table 2** for SAPPHIRE
- Population PK was described using a 2-compartment model incorporating time-varying body weight and age as covariates on clearance and volume of distribution[7]
  - Healthy volunteers and 186 participants with SMA were included in the PK dataset (TOPAZ, n=58; SAPPHIRE, n=128)
  - The age effect on clearance was implemented with a maturation function, allowing for age-dependent changes in clearance independent of changes in body weight
- PK/PD was characterized by an indirect response model with a drug effect on the output
  - 246 participants were included in the PK/PD dataset (TOPAZ, n=58; SAPPHIRE, n=188)
  - Baseline serum total latent myostatin values were used to anchor initial conditions of the equations to allow fitting of the absolute change
- An exposure-response model was developed using data from SAPPHIRE participants aged 2-12 years to characterize the relationship between change from baseline in Hammersmith Functional Motor Scale–Expanded (HFMSE) total score at Week 52 and total latent myostatin exposure
- Exposure response analyses for safety were performed using data from SAPPHIRE participants aged 2-21 years

Table 1. TOPAZ baseline demographics and clinical characteristics

	Ambulatory participants aged 5-21 y	Nonambulatory participants aged 5-21 y	Nonambulatory participants aged ≥2 y	
TOPAZ	Cohort 1: Apitegromab 20 mg/kg ± nusinersen (n=23)	Cohort 2: Apitegromab 20 mg/kg + nusinersen (n=15)	Cohort 3: Apitegromab 20 mg/kg + nusinersen (n=10)	Cohort 3: Apitegromab 2 mg/kg + nusinersen (n=10)[a]
Female, n (%)	15 (65.2)	8 (53.3)	5 (50.0)	3 (30.0)
Mean age at baseline (min, max), y	12.6 (7, 21)	11.7 (8, 19)	3.8 (2, 6)	4.1 (2, 6)
Mean baseline weight (min, max), kg	46.0 (19, 98)	43.4 (19, 91)	16.1 (12, 20)	14.5 (8, 23)
SMA Type 2/3, %	0/100	33.0/67.0	100/0	100/0
Mean duration on nusinersen prior to trial[b] (min, max), mo	19.9 (12, 28)	24.2 (12, 39)	23.7 (17, 31)	24.3 (10, 34)

[a]Based on the results of the prespecified 6-month safety and efficacy interim analyses, Cohort 3 participants who were randomized to receive apitegromab 2 mg/kg were reassigned to receive apitegromab 20 mg/kg after completion of the treatment period. [b]Time on nusinersen prior to study is estimated as 2 months (for the loading dose) plus 4 months for each maintenance dose plus the time from the last dose to the first day on study treatment (computed as a difference in days divided by 30); not presented for Cohort 1 apitegromab monotherapy participants.
SMA, spinal muscular atrophy.

Table 2. SAPPHIRE baseline demographics and clinical characteristics

	Nonambulatory participants aged 2-12 y			Nonambulatory participants aged 13-21 y	
SAPPHIRE	Placebo + SMN-targeted treatment (n=50)	Apitegromab 20 mg/kg + SMN-targeted treatment (n=53)	Apitegromab 10 mg/kg + SMN-targeted treatment (n=53)	Placebo + SMN-targeted treatment (n=10)	Apitegromab 20 mg/kg + SMN-targeted treatment (n=22)
Female, n (%)	25 (50.0)	26 (49.1)	23 (43.4)	5 (50.0)	15 (68.2)
Mean age at screening (min, max), y	8.1 (3, 12)	7.9 (2, 12)	7.4 (2, 12)	15.2 (13, 18)	16.1 (13, 21)
Mean baseline weight (min, max), kg	27.0 (11, 58)	25.9 (10, 64)	26.2 (14, 54)	49.0 (35, 62)	50.2 (27, 74)
SMA Type 2/3, %	94.0/6.0	90.6/9.4	83.0/17.0	60.0/40.0	40.9/59.1
SMN-targeted treatment at randomization					
Nusinersen/risdiplam, %	80.0/20.0	77.4/22.6	75.5/24.5	60.0/40.0	54.5/45.5
Mean duration of nusinersen/risdiplam, y	5.5/2.7	5.3/3.5	4.4/3.0	6.7/3.3	5.9/3.8
Number of SMN-targeted treatments, 1/2, %	86.0/14.0	84.9/15.1	86.8/13.2	80.0/20.0	90.9/9.1

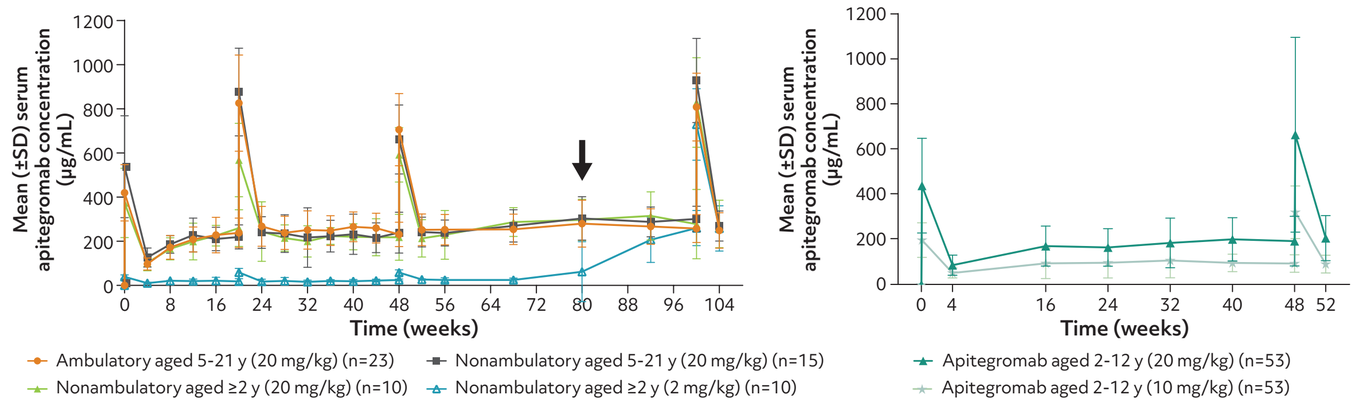
SMA, spinal muscular atrophy; SMN, survival motor neuron.

RESULTS

PK and PD

- Following IV administration, mean serum apitegromab PK was linear and dose proportional across the trials (**Figure 2**)
- No clinically meaningful differences in PK or PD exposure parameters, based on weight-adjusted doses, were observed according to weight, age, age group, SMN-targeted treatment type, race, ambulatory status, antidrug antibodies status, or sex, indicating no need for dose adjustments (**Figure S1**, accessible by QR code)

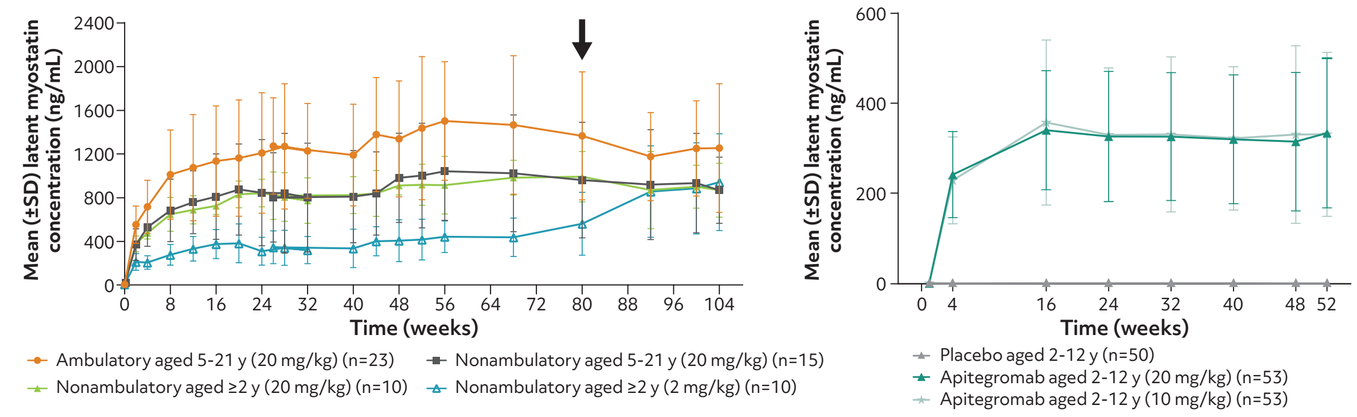
Figure 2. Serum apitegromab concentration–time profiles



[a]After completing the initial 52-week treatment period, TOPAZ participants were given the option to enroll in up to 3 open-label, 52-week extension periods to continue receiving apitegromab 20 mg/kg Q4W for a total of 4 years. [b]Participants in Cohort 3 receiving apitegromab 2 mg/kg during the 52-week treatment period were transitioned to the 20 mg/kg dose in the extension periods; most transitioned by Week 80 (arrow), and all were transitioned by Week 100. [c]PK samples shown are collected before and after infusion at Weeks 0, 20, 48, and 100, and only after infusion for all other time points. [d]PK samples shown were collected before and after infusion at Weeks 1 and 48 and only after infusion for all other time points.
PK, pharmacokinetics; Q4W, once every 4 weeks; SD, standard deviation.

- Following apitegromab dosing, robust and sustained increases in serum total latent myostatin were observed across trials
- In TOPAZ, dose-dependent target engagement was observed, with an ≈2.3-fold higher serum total latent myostatin concentration for the 20 mg/kg dose group compared with the 2 mg/kg dose group (**Figure 3A**)
- In SAPPHIRE, superimposable mean serum total latent myostatin concentration-time profiles were observed for the 10 mg/kg and 20 mg/kg dose groups (**Figure 3B**)

Figure 3. Serum total latent myostatin concentrations over time



[a]The methodology used to assess latent myostatin concentrations differed between TOPAZ and SAPPHIRE trials. [b]PD samples shown are collected before infusion. [c]Participants in Cohort 3 receiving apitegromab 2 mg/kg during the 52-week treatment period were transitioned to the 20 mg/kg dose in the extension periods; most transitioned by Week 80 (arrow), and all were transitioned by Week 100.
PD, pharmacodynamics; SD, standard deviation.

Exposure-response analyses

- The final model related HFMSE change from baseline to total latent myostatin C_{min}. The model-predicted, placebo-corrected changes from baseline were 1.66 and 1.67 points for apitegromab 10 mg/kg and 20 mg/kg, respectively (**Table 3**), consistent with the least squares mean difference of 1.8 points in the primary efficacy analysis of combined dose (apitegromab 10 mg/kg and 20 mg/kg) vs placebo in SAPPHIRE[5]
  - Concentrations of total latent myostatin were almost completely overlapping across doses (**Figure S2**, accessible by QR code)
- Apitegromab exposures in participants with adverse events (AEs) of Grade ≥3 and serious AEs were similar compared with participants without respective AEs; thus, no exposure-safety relationships were identified (**Figures S3**, **S4**, accessible by QR code)

Table 3. Model-predicted change from baseline in HFMSE total score at Week 52 in SAPPHIRE participants aged 2–12 years

Treatment	Total latent myostatin C_{min}, ng/mL	Age,[a] y	Predicted change from baseline of HFMSE	Placebo-corrected change from baseline of HFMSE
Placebo	1.24	8.9	-0.65	NA
Apitegromab 10 mg/kg Q4W	311	8.9	1.01	1.66
Apitegromab 20 mg/kg Q4W	318	8.9	1.02	1.67

[a]Model-predicted change from baseline is presented for a typical participant in the population aged 2-12 years in SAPPHIRE, with a median age at Week 52 of 8.9 years.
C_{min}, minimum concentration; HFMSE, Hammersmith Functional Motor Scale–Expanded; NA, not applicable; Q4W, once every 4 weeks.

CONCLUSIONS

- Given the absence of meaningful improvements in efficacy and no difference in safety with a 2-fold increase in dose, the recommended dose of apitegromab is 10 mg/kg
- Exposure-response modeling of HFMSE total scores at Week 52 confirmed that apitegromab demonstrated an efficacious response compared with placebo in SAPPHIRE
- Overall, clinical PK, PK/PD, exposure-efficacy, and exposure-safety analyses provide support for the efficacy and safety of the proposed 10 mg/kg Q4W dosing regimen of apitegromab treatment for patients with SMA

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Disclosures

GST, **YX**, **SMC**, **BY**, and **JLM** are employees of and stockholders in Scholar Rock, Inc. **AS**, **SB**, **NHG**, and **KK** are paid contractors of Scholar Rock, Inc.

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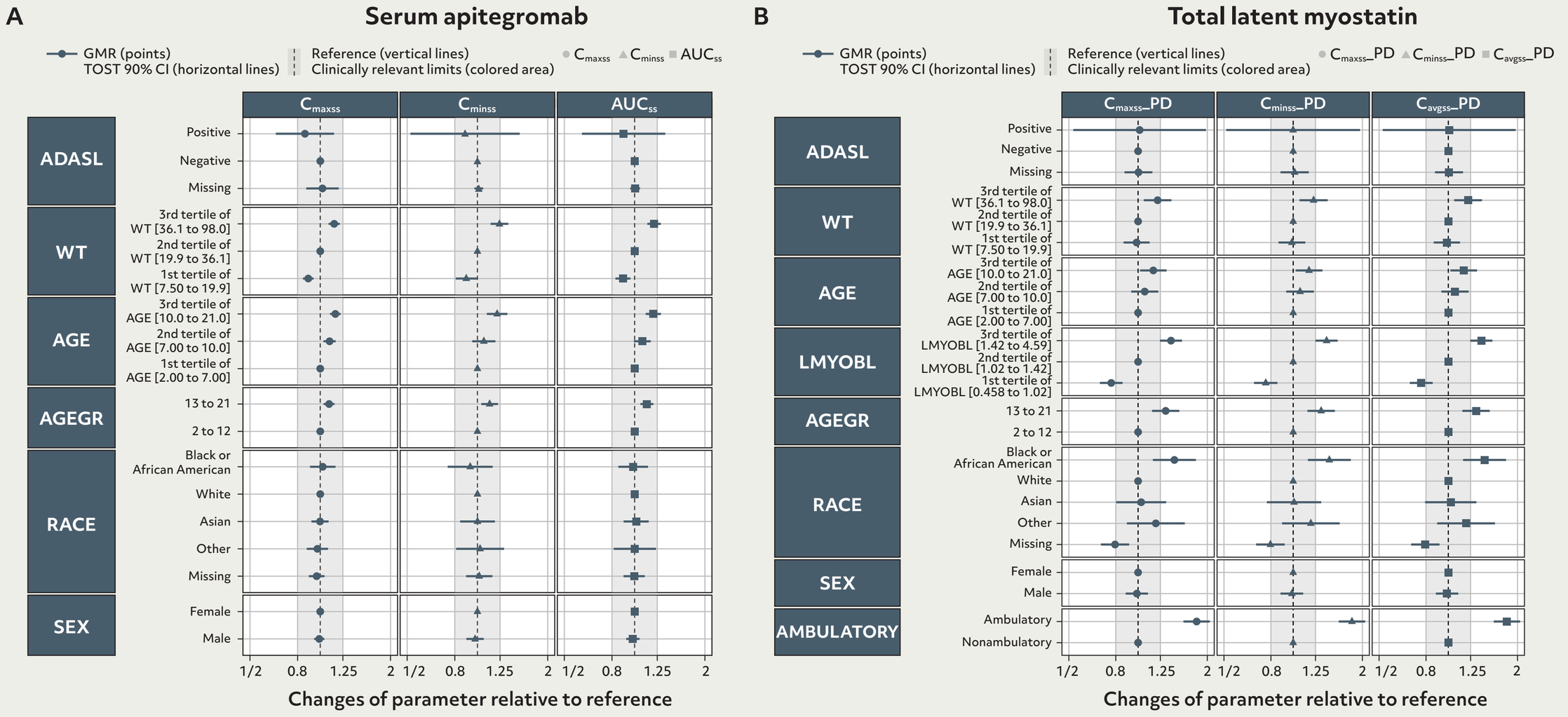
SUPPLEMENTARY MATERIAL

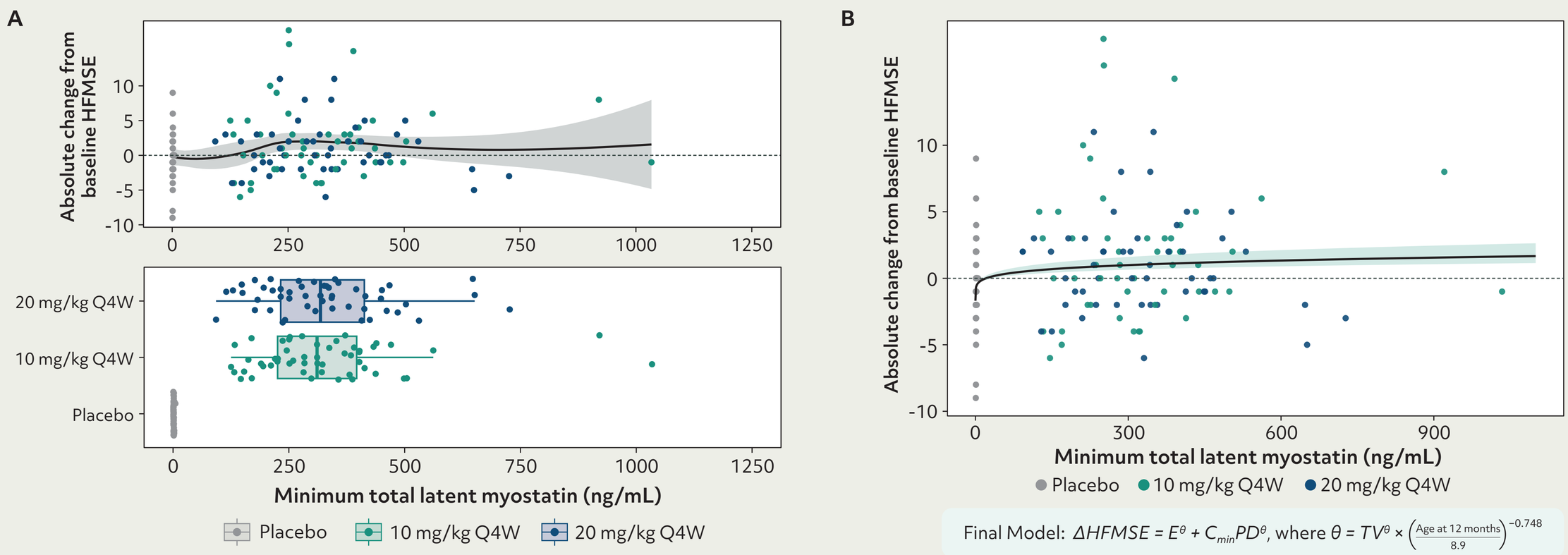
Figure S1. Impact of covariates and variables of interest[a]



[a]Individual post hoc parameter estimates from the final PK and PK/PD models were used to simulate steady-state time profiles; the derived exposure metrics were used to compare exposure between subgroups of covariates and variables of interest.

ADA, antidrug antibodies; ADASL, subject-concentration ADA status; AGEGR, age group; AUC_{ss}, area under the serum concentration-time curve at steady state over a dosing interval; C_{avgss}, average serum concentration at steady state; CI, confidence interval; C_{maxss}, maximum serum concentration at steady state; C_{minss}, minimum serum concentration at steady state; GMR, geometric mean ratio; LMYOBL, total latent myostatin at baseline; PD, pharmacodynamics; TOST, two one-sided test; PK, pharmacokinetics; WT, body weight.

Figure S2. Exposure–response model change from baseline in HFMSE score and total latent myostatin exposure C_{min} at Week 52



In A, circles represent the matched pairs of observed data for absolute change from baseline in HFMSE total score and model-predicted minimum total latent myostatin concentrations for the top panel and model-predicted minimum total latent myostatin concentrations for the bottom panel. The black line and the shaded area represent the LOESS line with 95% CI. In B, the green-shaded area represents the predictions for ages 6.9 years (upper end) and 10.9 years (lower end), and the solid black line represents the prediction for the median age of 8.9 years.

θ, exponent in the power model that related the total latent myostatin exposure to change from baseline in HFMSE; CI, confidence interval; $C_{min}PD^{\theta}$, total latent myostatin C_{min} at Week 52 in participants; C_{min}, minimum serum concentration; E^{θ}, the estimated intercept of change from baseline; HFMSE, Hammersmith Functional Motor Scale–Expanded; LOESS, locally weighted scatterplot smoothing; Q4W, once every 4 weeks; TV^{θ}, typical value of θ.

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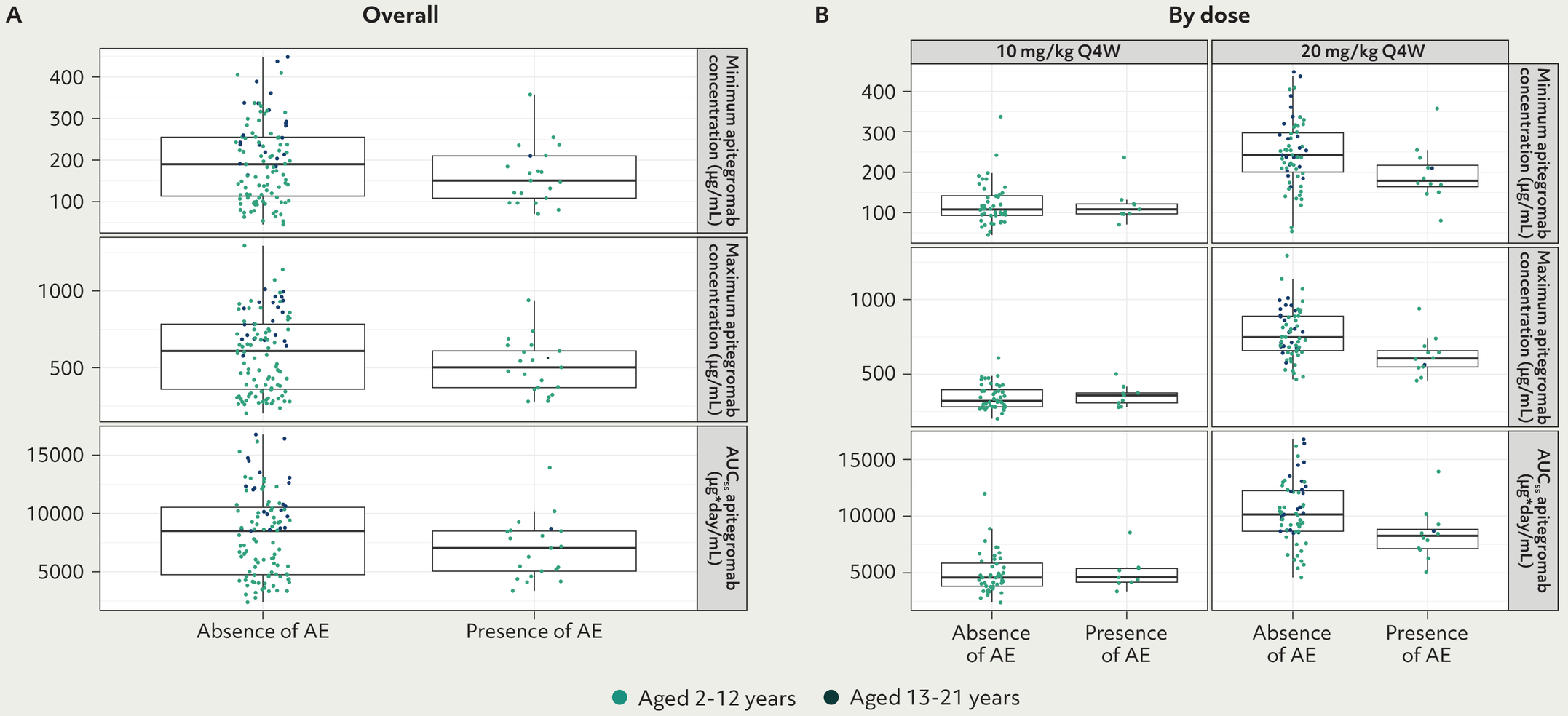
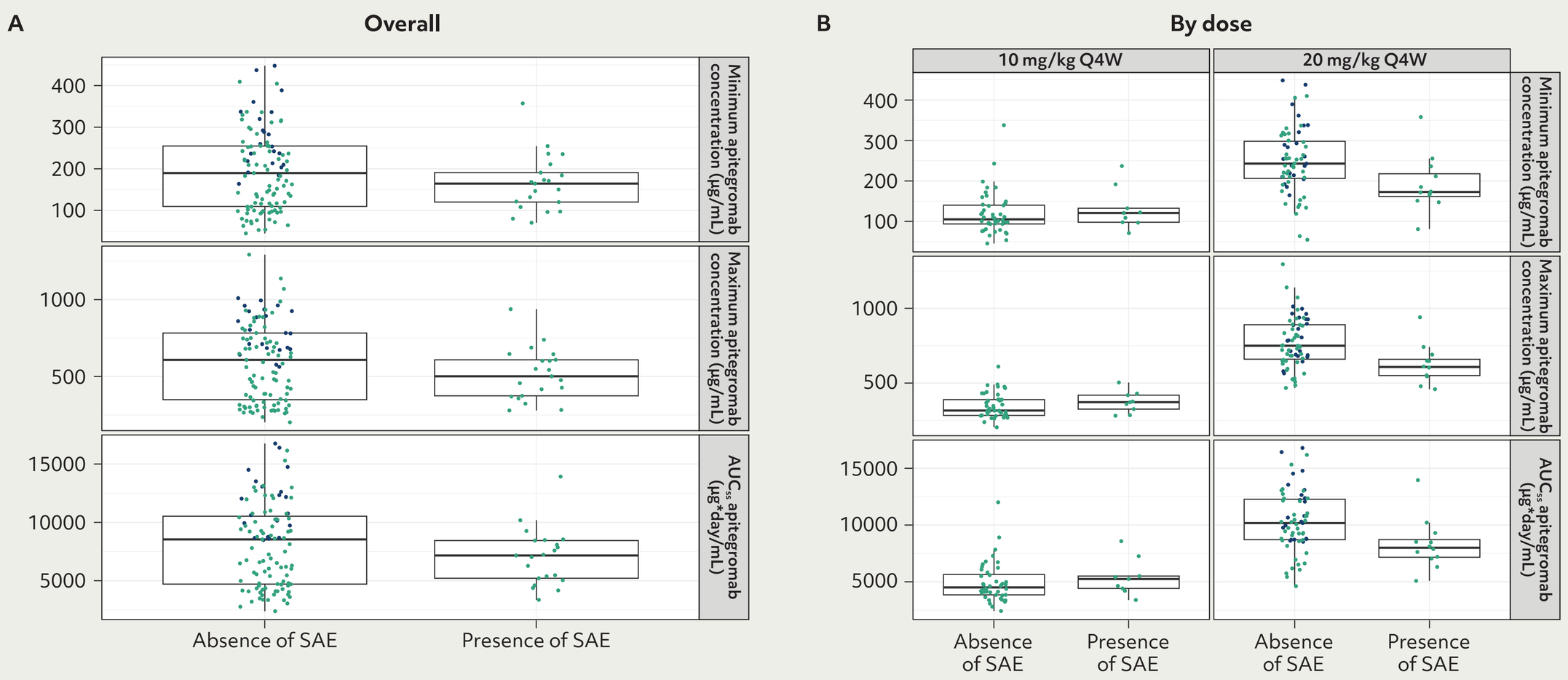
SUPPLEMENTARY MATERIAL

Figure S3. Relationship between Grade ≥3 adverse events and apitegromab exposures



AE, adverse event; AUC_{ss}, area under the serum concentration-time curve at steady state over a dosing interval; Q4W, once every 4 weeks.

Figure S4. Relationship between serious adverse events and apitegromab exposures



AUC_{ss}, area under the serum concentration-time curve at steady state over a dosing interval; Q4W, once every 4 weeks; SAE, serious adverse event.

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