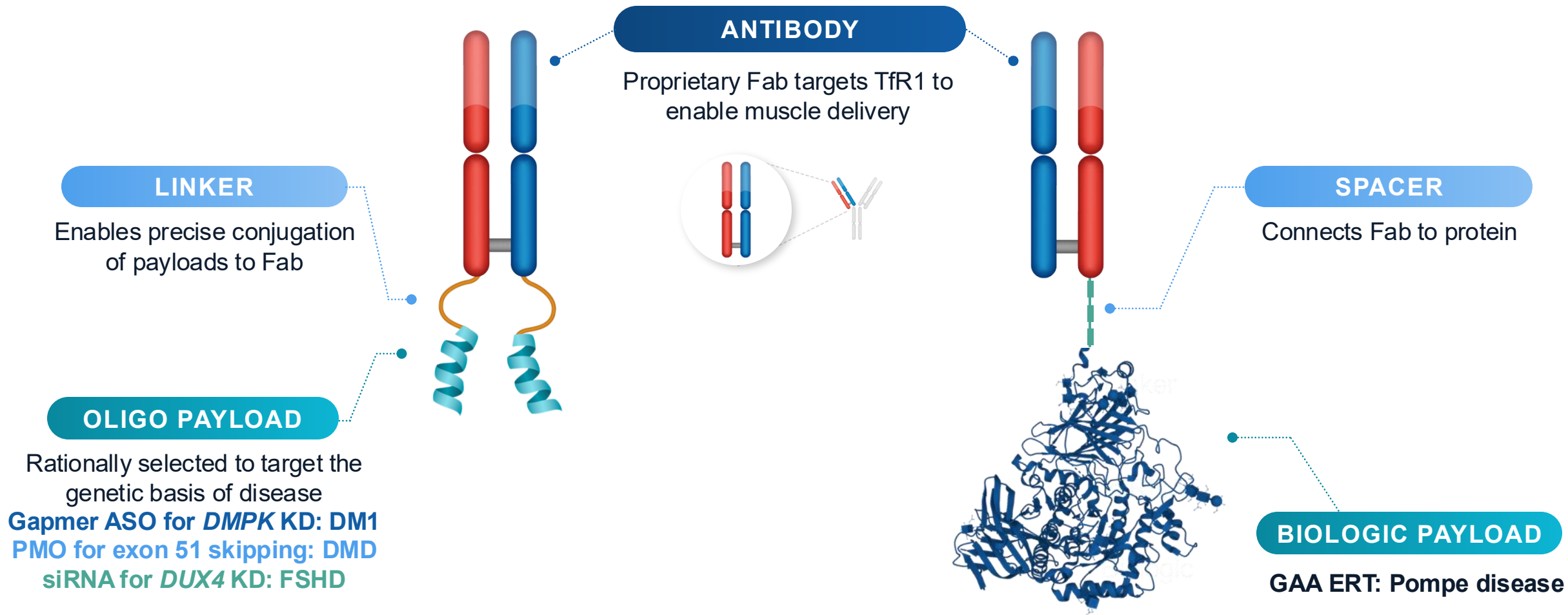


The FORCE™ Platform Delivers Acid Alpha-Glucosidase to Muscle as well as Central Nervous System and Resolves Pathology in Pompe Disease Mice

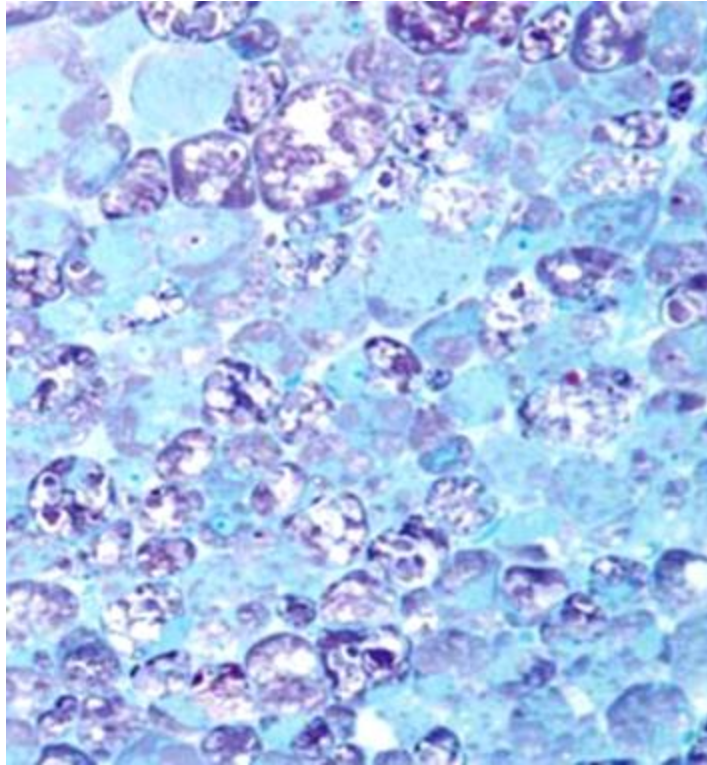
Tyler Picariello, Ph.D.
Director, Neuromuscular Research

FORCE Platform Modularity Enables Diversified Pipeline to Address DM1, DMD, FSHD, and Pompe Disease

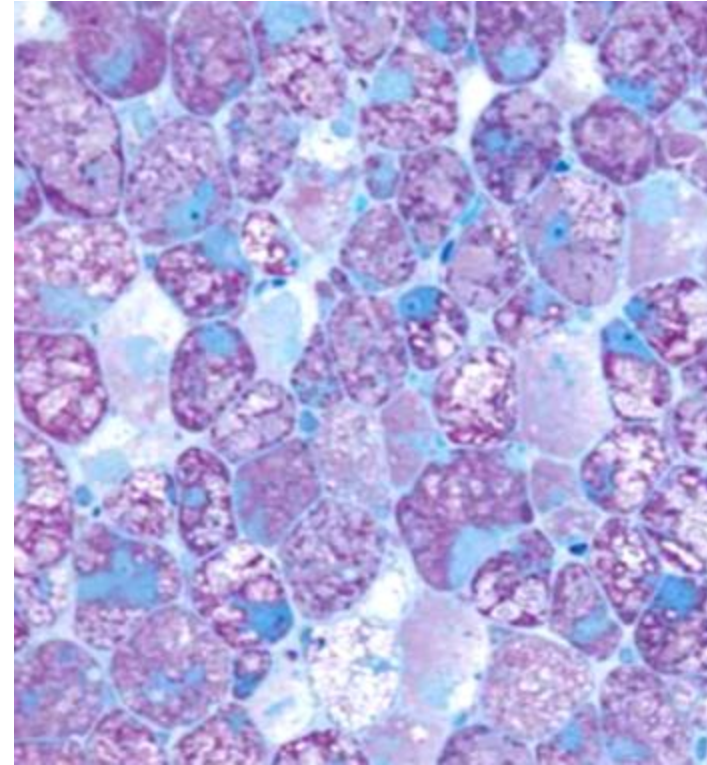


Pompe Standard of Care Requires Frequent Dosing, has Inadequate Efficacy in Skeletal Muscle, and Does not Address the CNS

Quadriceps of a Pompe patient treated with ERT weekly for 52 weeks^{1,2}



Glycogen accumulation
pre-treatment

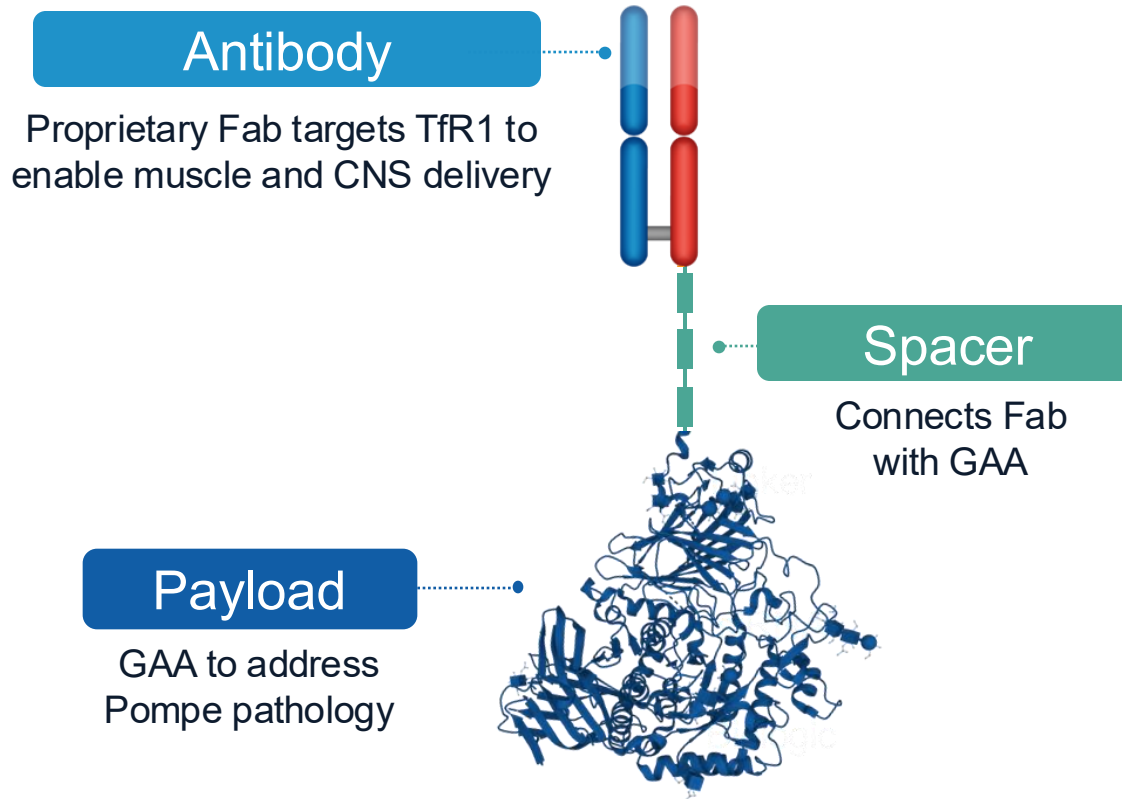


Glycogen accumulation
continues despite treatment

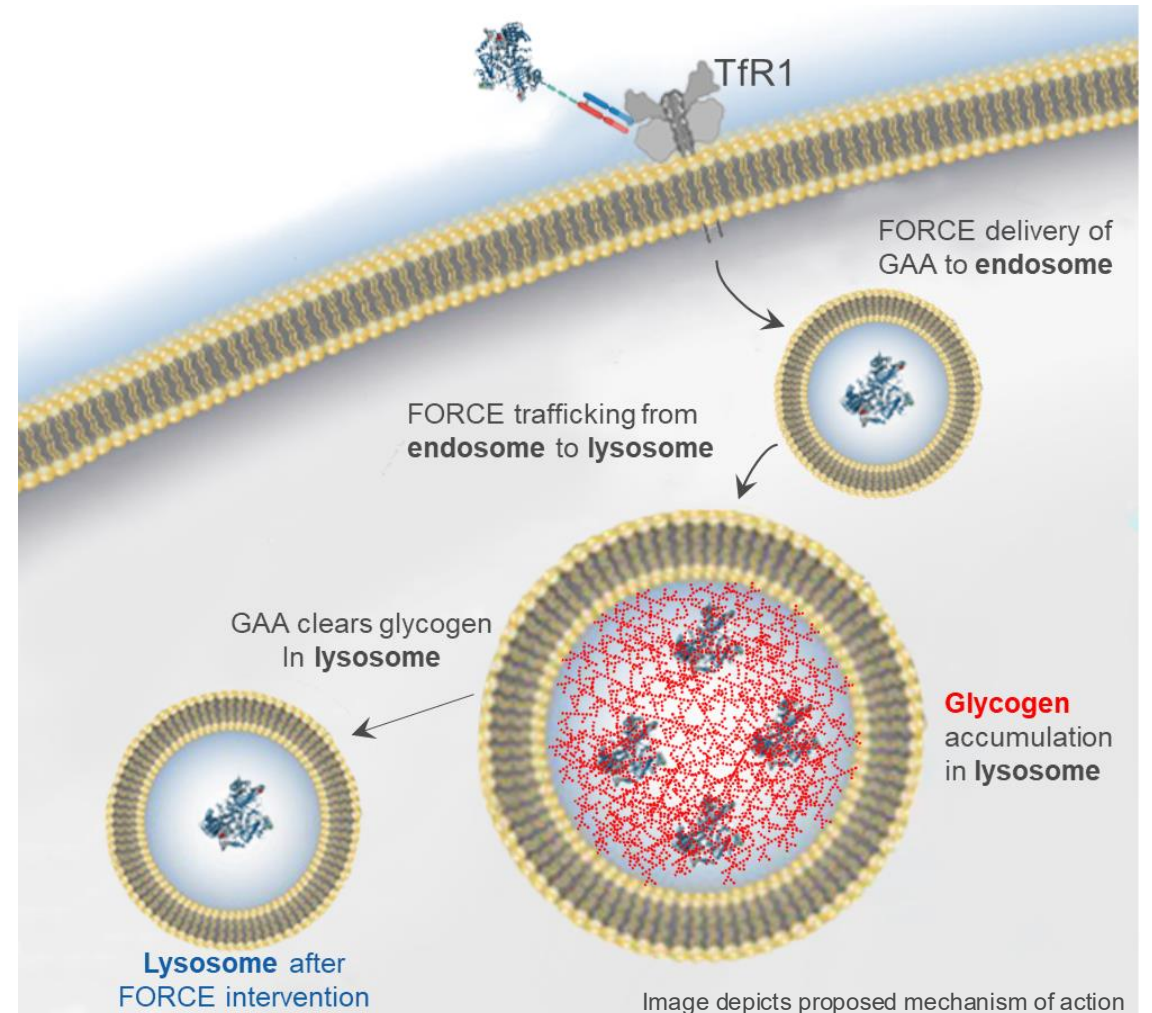
ERT does not address CNS manifestations that emerge as IOPD patients survive into adulthood^{3,4}

FORCE-GAA Designed to Improve Efficacy of ERT in Pompe Disease

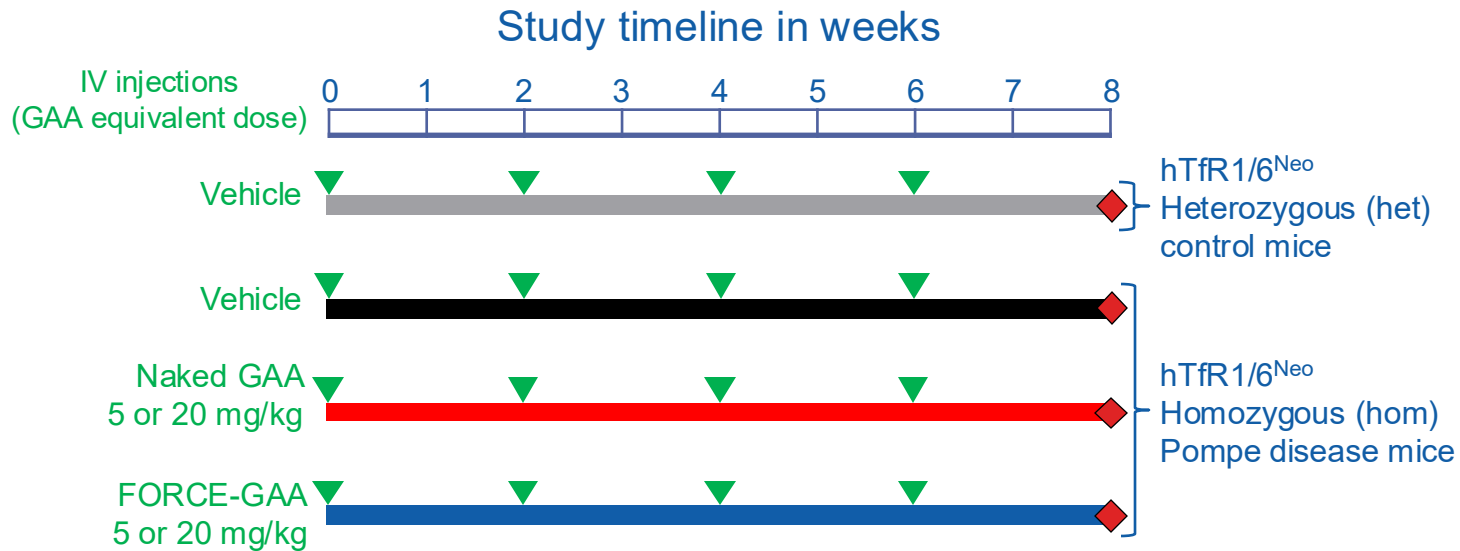
FORCE-GAA enables TfR1-targeted ERT



FORCE-GAA delivers to the endo-lysosomal system



FORCE-GAA was Compared to Naked GAA in a Study Mimicking SOC Q2W Dosing Regimen



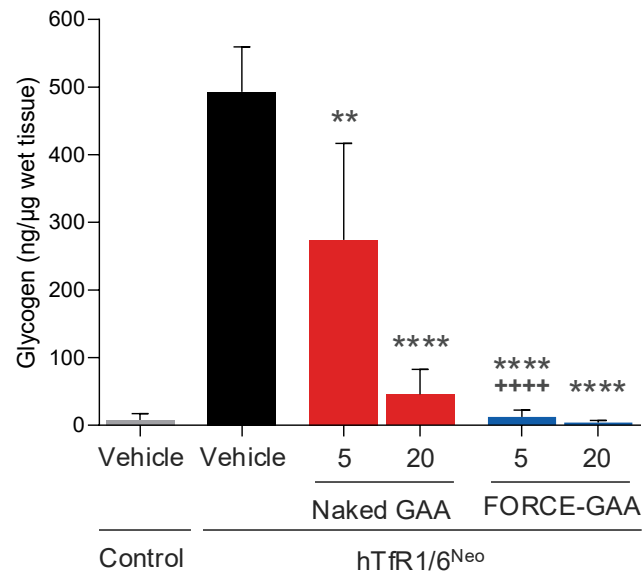
Readouts:

- Muscle and CNS datasets
 - Total tissue glycogen levels
 - Muscle and CNS histology with PAS
 - Muscle and CNS lysosome staining with LAMP1
 - CNS GFAP and IBA1 staining
- Serum neurofilament light chain (NF-L) levels

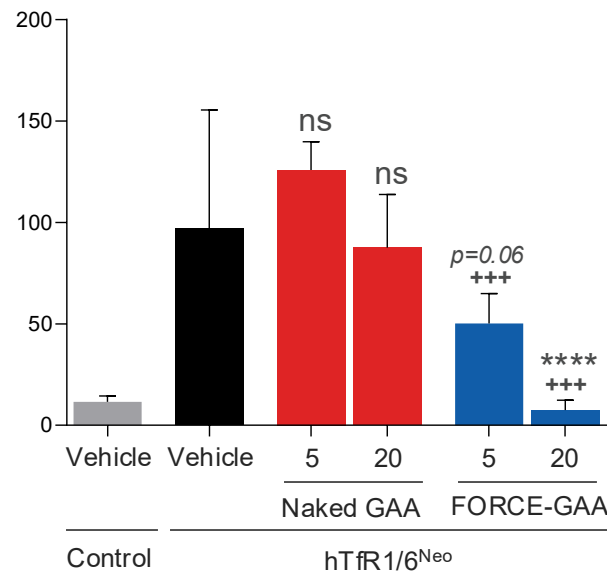
FORCE-GAA Achieves Superior Glycogen Clearance in Muscle Compared to Naked GAA Using the SOC Dosing Regimen



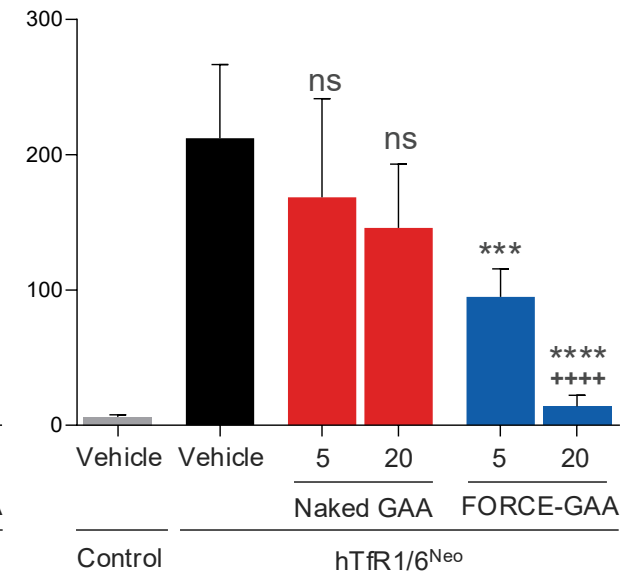
Heart



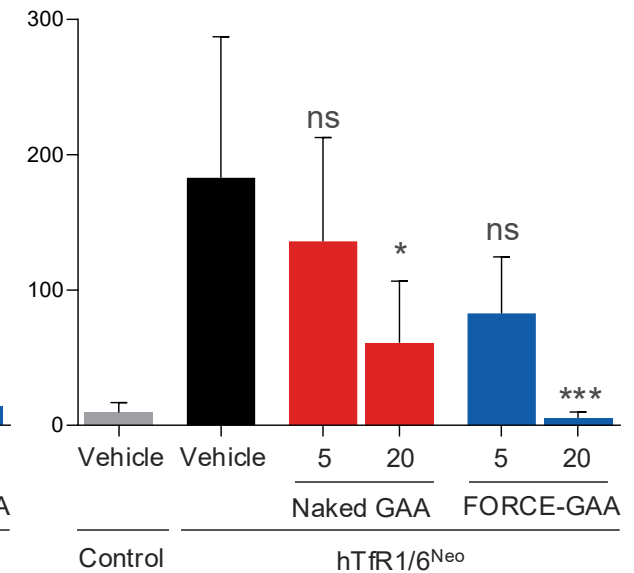
Diaphragm



Quadriceps

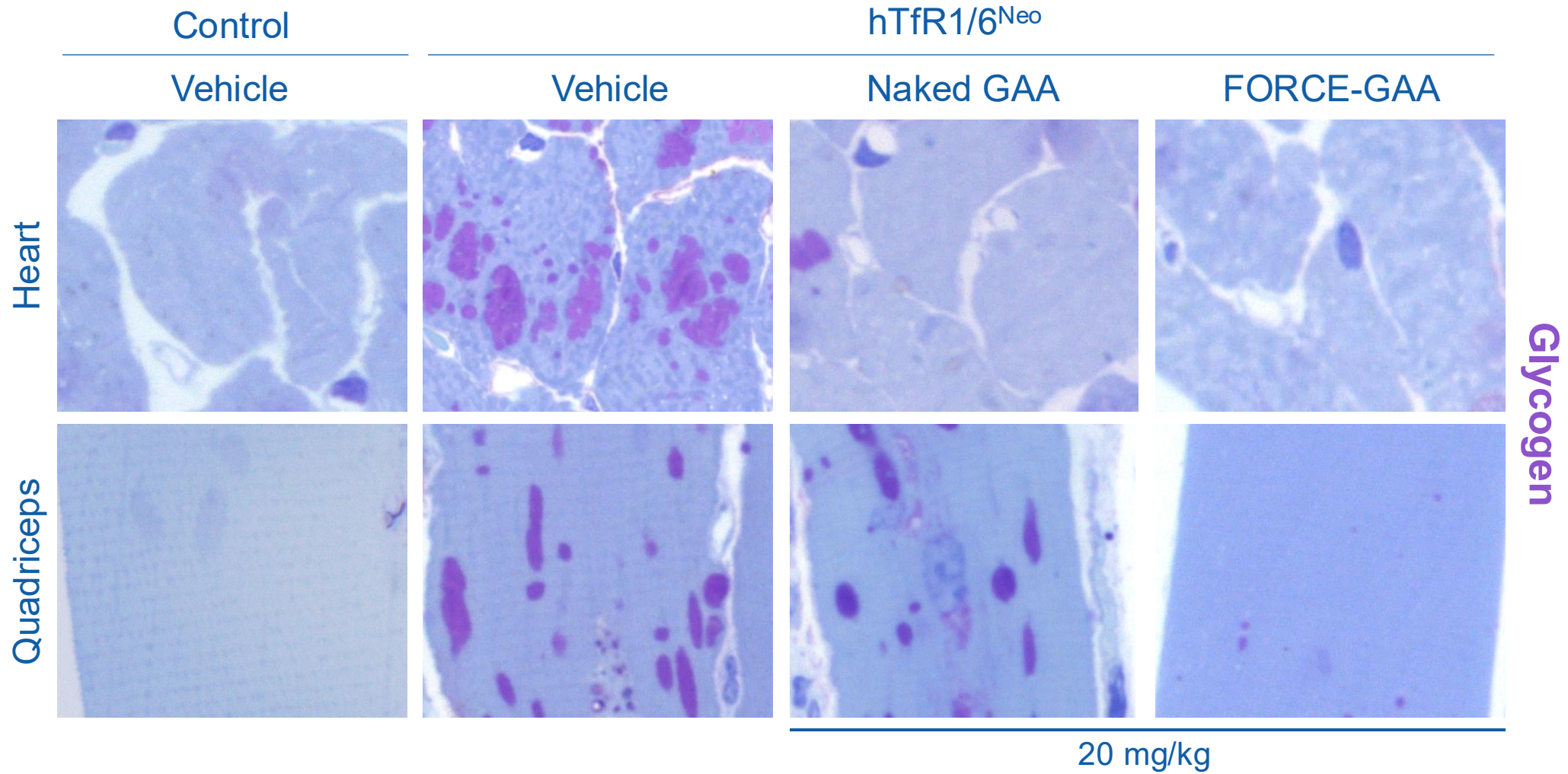


Soleus



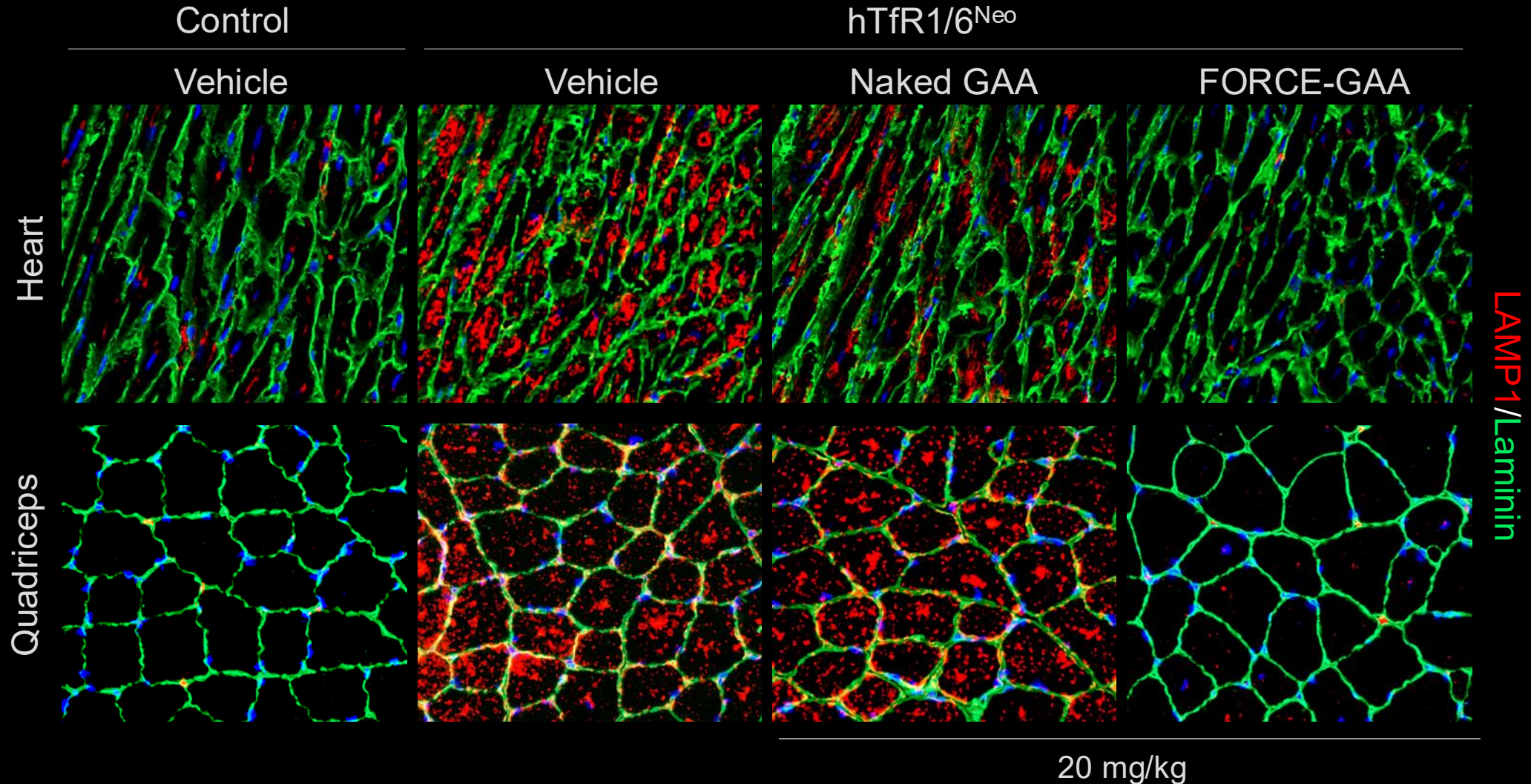
Notes: Doses are mg/kg GAA-equivalents. Mice were dosed on day 0 and weeks 2, 4, and 6, analyzed on week 8. Data are means + SD; n = 4-7. Control mice are hTfR1(Het)/6^{Neo}(Het); hTfR1/6^{Neo} mice are hTfR1(Het)/6^{Neo}(Hom); Asterisks indicate statistical significance compared to Vehicle treated Pompe mice; Plus signs indicate statistical significance compared to matched naked GAA dose; Statistical significance compared by ANOVA * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$; ***** $p < 0.00001$.

FORCE-GAA Achieves Superior Glycogen Clearance in Muscle Compared to Naked GAA Using the SOC Dosing Regimen



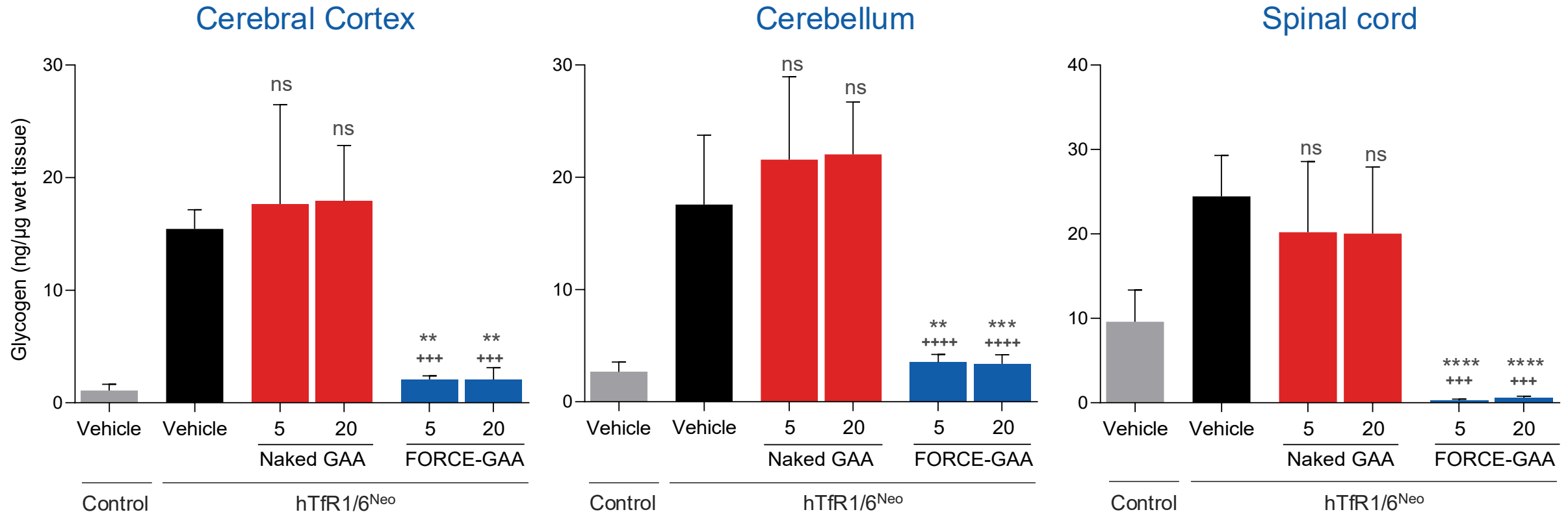
Notes: Dose is 20 mg/kg GAA-equivalents. Mice were dosed on day 0 and weeks 2, 4, and 6, analyzed on week 8. Control mice are hTfR1(Het)/6^{Neo}(Het); hTfR1/6^{Neo} mice are hTfR1(Het)/6^{Neo}(Hom).

FORCE-GAA Outperforms Naked GAA and Demonstrates Superior Reduction of Lysosomal Enlargement in Muscle Using SOC Dosing



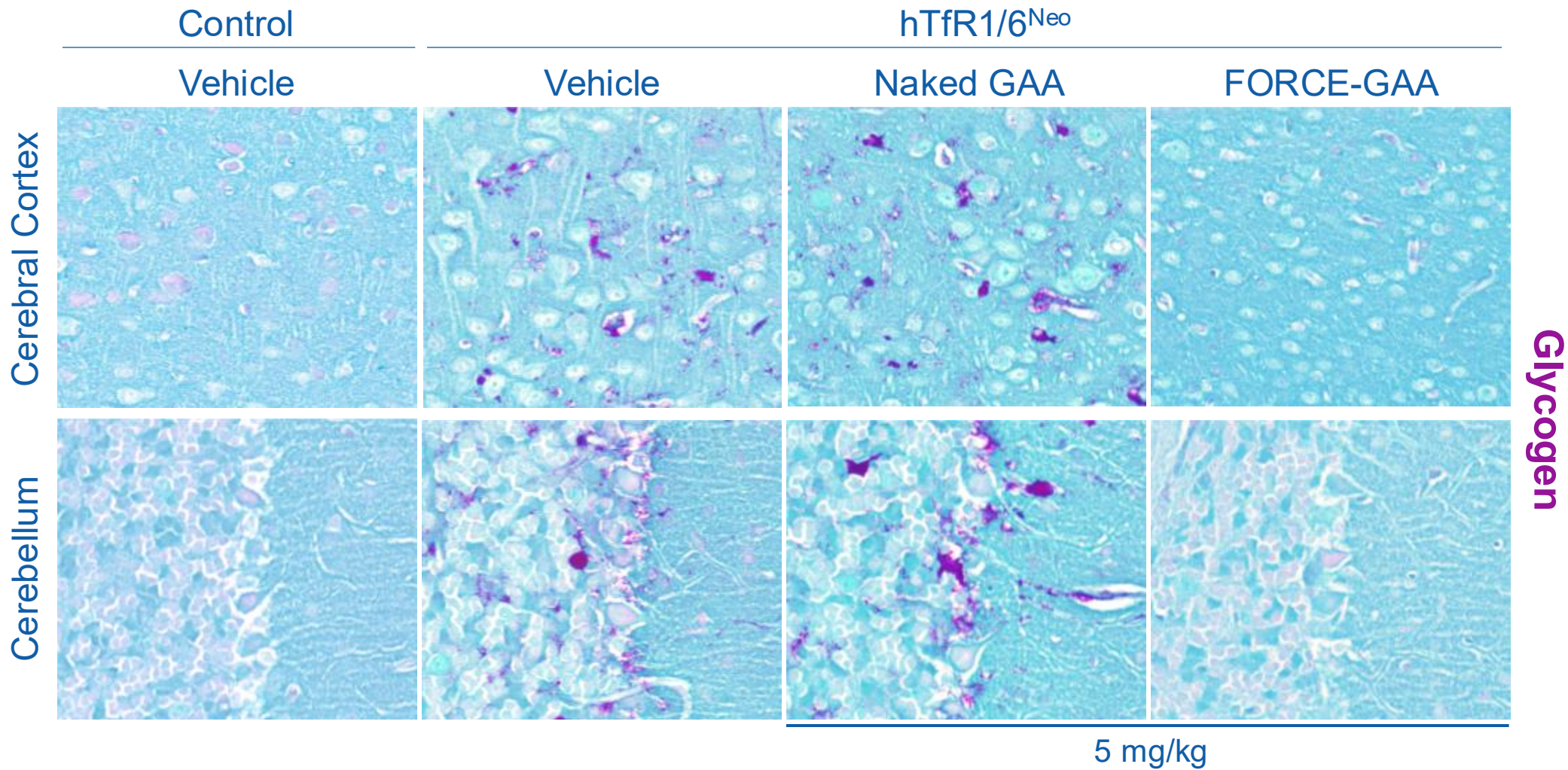
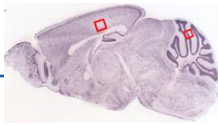
Notes: Dose is 20 mg/kg GAA-equivalents. Mice were dosed on day 0 and weeks 2, 4, and 6, analyzed on week 8. Control mice are hTfR1(Het)/6^{Neo}(Het); hTfR1/6^{Neo} mice are hTfR1(Het)/6^{Neo}(Hom).
LAMP1 = Lysosome associated membrane protein 1.

FORCE-GAA Clears Glycogen in CNS with SOC Dosing Regimen



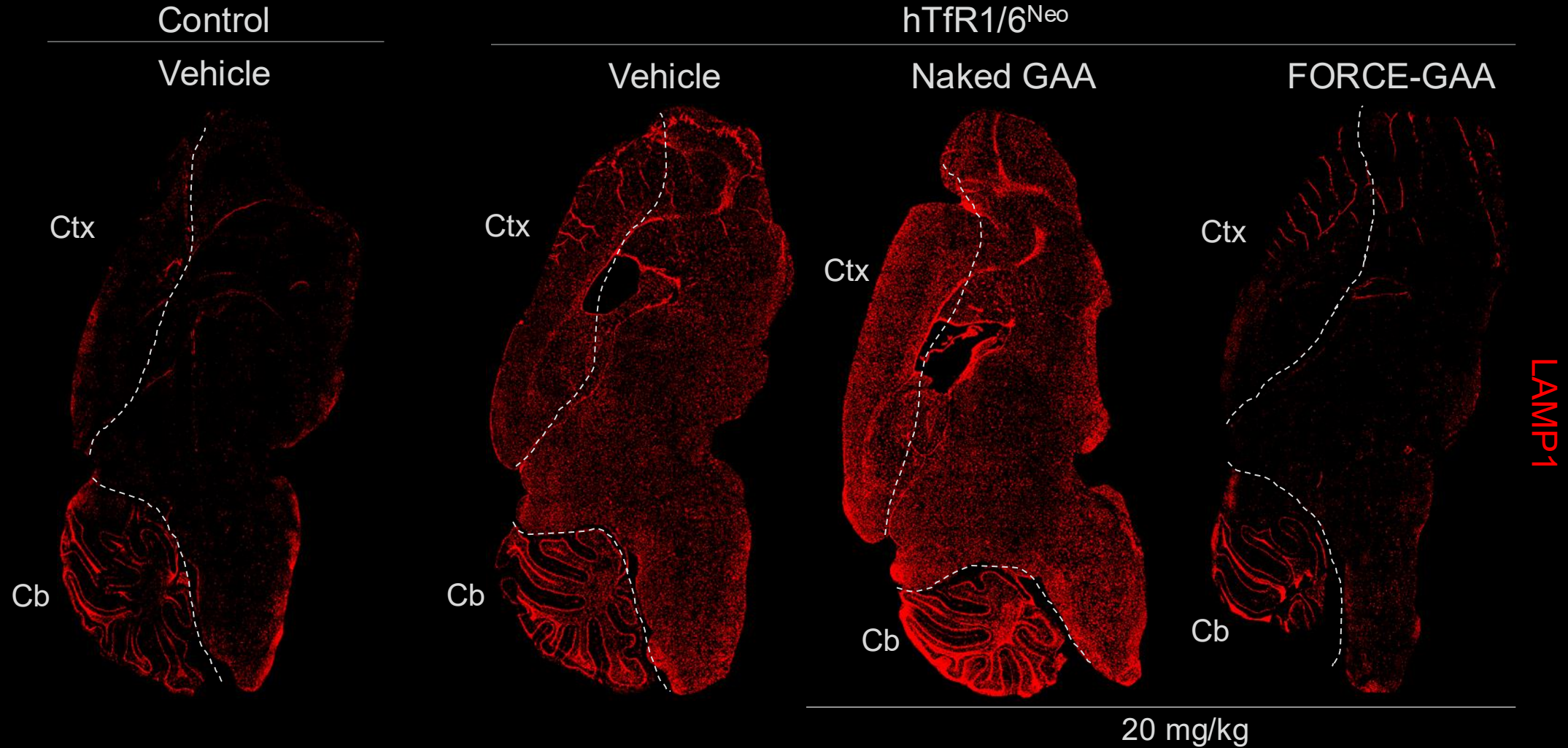
Notes: Doses are mg/kg GAA-equivalents. Mice were dosed on day 0 and weeks 2, 4, and 6, analyzed on week 8. Data are means + SD; n = 4-7. Control mice are hTfR1(Het)/6^{Neo}(Het); hTfR1/6^{Neo} mice are hTfR1(Het)/6^{Neo}(Hom); Asterisks indicate statistical significance compared to Vehicle treated Pompe mice; Plus signs indicate statistical significance compared to matched naked GAA dose; Statistical significance by ANOVA *** $p < 0.001$; ****, + p < 0.0001.

FORCE-GAA Clears Glycogen in CNS with SOC Dosing Regimen



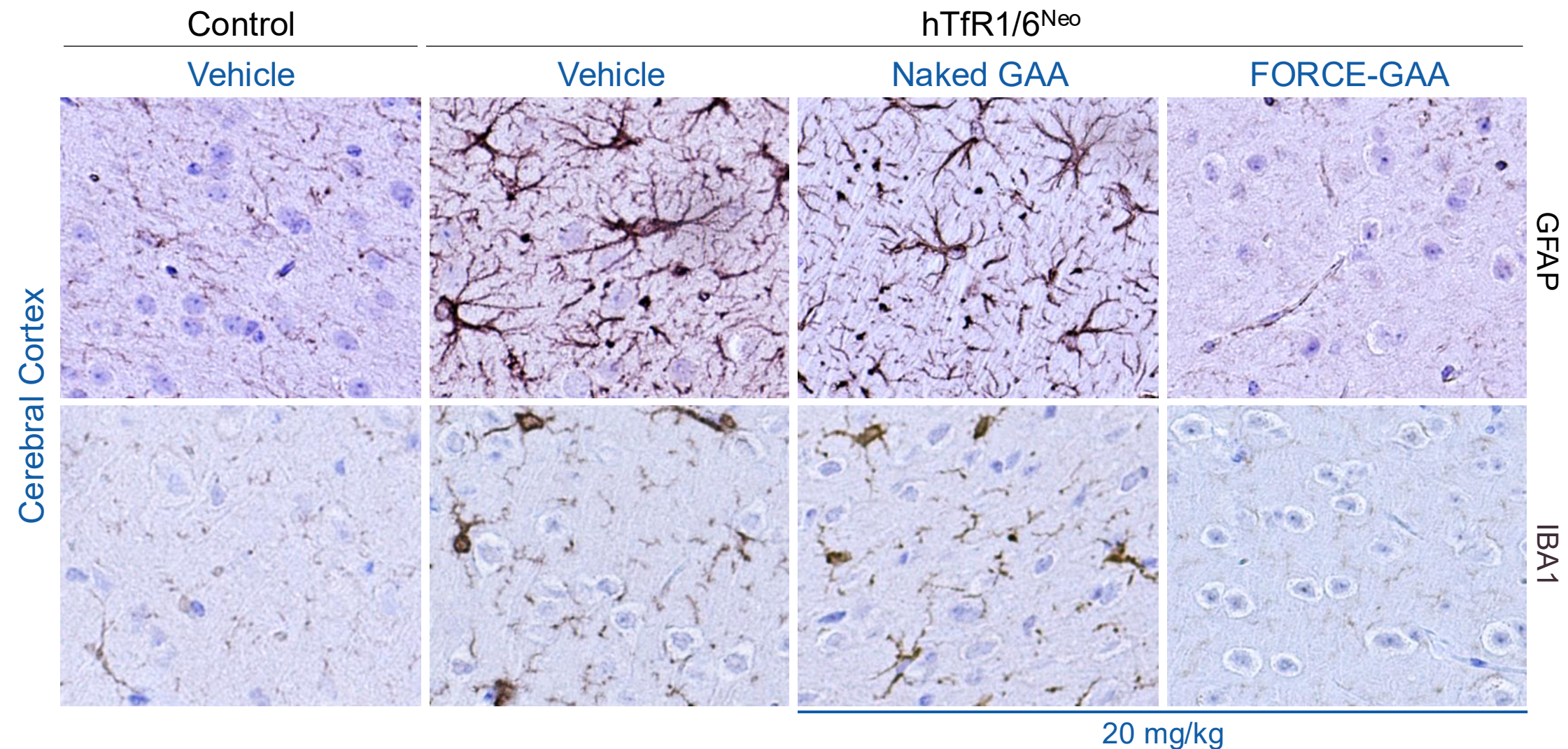
Notes: Dose is 5 mg/kg GAA-equivalents. Mice were dosed on day 0 and weeks 2, 4, and 6, analyzed on week 8. Control mice are hTfR1(Het)/6^{Neo}(Het); hTfR1/6^{Neo} mice are hTfR1(Het)/6^{Neo}(Hom).

FORCE-GAA Achieves Widespread Lysosomal Size Normalization in CNS Using SOC Dosing



Notes: Dose is 20 mg/kg GAA-equivalents. Mice were dosed on day 0 and weeks 2, 4, and 6, analyzed on week 8. Control mice are hTfR1(Het)/6^{Neo}(Het); hTfR1/6^{Neo} mice are hTfR1(Het)/6^{Neo}(Hom).
Cb = cerebellum; Ctx = cortex; LAMP1 = Lysosome associated membrane protein 1.

FORCE-GAA Substantially Reduces Neuroinflammation in the CNS



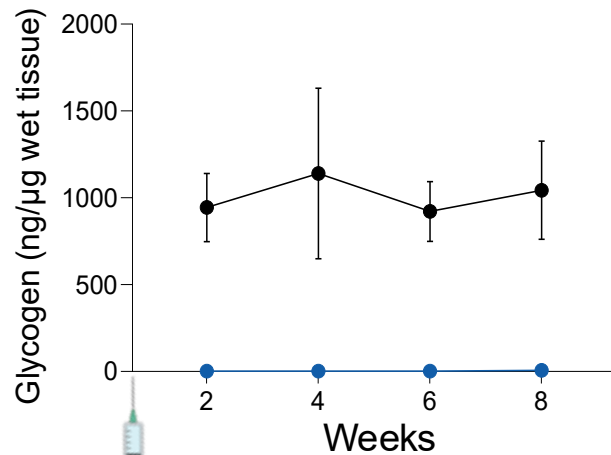
Notes: Dose is 20 mg/kg GAA-equivalents. Mice were dosed on day 0 and weeks 2, 4, and 6, analyzed on week 8. Control mice are hTfR1(Het)/6^{Neo}(Het); hTfR1/6^{Neo} mice are hTfR1(Het)/6^{Neo}(Hom).
 GFAP = Glial fibrillary acidic protein; IBA1 = Ionized calcium binding adaptor molecule 1.

FORCE-GAA Demonstrates Potential for Infrequent Dosing

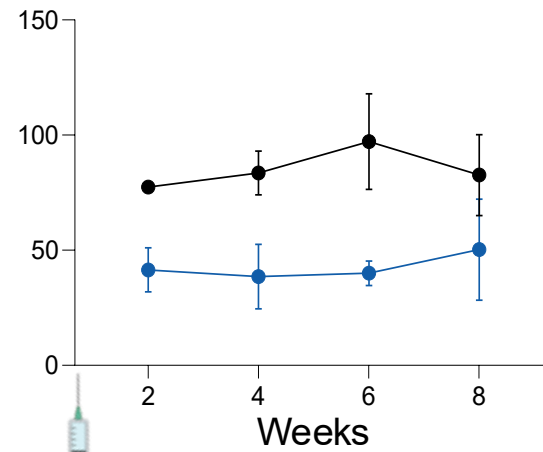


FORCE-GAA Achieves Durable Glycogen and Serum NF-L Reduction

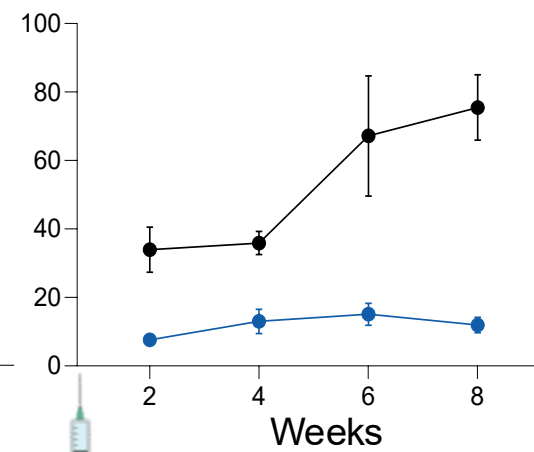
Heart



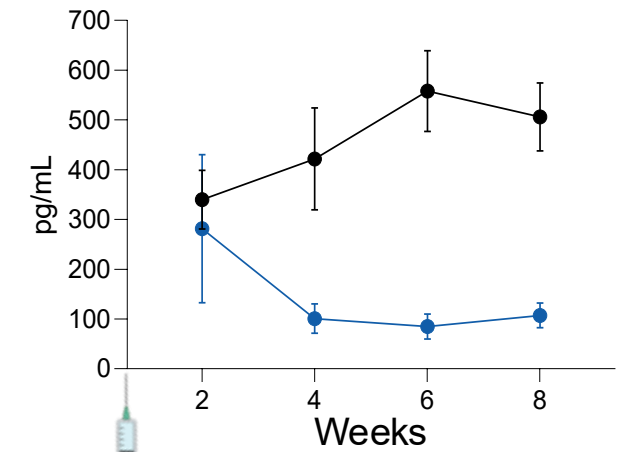
Quadriceps



Cerebral cortex



Serum NF-L



IV injection

IV injection

IV injection

IV injection

● Vehicle ● 20 mg/kg FORCE-GAA

Notes: Dose is mg/kg GAA-equivalents. Mice were dosed on day 0; analyzed on week 2, 4, 6, and 8. Data are means $\pm$ SD; n = 3-4.

Conclusions

- FORCE-GAA displayed superior efficacy in cardiac and skeletal muscle compared to naked GAA in a well-established mouse model of Pompe disease
- FORCE enables effective ERT delivery throughout the CNS that translates into normalization of serum NF-L levels in a mouse model of Pompe disease
- Durability of pharmacodynamics in muscle and CNS indicates potential for monthly or less frequent dosing
- Modularity of FORCE as delivery platform for muscle and CNS is demonstrated with a biologic payload

Data support applicability of the FORCE platform for the treatment of Pompe

Acknowledgements

Research and Development

Special thanks

- Beth Thurberg
- Nancy Andrews



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