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

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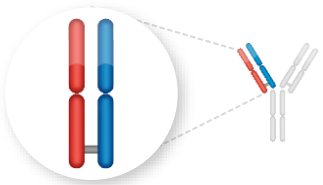
The FORCE platform and FORCE-GAA are investigational or otherwise in development and have not been approved as safe or effective by the FDA or any other regulatory authority.

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

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



LINKER

Enables precise conjugation of payloads to Fab

SPACER

Connects Fab to protein

OLIGO PAYLOAD

Rationally selected to target the genetic basis of disease

Gapmer ASO for *DMPK* KD: DM1

PMO for exon 51 skipping: DMD

siRNA for *DUX4* KD: FSHD

BIOLOGIC PAYLOAD

GAA ERT: Pompe disease

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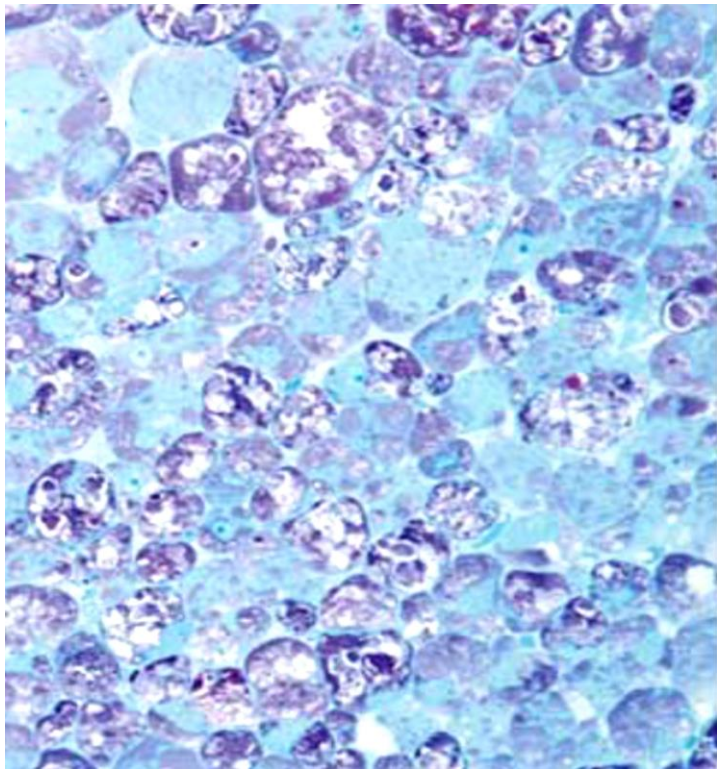
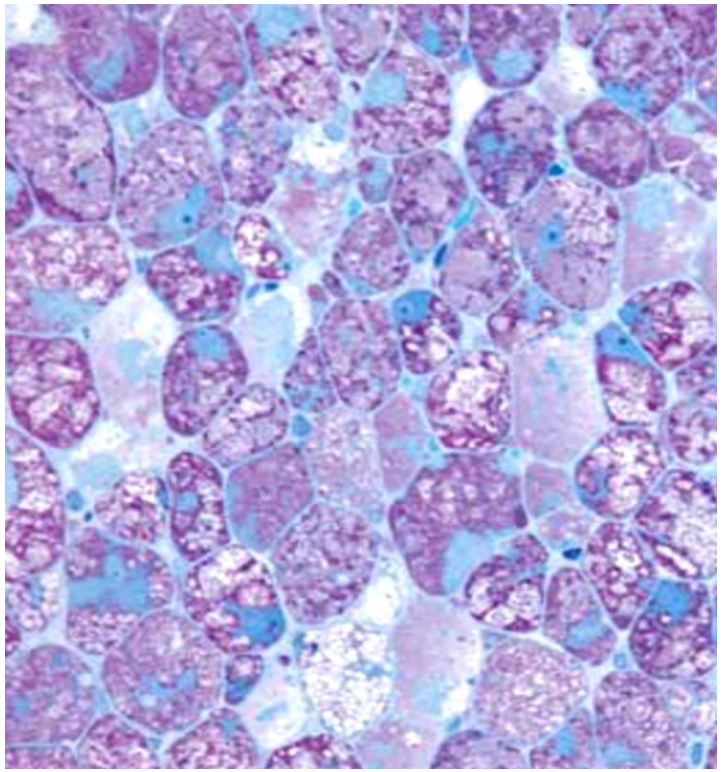
Pompe Standard of Care Requires Frequent Dosing, has Inadequate Efficacy in Skeletal Muscle, and Does not Address the CNS

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]

Notes: [1] Thurberg, B. *et al*., 2006; [2] Fiumara, A., 2014; [3] Stevens, D., et al., 2022; [4] Mackenbach, M.J. et al., 2023. The FORCE platform and FORCE-GAA are investigational or otherwise in development and have not been approved as safe or effective by the US FDA, EMA, or any regulatory authority.

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

FORCE-GAA enables TfR1-targeted ERT

Antibody

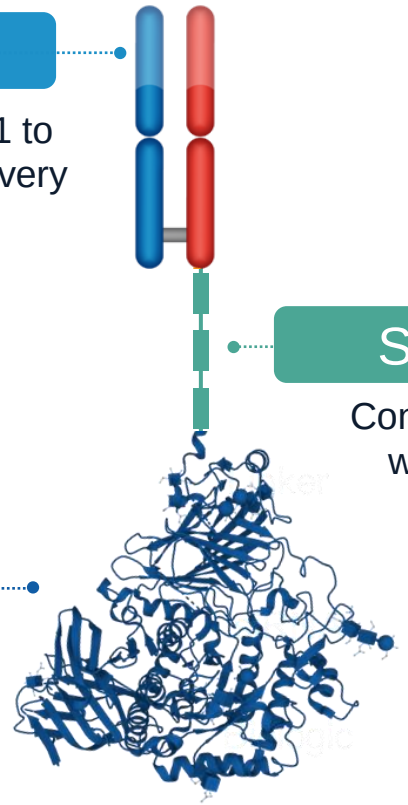
Proprietary Fab targets TfR1 to enable muscle and CNS delivery

Spacer

Connects Fab with GAA

Payload

GAA to address Pompe pathology



FORCE-GAA delivers to the endo-lysosomal system

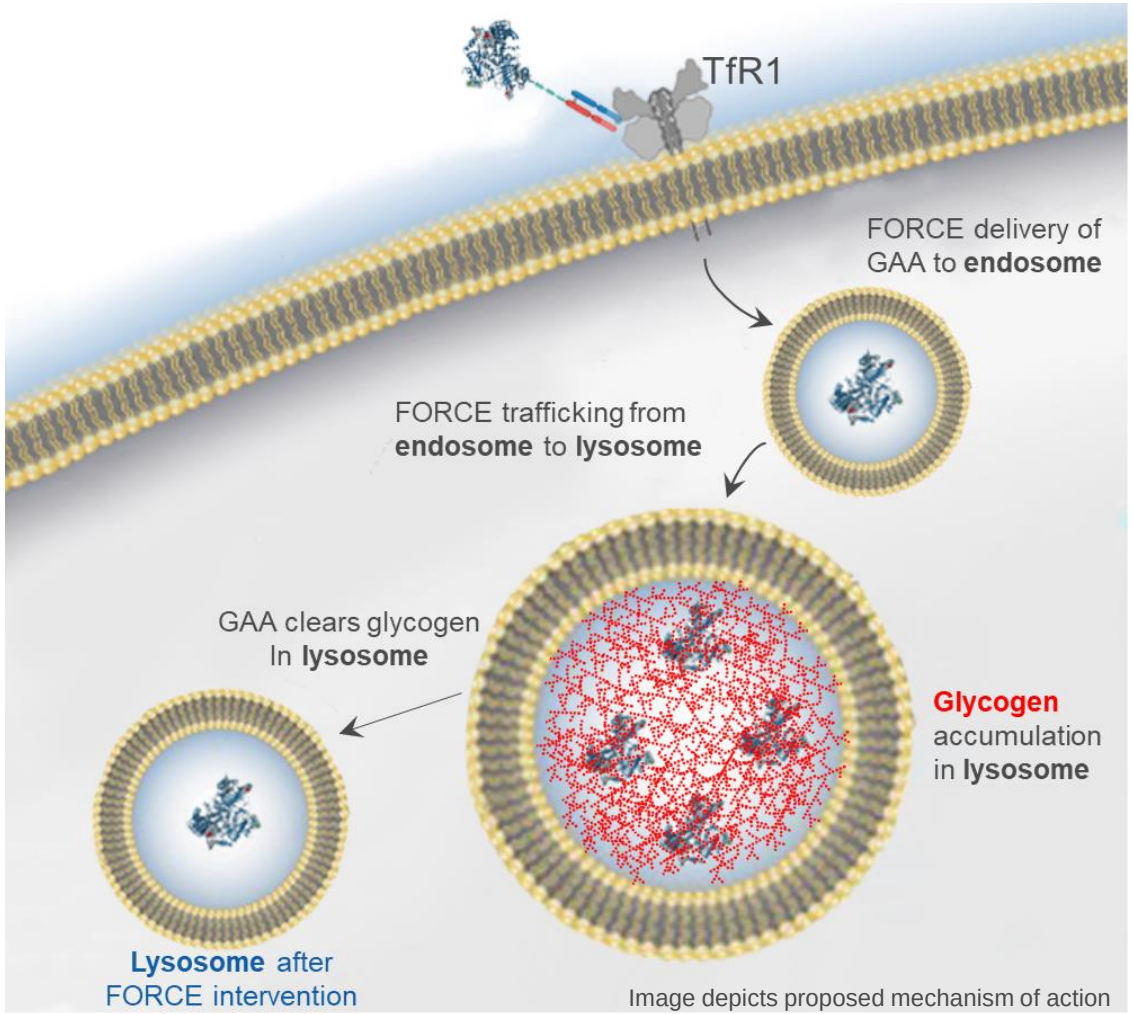
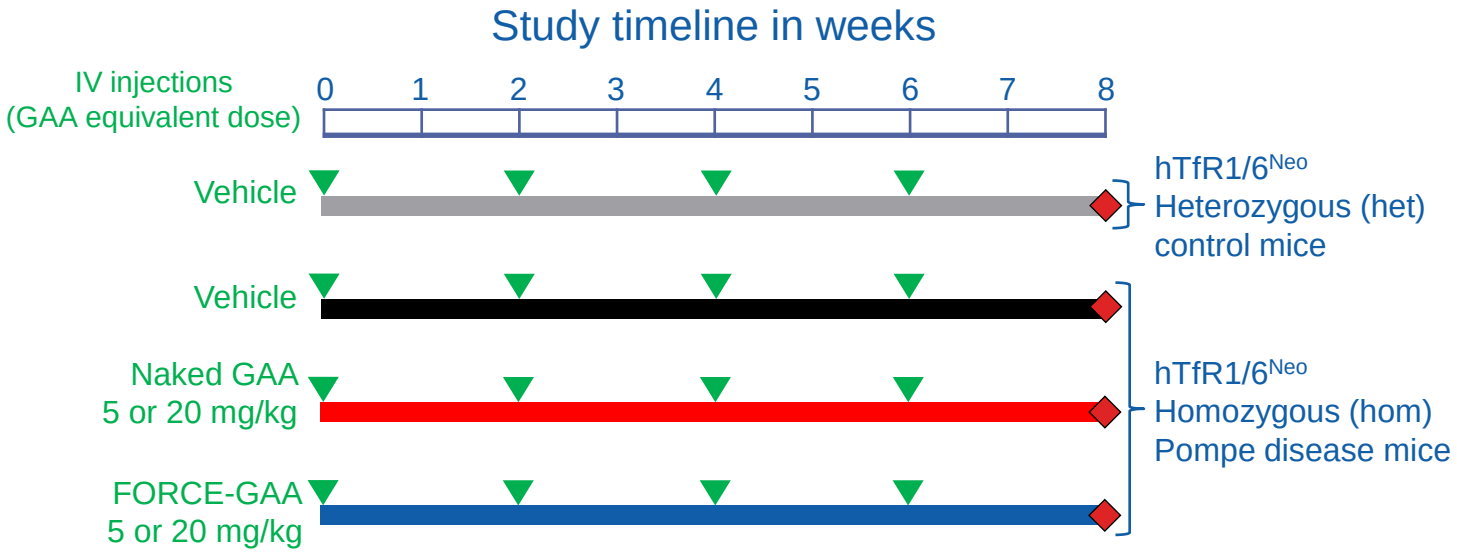


Image depicts proposed mechanism of action

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

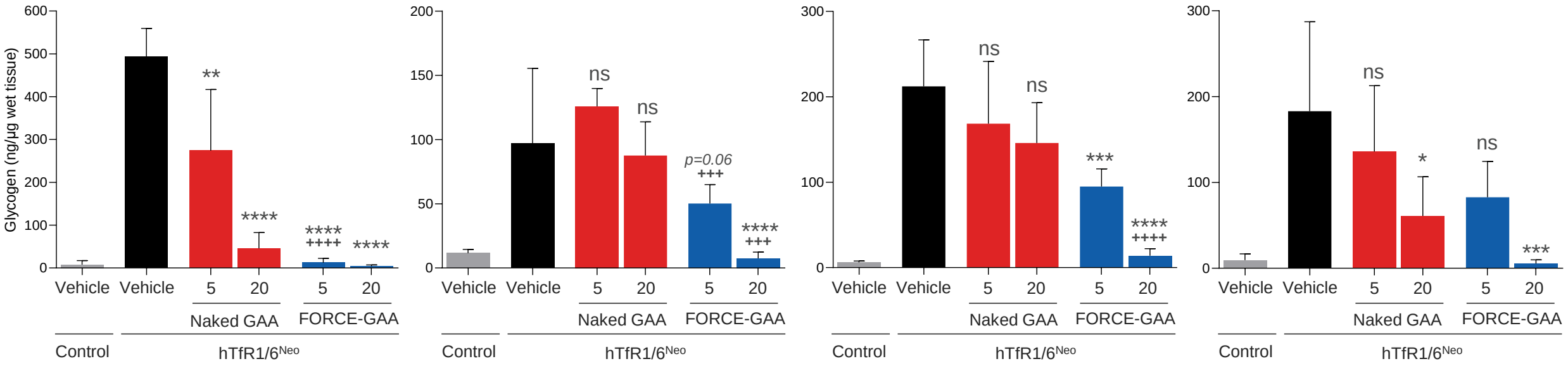


Readouts:

- 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

Notes: Doses are mg/kg GAA-equivalents. GFAP = Glial Fibrillary Acidic Protein; IBA1 = Ionized calcium-binding adaptor molecule 1; LAMP1 = lysosome associated membrane protein 1; PAS = Periodic acid-Schiff Stain. The FORCE platform and FORCE-GAA are investigational or otherwise in development and have not been approved as safe or effective by the US FDA, EMA, or any regulatory authority.

FORCE-GAA Achieves Superior Glycogen Clearance in Muscle Compared to Naked GAA Using the 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 compared by ANOVA $^{*,+}$ *p < 0.05*; ** *p < 0.01*; $^{***,+++}$ *p < 0.001*; $^{****,++++}$ *p < 0.0001*. The FORCE platform and FORCE-GAA are investigational or otherwise in development and have not been approved as safe or effective by the US FDA, EMA, or any regulatory authority.

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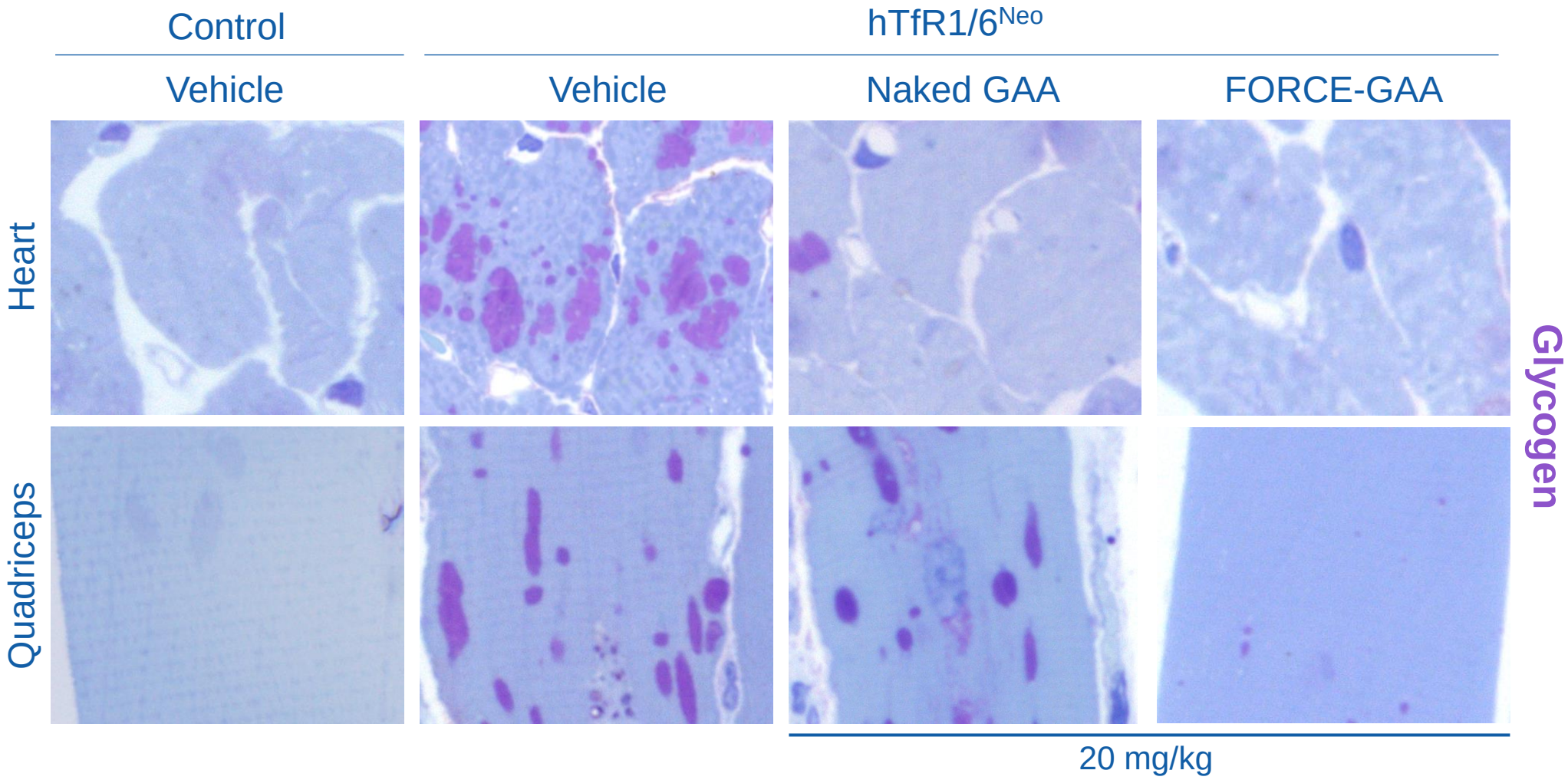

Notes: Dose is 20 mg/kg GAA-equivalents. Mice were dosed on day 0 and weeks 2, 4, and 6, analyzed on week 8. Control mice are hTfR1(Het)/6^{Neo}(Het); hTfR1/6^{Neo} mice are hTfR1(Het)/6^{Neo}(Hom).
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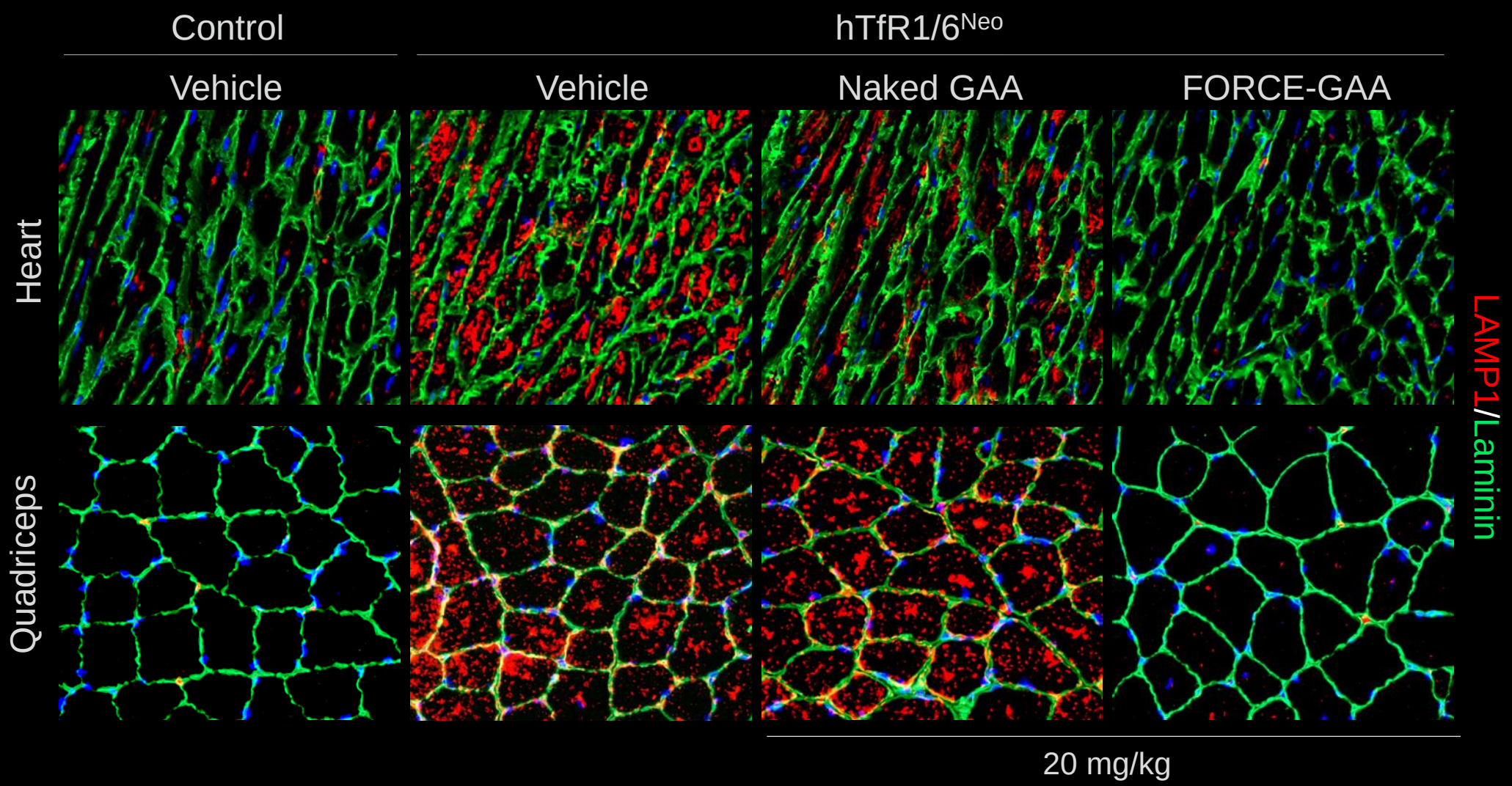
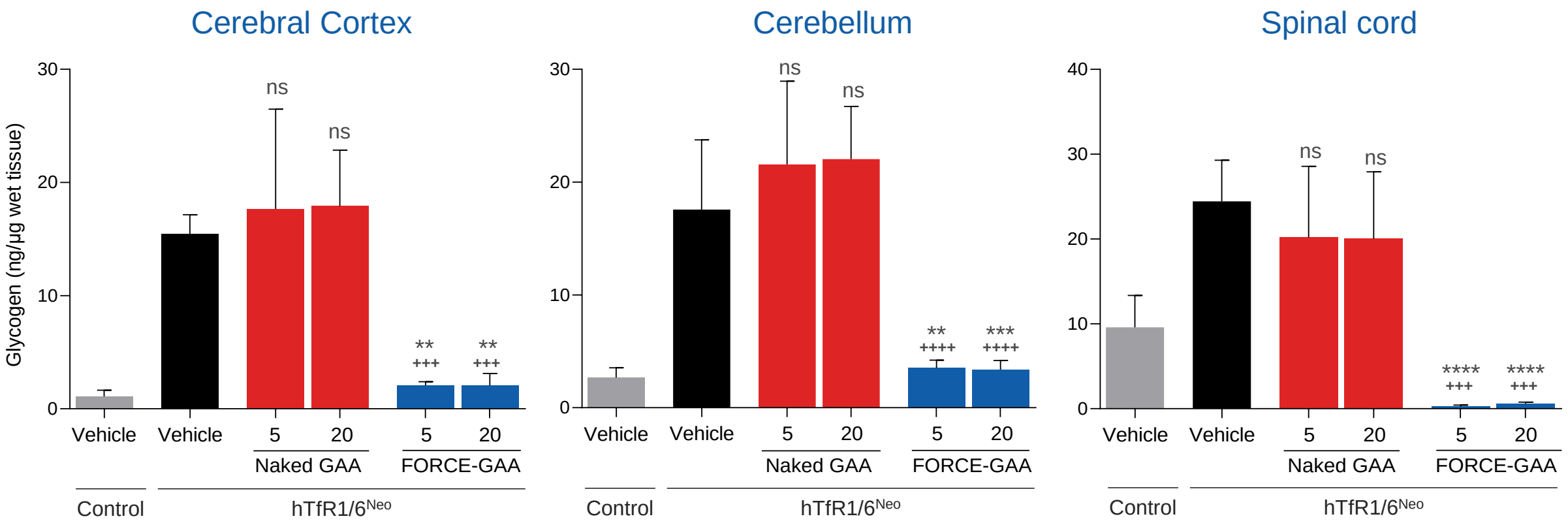
FORCE-GAA Outperforms Naked GAA and Demonstrates Superior Reduction of Lysosomal Enlargement in Muscle Using SOC Dosing



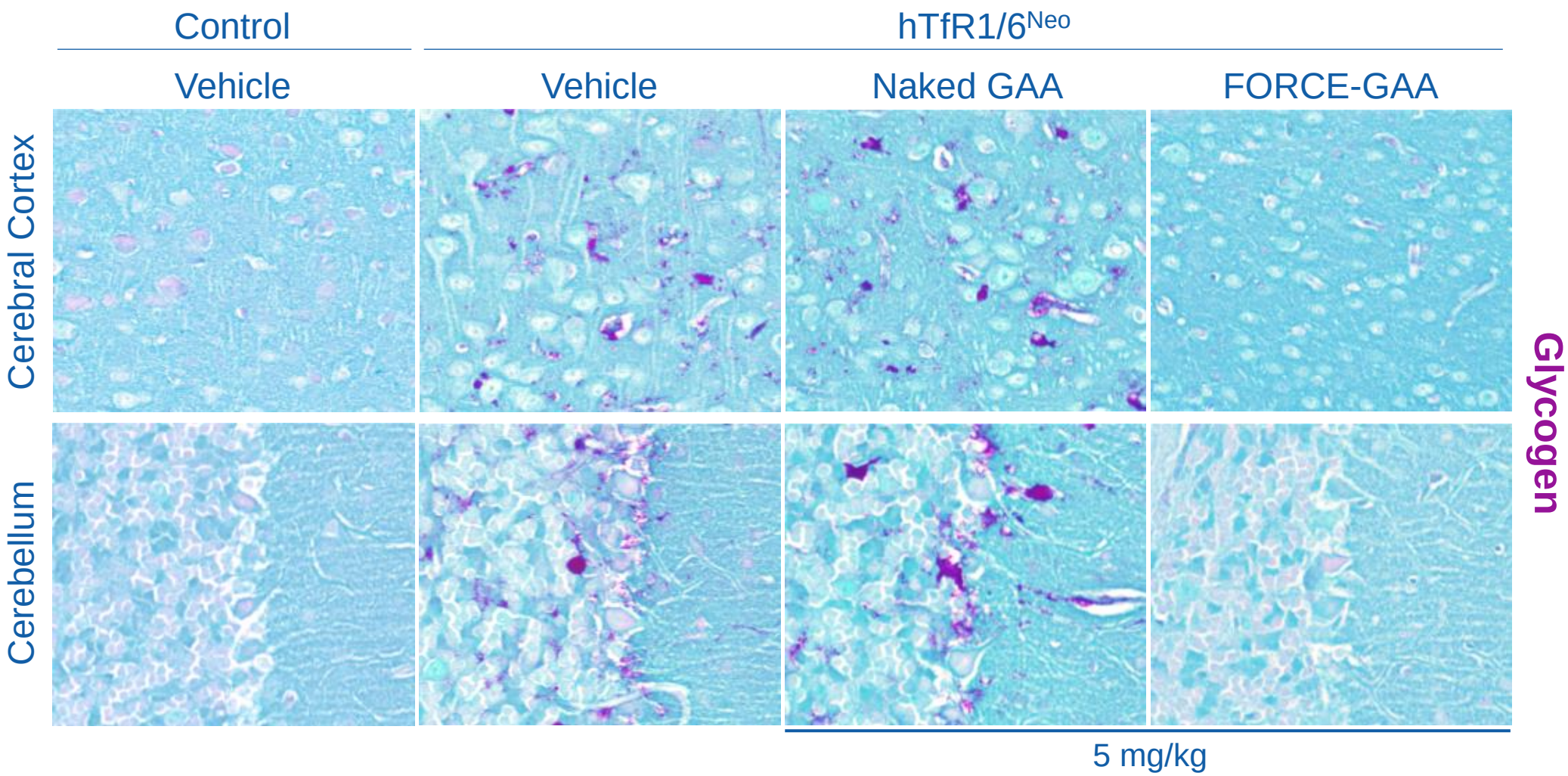
Notes: Dose is 20 mg/kg GAA-equivalents. Mice were dosed on day 0 and weeks 2, 4, and 6, analyzed on week 8. Control mice are hTfR1(Het)/6^{Neo}(Het); hTfR1/6^{Neo} mice are hTfR1(Het)/6^{Neo}(Hom). LAMP1 = Lysosome associated membrane protein 1 The FORCE platform and FORCE-GAA are investigational or otherwise in development and have not been approved as safe or effective by the US FDA, EMA, or any regulatory authority.

FORCE-GAA Clears Glycogen in CNS with SOC Dosing Regimen



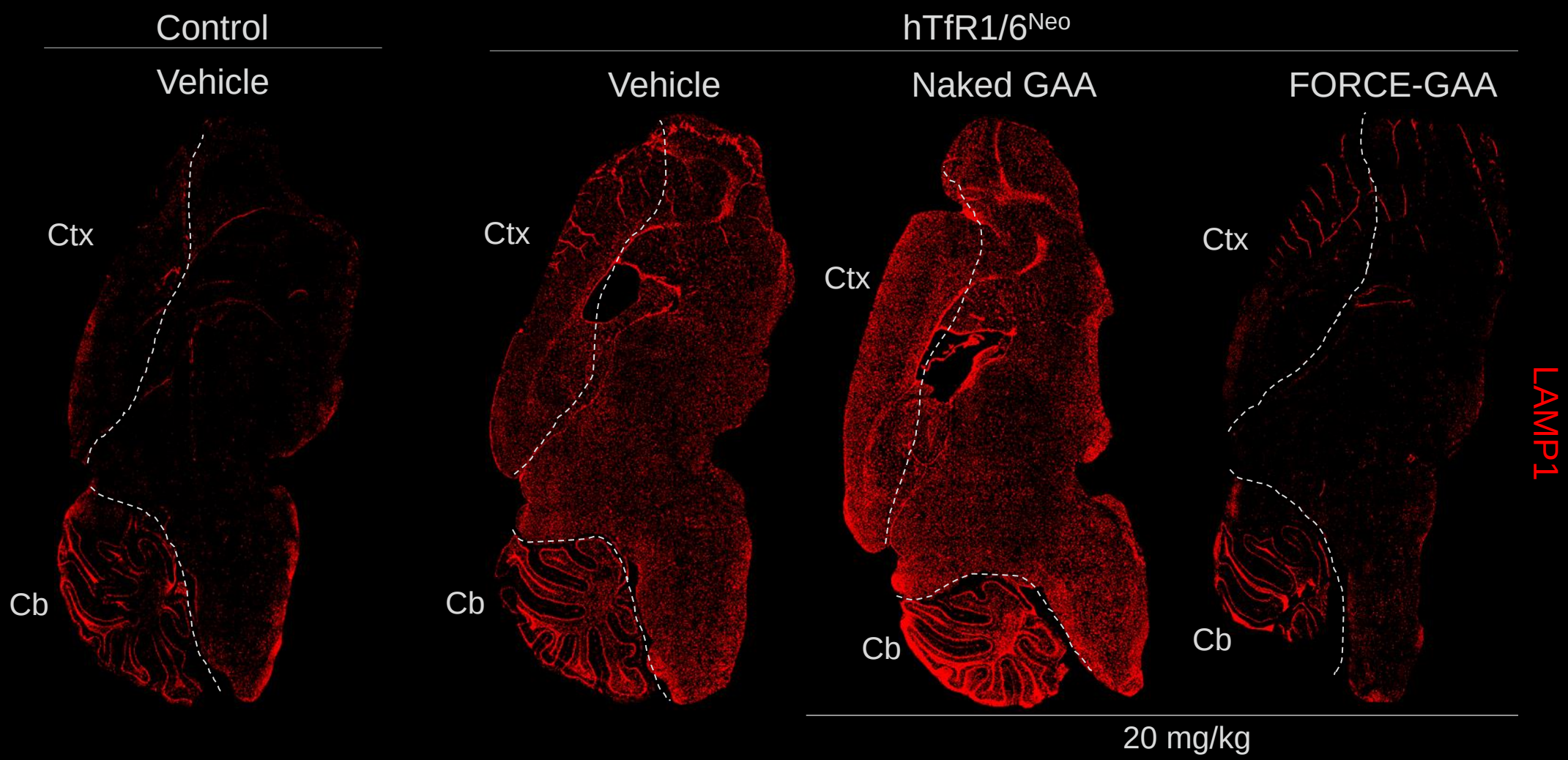
Notes: Doses are mg/kg GAA-equivalents. Mice were dosed on day 0 and weeks 2, 4, and 6, analyzed on week 8. Data are means + SD; n = 4-7. Control mice are hTfR1(Het)/6^{Neo}(Het); hTfR1/6^{Neo} mice are hTfR1(Het)/6^{Neo}(Hom); Asterisks indicate statistical significance compared to Vehicle treated Pompe mice; Plus signs indicate statistical significance compared to matched naked GAA dose; Statistical significance by ANOVA $^{***}p < 0.001$; ****, $^{++++}p < 0.0001$. The FORCE platform and FORCE-GAA are investigational or otherwise in development and have not been approved as safe or effective by the US FDA, EMA, or any regulatory authority.

FORCE-GAA Clears Glycogen in CNS with SOC Dosing Regimen



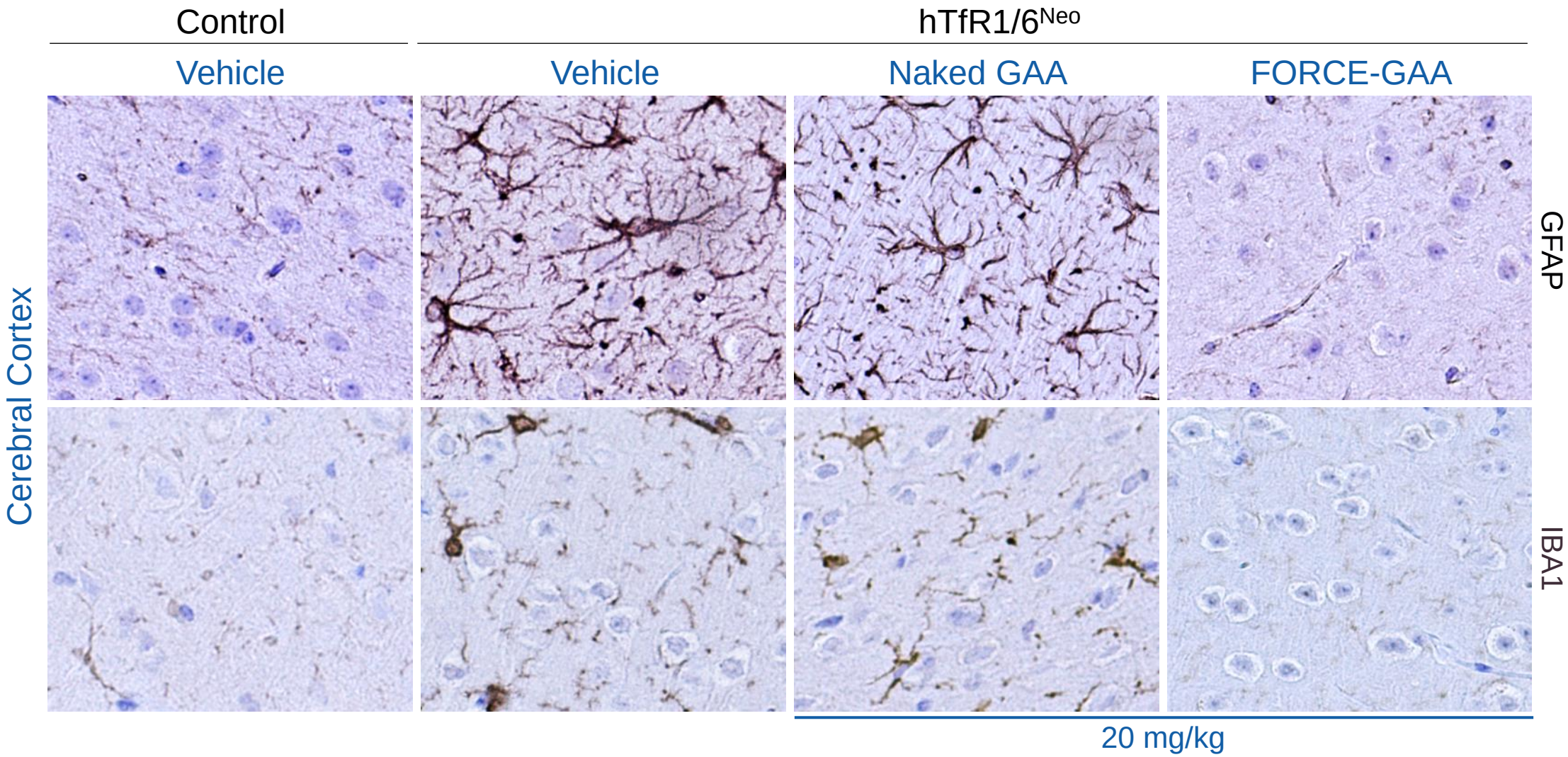
Notes: Dose is 5 mg/kg GAA-equivalents. Mice were dosed on day 0 and weeks 2, 4, and 6, analyzed on week 8. Control mice are hTfR1(Het)/6^{Neo}(Het); hTfR1/6^{Neo} mice are hTfR1(Het)/6^{Neo}(Hom). The FORCE platform and FORCE-GAA are investigational or otherwise in development and have not been approved as safe or effective by the US FDA, EMA, or any regulatory authority.

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. The FORCE platform and FORCE-GAA are investigational or otherwise in development and have not been approved as safe or effective by the US FDA, EMA, or any regulatory authority.

FORCE-GAA Substantially Reduces Neuroinflammation in the CNS



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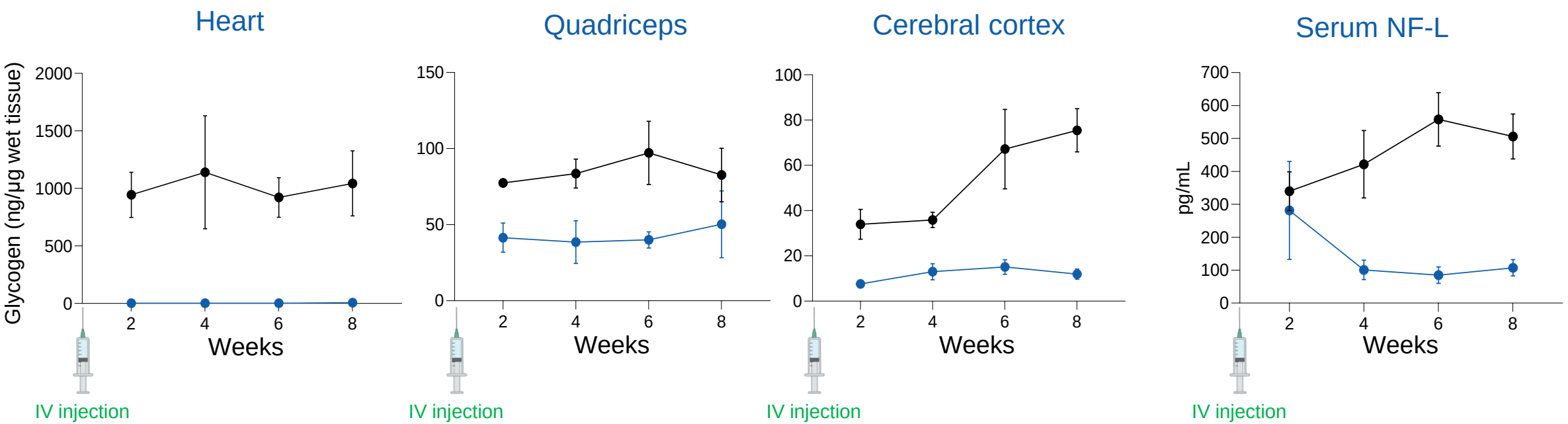
FORCE-GAA Demonstrates Potential for Infrequent Dosing

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



Notes: Dose is mg/kg GAA-equivalents. Mice were dosed on day 0; analyzed on week 2, 4, 6, and 8. Data are means ± SD; n = 3-4. The FORCE platform and FORCE-GAA are investigational or otherwise in development and have not been approved as safe or effective by the US FDA, EMA, or any regulatory authority.

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

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Acknowledgements

Research and Development

Special thanks

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