DYNE-401 demonstrates potential to deliver functional improvement in Pompe disease with low and infrequent dosing

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BACKGROUND

The FORCE™ platform is a versatile therapeutic approach that enables delivery of biologics and oligonucleotides to muscle and CNS via a fragment antigen binding antibody (Fab) highly specific for human transferrin receptor type 1 (TfR1). Traditional enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase (GAA) delivered via the mannose-6-phospate receptor is the current standard of care (SOC) for Pompe disease. Unfortunately, the SOC has insufficient efficacy in skeletal muscle and does not address the central nervous system (CNS) manifestations of Pompe. Traditional ERT also requires frequent bi-weekly dosing and high dose levels. DYNE-401 was developed using the FORCE platform and has the potential to address the limitations of SOC by improving GAA uptake in muscle and enabling CNS delivery. We assessed the potential for reduced dosing frequency and lower dose levels in a hTfR1 expressing mouse model of Pompe disease (hTfR1/6^{Neo}). Monthly intravenous administration of DYNE-401 led to dose dependent glycogen clearance in muscle. Glycogen reduction was also associated with functional improvement. DYNE-401 normalized glycogen levels in the CNS at the lowest dose tested. DYNE-401 achieved similar effects in muscle and CNS when administered once every other month to hTfR1/6^{Neo} mice. Even with this infrequent dosing regimen, DYNE-401 retained the ability to normalize serum neurofilament light chain levels, indicating correction of neuronal damage. These data demonstrate the potential of low and infrequent dosing with DYNE-401 to deliver functional improvement in Pompe disease.

Figure 1. Dyne FORCE Platform modularity enables a diversified pipeline

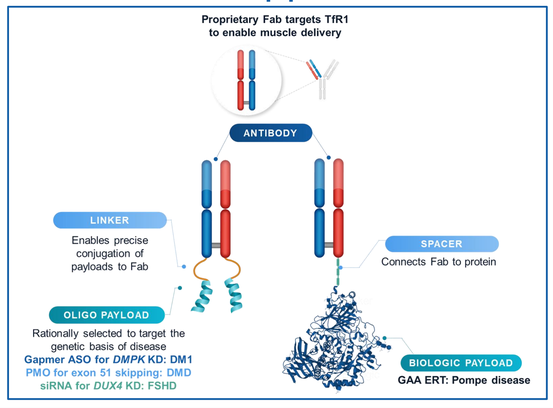
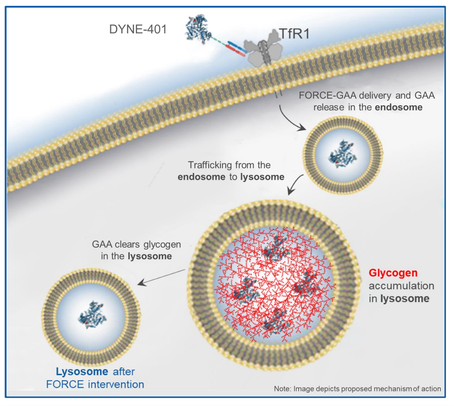
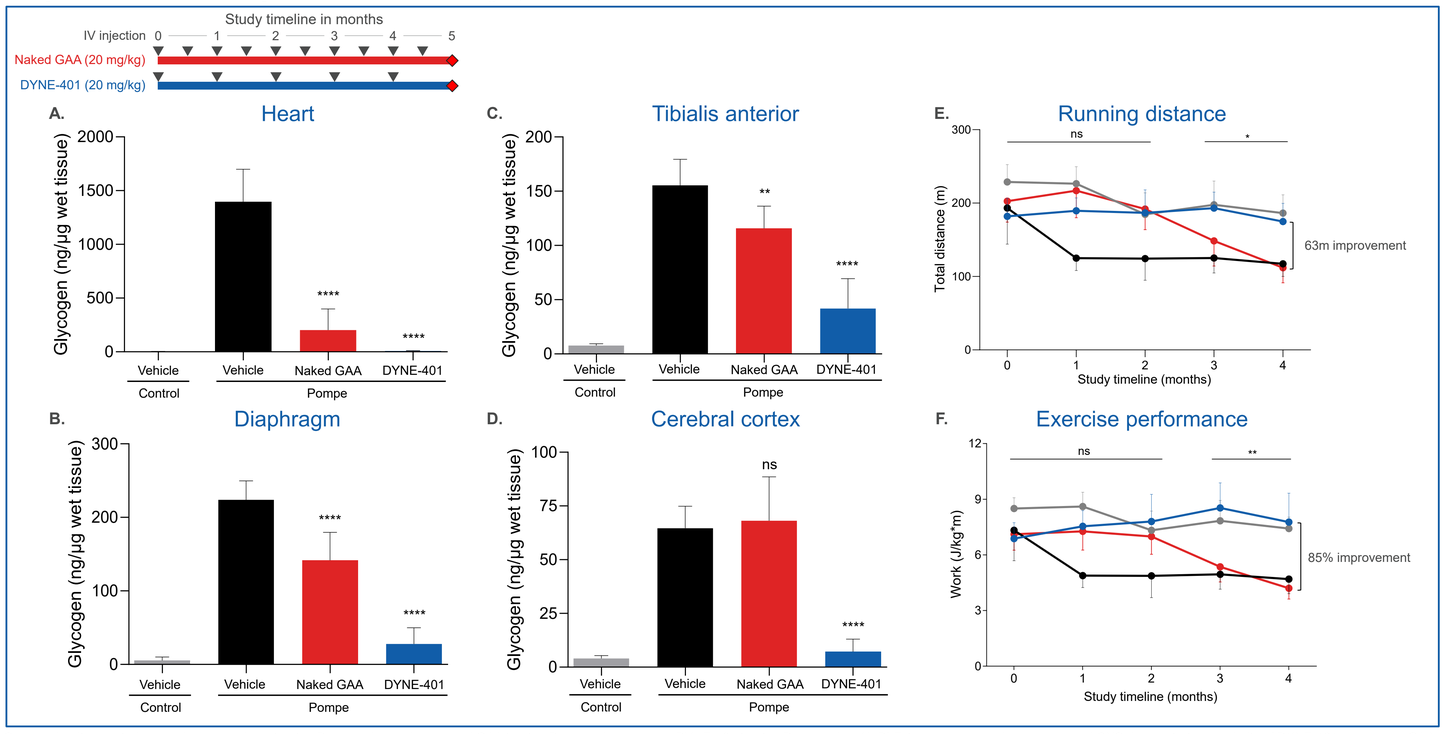


Figure 2. DYNE-401 delivers GAA to the lysosome



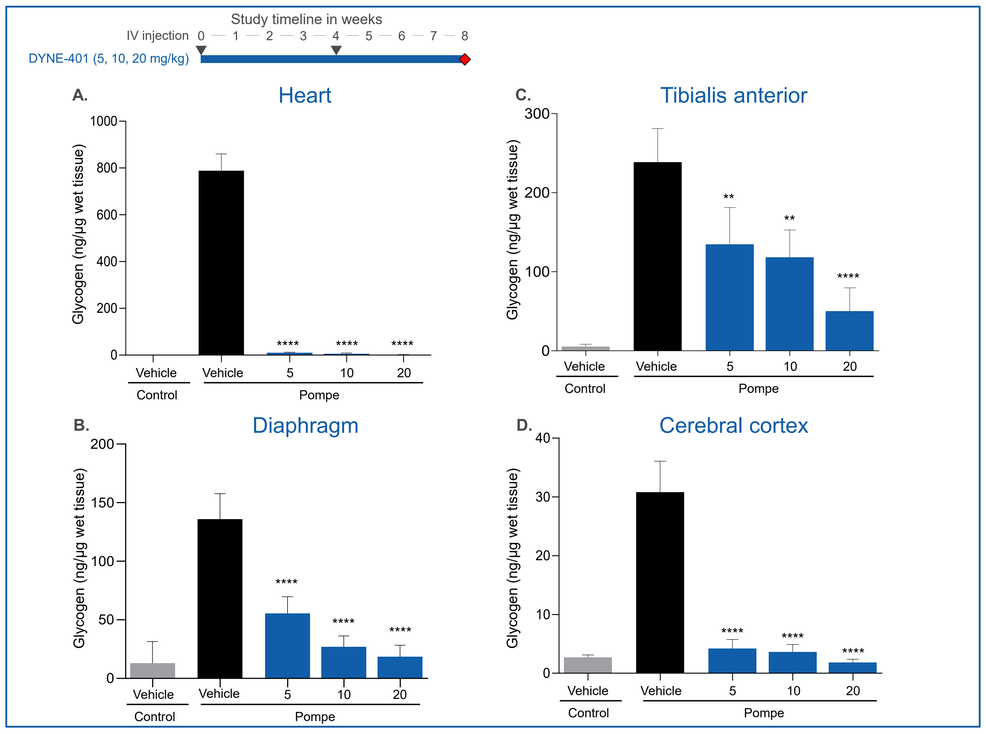
RESULTS

Figure 3. Monthly (Q4W) DYNE-401 clears glycogen in muscle and CNS and sustains functional improvement compared to biweekly (Q2W) naked GAA in Pompe mice.



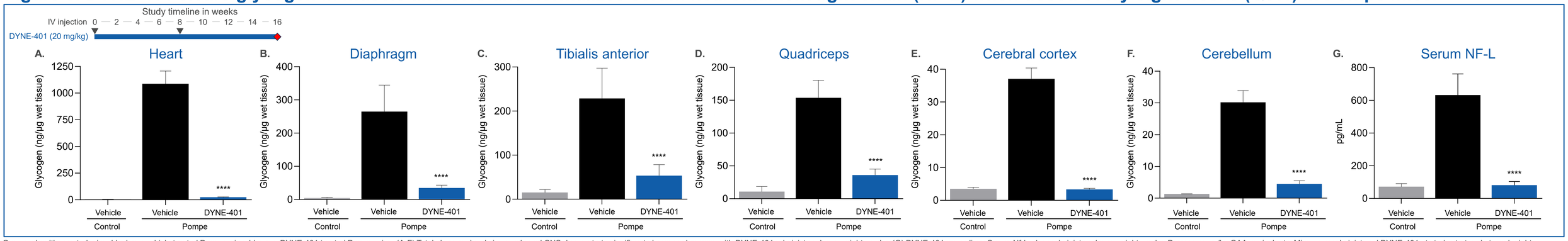
Grey are healthy control mice, black are vehicle treated Pompe mice, red are naked GAA treated Pompe mice, blue are DYNE-401 treated Pompe mice. (A-D) Total glycogen levels in muscle and CNS demonstrate superiority of DYNE-401 over naked GAA in Pompe disease mice. (E and F) DYNE-401 treatment led to significant and sustained improvements in total running distance and treadmill work compared to vehicle or naked GAA treated Pompe mice. Doses are mg/kg GAA equivalents. Mice were administered naked GAA every other week or DYNE-401 once a month for the duration of the study. Tissues were analyzed 5 months after study start. N=7-9 mice per group, mice were approximately 24 weeks of age at study start; biochemical data are mean ± SD; data analyzed by one-way ANOVA followed by Turkey's multiple comparisons; ** = *p≤0.01*, **** = *p ≤ 0.0001*; functional data are mean ± SEM; Data analyzed by one-way ANOVA followed by Dunnett's multiple comparisons test; ** = *p≤0.01*.

Figure 4. Monthly (Q4W) DYNE-401 clears glycogen in muscle and CNS with low doses of GAA in Pompe mice.



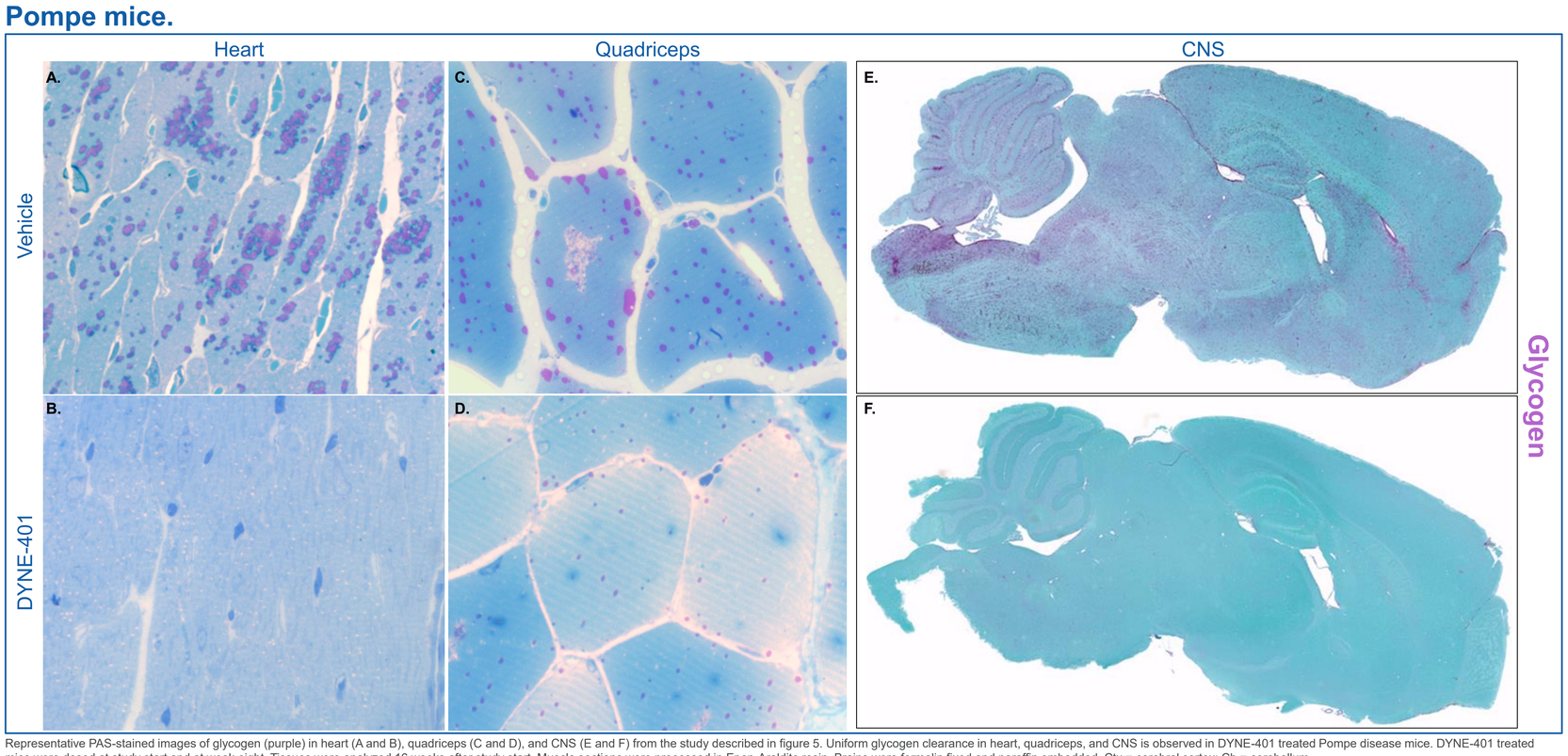
Grey are healthy control mice, black are vehicle treated Pompe mice, blue are DYNE-401 treated Pompe mice. (A-D) Total glycogen levels in muscle and CNS demonstrate dose dependent glycogen clearance with DYNE-401 in Pompe disease mice. Doses are mg/kg GAA equivalents. Mice were administered DYNE-401 once a month for the duration of the study. Tissues were analyzed 8 weeks after study start. N=4-5 mice per group, mice were approximately 10 weeks of age at study start; biochemical data are mean + SD; data analyzed by one-way ANOVA followed by Turkey's multiple comparisons; ** = *p≤0.01*, **** = *p ≤ 0.0001*.

Figure 5. DYNE-401 clears glycogen in muscle and CNS and normalizes serum neurofilament light chain (NF-L) when dosed every eight weeks (Q8W) in Pompe mice.



Grey are healthy control mice, black are vehicle treated Pompe mice, blue are DYNE-401 treated Pompe mice. (A-F) Total glycogen levels in muscle and CNS demonstrate significant glycogen clearance with DYNE-401 administered every eight weeks. (G) DYNE-401 normalizes Serum Nf-L when administered every eight weeks. Doses are mg/kg GAA equivalents. Mice were administered DYNE-401 at study start and at week eight. Tissues were analyzed 16 weeks after study start. N=4-5 mice per group, mice were approximately 10 weeks of age at study start; biochemical data are mean + SD; data analyzed by one-way ANOVA followed by Turkey's multiple comparisons; * = *p≤0.05*, ** = *p≤0.01*, *** = *p≤0.001*, **** = *p ≤ 0.0001*.

Figure 6. DYNE-401 achieves uniform glycogen clearance in muscle and CNS when dosed every eight weeks (Q8W) in Pompe mice.



Representative PAS-stained images of glycogen (purple) in heart (A and B), quadriceps (C and D), and CNS (E and F) from the study described in figure 5. Uniform glycogen clearance in heart, quadriceps, and CNS is observed in DYNE-401 treated Pompe disease mice. DYNE-401 treated mice were dosed at study start and at week eight. Tissues were analyzed 16 weeks after study start. Muscle sections were processed in Epon-Araldite resin. Brains were formalin fixed and paraffin embedded. Ctx = cerebral cortex; Cb = cerebellum

CONCLUSIONS

- DYNE-401 demonstrates superior efficacy in muscle compared to naked GAA in a well-established mouse model of Pompe disease
- DYNE-401 addresses CNS pathology in Pompe mice
- DYNE-401 has the potential to deliver functional improvement in Pompe disease with infrequent dosing
- FORCE is modular drug delivery platform that enables muscle and CNS distribution of biologics as well as oligonucleotide payloads

DYNE-401 demonstrates potential for low, infrequent dosing and potential to deliver functional improvement in Pompe disease

DISCLOSURE INFORMATION: All authors are employees or advisors of Dyne Therapeutics Inc. and may hold Dyne stock and/or stock options. Data previously presented: Picariello, T. et al., (2026) *Molecular Genetics and Metabolism,* 147;(2).

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