Centyrin-targeted glycogen synthase-1 siRNA conjugates: A novel, muscle targeted glycogen reduction therapy for the treatment of Pompe Disease

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Abstract

Pompe disease is a lysosomal storage disease characterized by loss of function mutations in acid alpha glucosidase (GAA), an enzyme responsible for the degradation of lysosomal glycogen in muscle tissues, and consequent pathogenic accumulation of glycogen[1]. In muscle tissue, the enzyme responsible for synthesizing glycogen is called glycogen synthase 1 (Gys1). Reducing the production of glycogen via decreasing levels of *Gys1* mRNA and GYS1 protein may provide an effective strategy for the treatment of Pompe disease that would be an alternate approach to the current standard of care, enzyme replacement therapy. We have designed a Centyrin targeting CD71 receptor (Transferrin receptor 1, TfR1) conjugated to a GYS1 specific siRNA to achieve muscle selective GYS1 reduction and rebalancing of muscle glycogen levels. Single and repeat dose studies were conducted using a mouse specific surrogate Centyrin-siRNA conjugate targeting CD71 and *Gys1* mRNA in the Pompe ($GAA^{-/-}$) knockout mouse model. Single doses of Centyrin-siRNA conjugate resulted in >80% reduction in *Gys1* mRNA levels and > 90% reduction in expression of GYS1 protein at the 10 mg/kg dose level after 4 weeks. The *Gys1* mRNA effects were observed out to 6 weeks post single dose with return to baseline by 12 weeks in the muscle. Reductions in GYS1 protein expression were observed out to 12 weeks in muscle. Dose-response modeling resulted in ED50 estimates ranging from 1-3 mg/kg for *Gys1* mRNA. Minimal to no decrease of *Gys1* mRNA or GYS1 protein were detected in liver or kidney. Decreases in *Gys1* mRNA and GYS1 protein led to a significant decrease in skeletal muscle glycogen of up to 67% in repeat dose studies. Subsequent studies have demonstrated robust *Gys1* mRNA and GYS1 protein reductions with quarterly dosing, indicating the potential to dose Centyrin-siRNA conjugates every 3 months. ABX1100, the CD71 Centyrin- Gys1 siRNA clinical candidate demonstrates robust *Gys1* mRNA knockdown in nonhuman primates and a favorable safety profile. These data provide the basis for studying Centyrin-siRNA conjugates in patients with Pompe disease. Pre-clinical studies are ongoing to support an IND in 2023.

Figure 1: Toxic glycogen buildup in Pompe disease is reduced by decreasing expression of glycogen synthase-1 (GYS1) mRNA and protein

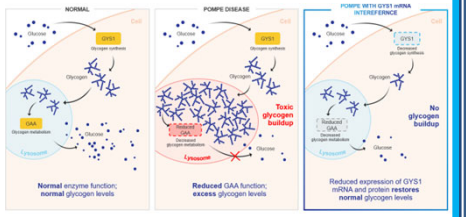
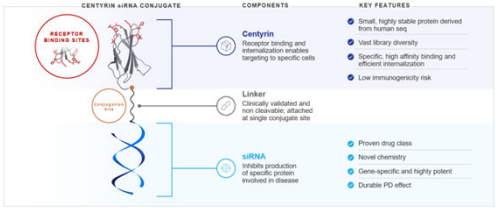


Figure 2: Centyrin-siRNA conjugates possess key attributes required for extrahepatic delivery of siRNA



Single dose of CD71 Centyrin-Gys1 siRNA reduces *Gys1* mRNA and Protein in Pompe Mice

Figure 3: Single-dose, Dose Range Study Design in Pompe mice

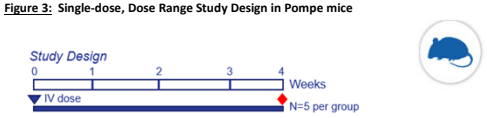
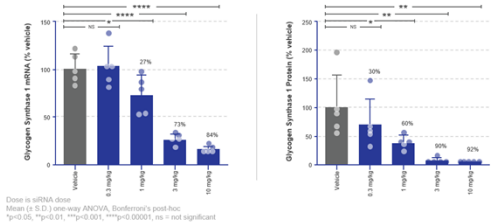


Figure 4: Dose-response of Gys1 mRNA and protein reduction in Pompe Mice in the Gastrocnemius 4 weeks after single dose



Repeat dosing of CD71 Centyrin-Gys1 siRNA reduces Gys1 mRNA and protein, glycogen, and creatinine kinase in Pompe Mice

Figure 5: Repeat-dose Study Design in Pompe Mice

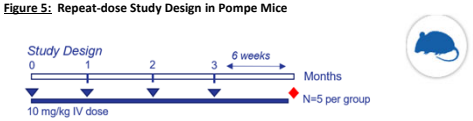


Figure 6: Monthly dosing of CD71 Centyrin-Gys1 siRNA conjugate demonstrates efficient Gys1 mRNA and protein reduction in Pompe mouse muscle tissue

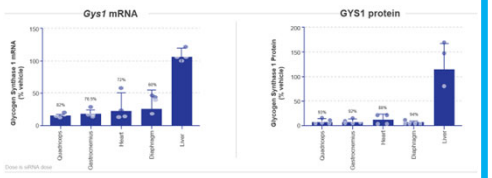
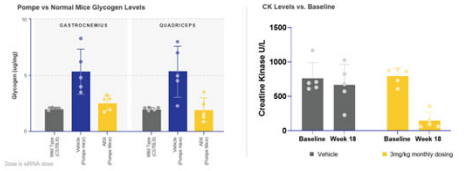
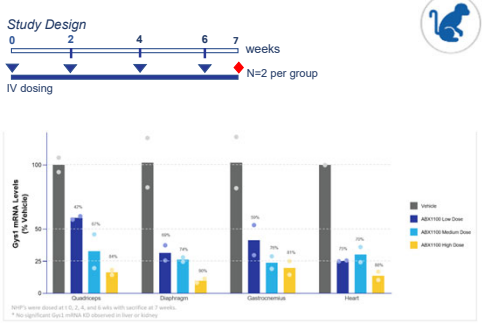


Figure 7: Monthly dosing of CD71 Centyrin-Gys1 siRNA conjugate demonstrates efficient glycogen and creatinine kinase reduction in Pompe mouse muscle tissue



ABX1100 activity in Non-human primates' muscle after biweekly dosing

Figure 8: Repeat dose Study Design in NHPs



No in-life adverse events, abnormal labs, ECGs or histopathology findings

Summary and Conclusions

- Proof of concept of muscle-specific targeting of Gys1 mRNA via Centyrin-siRNA conjugates in murine Pompe model and in NHPs
- Durable mechanism of action demonstrated
- Glycogen reduction and corresponding CK biomarker reduction established in Pompe mouse
- Convenient dosing, wide therapeutic window, no toxicities in initial NHP study

References

1. Lim JA, Li L, Raben N. *Front Aging Neuurosci.* 2014.