Peer Review File

Article Information: https://dx.doi.org/10.21037/atm-24-135

Reviewer A

well written;
all major topics discussed and reviewed
no major comments

Comment 1: # Line 20 and following: please add "age of onset" in discussing the differences between infantile and late onset.
Reply 1: Thank you for this recommendation. The differentiating feature between LOPD and IOPD is absence of cardiomyopathy in 1st year of life. While historically LOPD was considered to present later in life and have a milder disease course, recent evidence – including from a cohort of LOPD children diagnosed via newborn screening – has shown that LOPD can present as early as infancy (PMIDs 35123877, 30655185, 37670900). Respectfully, we did not add "age of onset" to the list of differentiating features between IOPD and LOPD as requested because it would imply that there are no detectable features of LOPD in infants. Rather, the following sentences in lines 27-31 expands on the age of onset of IOPD and LOPD: "The phenotypic spectrum of Pompe disease includes infantile-onset and late-onset Pompe disease (IOPD and LOPD, respectively) based on the levels of residual endogenous GAA activity and the presence/absence of cardiomyopathy in the first year of life. IOPD manifests as severe early cardiomyopathy, while LOPD can present at any age and had been previously categorized as juvenile-, childhood-, and adult-onset forms."

Comment 2: # a comment about the occurrence of genetic variants of GYS in the general population (see GnomAd) their possible effect or interaction with the small molecule and discussion about the need to assess the GYS status of patients to be enrolled in new studies, distribution of GYS variants in Pompe, could be added, and certainly will improve the paper.
Reply 2:
We appreciate the suggestion and have added the following text (in blue) starting at line 174 to address these concerns:
"At this time, it is unclear to what level GYS1 activity can be reduced without negative effects. *GYS1* loss-of-function (LOF) variants appear to be rare in the general population. In the recently released and updated gnomAD v4.1, 692 predicted *GYS1* LOF alleles are reported across approximately 160,000 sequenced alleles for an allele frequency of 0.0004. Though rare in the general population, we would encourage screening patients for *GYS1* LOF variants prior to initiating treatment with a GYS1 inhibitor. Complete or near complete loss of GYS1 activity, as seen in patients with biallelic loss-of-function variants in *GYS1* (GSD type 0b), can lead to muscle weakness and fatal cardiac arrythmias (Kollberg et al., 2007; Sukigara et al., 2012)."

Reviewer B

This is an excellent and very comprehensive editorial, obviously written by an expert in the field of basic research in Pompe disease.
Author view is very nuanced, and thoughts about the topic of future clinical trials design is very relevant.

Comment 1: I have only a minor remark: I suggest to modify the sentence line 34 " Persistent glycogen buildup is also noted in cardiac and skeletal muscle tissues despite..." as to my opinion a huge limitation of ERT efficacy in LOPD is related to autophagy disturbances as well in skeletal muscle.
Reply 1: Thank you for this recommendation. We have modified the text starting at line 40 to emphasize the limitation of ERT efficacy in skeletal muscle:
Notably, poor biodistribution and inefficient rhGAA uptake by skeletal muscle cells result in inadequate clearance of glycogen in this tissue. In addition, residual glycogen accumulation is also noted in cardiac tissue despite improvements in cardiomyopathy and cardiac function.