Immunogenicity of cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo in late-onset Pompe disease: a Phase III, randomized study (PROPEL)

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INTRODUCTION

- Pompe disease is a rare, autosomal recessive lysosomal disorder caused by variants of the *GAA* gene.[1,2]
- Alglucosidase alfa, a recombinant human acid alpha glucosidase (rhGAA) enzyme, is one of the approved treatments and has been shown to improve outcomes in patients with late-onset Pompe disease (LOPD).[3,4]
- Cipaglucosidase alfa/miglustat is an investigational, two-component therapy that has been shown to improve outcomes in patients with Pompe disease[5]
  - Cipaglucosidase alfa is a novel bis-mannose 6-phosphate (M6P)-enhanced rhGAA for improved uptake and processing by target tissues, including muscle
  - Miglustat is a small molecule that stabilizes cipaglucosidase alfa in blood and enhances delivery of active enzyme to tissues.

OBJECTIVE

- To assess the effects of anti-drug antibodies (ADAs) to cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo on efficacy (6-minute walking distance [6MWD], forced vital capacity [FVC]), diagnostic biomarkers (creatine kinase [CK], hexose tetrasaccharide [Hex4]) and safety, using data from studies ATB200-02 (Phase II) and ATB200-03 (PROPEL; Phase III).

METHODS

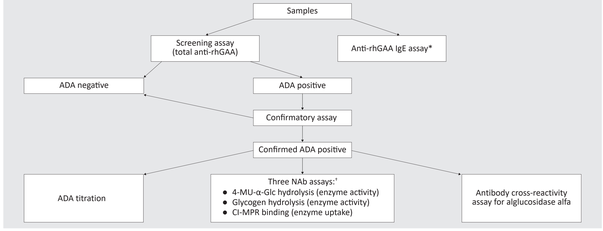
Study design

- The ATB200-03 study design has been previously described[5] and is shown in **Supplementary Figure 1**, which is accessible via quick response (QR) code.
- The impact of ADAs and neutralizing antibodies (NAbs) on the following factors was assessed:
  - Clinical efficacy: 6MWD and FVC
  - Biomarkers: CK and Hex4
  - Pharmacokinetics (PK): area under the curve (AUC) and peak plasma concentration (C_{max})
  - Safety.

ADA assay technique and strategy

- A three-tiered assay strategy was developed in accordance with US Food and Drug Administration (FDA) guidance (**Figure 1**).
- The ADA assessment used a novel, highly sensitive, electrochemiluminescence (ECL)-based immunoassay (**Supplementary Figure 2**).
- The Meso Scale Discovery bridging format (Meso Scale Diagnostics, MD, USA) may enable or improve detection of low-affinity ADAs and may have better drug tolerance in test samples compared with enzyme-linked immunosorbent assay (ELISA) and other platforms.[6]
- For the ECL-based assay, a validated cutoff was established using 75 enzyme replacement therapy (ERT)-naïve human dipotassium ethylenediaminetetraacetic acid (K2 EDTA) plasma samples.
- The in-study cutoff from predose (baseline) plasma samples (ERT-naïve patients in ATB200-03) was similar to the validated cutoff.
- The assay sensitivity was ≤100 ng/mL (screening assay: 8.07 ng/mL), and the minimum required dilution was 100-fold.

Figure 1. Overview of tiered immunogenicity testing strategy and assays



*For all patients at baseline, and as needed in patients who experienced an IAR; †For alglucosidase alfa, results were only summarized from two NAb assays (4-MU-α-Glc hydrolysis and glycogen hydrolysis) and not CI-MPR binding because of fundamental differences in cipaglucosidase alfa M6P versus alglucosidase alfa M6P; method-bridging experiments with both forms of rhGAA were not performed in the validation of the CI-MPR NAb assay. 4-MU-α-Glc, 4-methylumbelliferone-α-D-glucopyranoside; CI-MPR, cation-independent M6P receptor; IAR, infusion-associated reaction; IgE, immunoglobulin E.

- All assay dilutions, including the minimum required dilution, were factored into the final reported titer values.
- To assess the impact of ADAs as a covariate on treatment outcomes of cipaglucosidase alfa plus miglustat or alglucosidase alfa plus placebo, model-based analyses were performed using pooled data from studies ATB200-02 and ATB200-03.
- Population PK analyses were performed to quantify the effects of immunogenicity markers on cipaglucosidase alfa exposure.
- Analysis of each of the immunogenicity marker effects on 6MWD and FVC following cipaglucosidase alfa or alglucosidase alfa administration was conducted with graphical investigation and estimation of covariate effects of immunogenicity on drug effect.

RESULTS

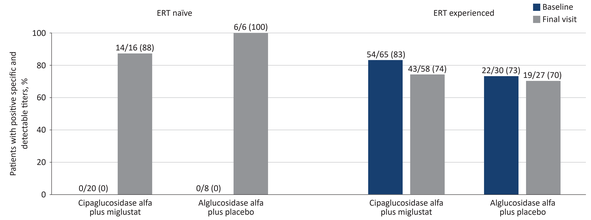
Patient disposition

- An overview of the baseline patient population for the modeled analyses is shown in **Supplementary Figure 3**.

ADAs

- In the ATB200-03 study, the majority of ERT-experienced patients had detectable titers (≥100) for ADAs at baseline, while no ERT-naïve patients had detectable baseline titers (**Figure 2**)
  - Among ERT-naïve patients, no patients in either treatment group had detectable titers at baseline; the majority had detectable titers at their final visit
  - Among ERT-experienced patients, the majority had detectable titers at baseline and remained stable in both treatment groups.

Figure 2. Patients with detectable ADA titers by ERT experience in the ATB200-03 study



n/N = number of patients with ADAs/total number of patients with data available at a given time point.

- Using the highly sensitive ECL-based assay, a broad range of titers was observed, independent of ERT status (**Table 1**)
  - Because of the differences in the assays, the titer values and rates of immunogenicity observed in these studies cannot be compared with previous reports from other rhGAA-based ERTs.

Table 1. Total ADA titer at baseline and last study visit in the ATB200-03 study

	Visit	Total ADA titer, median (range)
Cipaglucosidase alfa plus miglustat		
ERT experienced	**Baseline** (day 1)	**12,800** (<100–52,428,800)
	Last visit (day 364)	**102,400** (<100–6,553,600)
ERT naïve	**Baseline** (day 1)	N/D*
	Visit 5 (day 28)	**100** (<100–100)
	Last visit (day 364)	**12,800** (<100–204,800)
Alglucosidase alfa plus placebo		
ERT experienced	**Baseline** (day 1)	**9600** (100–819,200)
	Last visit (day 364)	**3200** (<100–1,638,400)
ERT naïve	**Baseline** (day 1)	N/D*
	Visit 5 (day 28)	**200** (<100–400)
	Last visit (day 364)	**2400** (400–51,200)

Titer values below the assay minimum required dilution of 100 were imputed to 0.1. *Not positive specific or had no detectable titers as per the tiered approach. N/D, not detectable.

Neutralizing antibodies

- The presence of post-baseline NAbs that inhibit rhGAA enzyme activity was similarly low between patients treated with either cipaglucosidase alfa or alglucosidase alfa (**Table 2**).

Table 2. Presence of post-baseline NAbs in ATB200-03

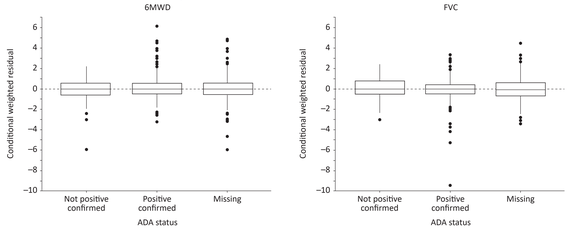
	Cipaglucosidase alfa plus miglustat, n (%)		Alglucosidase alfa plus placebo, n (%)	
	ERT experienced (n=65)	ERT naïve (n=20)	ERT experienced (n=30)	ERT naïve (n=8)
Glycogen NAb only	0	0	0	0
4-MU-α-Glc NAb only	0	0	0	0
Both 4-MU-α-Glc and glycogen NAbs	2 (3)	1 (5)	1 (3)	0

Data are n (%) patients with a detectable titer (≥100). The CI-MPR binding NAb assay cannot be compared between cipaglucosidase alfa and alglucosidase alfa; the assay was done only for cipaglucosidase alfa because of fundamental differences between cipaglucosidase alfa M6P and alglucosidase alfa M6P.

Immunogenicity impact assessments (studies ATB200-02 and ATB200-03 combined)

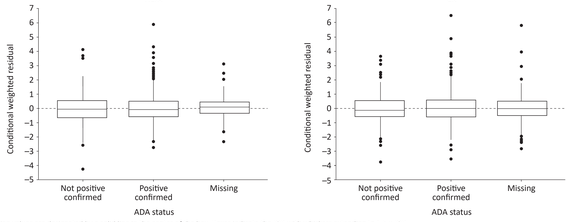
- Overall, immunogenicity markers did not have a clear association with efficacy assessments (**Figure 3**), diagnostic biomarkers (**Figure 4**), PK (**Figure 5**), as shown in representative covariate plots of conditional weighted residuals against ADA status
  - Analyses of the covariate effects of immunogenicity on modeled drug effects also suggested that there was no objective impact (data not shown).
- Analyses of the impact of immunogenicity on safety evaluated the frequency and severity of adverse events (AEs) in different system organ classes by antibody presence and maximum titer (studies ATB200-02 and ATB200-03 combined)
  - No clear associations between AEs and immunogenicity were observed
  - Similarly, there was no clear association between IAR occurrence and total ADA titer or the incidence of anti-rhGAA IgE.

Figure 3. Covariate plots showed no notable trends on the impact of ADA titers on 6MWD or FVC (studies ATB200-02 and ATB200-03 combined)



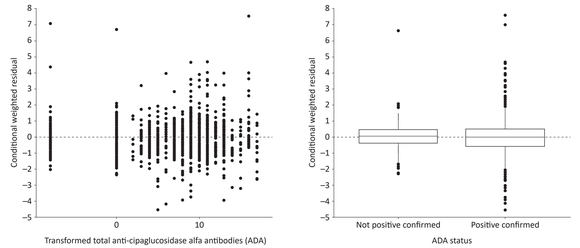
Median values are designated by a solid line in the center of the box. Boxes indicate the IQR with whiskers extending to 1.5 × IQR. A dashed black line at y = 0 is included as a reference. IQR, interquartile range.

Figure 4. Covariate plots showed no associations between ADAs and Hex4 or CK (studies ATB200-02 and ATB200 03 combined)



Median values are designated by a solid line in the center of the box. Boxes indicate the IQR with whiskers extending to 1.5 × IQR. A dashed black line at y = 0 is included as a reference.

Figure 5. Immunogenicity markers were not clearly associated with cipaglucosidase alfa, alglucosidase alfa or miglustat exposure (studies ATB200-02 and ATB200-03 combined)



Median values are designated by a solid line in the center of the box. Boxes indicate the IQR with whiskers extending to 1.5 × IQR.

CONCLUSIONS

- In the ATB200-03 study of LOPD, a wide range of ADA titers was observed, though the incidence of enzyme-activity NAbs was low and similar between treatment arms.
- Using modeling-based population analyses of combined data from two LOPD studies, overall, immunogenicity markers such as ADA, regardless of ERT-naïve or ERT-experienced status:
  - Did not have an impact on cipaglucosidase alfa plus miglustat or alglucosidase alfa effects on 6MWD or FVC
  - Did not influence cipaglucosidase alfa plus miglustat or alglucosidase alfa effect on Hex4 and CK
  - Did not have an impact on cipaglucosidase alfa plus miglustat or alglucosidase alfa PK or safety.
- Overall, the clinical benefit:risk assessment of cipaglucosidase alfa plus miglustat for the treatment of patients with Pompe disease was not affected by the immunogenicity associated with cipaglucosidase alfa plus miglustat.
- Continued long-term monitoring in ongoing clinical studies for the impact of immunogenicity on outcomes is planned.

Acknowledgments

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This presentation shares information about Amicus Therapeutics' investigational therapy, cipaglucosidase alfa plus miglustat, which is in development for the treatment of Pompe disease. This investigational therapy is not approved by any regulatory agency at this time.

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References

1. Hers HG. *Biochem J* 1963;86:11–16.
2. Kishnani PS *et al. J Pediatr* 2004;144:S35–43.
3. Alglucosidase alfa [prescribing information]. Sanofi Genzyme; 2020.
4. Do HV *et al. Ann Transl Med* 2019;7:291.
5. Schoser B *et al. Lancet Neurol* 2021;20:1027–37.
6. Liang M *et al. Assay Drug Dev Technol* 2007;5:655–62.

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Supplement

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