Poster no. 059

Long-term follow-up of cipaglucosidase alfa/miglustat in ambulatory patients with Pompe disease: an open-label Phase I/II study (ATB200-02)

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INTRODUCTION

- Pompe disease is a rare, multisystemic, heterogenous lysosomal disorder characterized by progressive loss of muscle and respiratory function due to acid α-glucosidase (GAA) deficiency, an enzyme responsible for degrading lysosomal glycogen.[1–3]
- Enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA), alglucosidase alfa, is the first approved treatment for the disease[4]
  - While alglucosidase alfa has been shown to improve prognosis,[5] some patients do not respond, and many do not show a sustained benefit;[6] thus, substantial unmet clinical needs remain.[6]
- Another rhGAA, avalglucosidase alfa, was approved in 2021.[7]
- Cipaglucosidase alfa plus miglustat is an investigational, two-component therapy for Pompe disease comprising cipaglucosidase alfa, a novel bis-mannose-6-phosphate-enhanced rhGAA, administered in conjunction with miglustat, an enzyme stabilizer.[8,9]
- Results from the PROPEL study,[9] a 52-week, Phase III study of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in patients with Pompe disease were recently published; the open-label extension of this study is presented in Poster no. LB-59.
- Data from our Phase I/II study (ATB200-02) may provide a further understanding of the long-term effect of this investigational therapy.

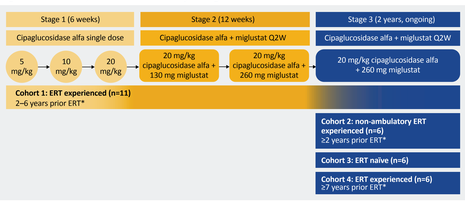
OBJECTIVE

- ATB200-02 (NCT02675465) is an ongoing, open-label, Phase I/II clinical trial that aims to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of cipaglucosidase alfa plus miglustat in adults with Pompe disease.
- Here, we report up to 48 months of efficacy and safety data for ambulatory patients with Pompe disease in the ATB200-02 study.

METHODS

- The ATB200-02 study is conducted in 17 centers across 6 countries, with 4 cohorts of patients enrolled at staggered timepoints.
- The study design is presented in **Figure 1**.

Figure 1. Phase I/II ATB200-02 study design



*With 20 mg/kg alglucosidase alfa Q2W. Q2W, every 2 weeks.

- A summary of the endpoints and cohorts we report is presented in **Table 1**.
- Available data for cohort 2, non-ambulatory ERT-experienced patients, are presented in the supplement, which is available via the QR code.
- Data were analyzed using descriptive statistics.

Table 1. Summary of endpoints and cohorts reported

Assessments	ERT experienced* (pooled data)		ERT naïve
	Cohort 1 2–6 years' prior ERT	Cohort 4 ≥7 years' prior ERT	Cohort 3
Motor function 6MWD	✓		✓
Respiratory function FVC	✓		✓
Muscle strength MMT lower extremity score	✓		✓
Biomarkers Hex4 (glycogen accumulation) and CK (muscle damage)	✓		✓
Safety	✓		✓

*With 20 mg/kg alglucosidase alfa Q2W. 6MWD, 6-minute walk distance; CK, creatine kinase; FVC, forced vital capacity; Hex4, glucose tetrasaccharide; MMT, manual muscle test.

RESULTS

Patients

- Baseline characteristics were representative of the Pompe disease population (**Table 2**).
- Due to the staggered timing of patient enrollment, the number of patients with data currently available decreases at later timepoints in this ongoing study.

Table 2. Baseline characteristics and patient disposition

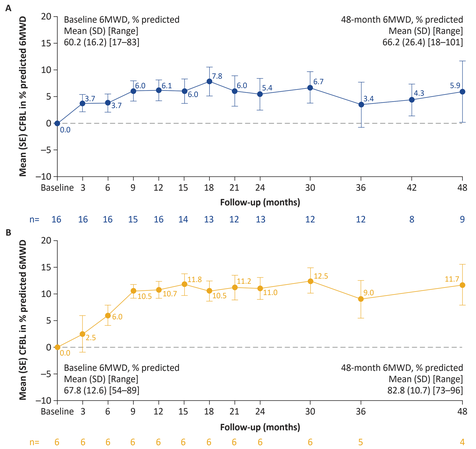
	ERT experienced		ERT naïve
	Cohort 1 2–6 years' prior ERT n=11*	Cohort 4 ≥7 years' prior ERT n=6	Cohort 3 n=6
Baseline† characteristics			
Median (range) age, years	50 (28–66)	43 (20–65)	51 (24–65)
Male patients, n (%)	9 (82)	2 (33)	1 (17)
Mean (SD) time on alglucosidase alfa, years	5.1 (1.3)	10.6 (2.1)	N/A‡
Mean (SD) 6MWD, % predicted	61.0 (13.4)	59.0 (21.4)	67.8 (12.6)
Mean (SD) sitting FVC, % predicted	52.6 (13.9)	65.3 (21.1)	57.2 (20.8)
Mean (SD) MMT lower extremity score	31.8 (1.9)	27.3 (3.7)	29.0 (1.7)
Patient disposition			
Ongoing in study, n (%)	9 (82)	6 (100)	6 (100)

*All enrolled patients were included in both the efficacy and safety populations, except one patient in cohort 1 who was excluded from the efficacy population as the patient withdrew consent prior to post-baseline efficacy assessments; †Baseline assessment is the last non-missing result on or prior to the administration of the first dose of study medication (20 mg/kg cipaglucosidase alfa + 260 mg miglustat co-administration dose); ‡One ERT-naïve patient had received one dose of alglucosidase alfa >6 months prior to study entry. N/A, not applicable; SD, standard deviation.

Motor function

- ERT-experienced cohorts showed durable mean improvements from baseline in 6MWD up to 48 months (**Figure 2A**).
- After 12, 24, 36 and 48 months of follow-up, 6MWD improved numerically from baseline in 13/16, 9/13, 6/12 and 6/9 ERT-experienced patients, respectively.
- The ERT-naïve cohort showed durable mean improvements from baseline in 6MWD up to 48 months (**Figure 2B**).
- After 12, 24, 36 and 48 months of follow-up, 6MWD improved numerically from baseline in 6/6, 6/6, 4/5 and 4/4 ERT-naïve patients, respectively.

Figure 2. CFBL in 6MWD in (A) ERT-experienced and (B) ERT-naïve patients

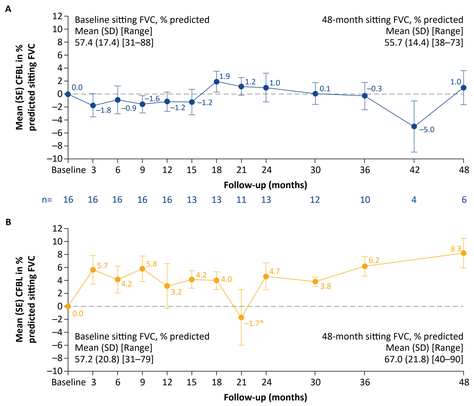


CFBL, change from baseline; SE, standard error.

Respiratory function

- Mean CFBL in FVC was generally stable for up to 48 months of follow-up in ERT-experienced cohorts (**Figure 3A**).
- After 12, 24, 36 and 48 months of follow-up, FVC improved (>3% points) or remained stable (±3% points) from baseline in 9/16, 11/13, 8/10 and 4/6 ERT-experienced patients, respectively.
- Mean CFBL in FVC improved numerically from baseline for up to 48 months of follow-up in the ERT-naïve cohort (**Figure 3B**).
- After 12, 24, 36 and 48 months of follow-up, FVC improved (>3% points) or remained stable (±3% points) from baseline in 5/6, 6/6, 5/5 and 4/4 ERT-naïve patients, respectively.

Figure 3. CFBL in FVC in (A) ERT-experienced and (B) ERT-naïve patients

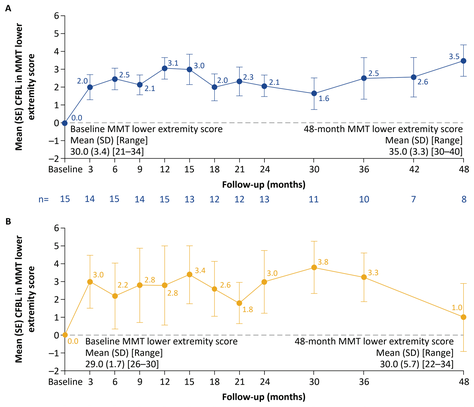


*One patient in the ERT-naïve cohort experienced a large drop in % predicted FVC at month 21, which returned to previous levels at the following visit (month 24).

Muscle strength

- Mean change in MMT lower extremity score improved numerically from baseline and improvements were generally maintained for up to 48 months of follow-up in both ERT-experienced and ERT-naïve cohorts (**Figures 4A** and **4B**).

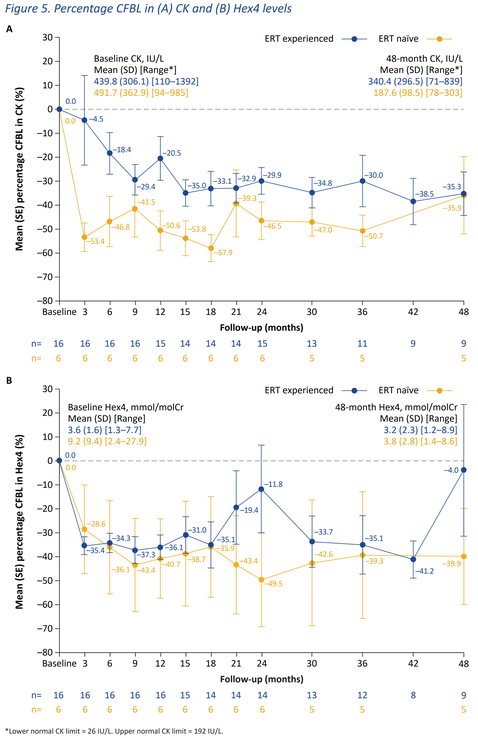
Figure 4. CFBL in MMT lower extremity score in (A) ERT-experienced and (B) ERT-naïve patients



Biomarkers

- During 48 months of follow-up, cipaglucosidase alfa plus miglustat was associated with mean reductions from baseline, in plasma CK (**Figure 5A**).
- After 12, 24, 36 and 48 months of follow-up, CK levels decreased numerically from baseline in 13/15, 14/15, 9/11 and 8/9 ERT-experienced patients, and in 6/6, 6/6, 5/5 and 4/5 ERT-naïve patients, respectively.
- During 48 months of follow-up, cipaglucosidase alfa plus miglustat was generally associated with mean reductions from baseline in urine Hex4 (**Figure 5B**).
- After 12, 24, 36 and 48 months of follow-up, Hex4 levels decreased numerically from baseline in 16/16, 11/14, 11/12 and 6/9 ERT-experienced patients, and in 5/6, 5/6, 4/5 and 4/5 ERT-naïve patients, respectively.

Figure 5. Percentage CFBL in (A) CK and (B) Hex4 levels



*Lower normal CK limit = 26 IU/L. Upper normal CK limit = 192 IU/L.

Safety

- **Table 3** summarizes treatment-emergent adverse events (TEAEs).
- Mean (SD) duration of treatment was 51.8 (21.46), 37.7 (4.13) and 54.7 (12.14) months in cohorts 1 (prior ERT 2–6 years), 4 (prior ERT ≥7 years) and 3 (ERT naïve), respectively.
- The most common TEAEs included fall, nasopharyngitis, arthralgia, headache and diarrhea; the majority of patients experienced only mild or moderate TEAEs that did not lead to study withdrawal.

Table 3. Summary of TEAEs

	ERT experienced n=17	ERT naïve n=6	Overall N=23
TEAEs, n (%)	17 (100)	6 (100)	23 (100)
TEAEs potentially related to treatment	11 (65)	4 (67)	15 (65)
Serious TEAEs	6 (35)	4 (67)	10 (44)
Serious TEAEs potentially related to treatment	1 (6)	2 (33)	3 (13)
TEAEs leading to study withdrawal	1 (6)*	0 (0)	1 (4)
Severe TEAEs	4 (24)	3 (50)	7 (30)
TEAEs leading to death	0 (0)	0 (0)	0 (0)
IARs	8 (47)	3 (50)	11 (48)

TEAEs have an onset date on or after first dose of study drug. *Diffuse large B-cell lymphoma. IAR, infusion-associated reaction.

Limitations

- As might be expected for a Phase I/II study of a rare disease therapy, the sample size was relatively small.
- The heterogenous nature of Pompe disease, spanning a wide spectrum of manifestations, disease severity, rates of progression, and responses to treatment, may have introduced variability into the dataset.
- Data were analyzed descriptively, with no statistical comparisons made.

CONCLUSIONS

- Results from up to 48 months of follow-up in ambulatory patients with Pompe disease from the ATB200-02 study of cipaglucosidase alfa plus miglustat showed:
  - ERT-experienced patients had durable mean improvements from baseline in motor function that were sustained for up to 48 months of follow-up, while respiratory function was stable and maintained over the same period: an improvement relative to the expected decline in many patients receiving long-term ERT[6]
  - ERT-naïve patients showed durable mean improvements from baseline in motor and respiratory function that were sustained for up to 48 months of follow-up
  - Mean levels of two biomarkers, Hex4 and CK, were either stable or decreased from baseline up to 48 months of follow-up, with decreases most notable in the ERT-naïve cohort
  - The safety profile of cipaglucosidase alfa plus miglustat was similar to that reported for alglucosidase alfa.[5]

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This presentation shares information about Amicus Therapeutics' investigational therapy, cipaglucosidase alfa/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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The presenter, Dr Barry J. Byrne, is a consultant/advisory board member for Pfizer, Amicus Therapeutics, Inc., and Sanofi; and owns stocks in Lacerta Therapeutics. Presenting author email address: barry.byrne@ufl.edu.

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