Long-term efficacy and safety of cipaglucosidase alfa/miglustat in ambulatory patients with Pompe disease: a Phase III open-label extension study (ATB200-07)

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Cipaglucosidase alfa plus miglustat is a novel, investigational, two-component therapy designed to address current challenges in ERT delivery for Pompe disease

1 Only 1% of an infused ERT reaches the target muscle due to **poor receptor binding and uptake**[1]

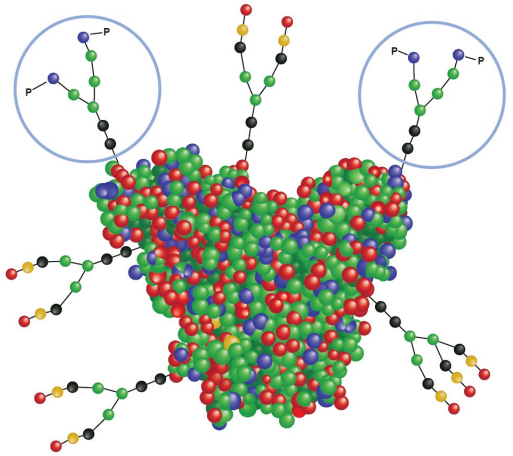
2 Once inside the target cell, ERT needs to be **fully processed** into the form that most effectively degrades glycogen[2]

3 Following infusion, ERTs are **rapidly inactivated** due to the pH of the blood[1]

Cipaglucosidase alfa (rhGAA)

Enhanced glycosylation with bis-M6P

Maximal receptor binding and uptake into target cells[3]



Synthesis within CHO cells results in cellularly derived bis-M6P N-glycans

Retained capacity for post-uptake processing into the most active form of the enzyme for degrading glycogen[3]

Miglustat (enzyme stabilizer)

Minimizes inactivation in the blood by binding to and **stabilizing** cipaglucosidase alfa during infusion and in circulation, which **increases availability of active enzyme** to muscles[3]

Bis-M6P, bis-mannose 6-phosphate; CHO, Chinese hamster ovary; ERT, enzyme replacement therapy; rhGAA, recombinant human acid α-glycosidase. 1. Do H *et al. Ann Transl Med* 2019;7:291; 2. Moreland RJ *et al. J Biol Chem* 2005;280:6780–91; 3. Xu S *et al. JCI Insight* 2019;4:e125358.

Cipaglucosidase alfa plus miglustat clinical trial overview

ATB200-03 Phase III PROPEL study (NCT03729362): compared the investigational two-component therapy cipaglucosidase alfa plus miglustat (cipa/mig) with alglucosidase alfa/placebo (alg/pla) in adult ambulatory patients with late-onset Pompe disease (LOPD) over 52 weeks[1]

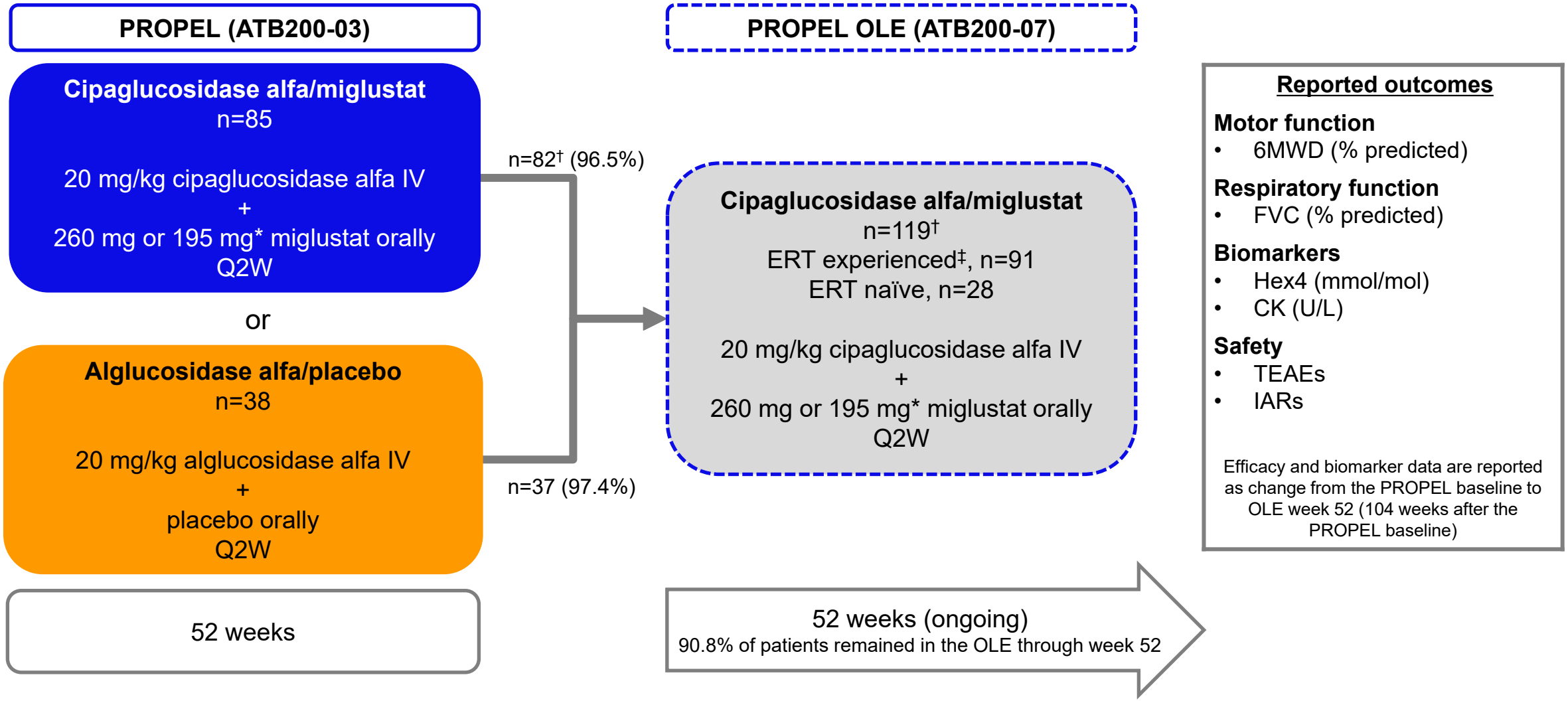
- While cipa/mig did not achieve statistical superiority over alg/pla for the primary endpoint of change in 6MWD from baseline to week 52, potentially clinically meaningful improvements in motor and respiratory function and biomarkers were seen at 52 weeks with cipa/mig versus alg/pla[1]

ATB200-07 (NCT04138277) is an ongoing, open-label extension (OLE) to evaluate the long-term safety and efficacy of cipa/mig in patients who completed the PROPEL study

We report **up to 52 weeks** (104 weeks after the PROPEL baseline) of **efficacy and safety data from ATB200-07**

6MWD, 6-minute walk distance. 1. Schoser B *et al. Lancet Neurol* 2021;20:1027–37.

ATB200-07 study design and patient disposition



*260 mg miglustat for patients weighing ≥50 kg and 195 mg for patients weighing ≥40 kg to <50 kg; †Includes one patient who enrolled on ATB200-07 but was never dosed; ‡ERT-experienced patients are defined as those treated with ERT (alglucosidase alfa) prior to their participation in the PROPEL study. 6MWD, 6-minute walk distance; CK, creatine kinase; FVC, forced vital capacity; Hex4, hexose tetrasaccharide; IAR, infusion-associated reaction; IV, intravenous; OLE, open-label extension; Q2W, every 2 weeks; TEAE, treatment-emergent adverse event.

Patient baseline characteristics in the OLE

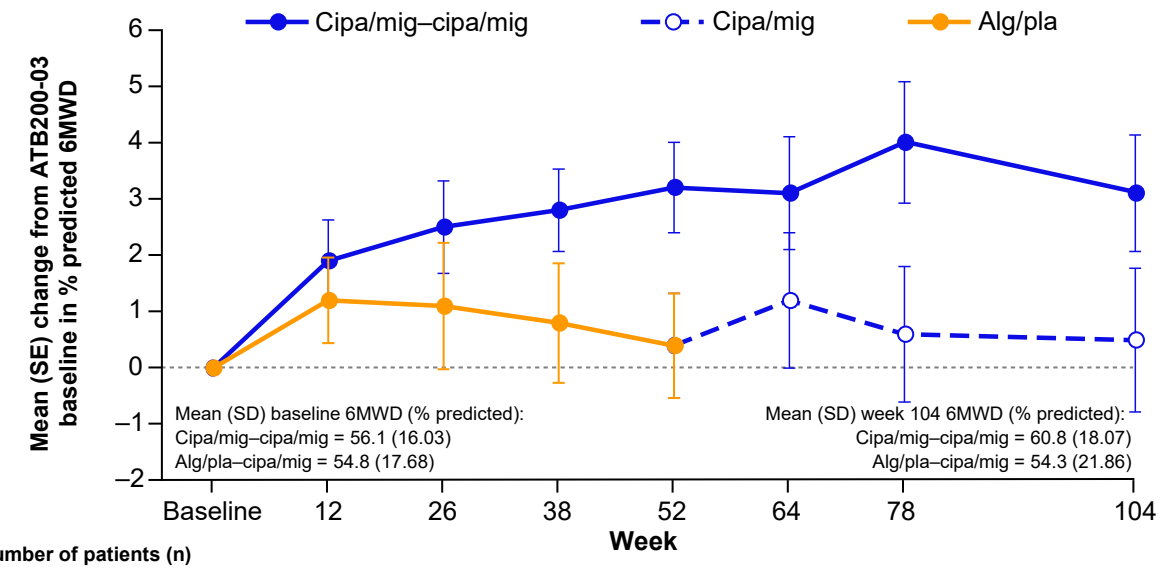
	Cipa/mig–cipa/mig n=81*	Alg/pla–cipa/mig n=37
Median (range) age, years	49 (20–75)	47 (23–67)
Male patients, n (%)	33 (40.7)	19 (51.4)
Race, n (%)		
Asian	3 (3.7)	1 (2.7)
Japanese	2 (2.5)	4 (10.8)
Black or African American	0	1 (2.7)
White	71 (87.7)	30 (81.1)
Other	5 (6.2)	1 (2.7)
ERT experienced, n (%)	61 (75.3)	29 (78.4)
Median (Q1–Q3) ERT duration, years†	7.6 (4.3–10.2)	7.1 (3.8–10.4)

- As only four patients in PROPEL did not continue into the OLE, patients in the OLE are representative of all randomized patients in PROPEL

*Excludes one patient who enrolled on ATB200-07 but was never dosed; †For ERT-experienced patients only. Alg/pla, alglucosidase alfa/placebo; cipa/mig, cipaglucosidase alfa/miglustat.

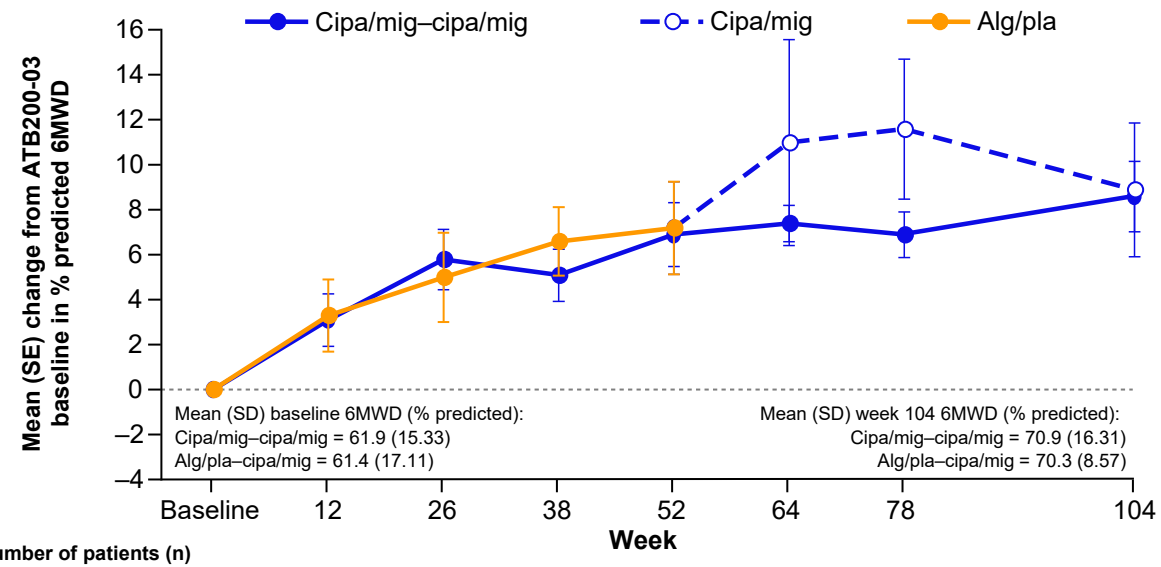
Improvement from the PROPEL baseline in % predicted 6MWD for the cipa/mig group was maintained throughout the OLE for ERT-experienced and ERT-naïve patients

ERT experienced



Number of patients (n)								
Cipa/mig–cipa/mig	62	61	54	58	61	55	56	56
Alg/pla–cipa/mig	29	29	27	28	29	27	26	26

ERT naïve*

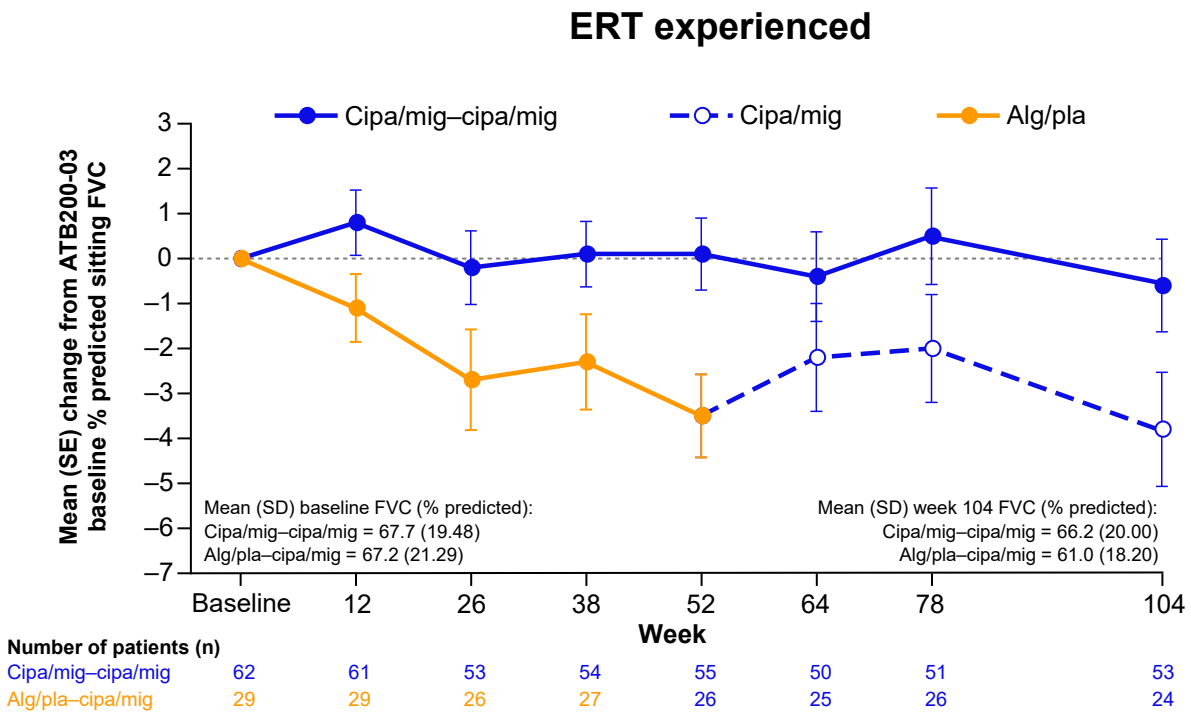


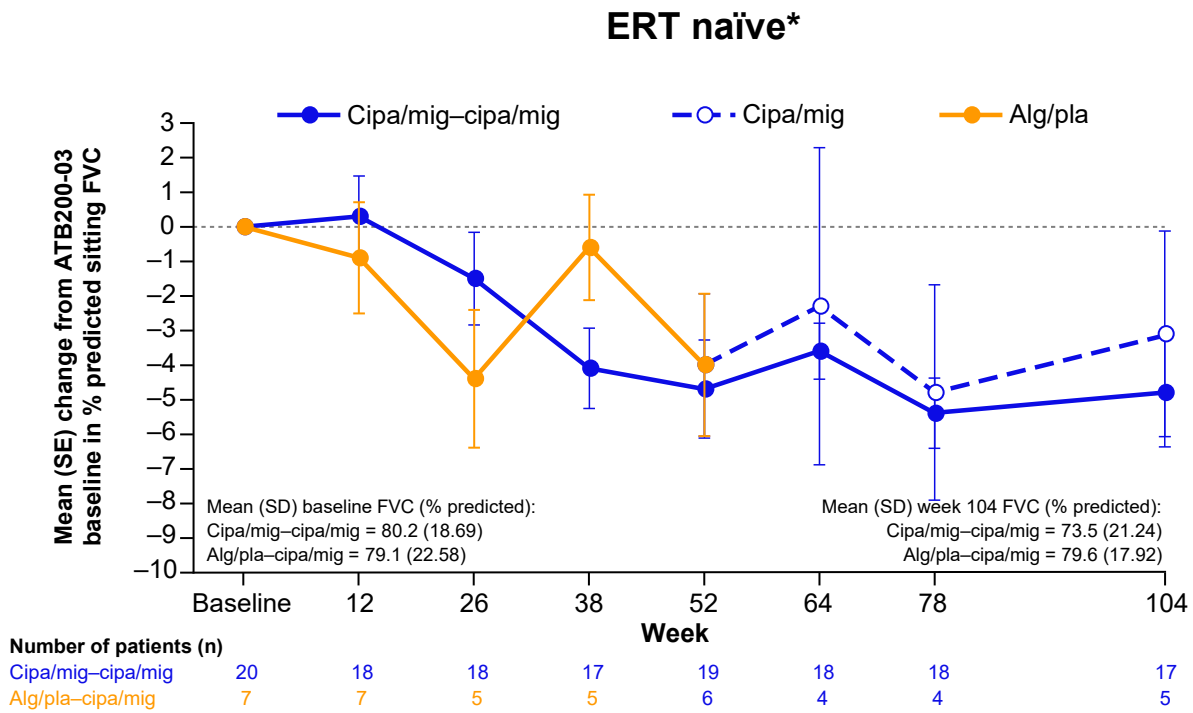
Number of patients (n)								
Cipa/mig–cipa/mig	20	19	17	20	20	18	19	18
Alg/pla–cipa/mig	7	7	6	7	7	5	6	7

- ERT-experienced and -naïve patients treated with cipa/mig throughout showed durable improvements in % predicted 6MWD in PROPEL that were maintained throughout the OLE to week 104
- ERT-experienced and -naïve patients who received alg/pla in PROPEL and switched to cipa/mig in the OLE showed stability in % predicted 6MWD throughout the OLE

*Excludes one outlier. SE, standard error.

Sitting % predicted FVC remained stable in ERT-experienced and ERT-naïve patients throughout the OLE for both PROPEL treatment groups

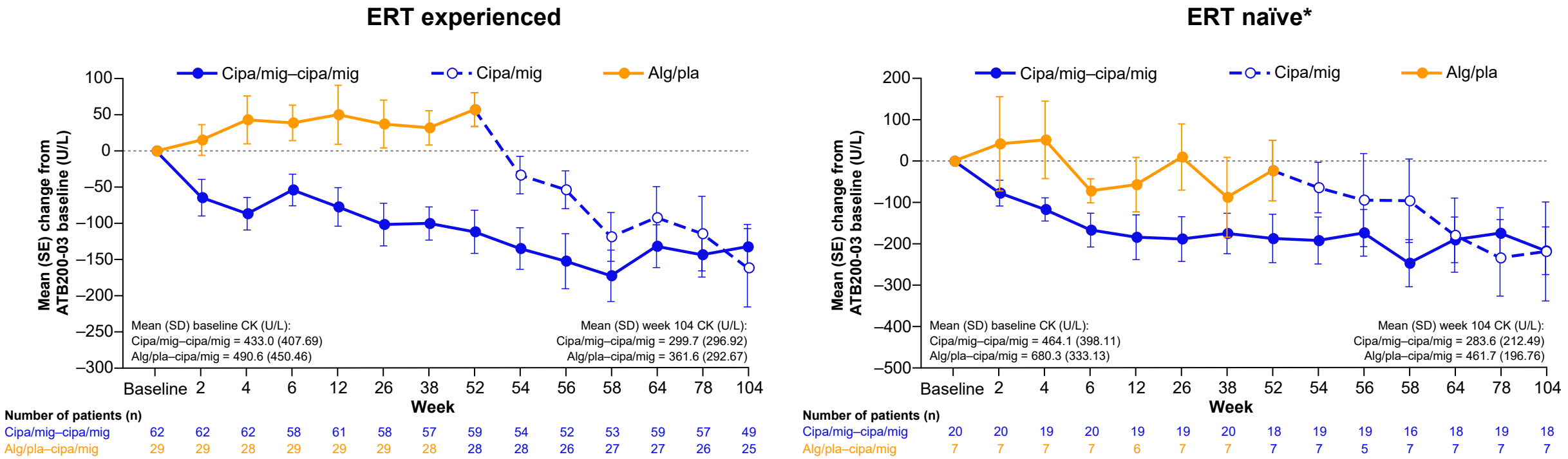




- ERT-experienced patients treated with cipa/mig throughout remained stable, while patients who received alg/pla in PROPEL experienced a decline in sitting % predicted FVC that stabilized after switching to cipa/mig in the OLE
- ERT-naïve patients in both treatment groups experienced some decline in PROPEL that stabilized in the OLE with no further decline in FVC to week 104

*Excludes one outlier.

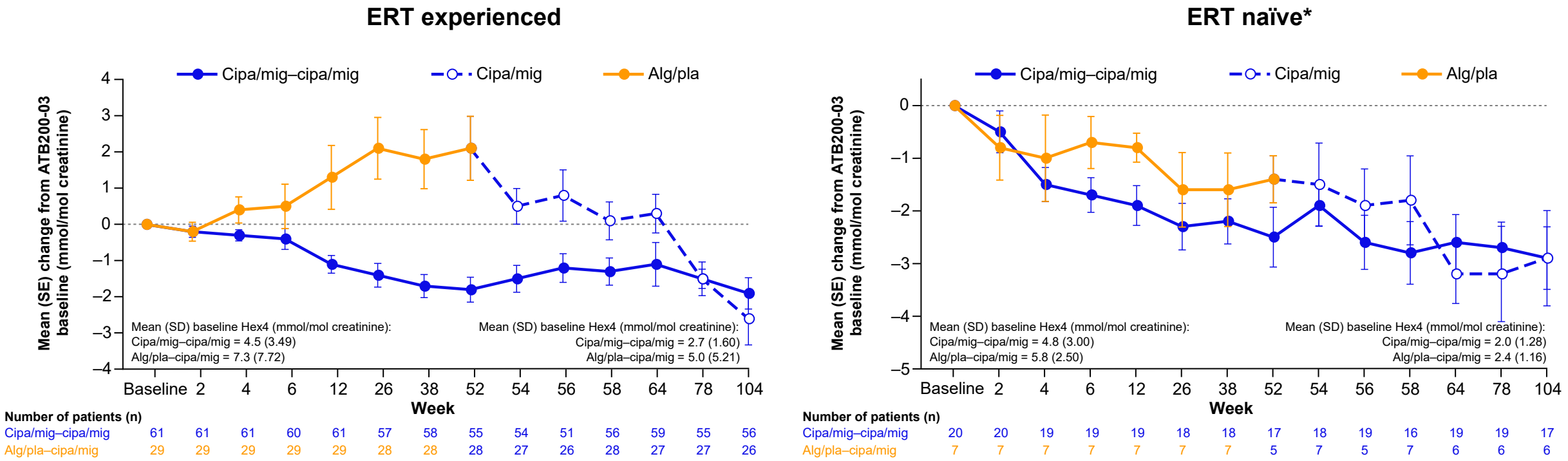
Cipa/mig treatment was associated with a durable reduction in serum CK during PROPEL and the OLE in both ERT-experienced and ERT-naïve patients



- ERT-experienced and -naïve patients treated with cipa/mig throughout showed a decline in serum CK levels during PROPEL that was maintained throughout the OLE
- ERT-experienced and -naïve patients who received alg/pla in PROPEL showed a slight increase or stability in serum CK levels to week 52, and a marked decline after switching to cipa/mig in the OLE

*Excludes one outlier.

Cipa/mig treatment was associated with a durable reduction in urine Hex4 during PROPEL and the OLE in both ERT-experienced and ERT-naïve patients



- ERT-experienced patients treated with cipa/mig throughout experienced a decline in urine Hex4 levels in PROPEL that stabilized during the OLE. ERT-experienced patients who received alg/pla in PROPEL experienced an increase in Hex4 and a marked decline after switching to cipa/mig in the OLE
- ERT-naïve patients experienced a decline in Hex4 levels during PROPEL in both treatment groups that stabilized or declined further during the OLE to week 104

*Excludes one outlier.

Safety summary

	Cipa/mig–cipa/mig n=85*	Alg/pla–cipa/mig n=37†
TEAEs, n (%)	84 (98.8)	36 (97.3)
TEAEs potentially related to treatment	37 (43.5)	15 (40.5)
Serious TEAEs	14 (16.5)	6 (16.2)
Serious TEAEs potentially related to treatment‡	1 (1.2)	2 (5.4)
TEAEs leading to study withdrawal during OLE	1 (1.2)§	2 (5.4)‖
TEAEs leading to death	0 (0)	0 (0)
IARs	27 (31.8)	10 (27.0)

- Most TEAEs were mild or moderate in severity
- The most common TEAEs included fall, headache, arthralgia, nasopharyngitis, myalgia and back pain
- Three patients withdrew from the study due to TEAEs experienced during the OLE
- No new safety signals were identified during the OLE

*Includes data from patients treated with cipa/mig in PROPEL who may or may not have continued cipa/mig in the OLE, including data from both PROPEL and the OLE; †Includes data from the OLE only; ‡Relatedness to treatment was determined by the investigator; §Urticaria; ‖Urticaria and hypotension, and anaphylaxis.

Study limitations

- The OLE was unblinded
- The heterogeneous 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
- As Pompe is a rare disease, the sample size was relatively small, particularly in the subgroup of ERT-naïve patients

Conclusions

- **ERT-experienced patients** who were treated with **cipa/mig through PROPEL and the OLE** showed improvements from baseline in 6MWD and biomarker levels and remained stable in FVC through PROPEL. All outcomes remained stable through the OLE to week 104
- For **ERT-naïve patients** who were treated with **cipa/mig through PROPEL and the OLE**, 6MWD and biomarker levels improved through PROPEL and remained stable through the OLE. FVC declined through PROPEL and stabilized over the OLE
- **ERT-experienced patients** who were treated with **alg/pla during PROPEL** remained stable in 6MWD and worsened in FVC and biomarker levels, and stabilized or improved after switching to cipa/mig in the OLE
- **ERT-naïve patients** who were treated with **alg/pla during PROPEL** and switched to cipa/mig in the OLE showed a similar pattern in 6MWD and FVC to ERT-naïve patients who were treated with cipa/mig throughout
- No new safety signals were identified in the OLE
- Overall, data demonstrate that treatment with cipa/mig up to 104 weeks was associated with a durable effect and was well tolerated, supporting the long-term benefits of cipa/mig treatment for patients with LOPD

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