# Results From ATB200-02: First-in-Human Study of ATB200 Co-Administered With AT2221 for Pompe Disease (18-Month Results)

Benedikt Schoser,[1] Drago Bratkovic,[2] Barry J. Byrne,[3] Paula Clemens,[4] Tarekegn Geberhiwot,[5] Ozlem Goker-Alpan,[6] Priya Kishnani,[7] Xue Ming,[8] Tahseen Mozaffar,[9] Peter Schwenkreis,[10] Kumaraswamy Sivakumar,[11] Ans T. van der Ploeg,[12] Jacquelyn Wright,[13] Swati Sathe,[13] Sheela Sitaraman,[13] Hjalmar Lagast,[13] Jay A. Barth,[13] Mark Roberts[14]

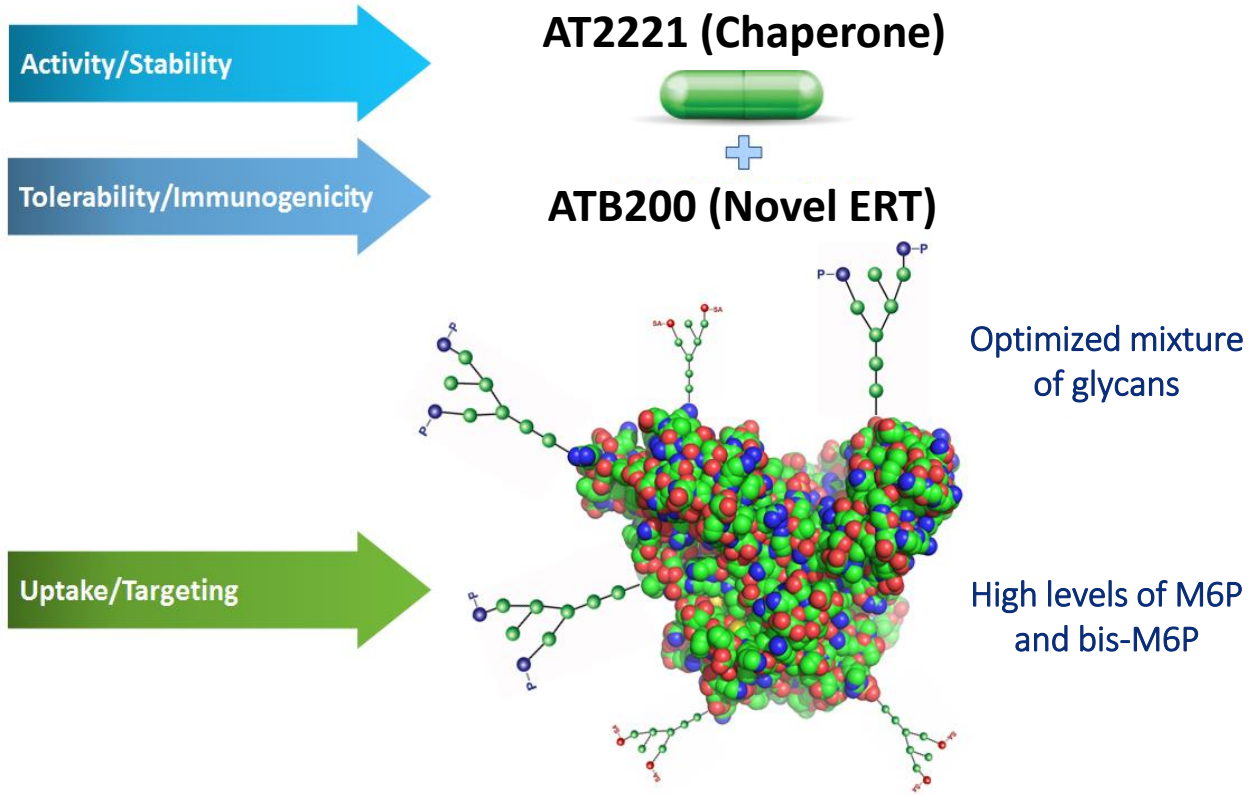
[1]Klinikum der Universität München-Neurologische Klinik, Friedrich-Baur-Institut, Munich, Germany; [2]PARC Research Clinic, Royal Adelaide Hospital, Adelaide, SA, Australia; [3]University of Florida, Gainesville, FL, USA; [4]University of Pittsburgh and Department of Veterans Affairs Medical Center, Pittsburgh, PA, USA; [5]University Hospital Birmingham NHS Foundation Trust, Queen Elizabeth Medical Center, Birmingham, UK; [6]O&O Alpan LLC, Fairfax, VA, USA; [7]Duke University Medical Center, Durham, NC, USA; [8]Rutgers New Jersey Medical School, Newark, NJ, USA; [9]University of California, Irvine, Orange, CA, USA; [10]Neurologische Klinik und Poliklinik des Berufsgenossenschaftlichen, Universitätklinikum Bergmannsheil, Bochum, Germany; [11]Neuromuscular Research Center, Phoenix, AZ, USA; [12]Erasmus MC University Medical Center, Rotterdam, The Netherlands; [13]Amicus Therapeutics, Inc., Cranbury, NJ, USA; [14]Salford Royal NHS Foundation Trust, Salford, UK;

# Benedikt Schoser Disclosure Information

- I have the following financial relationships to disclose:
  - Consultant for Amicus Therapeutics, Inc.
  - Consultant and member of speaker bureau for Audentes, Genzyme, Intiva, Lupin, Valerion and Vertex.
- I will discuss the following off-label use and/or investigational use in my presentation:
  - Data from a phase 1/2 trial of ATB200/AT2221 for the treatment of patients with Pompe disease
  - ATB200/AT2221 is an investigational therapy that has not been approved for commercial use

# AT-GAA (Acid α-Glucosidase) (ATB200/AT2221)

- AT2221: orally administered investigational chaperone given prior to infusion of ATB200
  - Shown to stabilize ERT in blood and maintain catalytic activity to enhance delivery of active enzyme to lysosomes[1,2]
- ATB200: investigational next-generation ERT
  - Designed with optimized glycosylation and high levels of mannose 6-phosphate residues for better uptake to target tissues




ERT=enzyme replacement therapy; M6P=mannose-6-phosphate.

1. Gotschall R et al. *Mol Genet Metab*. 2015;114(2):S49. Abstract 94. 2. Khanna R et al. Presented at: the 12th Annual WORLD*Symposium*™; February 29-March 4, 2016; San Diego, CA, USA.

# ATB200-02 Study Design (NCT02675465)

**Phase 1/2 Clinical Study to Evaluate Safety, Tolerability, PK, and PD of AT-GAA (ATB200/AT2221) at 16 Sites in 5 Countries**

## 18-Week Primary Treatment Period With Long-Term Extension (N=20)

**Cohort 1 (Ambulatory ERT-Switch, n=11)**

**ATB200**
5 mg/kg (wk 2)
10 mg/kg (wk 4)
20 mg/kg (wk 6)

→ **ATB200 20 mg/kg + AT2221 (Sub-Optimal Dose)** wks 8,10,12

→ **ATB200 20 mg/kg + AT2221 (Optimal Dose)** wk 14+

**Cohort 2 (Non-ambulatory ERT-Switch, n=4) & Cohort 3 (ERT-Naive, n=5)**

**ATB200 20 mg/kg + AT2221 (High Dose)** wk 2+

## Assessments:

- Safety/Tolerability
- Plasma PK
- Infusion-Associated Reactions
- Antibody & Cytokine Levels
- Pharmacodynamics
- Efficacy (long-term extension)

ERT=enzyme replacement therapy; PD=pharmacodynamics; PK=pharmacokinetics, wk=week.

# Baseline Characteristics

**Patients (N=20) enrolled across the 3 cohorts were representative of the overall LOPD population, with significant impairment at baseline**

| | Cohort 1 ERT-Switch Ambulatory n=11[a] | Cohort 2 ERT-Switch Nonambulatory n=4 | Cohort 3 ERT-Naive n=5 |
|---|---|---|---|
| **Age, mean years (min, max)** | 49.4 (28, 66) | 36.0 (18, 56) | 49.4 (24, 65) |
| **Sex, M:F** | 9:2 | 3:1 | 1:4 |
| **Time on alglucosidase alfa, mean years (SD)** | 4.8 (1.4)[b] | 8.9 (3.8) | NA |
| **6MWT, mean meters (SD)** | 392.0 (93.4) | NA | 399.5 (83.5) |
| **Upright FVC, mean % predicted (SD)** | 52.3 (13.2) | NA | 53.4 (20.3) |

6MWT=6-minute walk test; ERT=enzyme replacement therapy; FVC=forced vital capacity; LOPD=late-onset Pompe disease; NA=not applicable; SD=standard deviation.
[a]One patient in Cohort 1 discontinued after 18 weeks due to burden of travel; [b]Cohort 1 patients were required to have been on alglucosidase alfa for 2-6 years at baseline.

# 6-Minute Walk Test

**6MWT improved for both ERT-switch ambulatory and ERT-naive patients at Month 6 with continued benefit observed out to Month 18**

| All results are mean (SD), meter | Baseline | Change From Baseline | | |
|---|---|---|---|---|
| | | Month 6 | Month 12 | Month 18 |
| Cohort 1 ERT-Switch Ambulatory | n=10 | n=10 | n=10 | n=9[a] |
| | **397.2** (96.8) | **+23.9** (52.2) | **+42.2** (46.5) | **+51.7** (45.9) |
| Cohort 3 ERT-Naive | n=5 | n=5 | n=5 | n=5 |
| | **399.5** (83.5) | **+41.8** (29.4) | **+63.1** (29.1) | **+49.0** (28.3) |

- 6MWT increased in 7/10, 9/10, and 9/9 ERT-switch patients at Months 6, 12, and 18, respectively
- 6MWT increased in 5/5, 5/5, and 5/5 ERT-naive patients at Months 6, 12, and 18, respectively
- Timed motor function tests were consistent with 6MWT (not shown)

6MWT=6-minute walk test; ERT=enzyme replacement therapy; SD=standard deviation.
[a]Data for one patient is pending (visit had not occurred at time of interim data cut).

# Manual Muscle Test Score

**Increases were observed in manual muscle strength[a] in all patients at Months 6, 12, and 18**

| | Body Area | Baseline | | Change From Baseline | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Month 6 | | Month 12 | | Month 18 | |
| | | mean (SD) | n | mean (SD) | n | mean (SD) | n | mean (SD) | n |
| **ERT-switch Ambulatory** | **Total Body** Max score 80 | **66.4** (8.1) | 10 | **+2.5** (3.2) | 9 | **+3.3** (3.4) | 9 | **+4.5** (3.2) | 9 |
| **ERT-switch Non-Ambulatory** | **Upper Body** Max score 40 | **13.3** (12.2) | 3[b] | **+4.5** (0.7) | 2[bc] | **+2.7** (2.3) | 3[b] | **+4.3** (3.5) | 3[b] |
| **ERT-Naive** | **Total Body** Max score 80 | **66.9** (3.7) | 5 | **+0.3** (2.8) | 5 | **+1.1** (3.1) | 5 | **+2.0** (2.9) | 4[d] |

- Quantitative muscle strength testing[e] results were generally consistent with manual muscle test results

ERT=enzyme replacement therapy; SD=standard deviation. [a]Measured via the Medical Research Criteria (MRC) scale; [b]Baseline data missing for 1 patient; [c]One patient did not complete Month 6 assessment; [d]Manual muscle testing not completed for one patient; [e]Measured via hand-held dynamometer.

# Sitting Forced Vital Capacity (FVC, % Predicted)

**FVC was generally stable in ERT-switch ambulatory patients and increased in ERT-naive patients**

| | Baseline, mean (SD) | Change From Baseline, mean (SD) | | |
|---|---|---|---|---|
| | | Month 6 | Month 12 | Month 18 |
| Cohort 1 ERT-Switch Ambulatory | n=9[a] | n=9[a] | n=9[a] | n=8[a,b] |
| | **52.6** (14.7) | **−1.3** (4.1) | **−3.3** (6.1) | **−3.7** (7.0) |
| Cohort 3 ERT-Naive | n=5 | n=5 | n=5 | n=5 |
| | **53.4** (20.3) | **+4.2** (5.6) | **+4.4** (8.6) | **+5.0** (2.9) |

- FVC was stable or increased in 5/9, 6/9, and 5/8 ERT-switch patients at Months 6, 12, and 18, respectively
- FVC was stable or increased in 5/5, 4/5, and 5/5 ERT-naive patients at Months 6, 12, and 18, respectively

ERT=enzyme replacement therapy; SD=standard deviation.
[a]Baseline FVC not available for 1 patient in Cohort 1; [b]FVC for one patient in Cohort 1 pending (visit had not occurred at time of interim data cut). .

# Other Pulmonary Function Tests: MIP and MEP

**MIP was stable and MEP increased in ERT-switch ambulatory patients; MIP and MEP increased in ERT-naive patients**

| | Assessment | Baseline, mean (SD) | Change From Baseline, mean (SD) | | |
|---|---|---|---|---|---|
| | | | Month 6 | Month 12 | Month 18 |
| Cohort 1 ERT-Switch Ambulatory | | n=10 | n=10 | n=10 | n=9[a] |
| | MIP | **35.7** (11.0) | **+0.3** (4.6) | **0.0** (3.2) | **−2.8** (4.4) |
| | MEP | **72.6** (32.6) | **+16.1** (42.1) | **+28.6** (44.0) | **+30.2** (43.0) |
| Cohort 3 ERT-Naive | | n=5 | n=5 | n=5 | n=5 |
| | MIP | **32.6** (18.5) | **+11.0** (5.0) | **+5.2** (12.2) | **+6.2** (11.5) |
| | MEP | **60.6** (8.3) | **−0.4** (12.4) | **+8.6** (16.3) | **+9.8** (19.6) |

ERT=enzyme replacement therapy; MEP=maximal expiratory pressure; MIP=maximal inspiratory pressure; SD=standard deviation.
MIP and MEP measured in centimeters of water.
[a]Data for one patient in Cohort 1 pending (visit had not occurred at time of interim data cut).

# Fatigue Severity Scale (FSS)

**All cohorts were significantly impacted by fatigue at baseline and demonstrated a mean improvement in fatigue**

| | Baseline, mean (SD) | Change From Baseline, mean (SD) | | |
|---|---|---|---|---|
| | | Month 6 | Month 12 | Month 18 |
| Cohort 1 ERT-Switch Ambulatory | n=10 | n=10 | n=10 | n=9 |
| | **53.5** (7.7) | **−8.0** (10.7) | **−8.0** (6.5) | **−3.8** (12.2) |
| Cohort 2 ERT-Switch Nonambulatory | n=4 | n=4 | n=4 | n=3 |
| | **42.3** (14.6) | **+2.3** (8.7) | **−12.5** (10.0) | **−13.3** (2.1) |
| Cohort 3 ERT Naive | n=5 | n=5 | n=5 | n=5 |
| | **39.2** (12.7) | **−5.2** (11.7) | **−7.2** (7.5) | **−2.0** (7.5) |

ERT=enzyme replacement therapy; SD=standard deviation.

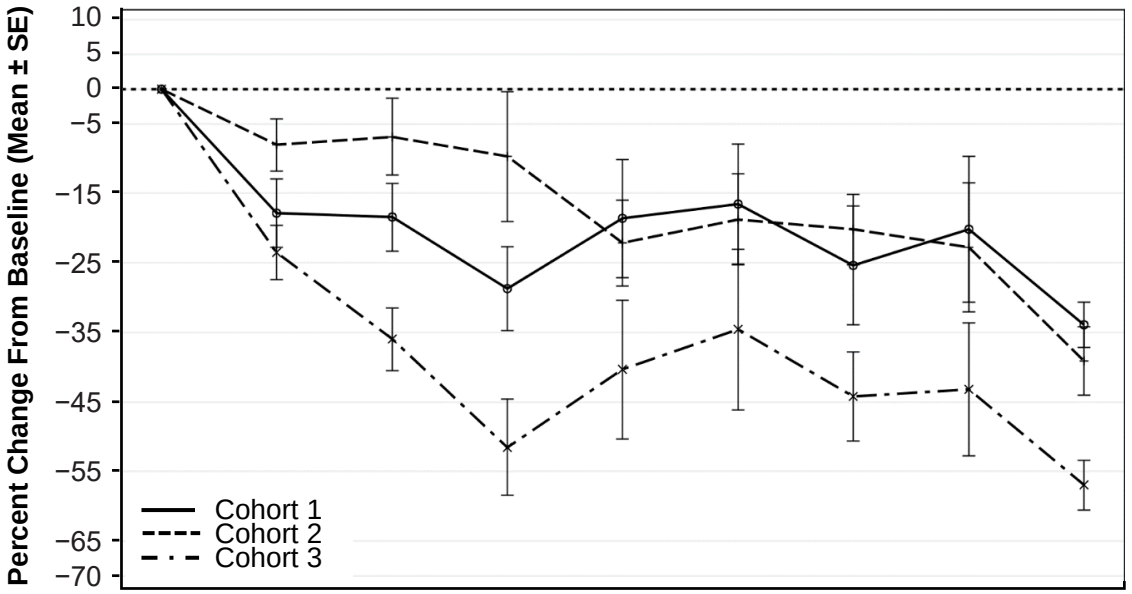
1. Grace J et al. *Parkinsonism Relat Disord*. 2007;13(7):442-445.

FSS consists of 9 questions, each scored on a scale from 1 to 7. Total scores range from 9 to 63, with higher values representing higher levels of fatigue due to the disease condition. The normative value in the healthy population is ~21.[1]

# CK and Hex4 Biomarkers

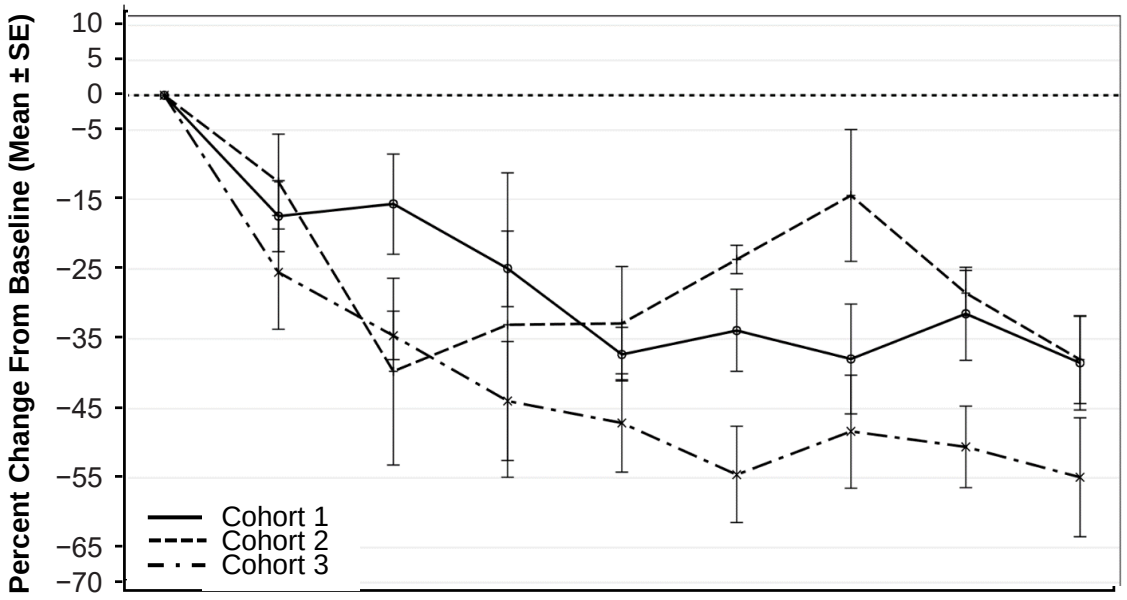
**All cohorts demonstrated persistent improvement in biomarkers of muscle damage (CK) and disease substrate (Hex4) for up to 18 months**

## Percent Change From Baseline for CK




| n | BL | W2 | W4 | M3 | M6 | M9 | M12 | M15 | M18 |
|---|---|---|---|---|---|---|---|---|---|
| Cohort 1 | 11 | 11 | 11 | 11 | 10 | 10 | 10 | 9 | 8 |
| Cohort 2 | 4 | 4 | 5 | 3 | 4 | 4 | 4 | 4 | 3 |
| Cohort 3 | 5 | 5 | 4 | 5 | 5 | 5 | 5 | 3 | 3 |

## Percent Change From Baseline for Hex4




| n | BL | W2 | W4 | M3 | M6 | M9 | M12 | M15 | M18 |
|---|---|---|---|---|---|---|---|---|---|
| Cohort 1 | 11 | 11 | 11 | 11 | 10 | 10 | 10 | 10 | 9 |
| Cohort 2 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 2 |
| Cohort 3 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 3 |

BL=baseline; CK=creatine kinase; Hex4=urine hexose tetrasaccharide; M=month; W=week.
Reported through interim data analysis; missing values either unable to be analyzed or not yet analyzed.

# Safety Summary at 18 Months of Treatment

**Safety data (N=20) for AT-GAA show that AEs have been generally mild and transient with very low rates of IARs (<1%) after 890+ total infusions across all cohorts**

- AEs were generally mild and transient
  - The most common treatment-emergent AEs[a] by decreasing frequencies were nasopharyngitis (10/20); fall (9/20); abdominal pain[b] and diarrhea (8/20); upper respiratory tract infection (7/20); arthralgia, nausea, fatigue, pain in extremities, and myalgia (6/20); and headache, tremor, oropharyngeal pain, and muscle spasms (5/20)
- For SAEs, 5 events occurred in 4 patients (severity: 3 moderate, 2 mild) and were unrelated to treatment. SAEs did not lead to treatment interruption or study discontinuation.
- 7 incidents of IARs in 5 patients in 890+ infusions, which were controlled by standard medication or premedication
  - 1 IAR event each in 3 ambulatory ERT-switch patients
  - 1 IAR event in a non-ambulatory ERT-switch patient
  - 3 IAR events in a ERT-naive patient
- Longest duration of treatment is 28+ months

AE, adverse events; ERT=enzyme replacement therapy; IAR, infusion-associated reaction; SAE=serious adverse event.
[a]Number of patients experiencing the AE; [b]Includes upper and lower abdominal pain.

# Conclusions at 18 Months of Treatment

**6MWT, an integrated measure of motor, cardiac, and pulmonary function, improved in ERT-switch ambulatory and ERT-naive patients out to Month 18**

- 6MWT showed continued benefit in ERT-switch and ERT-naive patients
- Timed motor function tests were generally consistent with 6MWT results in both ambulatory cohorts
- Muscle strength increased in all cohorts, including nonambulatory ERT-switch patients
- Pulmonary function
  - FVC, MIP, and MEP generally increased in ERT-naive patients
  - FVC, MIP, and MEP were generally stable in ERT-switch patients
- Fatigue Severity Scale
  - Improvement in fatigue score was observed in all cohorts
- Biomarkers and safety
  - CK and Hex4 levels decreased in all cohorts
  - AT-GAA (ATB200/AT2221) was generally well tolerated

6MWT=6-minute walk test; CK=creatine kinase; ERT=enzyme replacement therapy; FVC=forced vital capacity; Hex4=urine hexose tetrasaccharide; MEP=maximal expiratory pressure; MIP=maximal inspiratory pressure.

# Acknowledgments


- The authors thank the patients, their families, and Pompe disease patient organizations, as well as the study investigators
- ATB200-02 Clinical Trial Investigators: Drago Bratkovic, Barry J. Byrne, Paula R. Clemens, Tarekegn Geberhiwot, Ozlem Goker-Alpan, Priya Kishnani, Xue Ming, Mark Roberts, Peter Schwenkreis, Kumaraswamy Sivakumar, Ans T. van der Ploeg, Benedikt Schoser
- Amicus Therapeutics: Jacquelyn Wright, Sheela Sitaraman, Swati Sathe, Hjalmar Lagast, Jay A. Barth
- Third-party medical editing assistance was provided by ApotheCom (Yardley, PA)