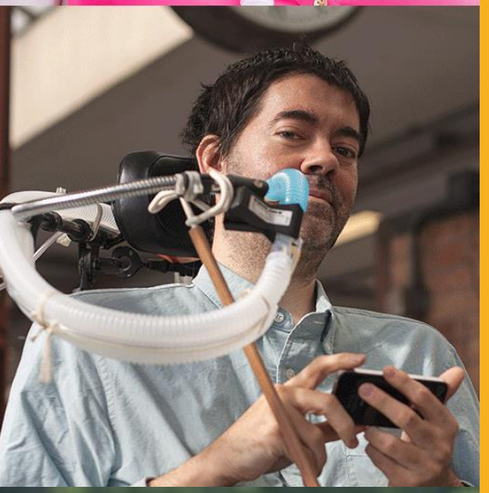
Amicus Pompe Overview & Pompe Data Highlights at 14th Annual World*Symposium*™

February 5-9, 2018 | San Diego, CA



Pompe Disease Overview

Dr. Priya Kishnani

14th Annual WORLDSymposium™ | February 5-9, 2018 | San Diego, CA

Disclosure Information

WORLD*Symposium*™ 2018 | *Dr. Priya Kishnani*

I have the following financial relationships to disclose:

Grant/Research support from: Genzyme
Honoraria from: Amicus Therapeutics, Genzyme

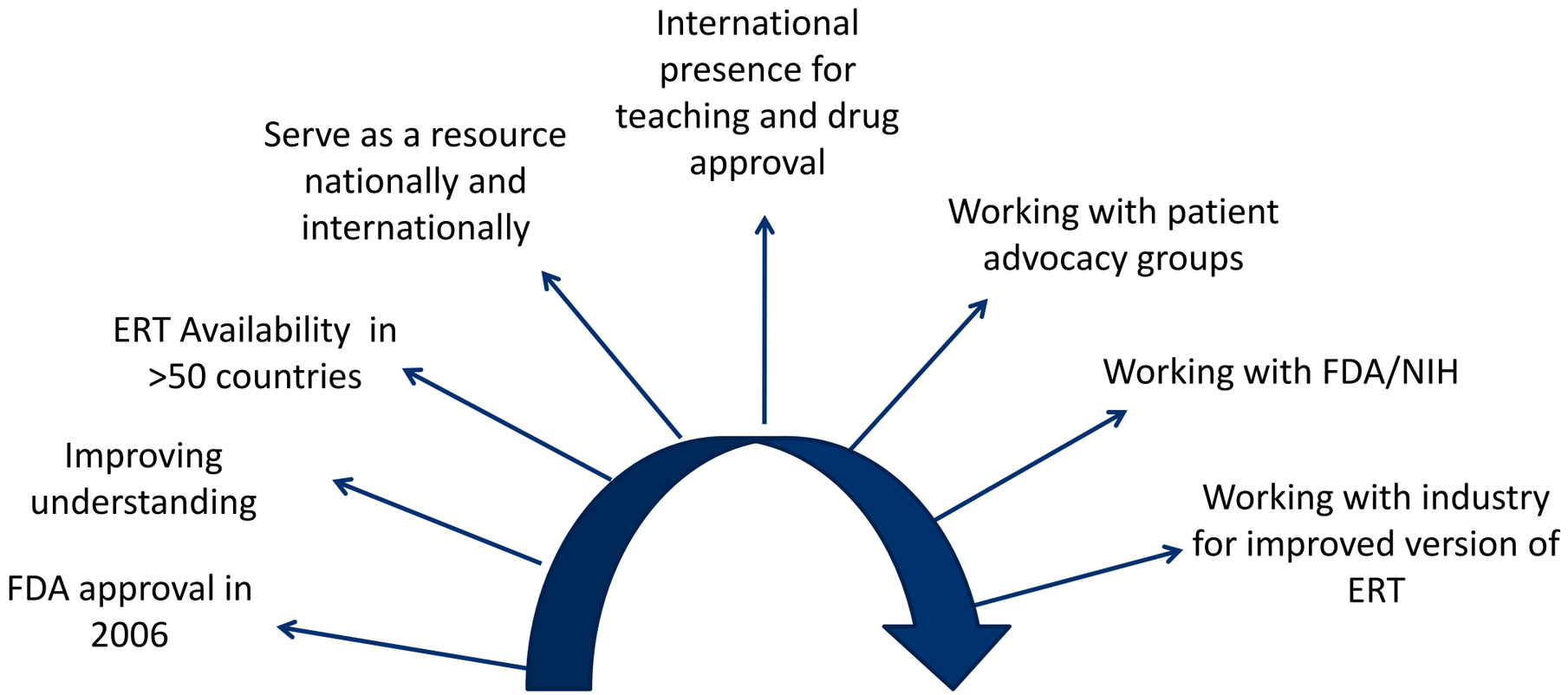
- and -

I will not discuss an off label use and/or investigational use in my presentation.

Our Team

- Over 70 members at Duke in Pompe disease clinical care/research
- Follow close to 250 Pompe patients at Duke
- Follow another 150-200 patients globally
- Provided care to patients from around the world- in person, telemedicine, email, phone
- Helped with drug approval in several countries including Singapore, Malaysia, Australia, Latin America, etc.
- Facilitated discussions with FDA and European Union for approval in US and EMEA
- Global outreach via charitable access programs in several countries including India, South Africa, China, Egypt, Israel, Peru, Brazil, Argentina, Chile, etc

Duke Contribution to the Field



Pompe Disease

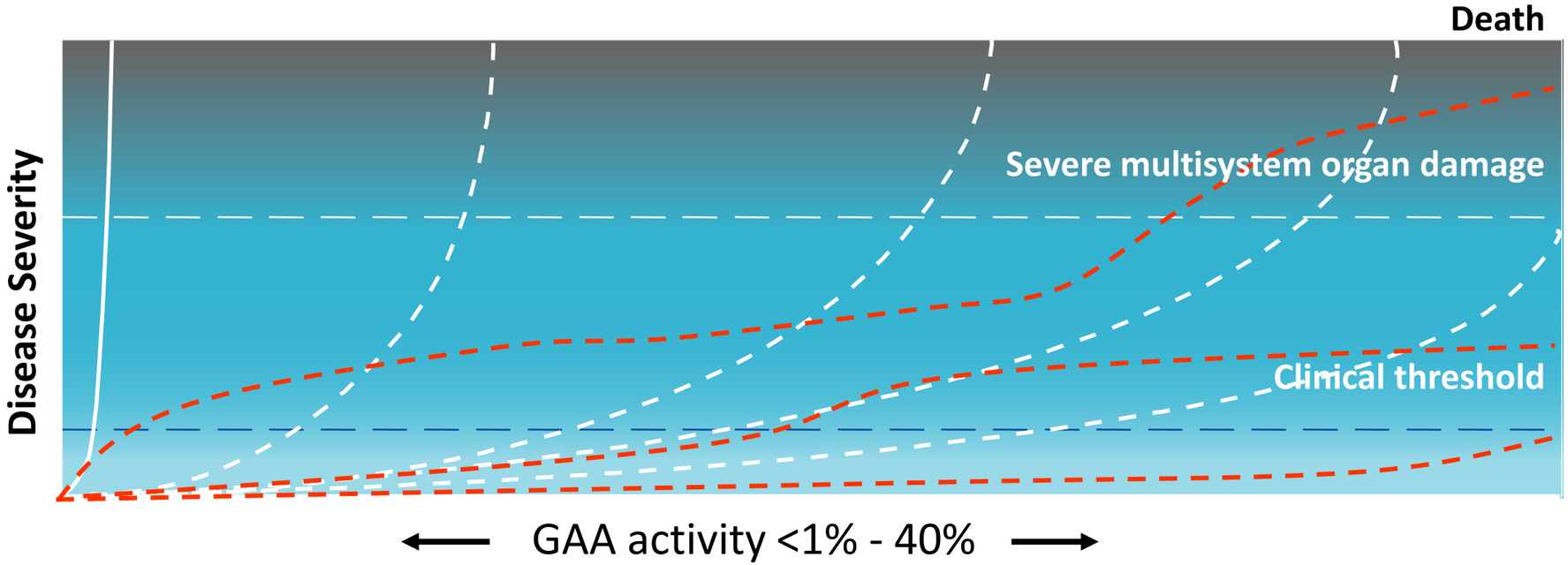
- Metabolic myopathy characterized by cardiac, skeletal and smooth muscle involvement with a continuum of disease severity
  - From early onset → rapid progression to death (infantile onset)
  - To later onset → slower progression, longer survival with marked morbidity (late onset)
- Deficiency of lysosomal enzyme, acid alpha-glucosidase (GAA)
- Glycogen accumulation → muscle tissue damage → functional impairment → permanent disability
- Variable rate of tissue damage in muscle

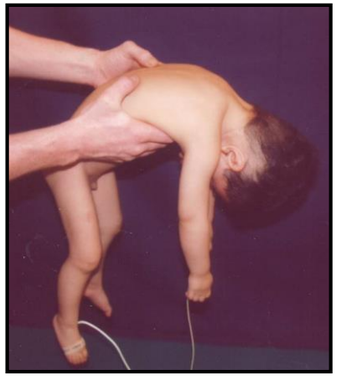
Pompe Disease

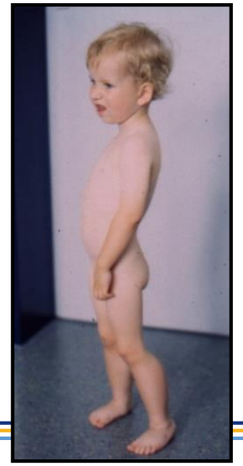
A continuum of disease caused by deficiency of acid alfa glucosidase (GAA)

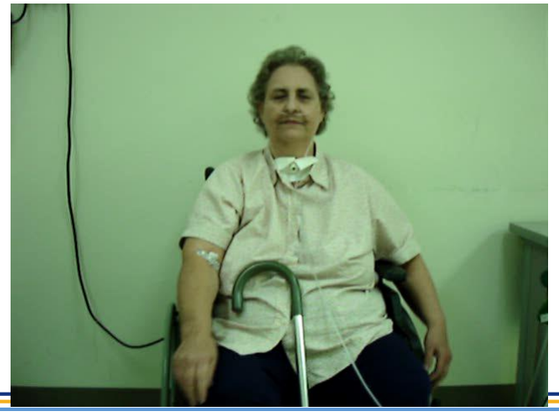
- Infantile Onset Pompe Disease (IOPD)
  - Presents in the *first few days* to months with hypotonia, generalized muscle weakness, macroglossia
  - Hypertrophic cardiomyopathy leads to death within the first year
- Late Onset (Juvenile and Adult) Pompe Disease (LOPD)
  - Characterized by respiratory and limb-girdle muscle weakness, resulting in significant morbidity and mortality
  - Lack of *severe* cardiac involvement
  - Early involvement of the diaphragm

Pompe Disease: A Continuum of Clinical Phenotypes



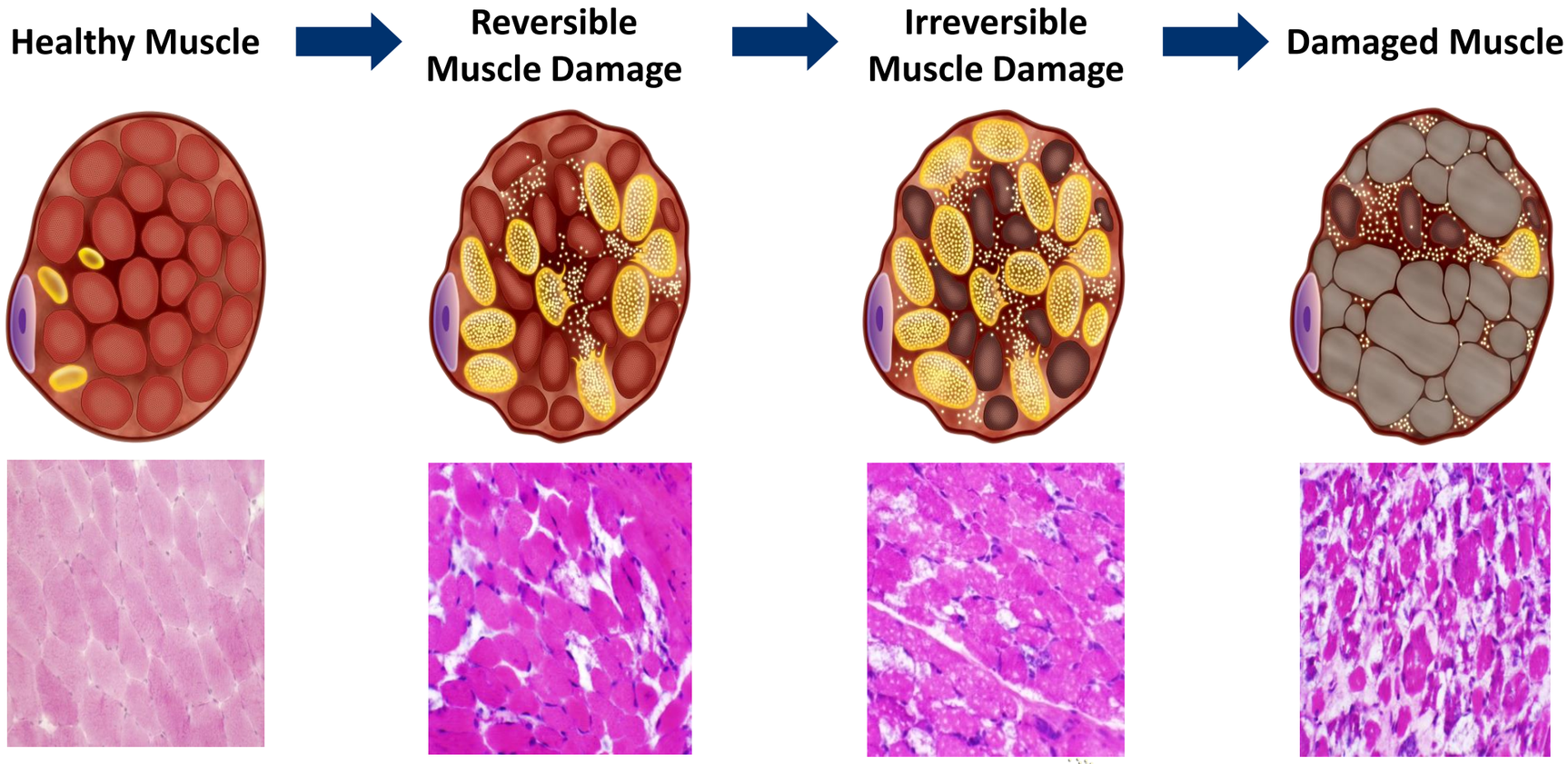






The Natural Course of Pompe Disease is a Progression From Healthy Muscle to Irreversible Muscle Damage

Untreated Pompe Disease



Courtesy of Dr. Priya Kishnani; Kishnani PR, et al. Am J Med Genet C Semin Med Genet. 2012;160C:1-7; Kishnani PR, et al. Genet Med. 2006;8:267-88.

Amicus Therapeutics®

Current Standard of Care and Factors Affecting Response to ERT

- Multidisciplinary
- Enzyme replacement therapy (ERT) with recombinant human GAA at 20 mg/kg every 2 weeks
- Factors Affecting Response to ERT
  - Degree of overall muscle damage and extent of preexisting pathology[2]
  - Age/Disease duration upon ERT initiation[2]
  - Predominance of Muscle fiber type (*i.e.,* type I *vs*. type II)[1]
  - Degree of disordered cellular processes, such as defective autophagy[1]
  - ACE polymorphism (D/D phenotype a poor prognostic factor)[4]
  - Cross-reactive immunologic material (CRIM) negative status[2]
  - Degree of any immunological reaction to therapy (high sustained titers and persistent titers)[3]

1. Raben, N et al. Enzyme replacement therapy in the mouse model of Pompe disease. Mol Genet Metab, 2003.
2. Kishnani, PS et al. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. Mol Genet Metab, 2010.
3. Banugaria, S et al. Persistence of high sustained antibodies to enzyme replacement therapy despite extensive immunomodulatory therapy in an infant with Pompe disease: need for agents to target antibody-secreting plasma cells. Mol Genet Metab, 2012.
4. P. De Fillipi et al. The angiotensin-converting enzyme insertion/deletion polymorphism modifies the clinical outcome in patients with Pompe disease

Long-term Issues and Emerging Phenotype in IOPD (Clinically Diagnosed and Treated)

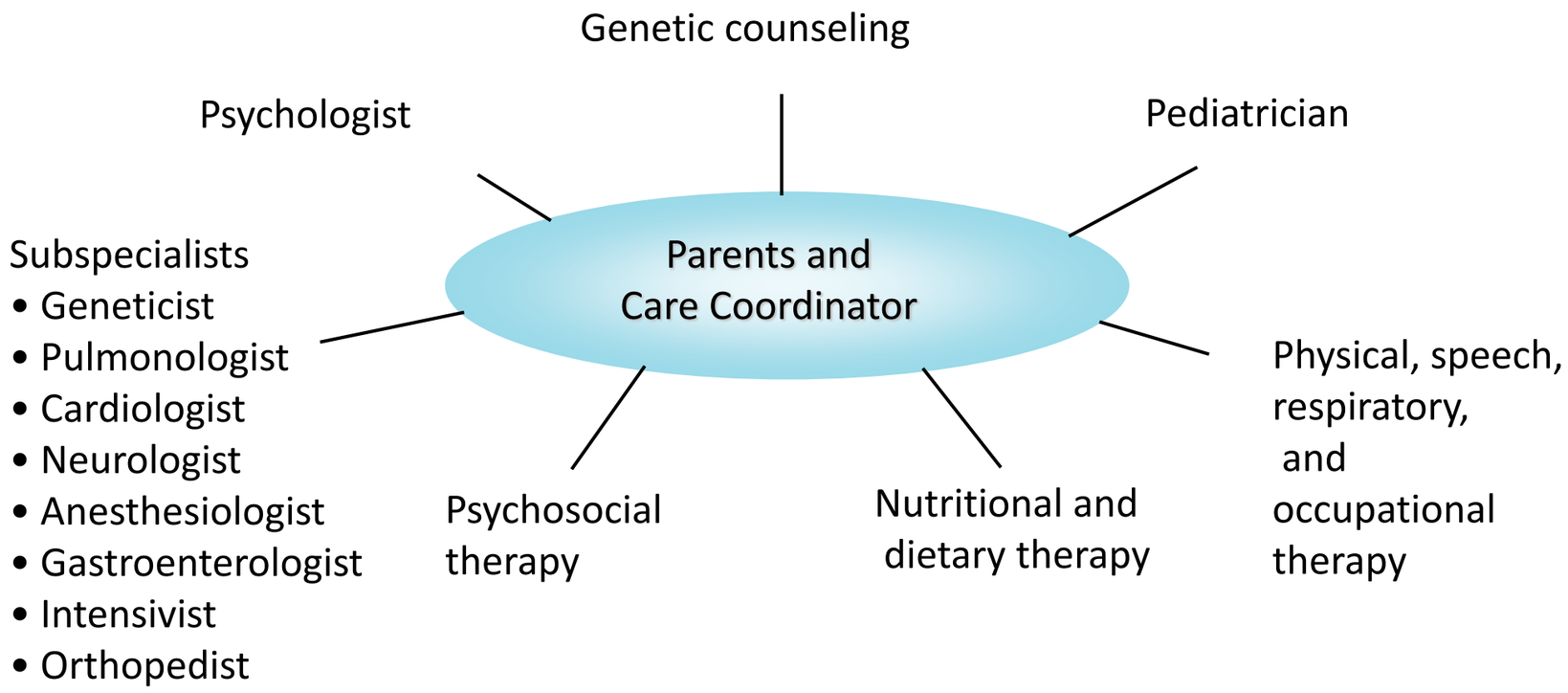
- **Cardiac**
  - Fibrosis
  - Cardiac arrhythmias
  - Dilatation of aorta
- **Neurologic**
  - Sensorineural hearing loss
  - Anterior horn cell involvement
  - Bulbar involvement
  - White matter changes, questions related to cognition
- **Speech acquisition**
  - Hypernasal speech due to velopharyngeal weakness and facial weakness
- **Ophthalmologic findings**
  - Ptosis-myogenic
  - Severe myopia
- **Sphincter issues**

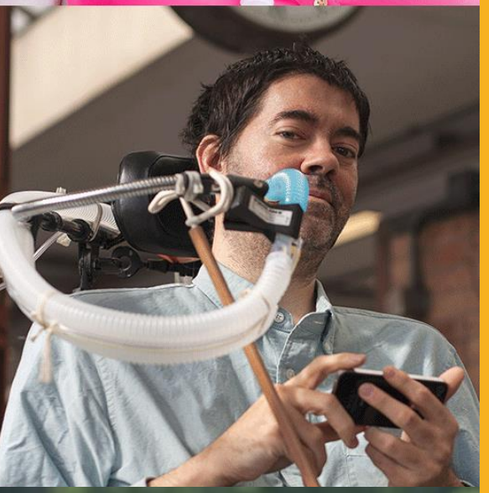
Prater SN, Banugaria SG, et al. The Emerging Phenotype of Long-Term Survivors with Infantile Pompe Disease. *Genetics in Medicine.* 2012; 14: 800-810.

Issues in Late Onset Pompe Disease

- Diagnosed late, very clinically heterogenous
- Response to current ERT typically noted in first 12-18 months, then a stabilization/decline
- Inefficient targeting of current ERT especially in skeletal muscle (poor M6P receptor in skeletal muscle)
- Immune response can occur
- Long duration of infusion

Pompe Disease Management Requires Coordination of Multi-Disciplinary Care





Updated Results From ATB200-02: A First-in-human, Open-label, Phase 1/2 Study of ATB200 Co-administered With AT2221 in Adults With Pompe Disease

Dr. Tahseen Mozaffar

Tahseen Mozaffar,[1] Sheela Sitaraman,[2] Jay A. Barth,[2] Swati Sathe,[2] on behalf of the ATB200-02 Clinical Trial Investigators (Drago Bratkovic, Barry J. Byrne, Paula Clemens, Tarekegn Geberhiwot, Ozlem Goker-Alpan, Priya Kishnani, Xue Ming, Peter Schwenkreis, Kumaraswamy Sivakumar, Ans T. van der Ploeg, Mark Roberts, Benedikt Schoser)

[1]University of California, Irvine, Orange, CA, USA; [2]Amicus Therapeutics, Inc., Cranbury, NJ, USA

14th Annual WORLDSymposium™ | February 5-9, 2018 | San Diego, CA

Disclosure Information

WORLD*Symposium*™ 2018 | *Dr. Tahseen Mozaffar*

I have the following financial relationships to disclose:

- Consultant for Amicus Therapeutics, Inc.
- Consultant and member of speaker bureau for Genzyme

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 in patients with Pompe disease
- ATB200 and AT2221 are investigational drugs that have not been approved for use in the United States

Overview of Novel Pompe Approach ATB200/AT2221

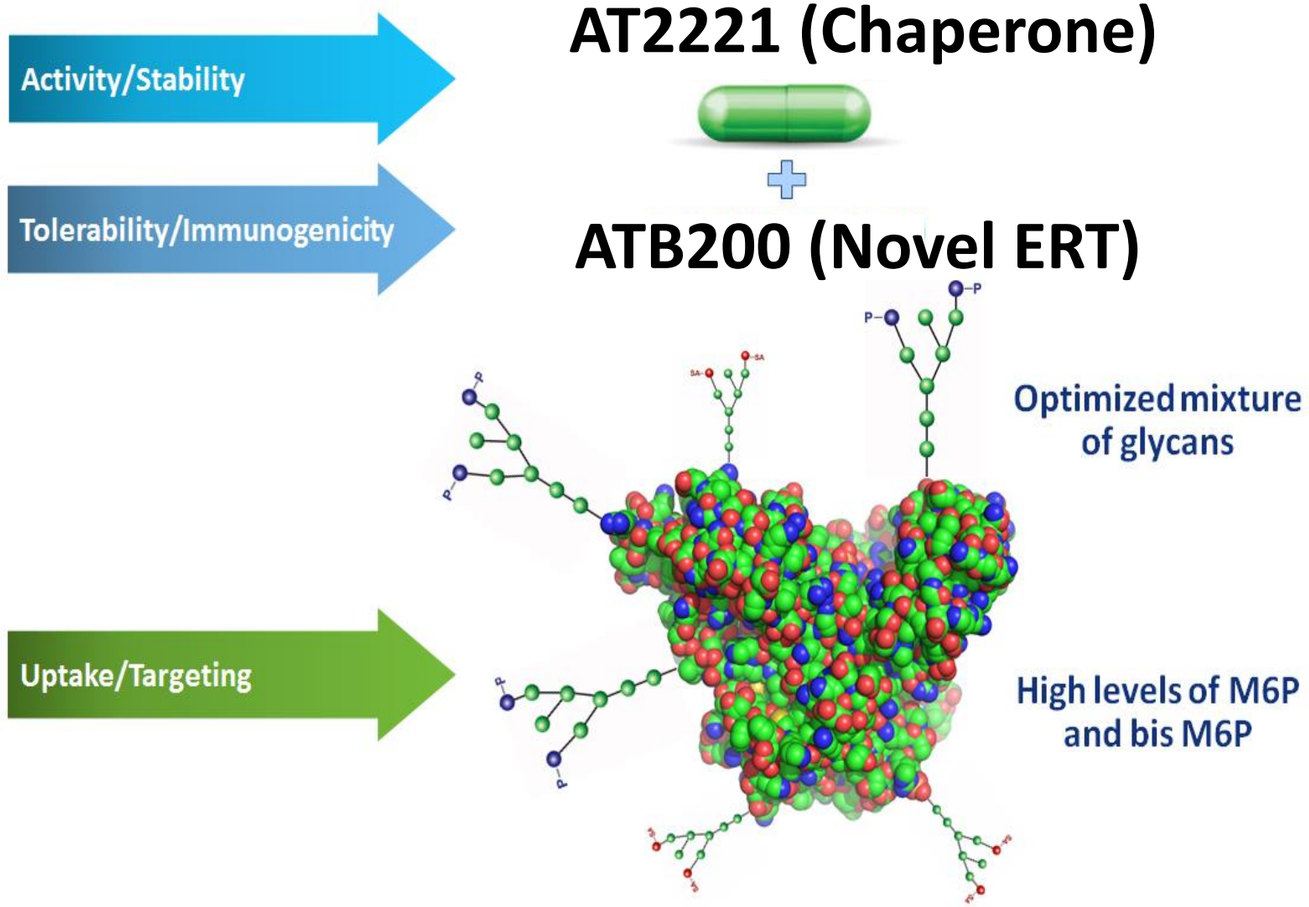
- Amicus Therapeutics is developing a combination therapeutic approach with two investigational agents:
  - Oral administration of pharmacological chaperone (PC), AT2221[1], prior to
  - IV infusion of ATB200 (rhGAA) enzyme replacement therapy (ERT)

GAA=acid α-glucosidase; rhGAA=recombinant human acid α-glucosidase.

1. Kishnani PS et al. *Genet Med.* 2006;8(5):267-288. 2. Bijvoet AGA et al. *Hum Mol Gen.* 1998;7(1):53-62.

ATB200 Co-administration With AT2221

- AT2221: orally administered investigational PC 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; PC=pharmacological chaperone

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

ATB200-02 Study Design (NCT02675465)

Phase 1/2 Clinical Study to Evaluate Safety, Tolerability, Pharmacokinetics (PK), and Pharmacodynamics (PD) of ATB200 + Chaperone (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
5mg/kg (wk 2)
10mg/kg (wk 4)
20mg/kg (wk 6)

→

ATB200 20mg/kg + AT2221 (Low Dose)
wks 8,10,12

→

ATB200 20mg/kg + AT2221 (High Dose)
wk 14+

Cohort 2 (Non-Ambulatory ERT-Switch, n=4) & Cohort 3 (ERT-Naïve, n=5)

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

Assessments:

- Safety/Tolerability
- Plasma PK
- Infusion-Associated Reactions
- Antibody & Cytokine Levels
- Pharmacodynamics
- Efficacy (Long-Term Extension)

Baseline Characteristics (N=20)

Patients Enrolled Across Three Cohorts are Representative of the Overall Late-Onset Pompe Population, with Significant Impairment at Baseline

	Cohort 1 ERT-Switch (N=11)	Cohort 2 ERT-Switch Non-ambulatory (N=4)	Cohort 3 ERT-Naïve (N=5)
Age, years, mean (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, years, mean (SD)	4.8 (1.42)[a]	8.9 (3.8)	-
6MWT, meters, mean (SD)	392.0 (93.4)	NA	399.5 (83.5)
FVC Upright, % predicted, mean (SD)	52.3 (13.2)	NA	53.4 (20.3)

NA=not applicable; SD=standard deviation.
[a]Cohort 1 patients were required to have been on alglucosidase alfa for 2-6 years at baseline.

6-Minute Walk Test (6MWT) (n=15)

6MWT Improved for Both ERT-Naïve and ERT-Switch Patients at Months 6 and 9 With Continued Benefit Observed Out to Month 12

6-Minute Walk Test (m); mean (SD)

	Baseline (n=10)	Change to Month 6 (n=10)	Change to Month 9 (n=10)	Change to Month 12 (n=8)
Cohort 1 ERT-Switch	**397.2** (96.8)	**+23.9** (52.2)	**+24.5** (40.8)	**+57.4** (34.4)
	Baseline (n=5)	**Change to Month 6 (n=5)**	**Change to Month 9 (n=5)**	**Change to Month 12 (n=2)**
Cohort 3 ERT-Naïve	**399.5** (83.5)	**+41.8** (29.4)	**+63.5** (23.1)	**+86.8** (11.1)

- 6MWT increased in 7/10, 8/10, and 8/8 ERT-switch patients at Months 6, 9 and 12 respectively
- 6MWT increased in 5/5, 5/5, and 2/2 ERT-naïve patients at Months 6, 9 and 12 respectively

CFBL=change from baseline.

6-Minute Walk Test Patient-Level Data – Cohort 1 ERT-Switch (n=10)

6MWT Improved for ERT-Switch Patients at Months 6 and 9 With Continued Benefit Observed Out to Month 12

6-Minute Walk Test (m)

ID	Baseline	Change From Baseline		
		Month 6	Month 9	Month 12
1052	544	+51	+56	+112
1252	379	+125	+110	+103
1251	339	+21	+45	+73
1751	332	+8	+26	+45
1201	456	-5	+8	+41
1451	500	+55	+20	+33
1051	220	+29	+21	+30
1053	410	+38	+11	+22
1701	464	-4	-9	N/A
1601	328	-78	-43	N/A
Mean (SD)	**397.2** (96.8)	**+23.9** (52.2)	**+24.5** (40.8)	**+57.4** (34.4)

- 6MWT increased in 7/10, 8/10, and 8/8 ERT-switch patients at Months 6, 9 and 12 respectively

N/A = data not available (patients have not reached 12 month time point)

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6-Minute Walk Test Patient Level Data – Cohort 3 ERT-Naïve (n=5)

All Five ERT-Naive Patients Showed Increases in 6MWT Distance Out to Month 12

6-Minute Walk Test (m)

ID	Baseline	Change From Baseline		
		Month 6	Month 9	Month 12
3551	480	+41	+72	+95
3552	384	+62	+78	+79
3051	460	+79	+89	N/A
3554	406	+14	+44	N/A
3553	267	+13	+35	N/A
Mean (SD)	**399.5 (83.5)**	**+41.8 (29.4)**	**+63.5 (23.1)**	**+86.8 (11.1)**

- 6MWT increased in 5/5, 5/5, and 2/2 ERT-naïve patients at Months 6, 9 and 12 respectively

N/A = data not available (patients have not reached 12 month time point)

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Other Motor Function Tests (n=15)

Improvement in Other Motor Function Tests Is Consistent with an Overall Improvement in Motor Performance for Both ERT-Switch and ERT-Naïve Patients over 12 Months

Cohort	Assessment (sec)	Baseline Mean (SD), n=10	Change to Month 6 Mean (SD), n=10	Change to Month 9 Mean (SD), n=10	Change to Month 12 Mean (SD), n=8
Cohort 1: ERT-Switch	Timed up and Go	**10.5** (6.6)	**-1.8** (3.5)	**-1.2** (3.3)	**-1.0** (2.2)
	4 Stair Climb	**4.1** (2.7)	**-0.6** (1.6)	**-0.4** (1.6)	**-1.0** (1.5)
	10M walk	**7.4** (3.0)	**+0.1** (1.9)	**-0.1** (1.6)	**-0.5** (1.7)
	Gowers[#]	**7.9** (2.9)	**-1.1** (3.8)	4.5[b] (13.4)	**-2.6** (1.9)
	GSGC Score	**12.6** (4.8)	**+0.1** (3.9)	**+0.5** (4.6)	**-1.9** (2.2)
Cohort	**Assessment (sec)**	**Baseline Mean (SD), n=5**	**Change to Month 6 Mean (SD), n=5**	**Change to Month 9 Mean (SD), n=5**	**Change to Month 12 Mean (SD), n=2**
Cohort 3: ERT-Naïve	Timed up and Go	**9.4** (2.9)	**-1.0** (1.1)	**-0.6** (1.4)	**-1.8** (0.5)
	4 Stair Climb	**4.2** (1.5)	**-0.6** (0.3)	**0.0** (1.5)	**-0.4** (0.4)
	10M walk	**7.9** (3.0)	**-0.7** (1.1)	**-1.3** (1.0)	**-0.6** (0.0)
	Gowers	**13.9** (11.0)	**7.9**[c] (20.9)	**-1.6** (3.9)	**-2.1** (1.3)
	GSGC Score	**12.2** (3.6)	**-1.8** (3.8)	**-2.4** (3.4)	0.0 (1.4)

[#]N=9 Missing values not obtained due to patient refusal to perform test; [b] Median CFBL was -1.5 and 7/9 had decrease [c] Median CFBL was -0.8 and 4/5 had decrease

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Muscle Strength Testing (QMT), Manual Muscle Testing (MMT): Cohort 2

Substantial Increases Observed in Upper Extremity Strength in Non-Ambulatory ERT-Switch Patients at Month 6 and Month 9

Assessment	Muscle Group Tested	Baseline (n=4)	Change to Month 6 (n=4)	Change to Month 9 (n=4)
QMT- Quantitative Muscle Testing - Dynamometer (pounds force)	Shoulder Adduction *	**5.7** (8.8)	**+8.1** (12.8)	**+9.6** (12.3)
	Shoulder Abduction	**16.7** (18.1)	**+1.0** (6.6)	**+0.5** (9.3)
	Elbow Flex	**12.7** (13.7)	**+2.4** (15.9)	**+6.0** (19.3)
	Elbow Extension	**12.3** (13.9)	**+5.5** (4.7)	**+7.5** (8.2)
Assessment	**Muscle Group Tested**	**Baseline ** (n=3)**	**Change to Month 6 (n=3)**	**Change to Month 9 (n=3)**
MMT - Manual Muscle Testing (manual score)	Shoulder Adduction	**2.3** (2.1)	**+1.3** (2.3)	**0.0** (4.0)
	Shoulder Abduction	**2.7** (2.3)	**+0.5** (0.7)	**-1.0** (2.7)
	Elbow Flex	**4.3** (4.5)	**+1.7** (1.5)	**+1.7** (1.5)
	Elbow Extension	**4.0** (4.0)	**+1.7** (1.5)	**+1.7** (1.5)

CFBL=change from baseline.; * *Shoulder adduction not available for one subject;* ** Total Score MMT = 10 (R+L) N=3 due to assessment not being performed at some visits for some patients

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Forced Vital Capacity (FVC) Summary (n=14)

FVC Increased In ERT-Naïve Patients and was Generally Stable in ERT-Switch Patients

FVC (% Predicted); mean (SD)

Cohort 1 ERT-Switch*	**Baseline (n=9)**	**Change to Month 6 (n=9)**	**Change to Month 9 (n=9)**	**Change to Month 12 (n=7)**
	52.6 (14.7)	**-1.3** (4.1)	**-1.7** (3.9)	**-3.1** (4.8)
Cohort 3 ERT-Naïve	**Baseline (n=5)**	**CFBL M6 (n=5)**	**CFBL M9 (n=5)**	**CFBL M12 (n=2)**
	53.4 (20.3)	**+4.2** (5.6)	**+6.2** (5.3)	**+6.0** (7.1)

- FVC was stable or increased in 5/9, 6/9, and 3/7 ERT-switch patients at Months 6, 9 and 12 respectively
- FVC was stable or increased in 5/5, 5/5, and 2/2 ERT-naïve patients at Months 6, 9 and 12 respectively

CFBL=change from baseline.; *FVC not available for one subject

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Other Pulmonary Function Tests: MIP and MEP (n=15)

Overall MIP and MEP were Stable or Increased in Both ERT-Naïve and ERT-Switch Patients

MIP and MEP; mean (SD)

Patients	Assessment	Baseline (n=10)	Change to Month 6 (n=10)	Change to Month 9 (n=10)	Change to Month 12 (n=8)
Cohort 1: ERT-Switch	MIP	35.7 (11.0)	+0.3 (4.6)	-0.6 (3.0)	+0.3 (3.6)
	MEP	72.6 (32.6)	+16.1 (42.1)	+23.7 (38.1)	+36.8 (45.7)
Patients	**Assessment**	**Baseline (n=5)**	**Change to Month 6 (n=5)**	**Change to Month 6 (n=5)**	**Change to Month 12 (n=2)**
Cohort 3: ERT-Naïve	MIP	32.6 (18.5)	+11.0 (5.0)	+12.0 (10.3)	-0.5 (9.2)
	MEP	60.6 (8.3)	-0.4 (12.4)	+7.2 (15.3)	-2.0 (9.9)

CFBL=change from baseline. MIP & MEP measured in cmH_2O ; MEP=maximal expiratory pressure; MIP=maximal inspiratory pressure.

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Fatigue Severity Scale (FSS) (n=19)

All Cohorts Were Significantly Impacted By Fatigue at Baseline and Demonstrated a Mean Improvement After Receiving ATB200/AT2221

Fatigue Severity Scale; mean score (SD)

Cohort 1: ERT-Switch	**Baseline (n=10)**	**Change to Month 6 (n=10)**	**Change to Month 9 (n=10)**	**Change to Month 12 (n=8)**
	53.5 (7.7)	**-8.0** (10.7)	**-6.8** (6.8)	**-7.8** (6.0)
Cohort 2: Non-Ambulatory ERT-Switch	**Baseline (n=4)**	**Change to Month 6 (n=2)**	**Change to Month 9 (n=2)**	**N/A**
	54.0 (8.5)	**-3.5** (7.8)	**-6.5** (5.0)	N/A
Cohort 3: Naïve	**Baseline (n=5)**	**Change to Month 6 (n=5)**	**Change to Month 9 (n=5)**	**Change to Month 12 (n=2)**
	39.2 (12.7)	**-5.2** (11.7)	**-7.8** (7.5)	**-1.5** (2.1)

Fatigue Severity Scale (FSS) consists of 9 questions, each scored on a scale from 1-7. The total score ranges from 9 to 63, with higher values representing higher level of fatigue due to the disease condition. The normative value in healthy population is ~21 [1].

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

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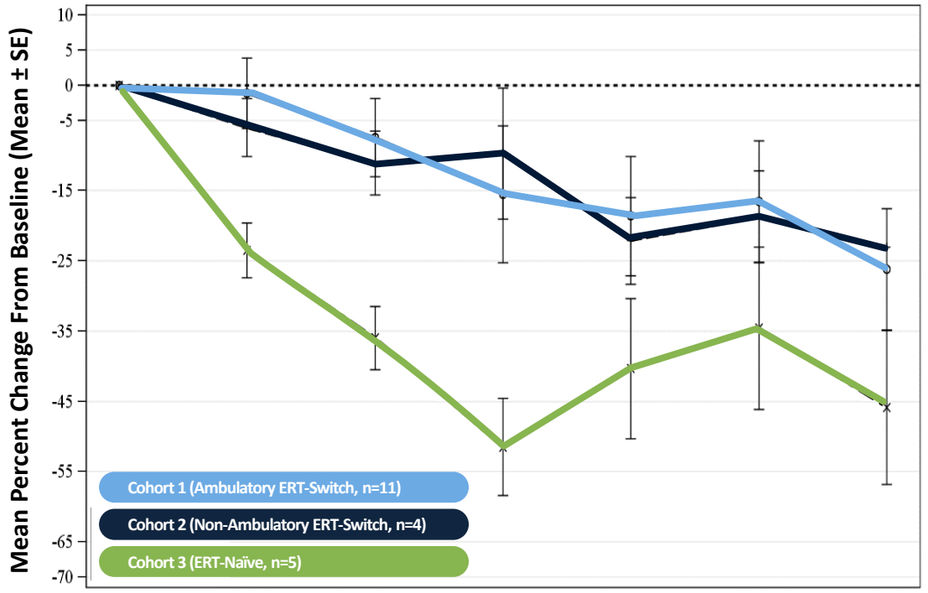
CK and Hex4 Biomarkers (n=20)

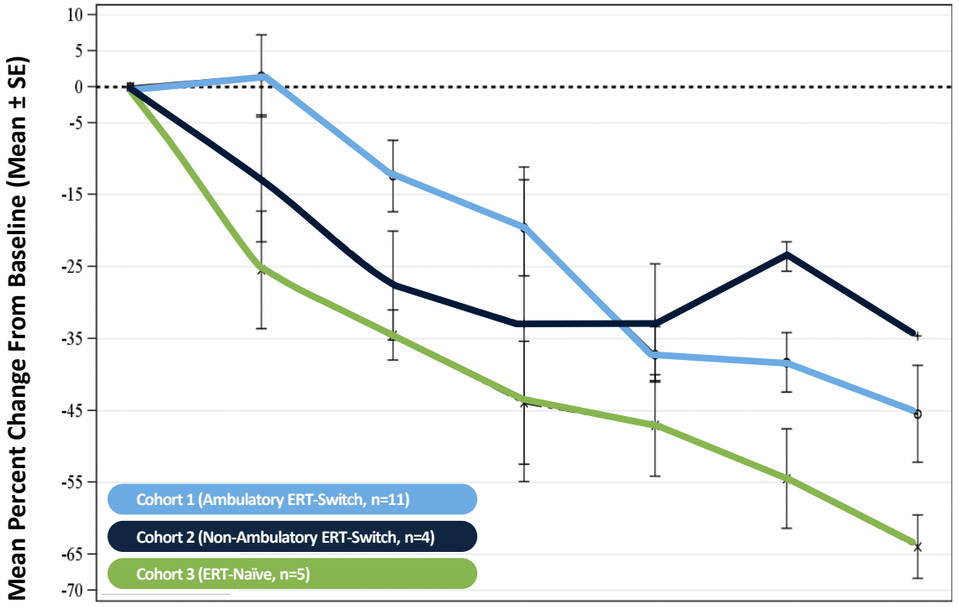
All Cohorts Demonstrated Persistent Improvement in Biomarkers of Muscle Damage (CK) and Disease Substrate (Hex4) For Up To 12 Months

Percent Change from Baseline for CK



Visit	BL	WK 2	WK 4	M3	M6	M9	M12
N	11,4,5	11,4,5	10,4,4	8,3,5	10,4,5	10,4,5	8,1,2

Percent Change from Baseline for Hex 4



Visit	BL	WK 2	WK 4	M3	M6	M9	M12
N	11,4,5	11,4,5	11,4,5	11,4,5	10,4,5	9,4,5	7,1,2

CK=creatine kinase; Hex4=urine hexose tetrasaccharide.
Missing values either unable to be analyzed or not yet analyzed.

Safety Summary (n=20)*

Safety Data for ATB200/AT2221 Show AEs Have Been Generally Mild and Transient with Very Low Rate of Infusion-Associated Reactions (< 1%) After 550+ Total Infusions Across All Cohorts

- AEs were generally mild and transient
  - Most common treatment emergent AEs (TEAEs) were abdominal pain** (8/20), diarrhea (8/20), nasopharyngitis (6/20), nausea (5/20), headache (5/20), upper respiratory tract infection (5/20).
- Three incidents of infusion-associated reactions in 550+ infusions which were controlled by standard premedication
  - One IAR event in one non-ambulatory ERT-switch patient (skin discoloration)
  - Two IAR events in one ERT-naïve patient (localized pruritus, erythema and burning sensation)
- Longest duration of treatment is 20+ months

AE, adverse events; IAR, infusion-association reaction.
*Reported through interim data analysis (maximum 20+ months)
**Includes upper and lower abdominal pain

Conclusions

- Muscle function
  - 6MWT distance generally improved in ERT-switch ambulatory and ERT-naïve patients out to month 12
  - Other motor function tests generally consistent with 6MWT results in both cohorts
  - Increases in elbow and shoulder muscle strength in non-ambulatory ERT-switch patients at Months 6 and 9
- Pulmonary function
  - FVC, MIP and MEP were generally stable in ERT-switch patients
  - FVC, MIP and MEP generally increased in ERT-naïve patients
- Fatigue Severity Scale
  - Improvement in fatigue score observed in all cohorts
- Biomarkers and Safety
  - CK and Hex4 levels decreased in all cohorts
  - ATB200/AT2221 was generally well tolerated, with low rate of infusion reactions

Data on file.

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Thank You

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