

alglucosidase alfa

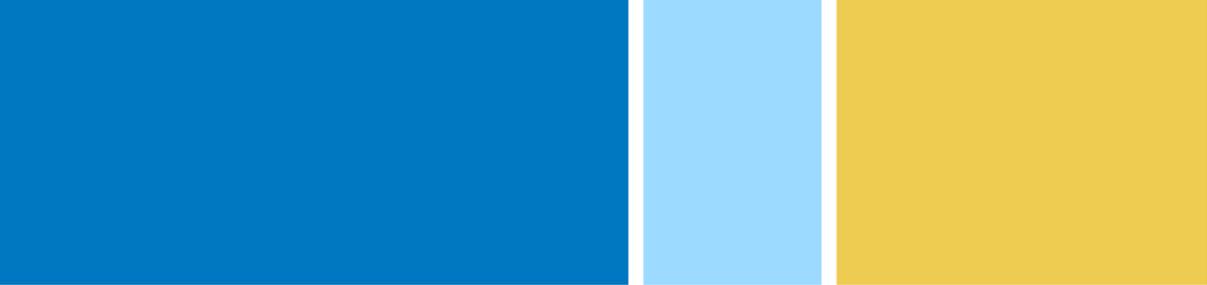
# Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Myozyme<sup>®</sup> (alglucosidase alfa)

October 21, 2008

Sponsor Presentation

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alglucosidase alfa

# Clinical Development of alglucosidase alfa in Late Onset Pompe Disease

**Alexander Kuta, PhD**

Group Vice President,  
Regulatory Affairs  
Genzyme Corporation



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# Agenda

## Introduction

**Alexander Kuta, PhD**

Group Vice President, Regulatory Affairs  
Genzyme Corporation

## Overview of Pompe Disease

**Priya Kishnani, MD**

Duke University Medical Center, Durham, NC

## Clinical Experiences with 2000 L Scale alglucosidase alfa

**Edward Kaye, MD**

Group Vice President, Clinical Research  
Genzyme Corporation

## Statistical Methods

**PK Tandon, PhD**

Senior VP, Biomedical Data Sciences and Informatics  
Genzyme Corporation

**Lee-Jen Wei, PhD**

Harvard University, Cambridge, MA

## Summary

**Alexander Kuta, PhD**

# Participating Experts Available to Committee

## Pompe Disease

### **Wuh – Liang (Paul) Hwu, MD, PhD**

National Taiwan University Hospital, Taipei, Taiwan

### **Dr. Robert Leshner**

Children's National Medical Center, Washington, DC

### **Ans van der Ploeg, MD, PhD**

Erasmus Medical Center, Rotterdam, Netherlands

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## Immunology

### **Gillian Shepherd, MD**

Weill Medical College, Cornell University, New York, NY

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## Pulmonology

### **Kevin K. Brown, MD**

National Jewish Medical and Research Center, Denver, CO

### **Kenneth Berger, MD**

New York University School of Medicine, New York, NY

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## Statistics

### **Lee-Jen Wei, PhD**

Harvard University, Cambridge, MA

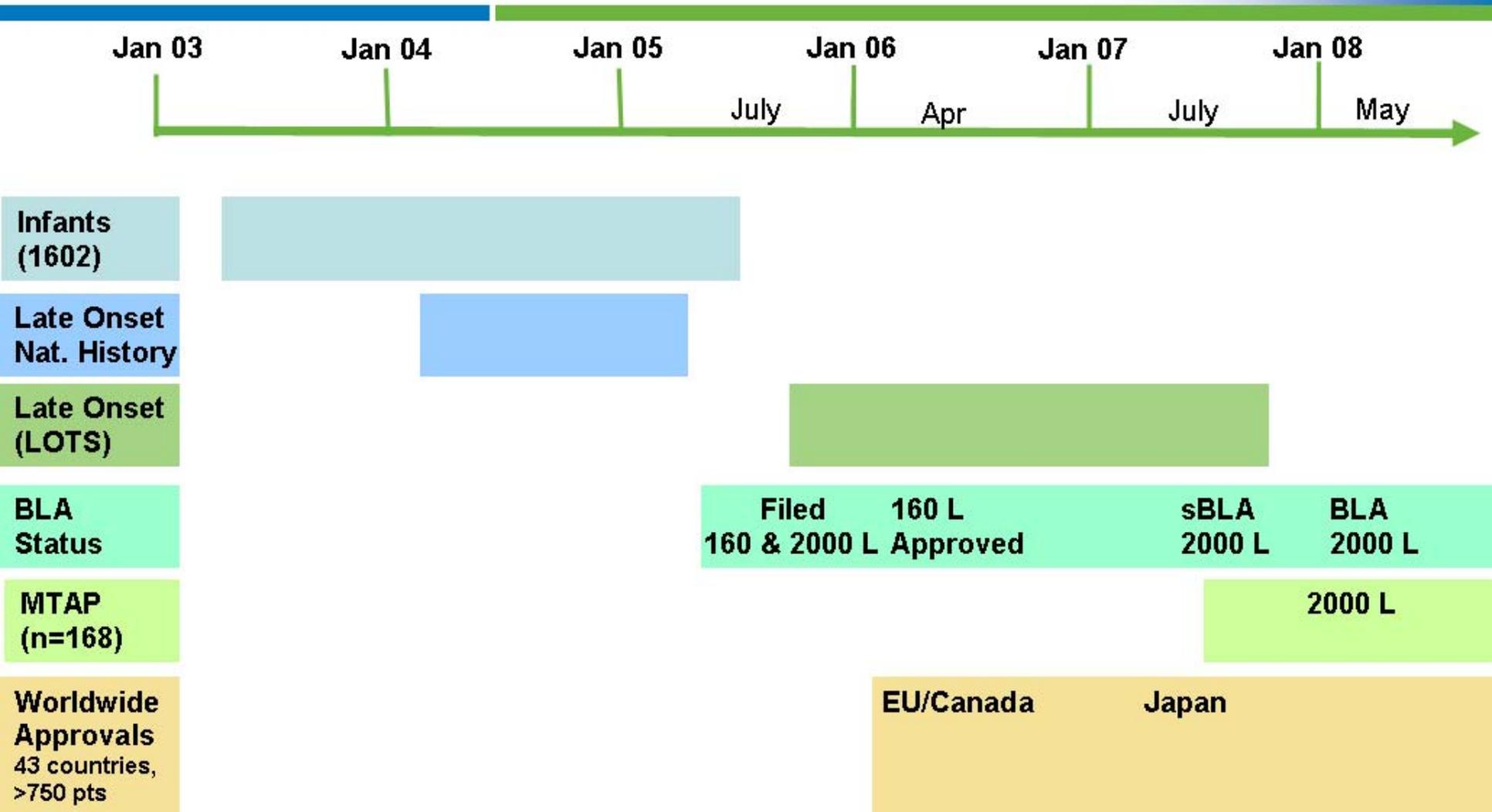
### **Ralph D'Agostino, Sr. PhD**

Boston University, Boston, MA

### **Cyrus Mehta, PhD**

President, Cytel, Inc., Cambridge, MA

# Myozyme Timeline



## Proposed Indication

- *alglucosidase alfa* is indicated for long-term use in patients with late onset Pompe disease (GAA deficiency). *alglucosidase alfa* has been shown to improve distance walked and stabilize pulmonary function in patients with late onset Pompe disease
- Proposed definition of late onset disease
  - Limited to patients with symptom onset >24 months without hypertrophic cardiomyopathy

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# Overview of Pompe Disease

**Priya S. Kishnani, MD**

Professor and Chief, Division of Medical Genetics  
Department of Pediatrics  
Duke University Medical Center  
Durham, NC

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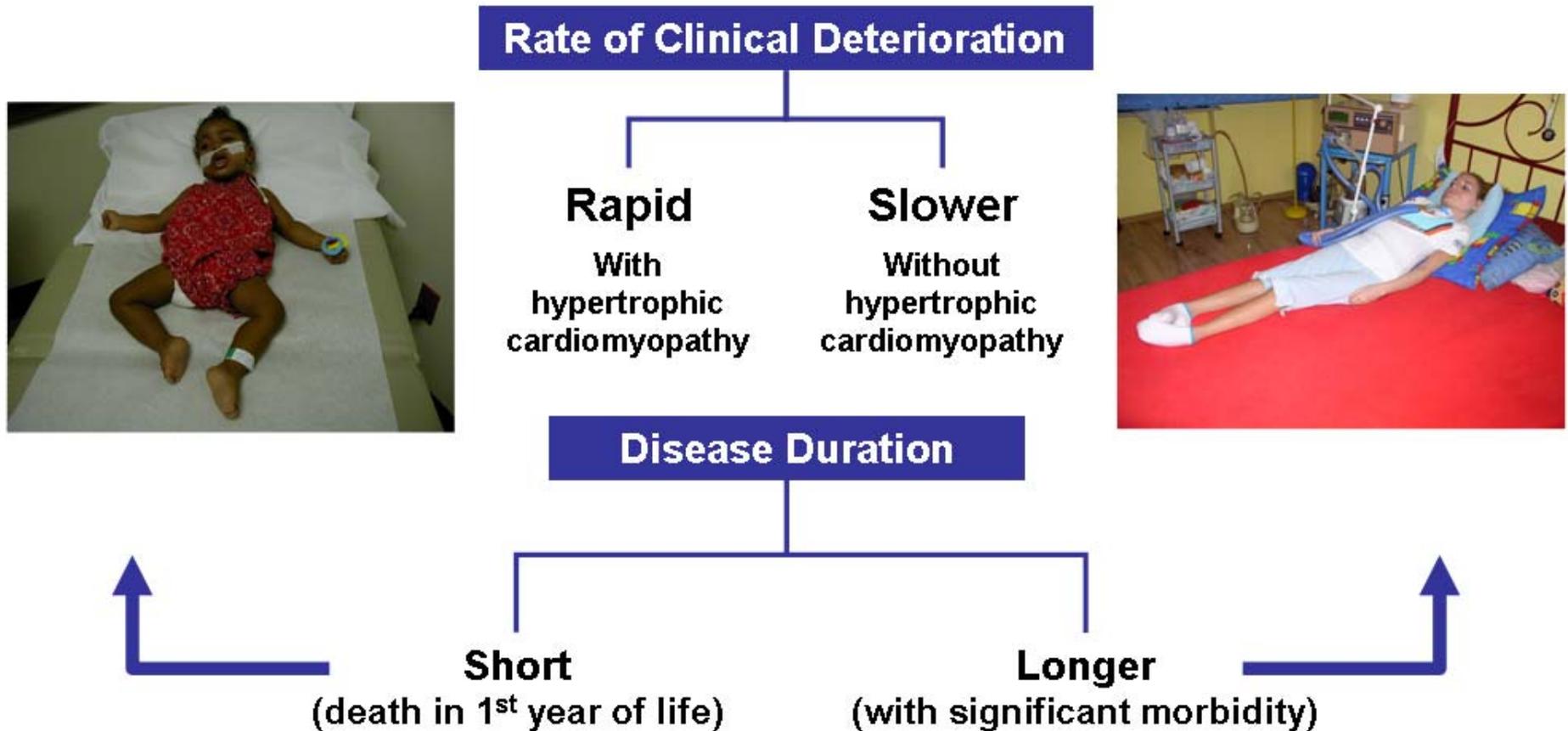
# Outline of Pompe Clinical Presentation

- Clinical spectrum of Pompe disease
- Natural history of Pompe disease
- Pathophysiology of Pompe disease
- Factors affecting treatment outcome of alglucosidase alfa in Pompe disease

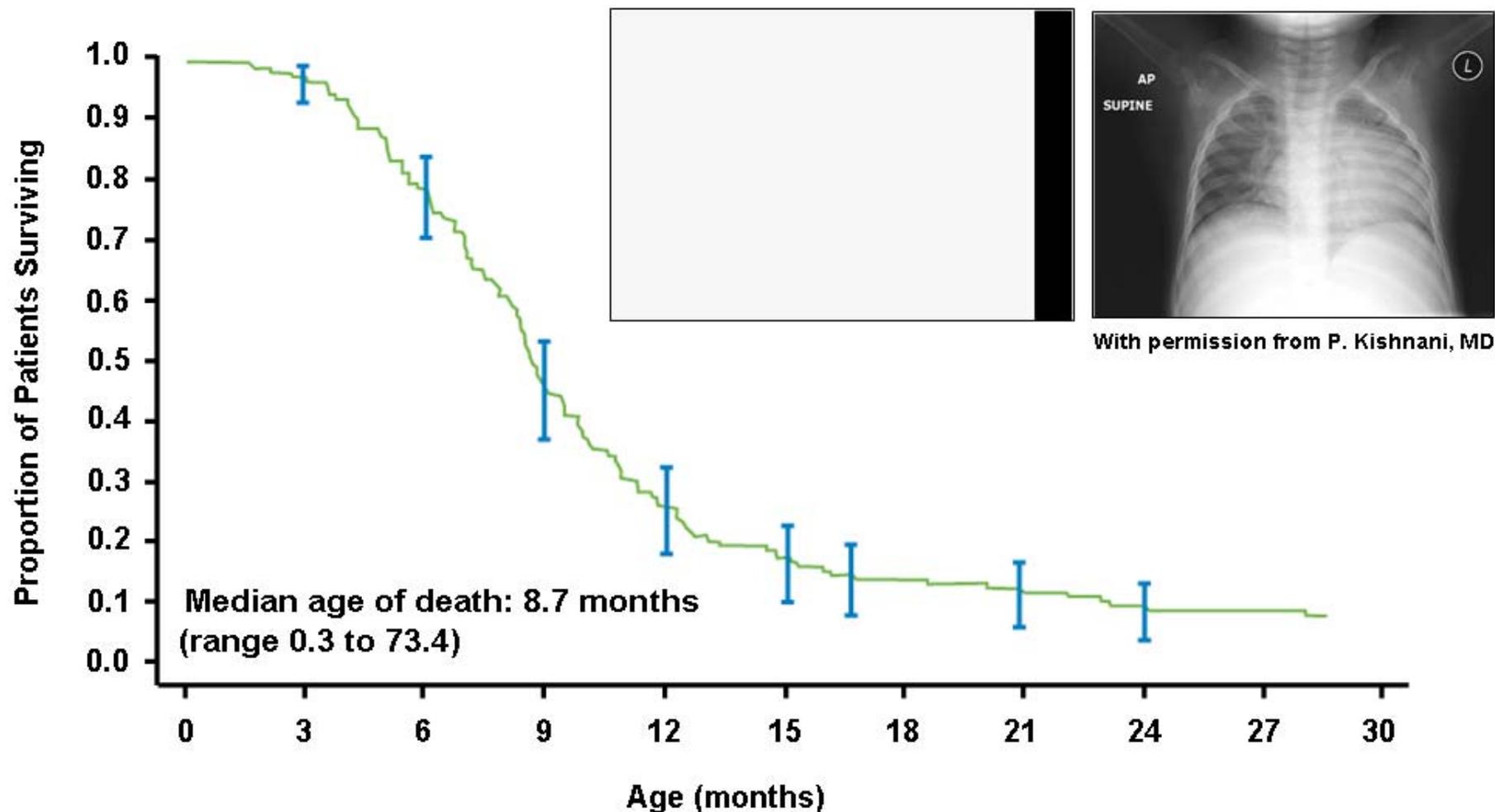
# Pompe Disease

- 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
- Very rare disease (estimated incidence 1:40,000)

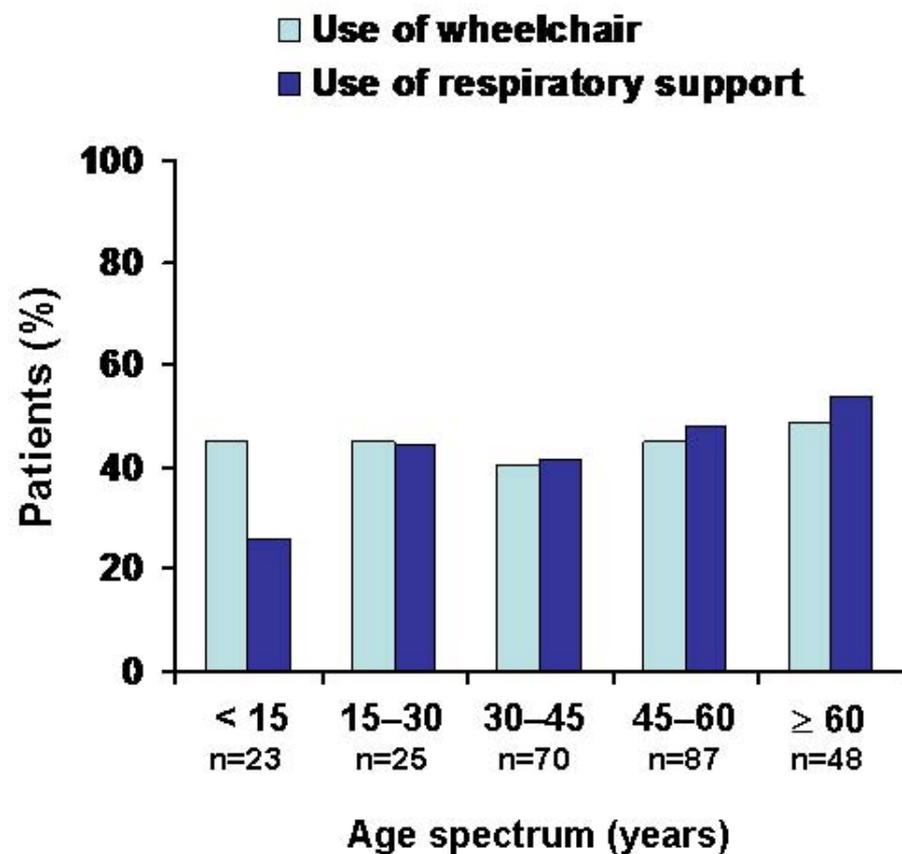
# Pompe Disease Presents as a Spectrum



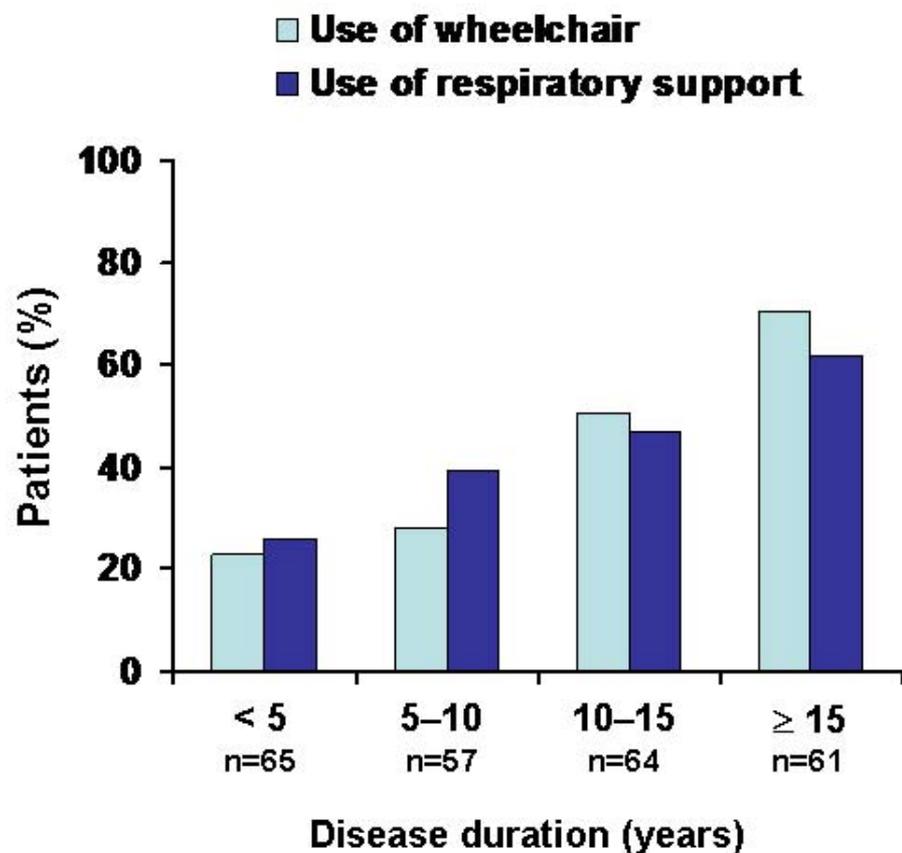
# Infantile Onset Pompe Disease: Rapidly Progressive and Often Fatal



# Late Onset Pompe Disease: Clinically Heterogeneous

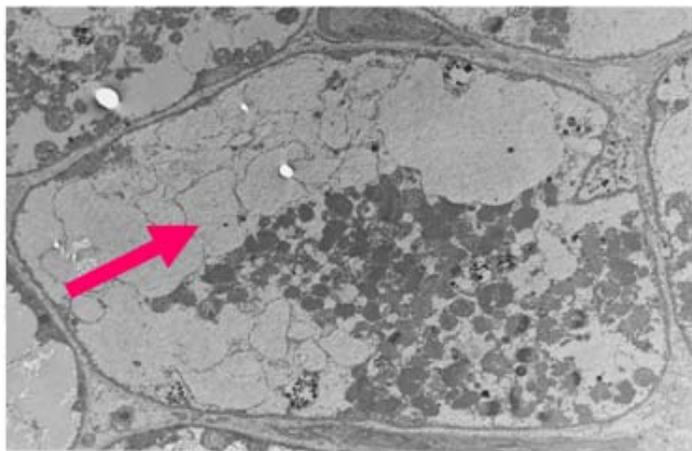
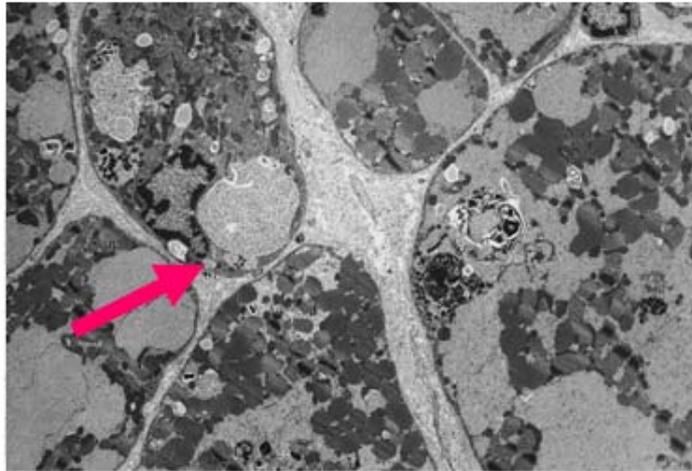


# Late Onset Pompe Disease: Relentlessly Progressive and Debilitating

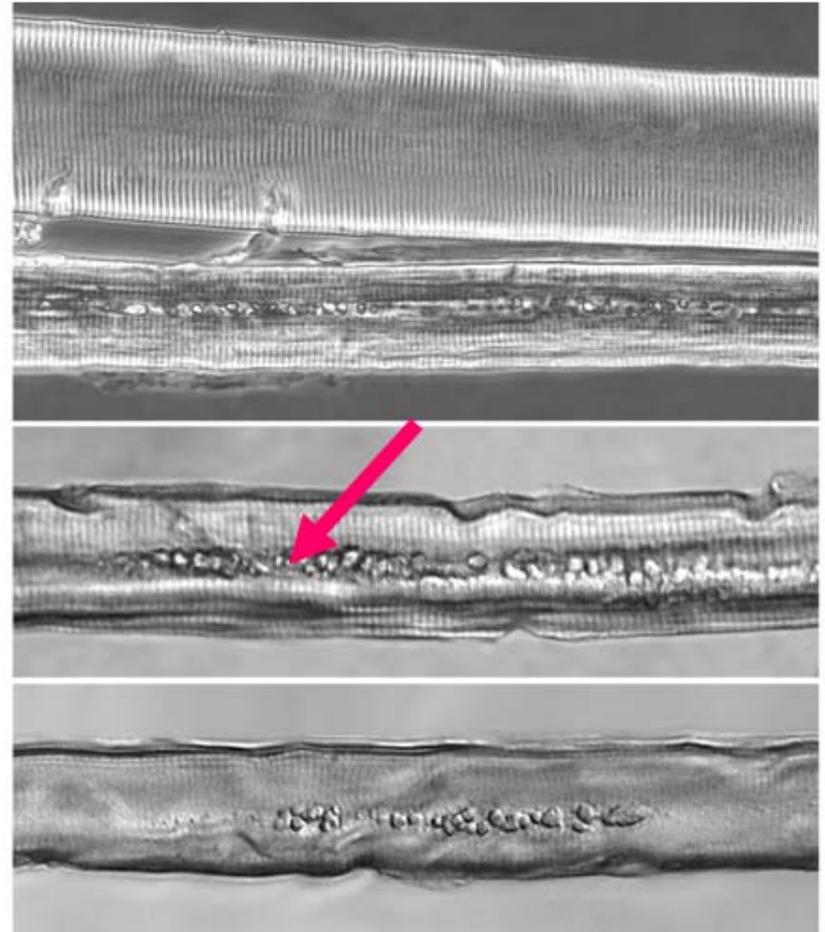


# Pathophysiology of Pompe Disease

Glycogen accumulation in lysosomes



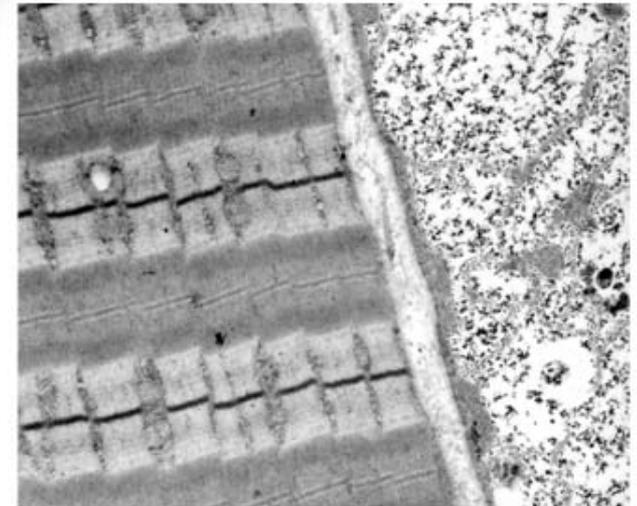
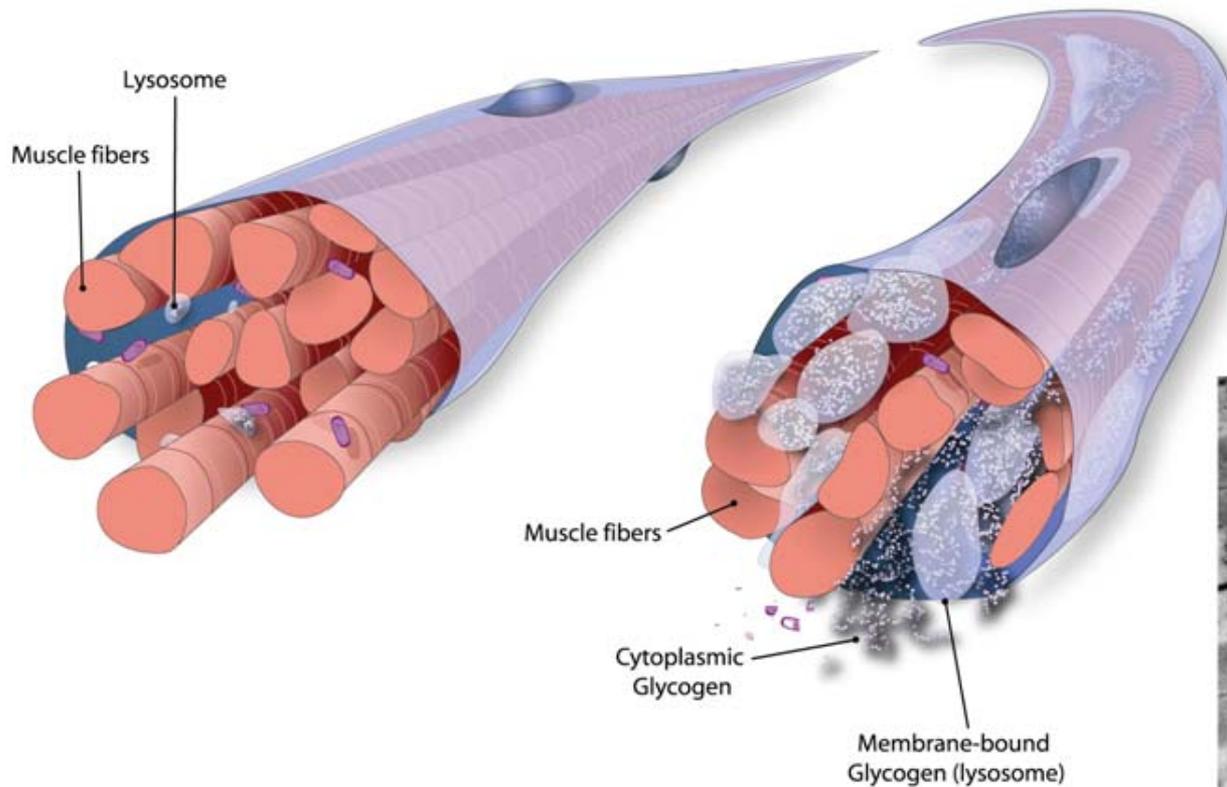
Defective autophagy



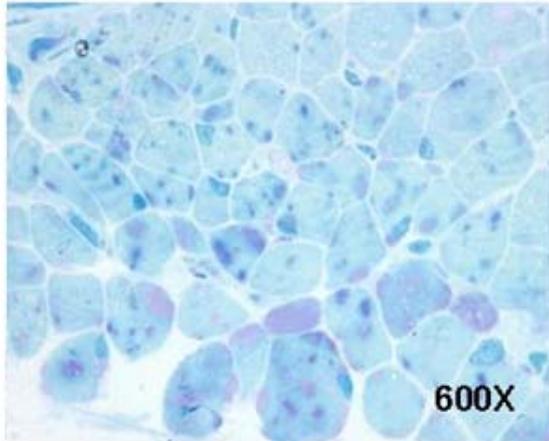
# Differential Involvement of Muscle Fibers in Pompe Disease

Normal Muscle Cell

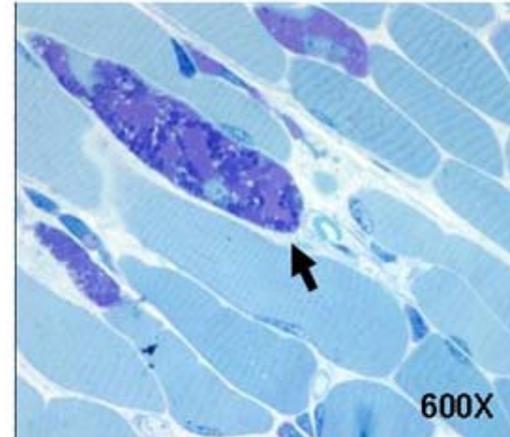
Affected Muscle Cell



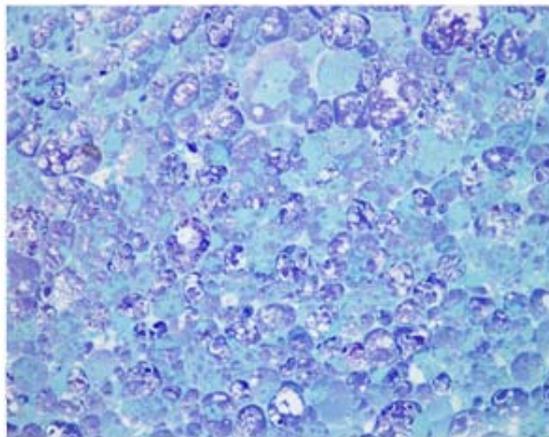
# Extent of Glycogen Clearance Depends on the Condition of Muscle Tissue Prior to Treatment



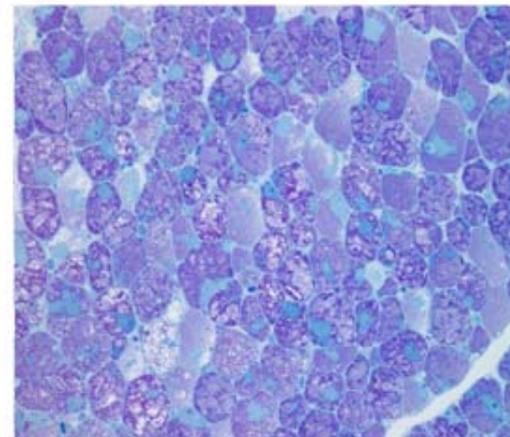
**Pre-treatment**



**6 Months Post-treatment**



**Pre-treatment**



**12 Months Post-treatment**

# Conclusions

- Pompe disease is a severe and progressive disease
- Profound clinical heterogeneity is observed in the late onset form of the disease
- If left untreated, the outcome is dismal
  - Death in infantile onset
  - Wheelchair/ventilator dependence and often death in late onset





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## **Clinical Experience with 2000 L alglucosidase alfa**

**Edward M. Kaye, MD**

Group Vice President, Clinical Research  
Genzyme Corporation



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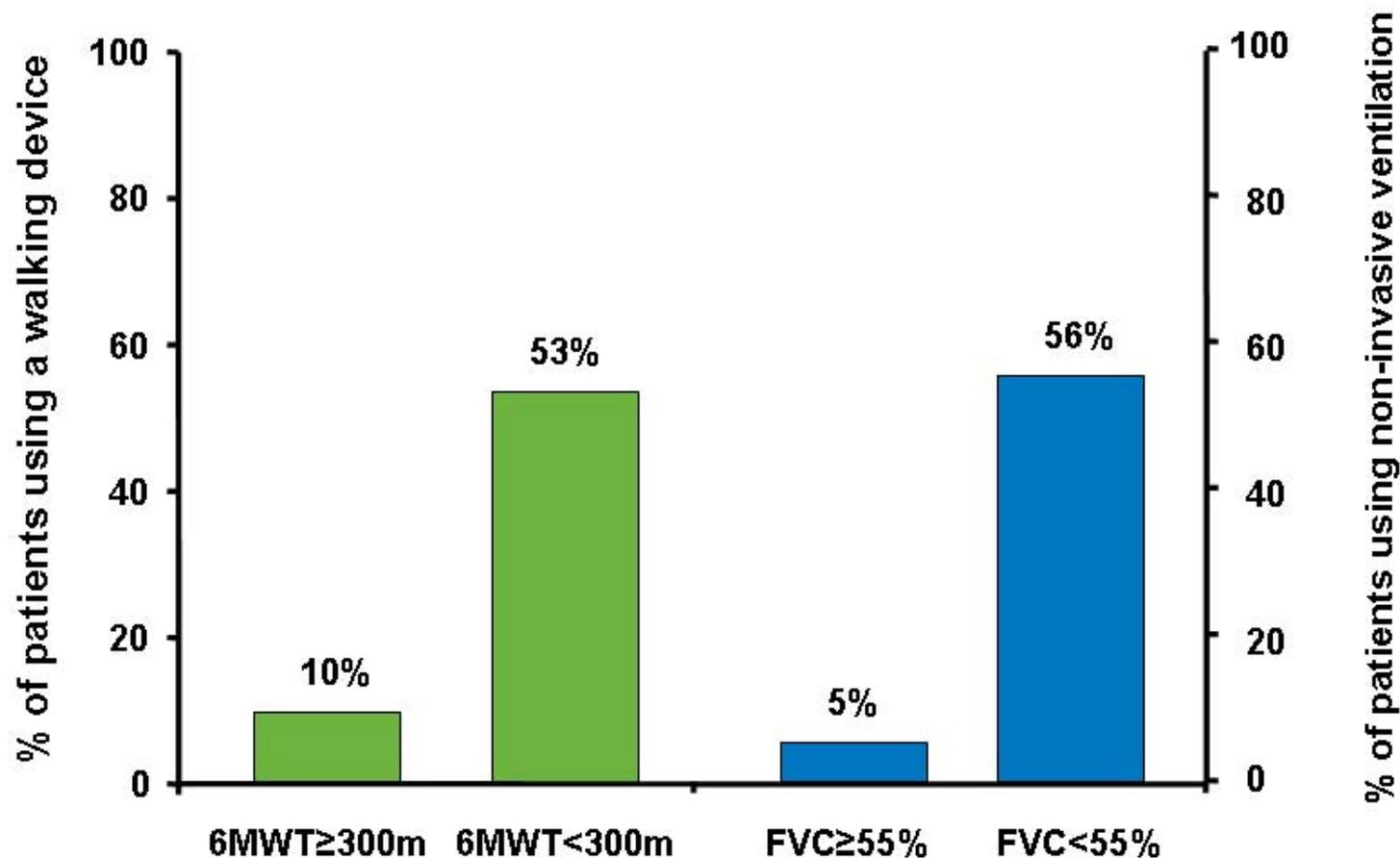
# Objectives

- Review the Late Onset Prospective Observational Study (LOPOS)
- Review the Late Onset Treatment Study (LOTS)
- Discuss age criteria for use of 2000 L material

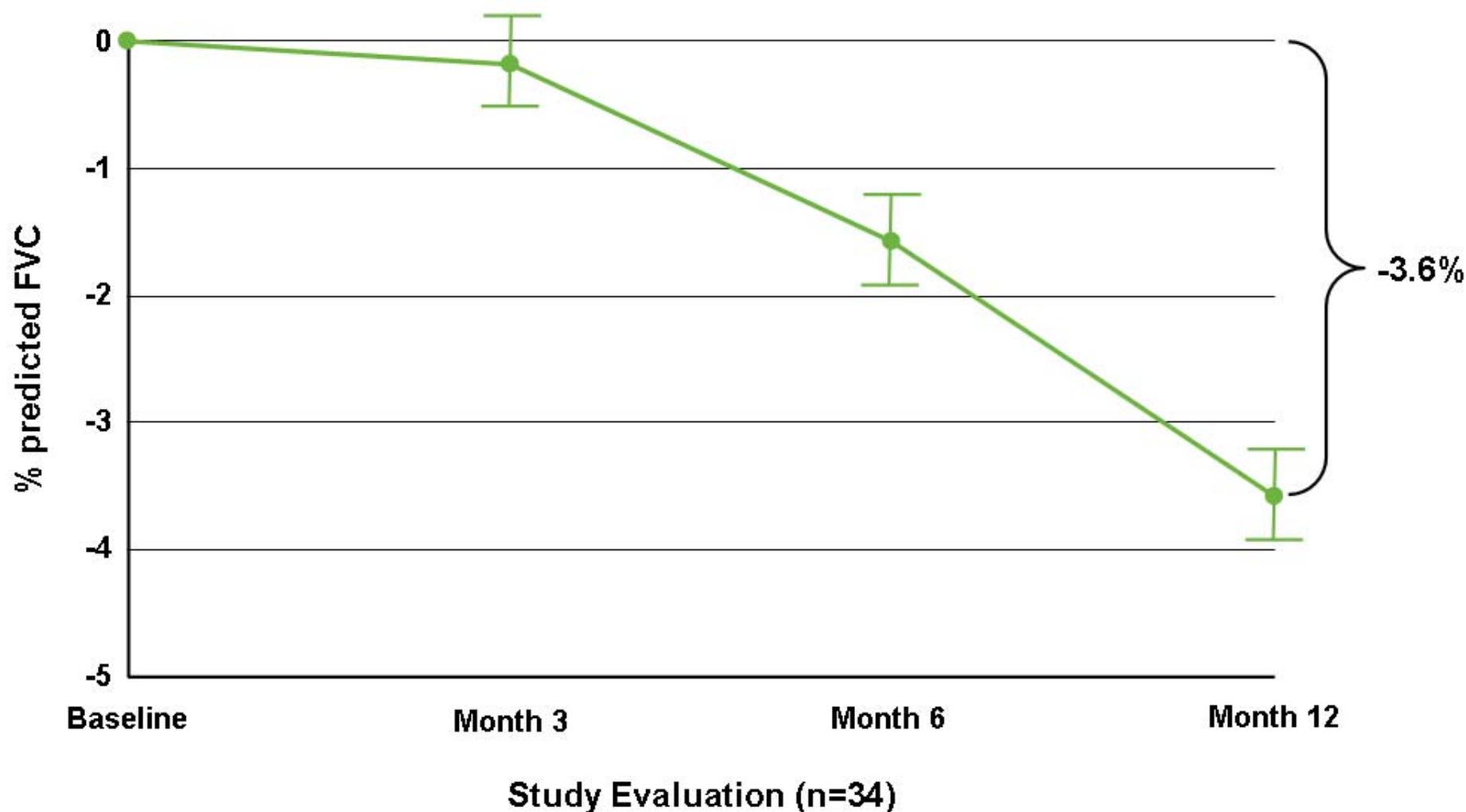
# Late Onset Observational Study (LOPOS)

- Prospective observational study of 58 ambulatory, invasive ventilator-free patients (age range 24-68)
  - 12-month duration
- Study conducted to characterize the clinical progression of late onset Pompe disease
  - Understand natural history to inform our selection of endpoints and estimates of sample size
  - 6MWT was performed only at the last study visit
  - Establish baseline level and rate of decline in % predicted forced vital capacity (FVC)

# 6MWT and FVC Associated with Use of Assistive Devices in LOPOS



# Statistically Significant Decline in Pulmonary Function Observed in 12-month Study Period



# LOTS: Clinical Trial Design Considerations

- Rare, clinically heterogeneous disease
  - Challenge to identify an eligible trial population
- Pompe disease is a neuromuscular disease with loss of mobility and respiratory failure
  - Limited number of possible endpoints
- What is the expectation of treatment?
  - Stabilization or improvement?
  - Extent of muscle damage may determine magnitude of response to treatment
- One chance to perform a placebo-controlled clinical trial

# Efficacy Endpoints

## Musculoskeletal

### Co-primary

- 6MWT distance walked

### Secondary

- QMT Leg score

### Tertiary

- QMT Arm score

## Respiratory

### Co-primary

- % predicted FVC

### Tertiary

- % predicted MEP
- % predicted MIP

## Quality of Life

### Secondary

- SF-36 PCS score

# Study Design

- Randomized, double-blind, placebo-controlled
  - 2:1 drug to placebo assignment
  - 20 mg/kg alglucosidase alfa or placebo IV administration qow
- Multi-center, multi-national
  - 90 patients enrolled at 8 sites in 3 countries
- Patients stratified for baseline disease severity
  - 6MWT distance  $\geq$  or  $<$ 300 m
  - % predicted FVC  $\geq$  or  $<$ 55%

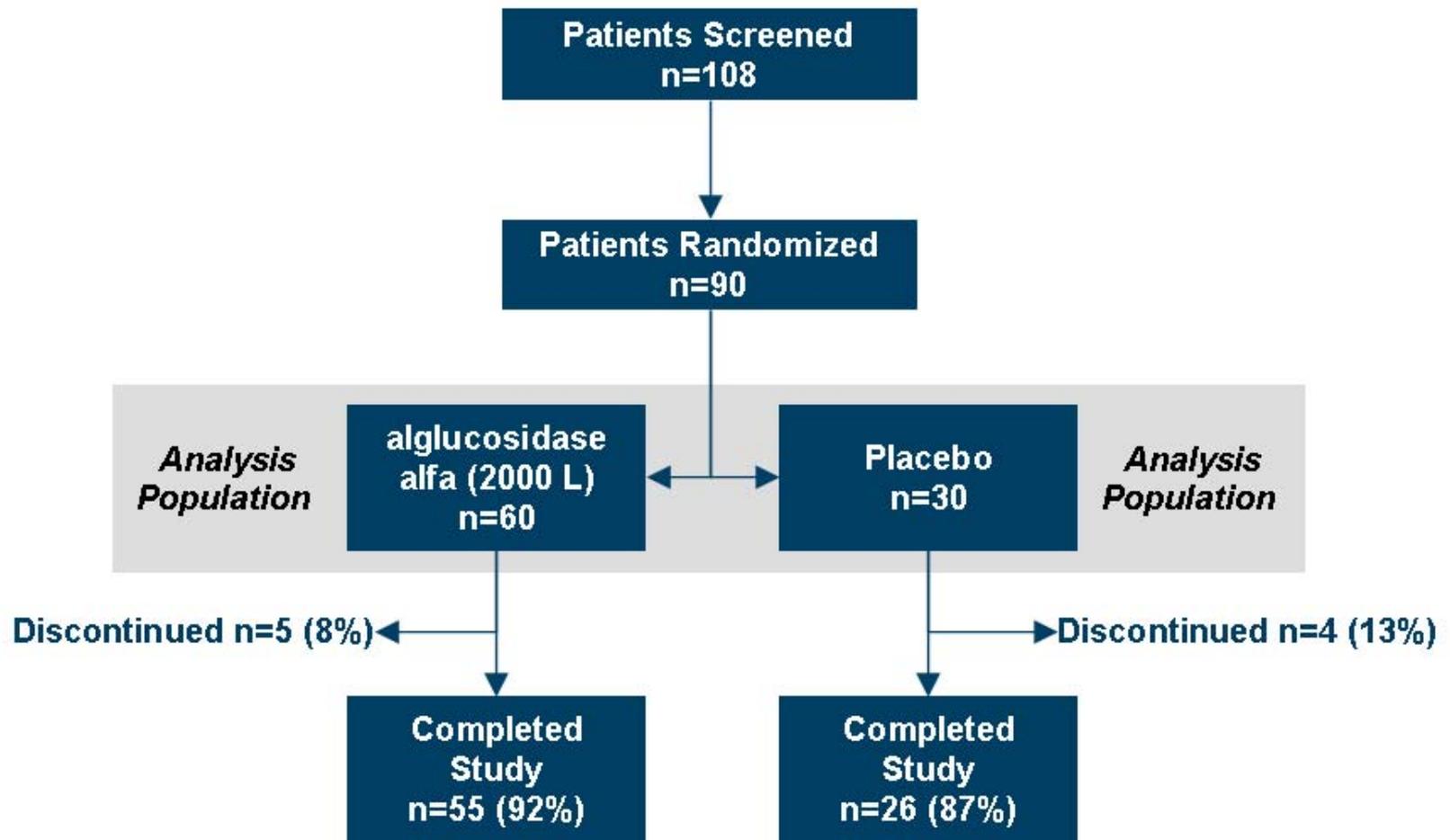
# Entry Criteria

- At least 8 years of age
  - Lower age limit for FVC reference standards and an age that ensured test compliance
- Ambulatory
- Not invasively ventilated
- Quantifiable evidence of:
  - Lower extremity muscle weakness
  - Diminished pulmonary function
  - Diaphragmatic weakness

# Statistical Methods

- Repeated measures analysis using a linear mixed effects (LME) model
  - Robust variance estimation
- ANCOVA analysis of the change from baseline to week 78

# Patient Disposition

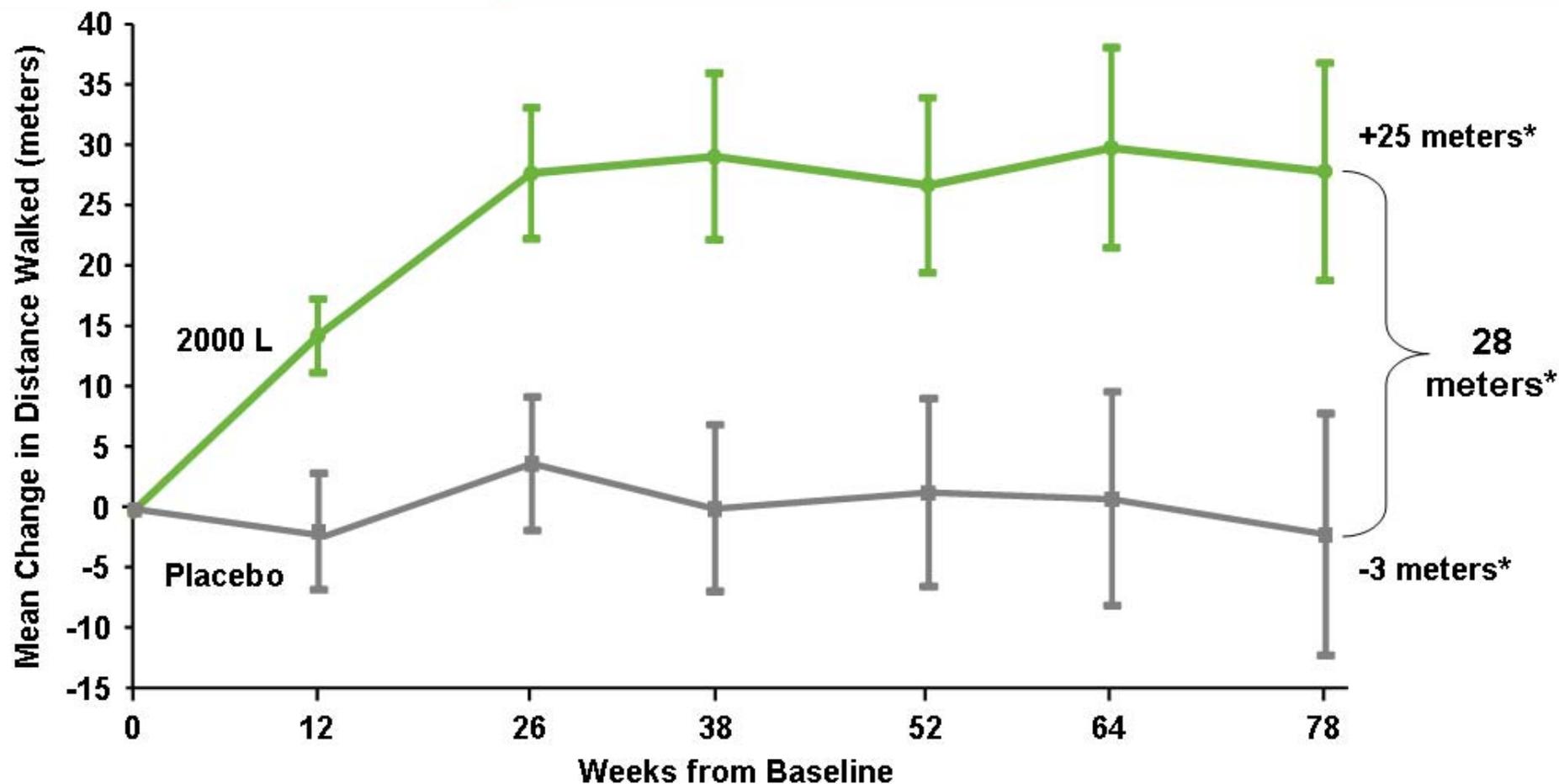


# Patient Demographics

		alglucosidase alfa (n=60)	Placebo (n=30)
Gender (%)	Male	57	37
	Female	43	63
Ethnicity (%)	Caucasian	95	90
Age at 1st infusion (yrs)	Median (range)	45 (16-70)	43 (10-68)
Time since symptom onset (yrs)	Median (range)	7.5 (<1-25)	7.6 (<1-31)
Baseline 6MWT distance (m)	Mean (SD)	332 (127)	318 (132)
	% predicted (SD)	52 (19)	50 (21)
Baseline % predicted FVC	% (SD)	55* (14)	53* (16)

\*Moderately severe restrictive respiratory disease by ATS standards

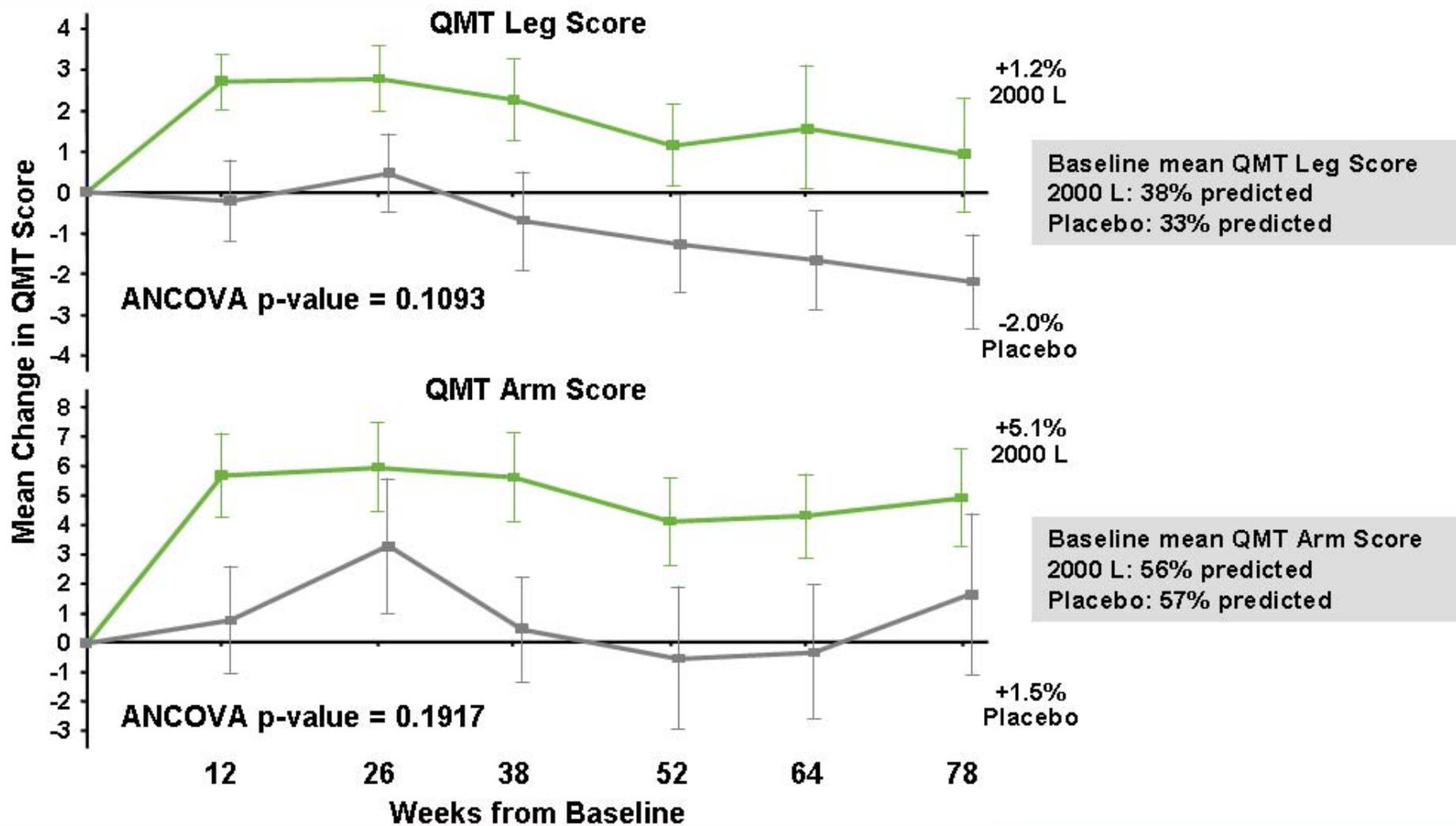
# 2000 L alglucosidase alfa Improves Walking Distance (6MWT)



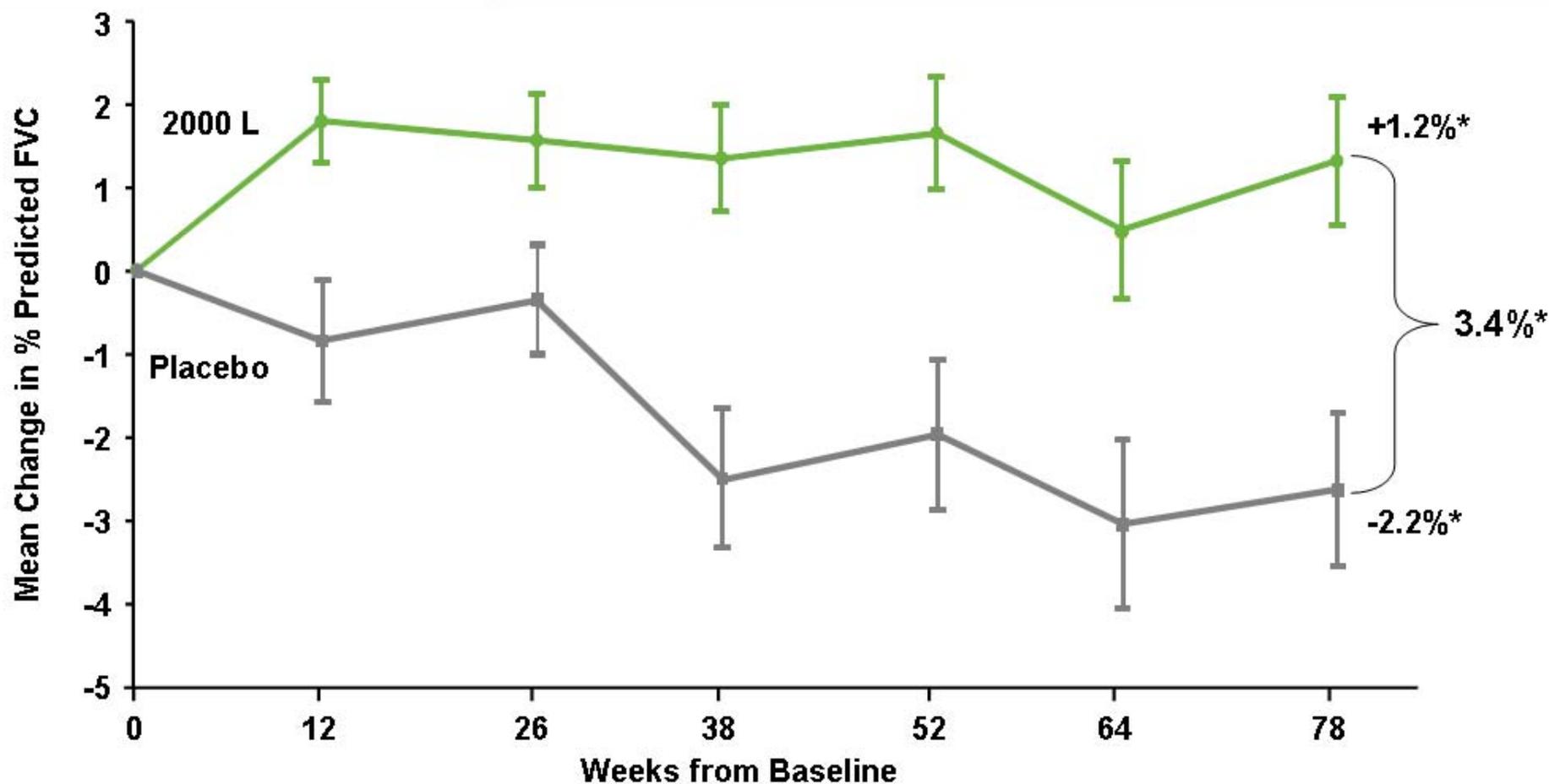
LME p-value = 0.0464  
ANCOVA p-value = 0.0347

\*ANCOVA estimate of mean

# Pattern of Proximal Muscle Response Supports 6MWT Results



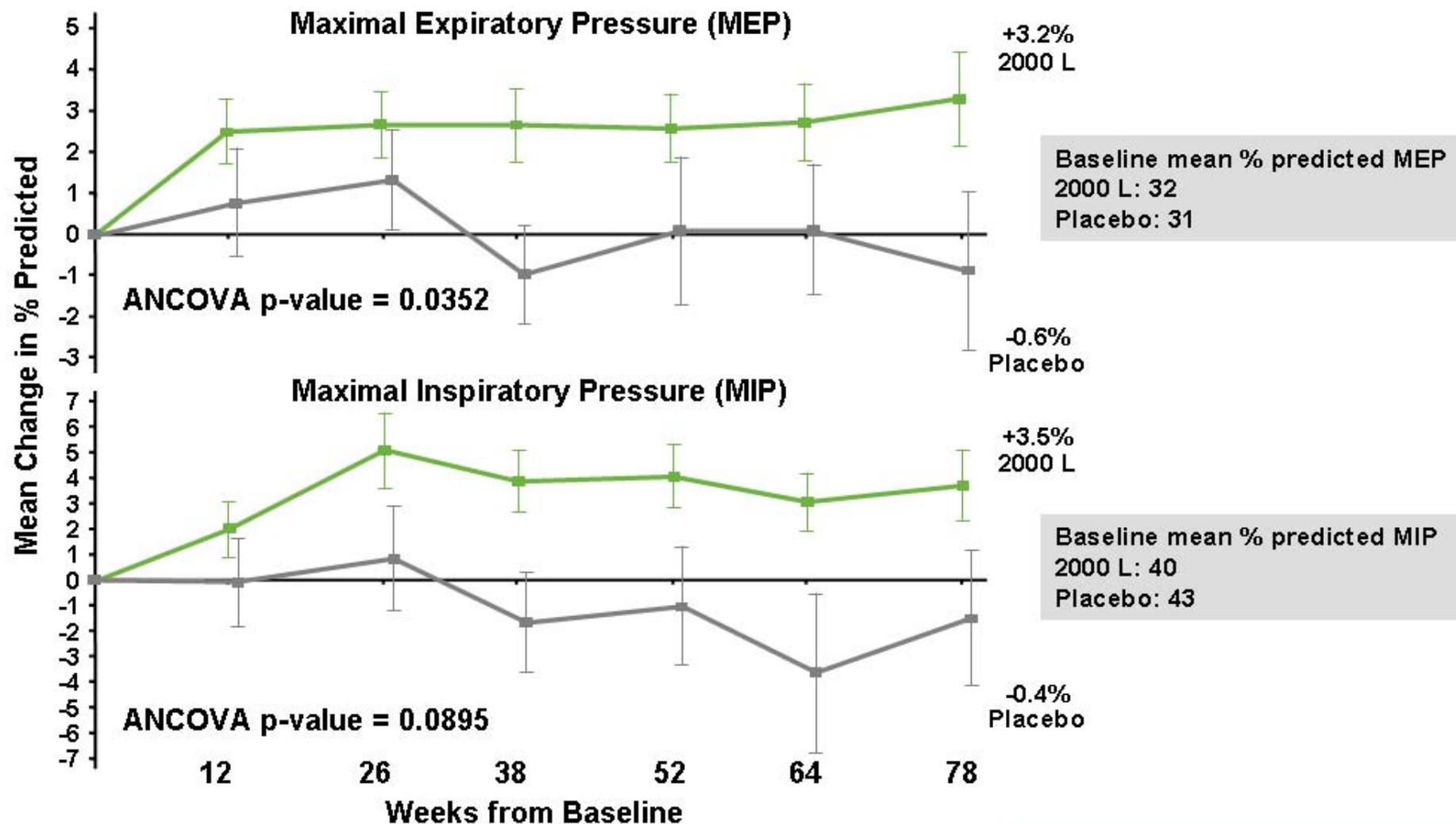
# 2000 L alglucosidase alfa Stabilizes Pulmonary Function (% Predicted FVC)



LME p-value = 0.0041  
ANCOVA p-value = 0.0055

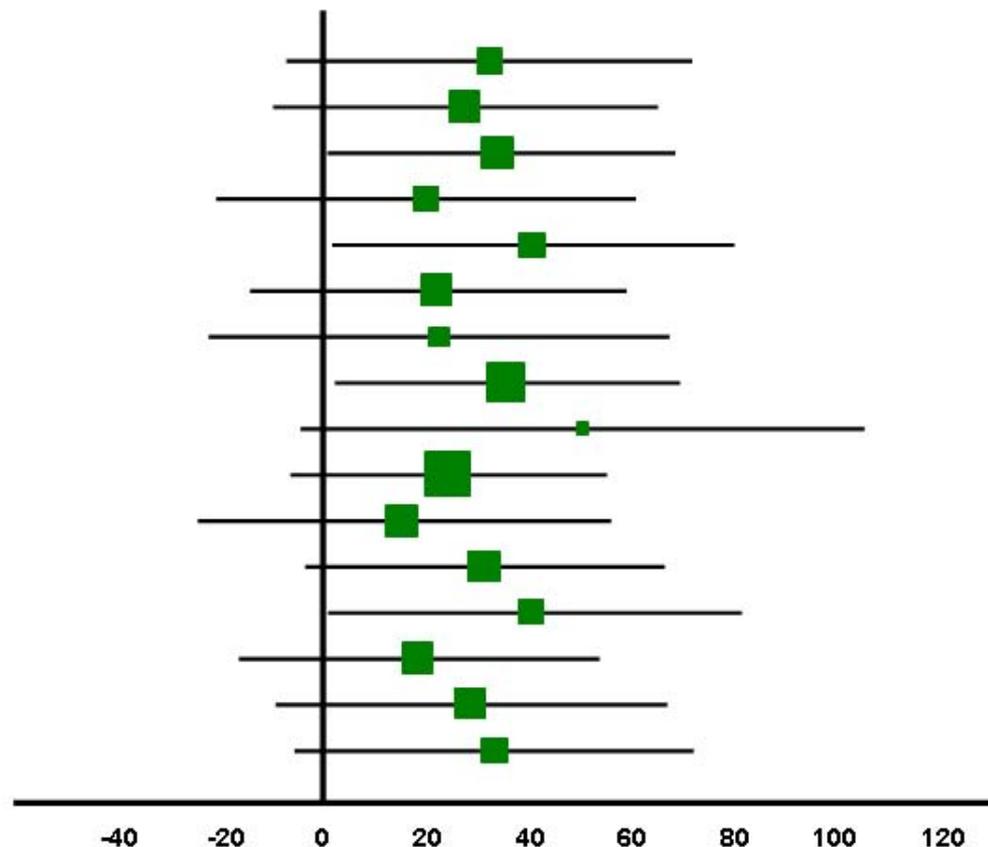
\*ANCOVA estimate of mean

# Pattern of Respiratory Muscle Response Supports FVC Results



# Observed Effect of 2000 L alglucosidase alfa on Walking Distance is Consistent

■ n=15-24   ■ n=25-34   ■ n=35-44   ■ n=45-54   ■ n=55-64   ■ n=65-74



Walking device used at Baseline  
 No walking device used at Baseline  
 Baseline 6MWT ≥300 m  
 Baseline 6MWT <300 m  
 Baseline FVC ≥55%  
 Baseline FVC <55%  
 Respiratory support device use at Baseline  
 No respiratory support device use at Baseline  
 Disease duration ≥15 years  
 Disease duration <15 years  
 Male  
 Female  
 Age ≥45  
 Age <45  
 GAA activity <9.8% Normal  
 GAA activity ≥9.8% Normal

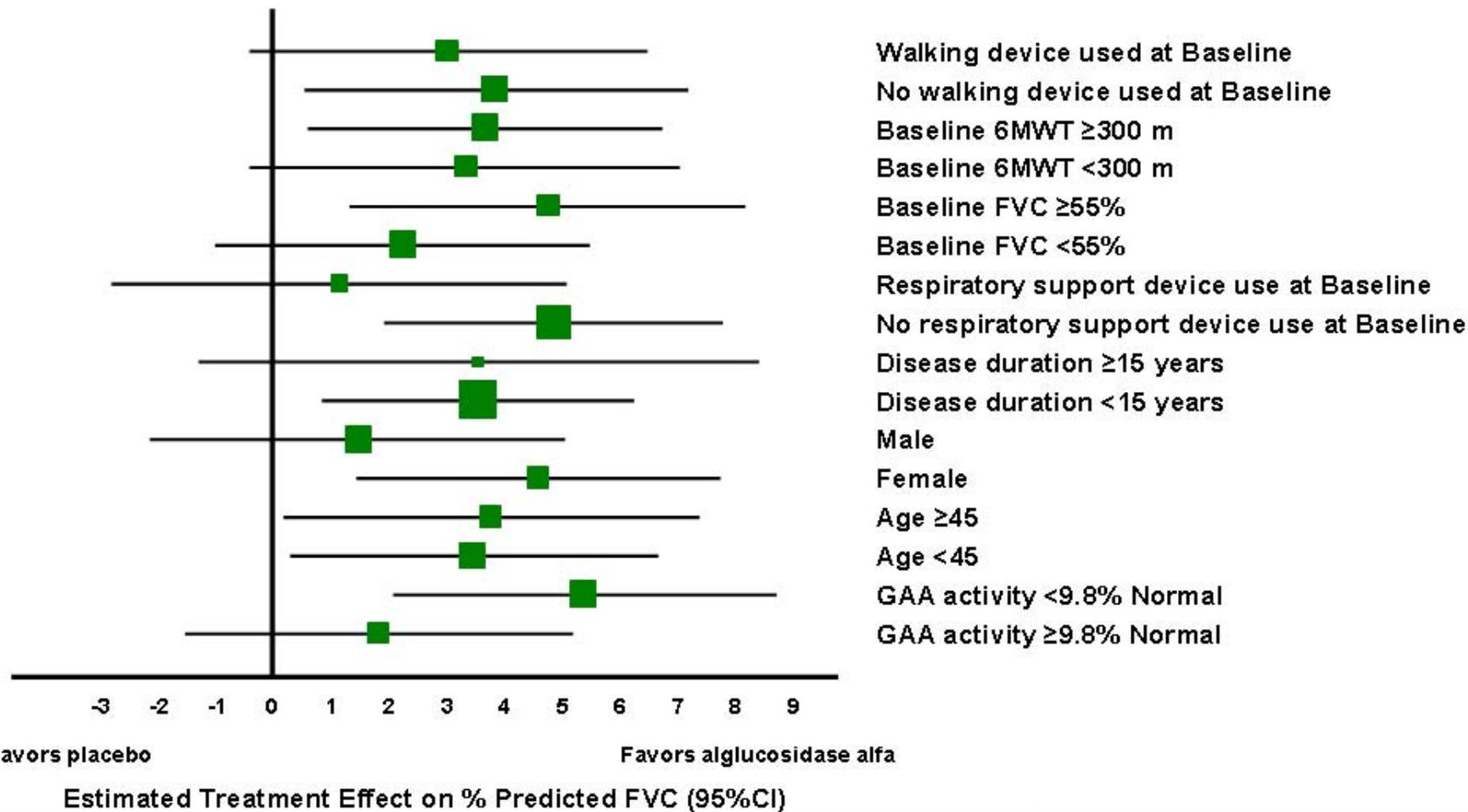
Favors placebo

Favors alglucosidase alfa

Estimated Treatment Effect on 6MWT Distance Walked (Meters)

# Observed Effect of 2000 L alglucosidase alfa on Pulmonary Function is Consistent

■ n=15-24   ■ n=25-34   ■ n=35-44   ■ n=45-54   ■ n=55-64   ■ n=65-74



# Effect Size is Comparable to Other Approved ERT Products

	Aldurazyme (laronidase) <sup>1</sup>	Elaprase (idursulfase) <sup>2</sup>	2000 L alglucosidase alfa
<b>Pivotal Study Design</b>			
Disease population	MPS-I	MPS-II	Pompe
Treatment duration	6 months	12 months	18 months
Number of patients treated	45	64	90
<b>6MWT distance walked</b>			
Effect size (p-value)	0.56 (0.039)	0.60 (0.0131)	0.48 (0.034)
<b>% predicted FVC</b>			
Effect size (p-value)	0.61 (0.028)	0.27 (not significant)	0.65 (0.006)

MPS=Mucopolysaccharidosis

<sup>1</sup>6MWT ES based on Wraith. *J Pediatr.* 2004; FVC ES based on data on file at Genzyme

<sup>2</sup>6MWT and FVC ES based on Muenzer. *Genet Med.* 2006.

Effect size=  $\frac{\text{treatment effect}}{\text{SD}}$



# **Late Onset Treatment Study (LOTS) Safety Results**

# AEs Occurred at Comparable Frequencies in Both Treatment Groups

Variable	alglucosidase alfa (n=60)		Placebo (n=30)	
	% Patients	Events	% Patients	Events
Any AEs	100	1445	100	851
SAEs	22		20	
Treatment Related AEs	53		57	
Infusion Associated Reactions (IARs)	28		23	
Anaphylactic Reactions	5		0	
Discontinuations due to AEs or Death	5		3	

# Serious Adverse Events (SAE): Comparable Frequency

- Frequency: approximately 20% in both groups
  - Most were unrelated to treatment
  - 1 patient in alglucosidase alfa group died due to unrelated causes
  - 4 events in treatment group
    - 3 (5%) with anaphylaxis
    - 1 tachycardia
  - 2 events in placebo group

# Anaphylactic Reactions

- 3/60 (5%) patients experienced anaphylactic reactions
  - 2 patients experienced IgE-mediated reactions
    - Both patients presented with respiratory and cutaneous reactions
    - Both patients were successfully rechallenged
  - 1 patient experienced angioedema of the tongue
    - Discontinued treatment due to the reaction
  - 4<sup>th</sup> patient classified as anaphylaxis by FDA
    - Patient with history of asthma (albuterol BID)
    - Intermittent mild to moderate wheezing
    - Recovered in a few minutes each time with infusion rate reduction and albuterol
- None of the patients had cardiovascular compromise

# Production of anti-GAA IgG Antibodies

- Assays: ELISA and confirmed by RIP
- Results:
  - All tested patients (n=59) in treatment group seroconverted
  - Median time to seroconversion: 4 weeks (range 4-12 weeks)
  - Median peak titer: 6,400 (range 200-819,200)
- Titers decreased from peak value in 61% of patients by the end of study

ELISA: Enzyme Linked Immunosorbent Assay

RIP: Radioimmunoprecipitation

# Titer of IgG Antibody: Impact on Safety and Efficacy

Parameter (IgG Peak Titer)	Quartile 1 (200-1600)	Quartile 2 (3200-3200)	Quartile 3 (6400-12800)	Quartile 4 (25600-819200)
Number of Patients % (n)	29% (17)	20% (12)	<b>27% (16)</b>	24% (14)
Patients with any SAE % (n)	29% (5)	16% (2)	25% (4)	7% (1)
Patients with any IAR % (n)	35% (6)	17% (2)	31% (5)	21% (3)
Change in 6MWT (m)* Mean (SD)	6 (54)	16 (25)	35 (77)	49 (80)
Change in % predicted FVC* Mean (SD)	0.8 (6)	1.8 (5)	1.5 (6)	1.1 (6)

\*Change from baseline to last observation

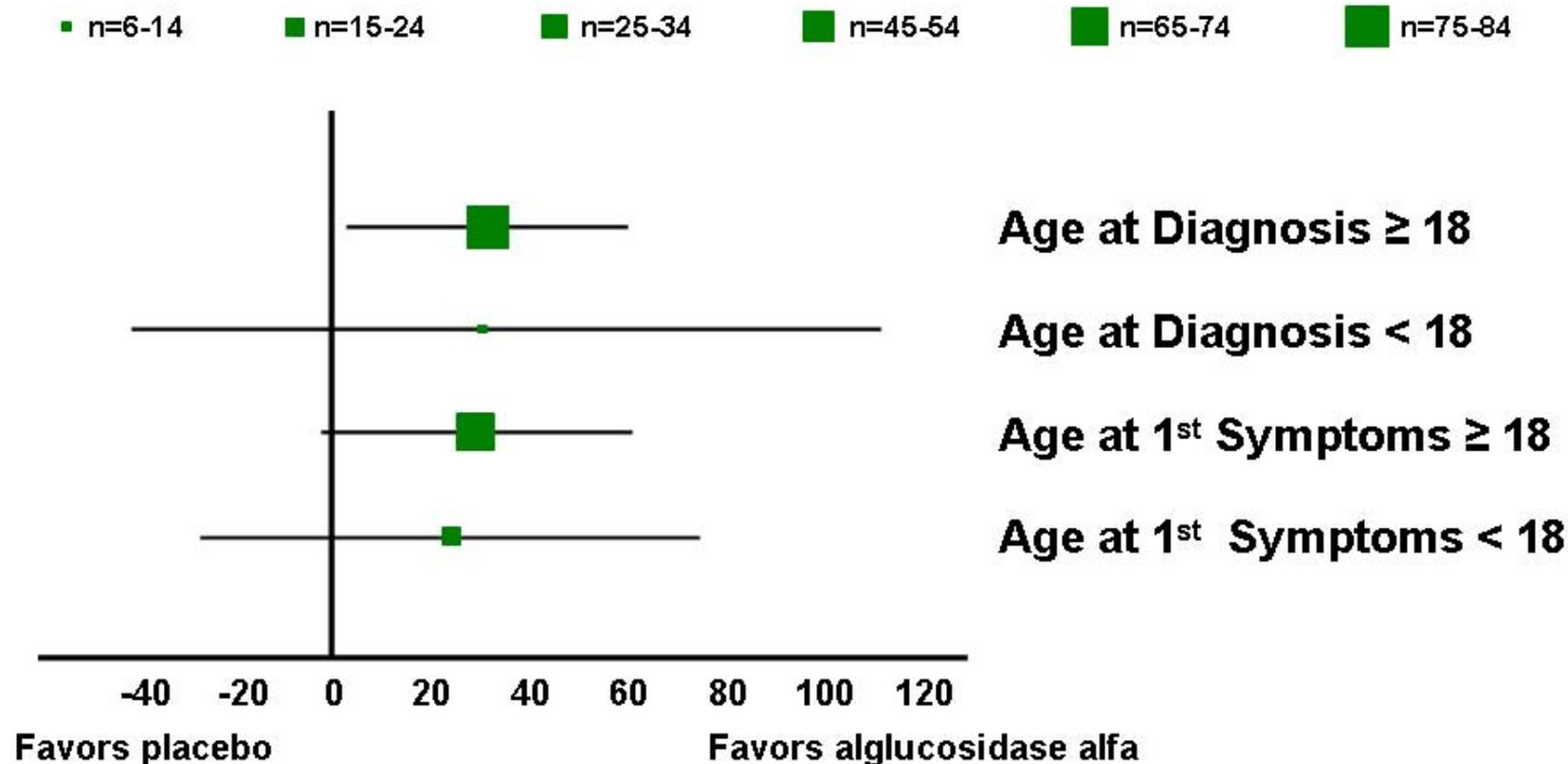
# Should There Be a Lower Age for 2000 L?

- 8 years of age?
  - Age used for LOTS was chosen to ensure testing compliance
- 18 years of age?
  - No rationale for restricting use to adult patients related to pathophysiology of Pompe disease

# Alternative Proposal

- Hypertrophic cardiomyopathy is the major clinical feature that differentiates infantile onset from late onset Pompe disease
- Proposal:
  - 2000 L material should be given to patients with Pompe disease without hypertrophic cardiomyopathy and older than 24 months

# Treatment Effect in 6MWT: Subgroups Based on Age



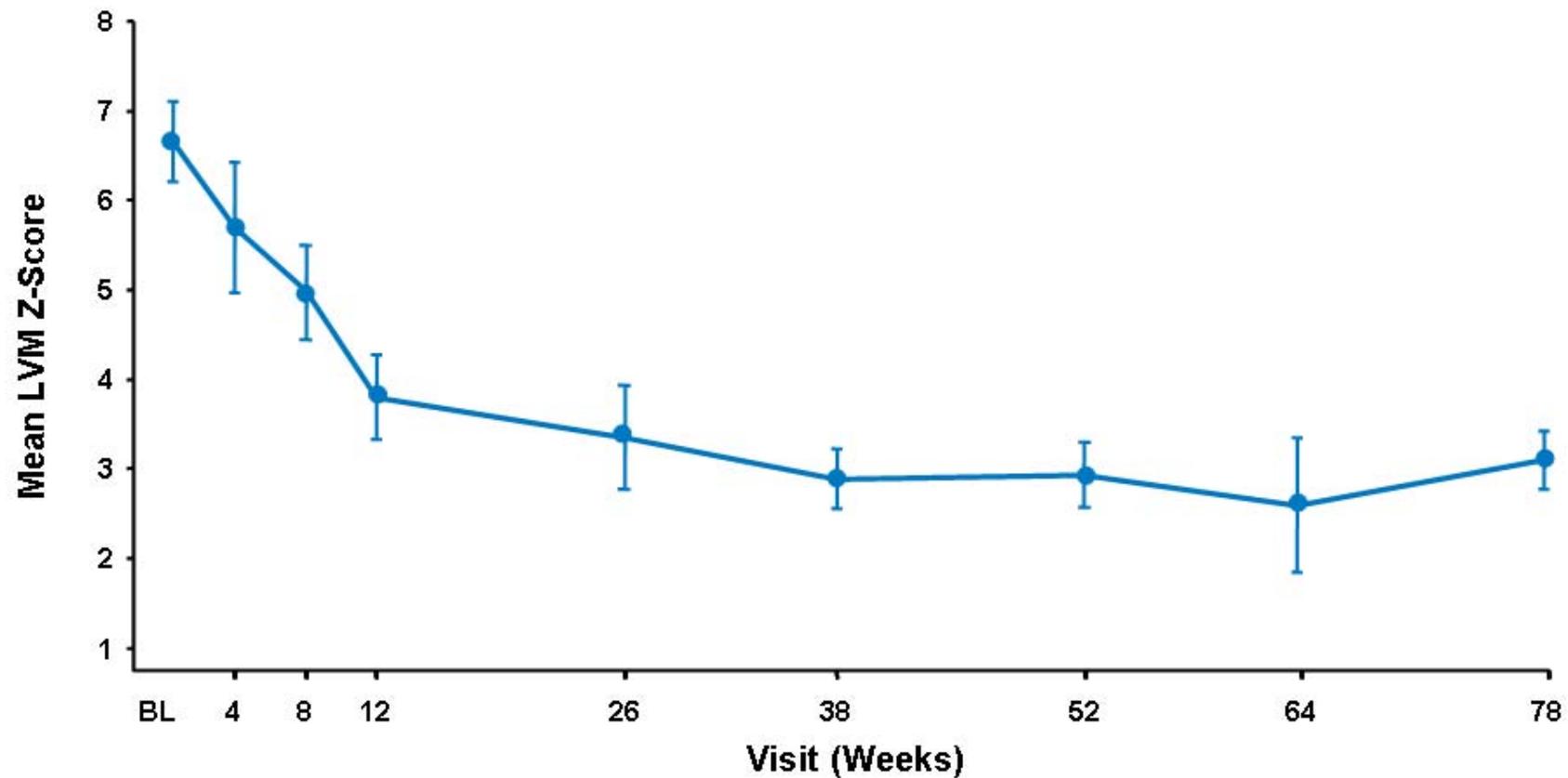
Estimated Treatment Effect on 6MWT (95%CI)

# Taiwan Infantile Onset Cohort: Overview

- Single-site, investigator-sponsored study of infantile onset Pompe patients conducted by Dr. Wuh-Liang (Paul) Hwu at NTUH
- 11 patients treated with alglucosidase alfa produced at the 2000 L scale
- Median age at treatment onset was 2 months (0.4-14)
- Patients were CRIM positive
- Median exposure was 71 weeks (22-116)
- Efficacy parameters evaluated included:
  - Survival
  - Ventilator status
  - Cardiac function
  - Motor development
  - Quadriceps muscle biopsy
- Spontaneous safety reporting



# Exposure to 2000 L Scale Results in Favorable Cardiac Response



Number of  
Observations

9

8

8

9

8

6

5

2

4

# Taiwan Cohort: Safety Summary

- Spontaneous AE reporting (3/11 patients) as of May 2008 (related)
  - 1 serious IgE-mediated anaphylactic reaction
    - Continue to receive treatment
  - 1 serious unlikely related event
    - Resolved
  - 1 non-serious IAR

# Risk/Benefit Summary

- **Demonstrated clinical benefit**
  - Improved distance walked and stabilized pulmonary function in late onset patients
    - Significant given natural history of progressive muscle weakness and loss of functional independence
  - Response in Taiwanese infants is reassuring for use in younger patients
- **Safety risks**
  - IARs: Mild or moderate and transient
  - Anaphylactic reactions: Infrequent
    - Manageable and majority of patients continue to receive treatment
  - High level of IgG antibodies to drug
    - No observed evidence of clinical impact
- **Favorable risk/benefit profile given proven clinical benefit in very rare population with no other treatment options**



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# Statistical Perspectives on LOTS Trial

**P.K. Tandon, PhD**

Senior Vice President

Biomedical Data Sciences and Informatics

Genzyme Corporation



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# Outline

- Statistical challenges in study design for Pompe disease
- Changes in the primary efficacy analysis plan
- Final efficacy analysis
- Rerandomization discussion – Dr. LJ Wei

## Statistical Challenges in LOTS Study Design

- Very rare disease; limited number of patients available for clinical trial
- A single chance to conduct placebo-controlled trial
- Lack of longitudinal natural history data on 6MWT in Pompe disease
- Concerned that in a progressive neuromuscular disease, long-term follow-up is needed

## Original Primary Efficacy Analysis Plan

- Treatment group difference at Week 52 for 6MWT and FVC
  - Hypothesis testing based on treatment group comparison at Week 52 adjusted for baseline
  - Use contrast from repeated measures ANCOVA

# Amended Primary Efficacy Analysis Plan

- Why was the plan changed?
  - Concerned that 52 weeks would not provide sufficient information
  - Decrease the chance of false negative study
- What was changed?
  - Fixed information design with interim analysis to possibly extend patient follow-up beyond 52 weeks (maximum 78 weeks)
  - Use linear mixed effect model (LME) to test difference in slopes
- All changes were prospectively defined in protocol and SAP and agreed to by FDA

# The Interim Analysis with Data at Week 38

- Performed by an independent statistical center reporting to DMC
- Using pre-specified rules, DMC recommended trial extension to 78 weeks
- Extension to 78 weeks depended on estimated variance, not on estimated treatment effect
  - No statistical penalty at final analysis
- Genzyme did not have access to interim analysis results until after study completion

# The Final Primary Efficacy Analysis

- During final analysis, pre-specified testing of key LME model assumptions was performed
  - LME model assumptions were violated
  - Commonly used robust method for standard error estimation was applied
- Key supportive analysis: ANCOVA to test change from baseline to Week 78 (FDA preference)
- Rerandomization test was one of the pre-specified sensitivity analyses

# Rerandomization Discussion

**Problems Using Re-Randomization  
Test Based on Minimization Treatment  
Allocation Rule as the Primary Efficacy  
Analysis**

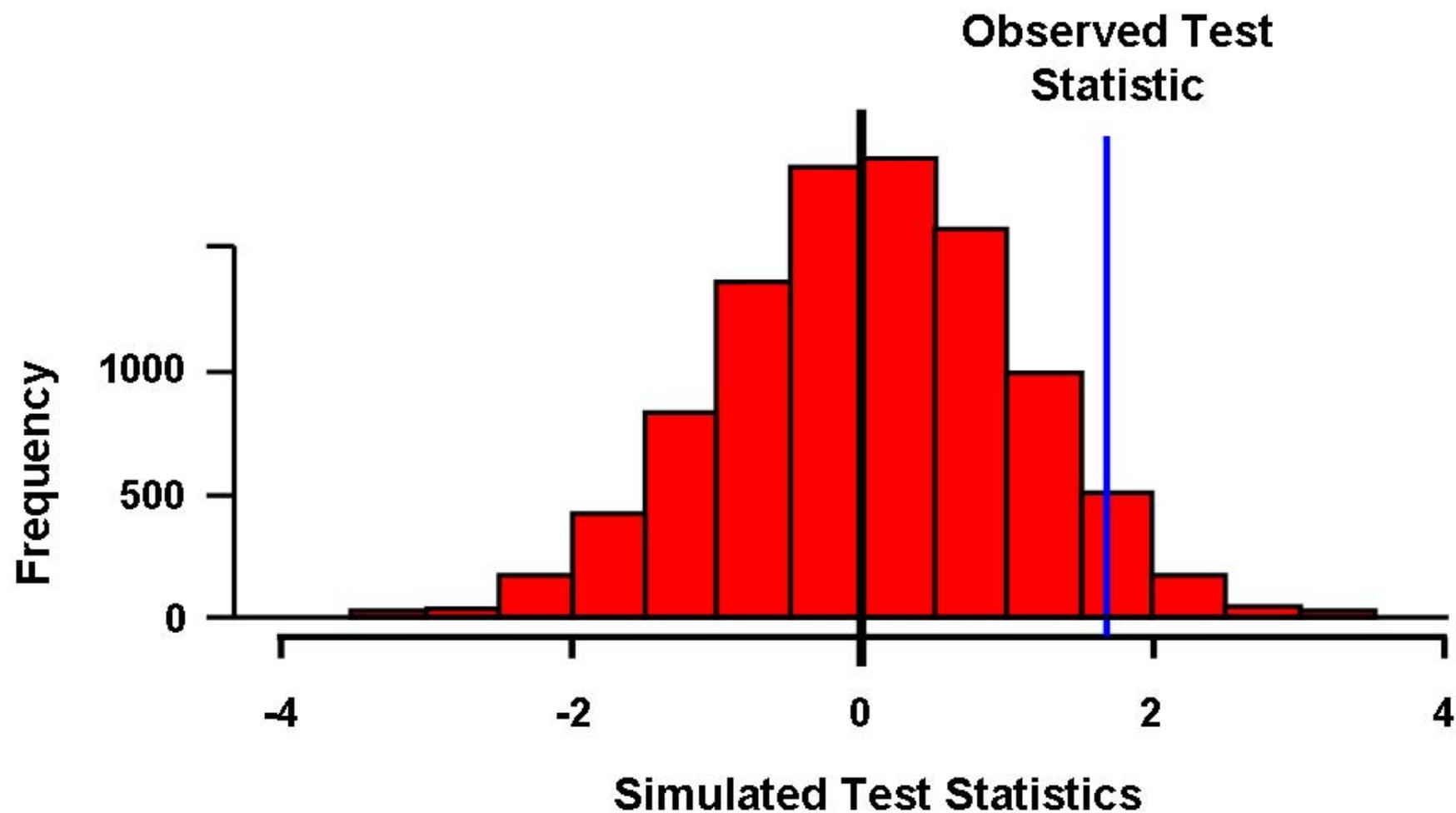
## LOTS Randomization Strategy

- In a multicenter, clinical trial with moderate sample size, a stochastic minimization treatment allocation rule is commonly used to balance treatment groups with respect to prognostic variables (Efron 1971; Pocock & Simon 1975; Wei 1977-78-80-82)
- After the trial is over, the same minimization allocation rule may be used to test for treatment difference (re-randomization test) (Wei et. al 1986-88)

# How to Construct a Re-Randomization Test?

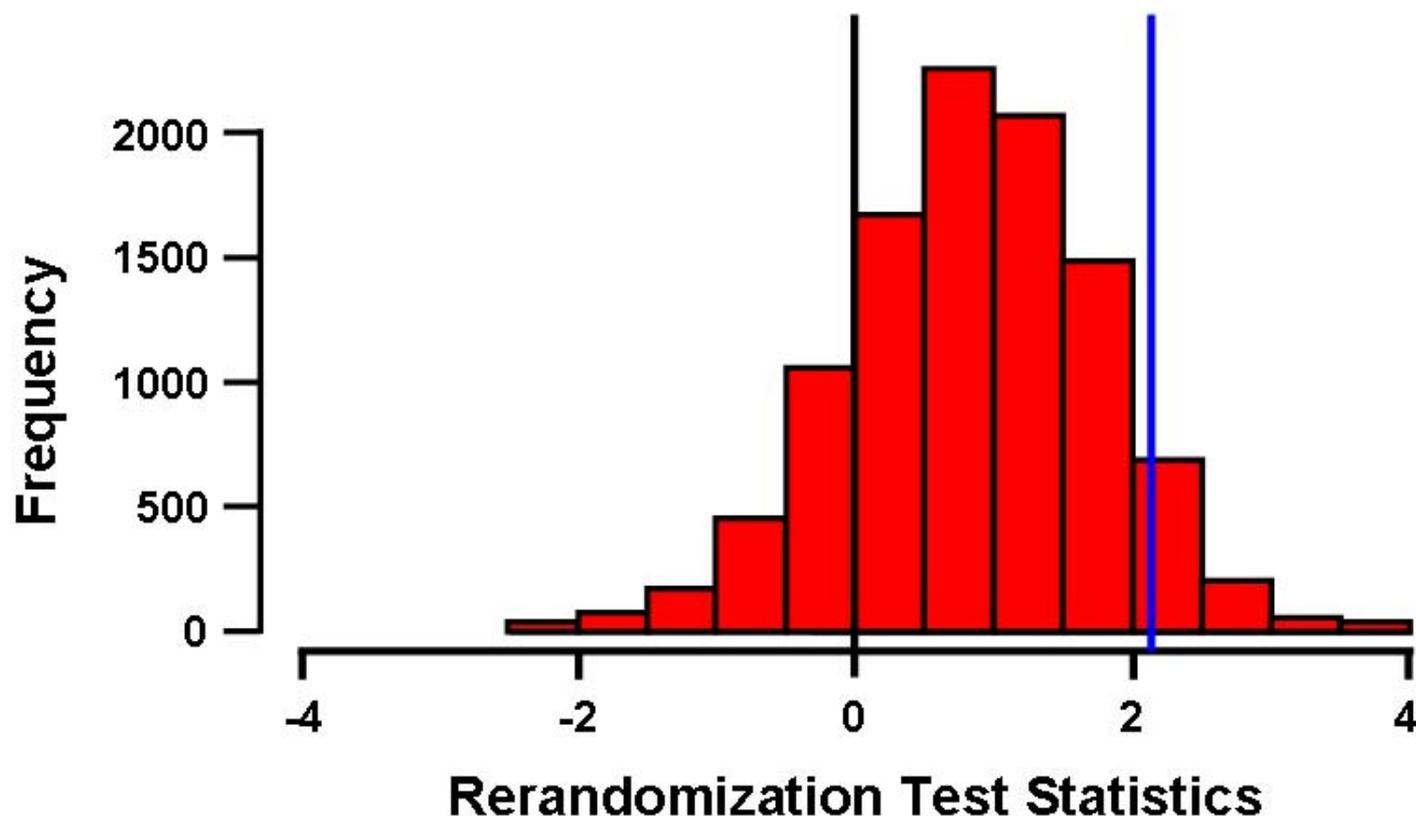
Patient	1	2	3	4	...	
Observed Change in 6MWT	35	20	21	40	...	Test Statistic
Obs. Rx Assignment	m	p	m	m	...	2.15
Rerand 1	M	P	P	M	...	0.63
Rerand 2	M	M	P	P	...	2.4
...						...

# Expected Histogram of Rerandomization Test Statistics



# Problem with Application of Rerandomization Test in Analysis of 6MWT

- Distribution of 6MWT ANCOVA test statistics



# Conclusions

- Rerandomization test may be considered as a sensitivity analysis and not as the primary analysis
- In this trial, p-values obtained from rerandomization test for 6MWT cannot be interpreted

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## Summary

**Alexander Kuta, PhD**

Group Vice President,  
Regulatory Affairs

Genzyme Corporation

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# Full Approval is Warranted

- Late Onset Treatment Study
  - Large study in rare disease population
  - Double-blind placebo controlled trial
  - Met Co-primary endpoints of 6MWT & % predicted FVC
  - Improvement of muscle strength and stabilization of pulmonary function are clinically meaningful in this progressively debilitating disease
- Global clinical experience and outcomes will continue to be collected and analyzed through the Pompe Registry and ongoing post-marketing commitments
- Value and feasibility of an additional clinical study comparing 2000 L to either placebo or 160 L are not clear

# Clinical Indication and Treated Population

- Indication:
  - *alglucosidase alfa* is indicated for long-term use in patients with late onset Pompe disease (GAA deficiency). *alglucosidase alfa* has been shown to improve distance walked and stabilize pulmonary function in patients with late onset Pompe disease
- Addressable Population:
  - 2000L scale: Limited to patients with symptom onset >24 months without hypertrophic cardiomyopathy
- Safeguards for restricted distribution:
  - REMS can effectively manage distribution after approval
  - Has already been achieved for 18 months with 2000L product in MTAP

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# **Endocrinologic and Metabolic Drugs Advisory Committee Meeting**

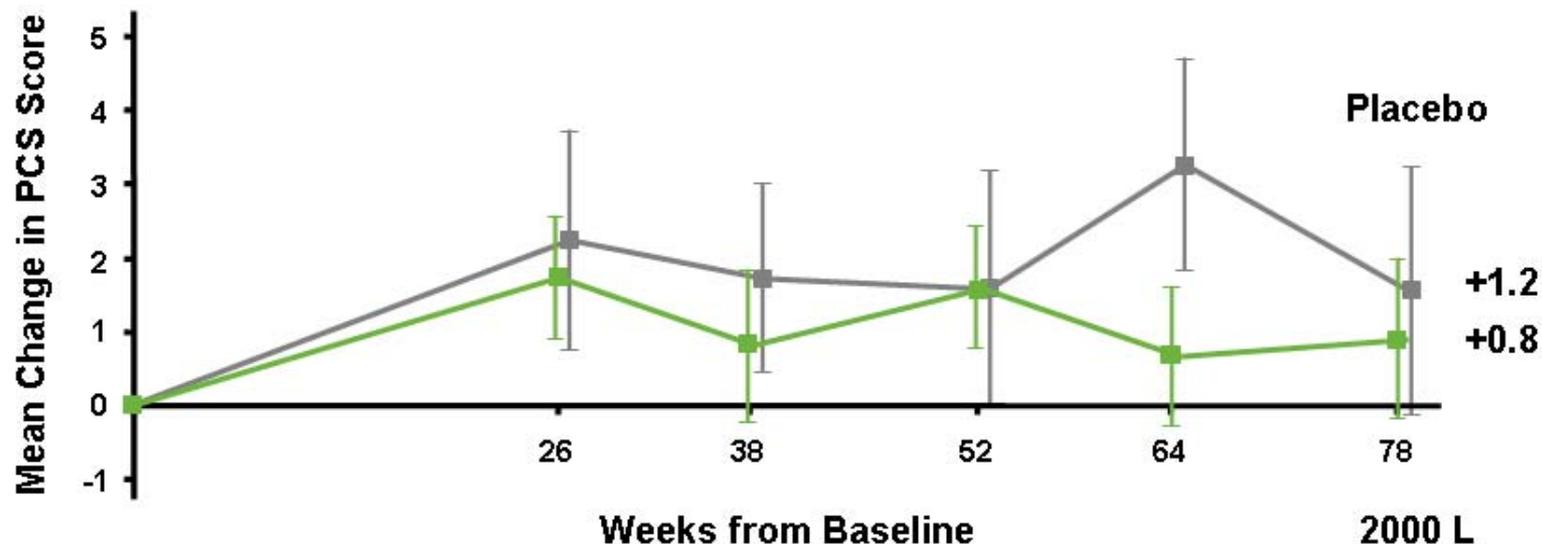
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# No Difference in Physical Health Status Observed Between 2000 L alglucosidase alfa and Placebo



**Baseline mean SF-36 PCS Score**

**2000 L: 34**

**Placebo: 35**

**US General Population Norms Mean=50 SD=10**

**ANCOVA p-value = 0.8333**

# Mini LOTS (AGLU02804): Patient Demographics

		2000 L alglucosidase alfa (n=5)
Gender	Male	3
	Female	2
Ethnicity	Caucasian	100 %
Age at 1st infusion	Range (yrs)	5.9 – 15.2
Age at diagnosis	Range (yrs)	0.8 – 6.5
Time since symptom onset	Range (yrs)	1.1 – 11.6
Exposure	(weeks)	74

# Mini LOTS (AGLU02804): Immunogenicity

Variable	Late onset patients tested N=5
Seroconversion rate	5 (100%)
Median time to seroconversion (range)	12 weeks (8-38 weeks)
Median peak titer (range)	3,200 (800-6,400)
Median last titer (range)	800 (800-6,400)
Inhibitory antibodies	None
IgG titers over time	Titers were generally low throughout the study period for all 5 patients