

Questions #1 & 2

1. Does the Committee believe LOTS has established the effectiveness of the 2000L product?
2. Consider the following decisional options for the 2000L product:
 - A. Not Approved
 - B. Accelerated Approval based on surrogate endpoint of FVC
 - C. Regular Approval

Question #3

3. If Approval is recommended (Accelerated or regular):
 - A. Should the 2000L product's use be restricted to adult-onset patients only?
 - B. If yes, what safeguards for communication and distribution should be implemented?
 - C. Should additional studies be required for efficacy?
 - D. Should additional studies be required for safety?

Alglucosidase Alfa 2000L Advisory Committee Clinical And Statistical Review

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Pompe Disease Background

- Named for JC Pompe, Dutch physician, 1932
- Ultra-rare, Orphan, autosomal recessive glycogen storage disease (GSD II)
- Deficiency of enzyme acid- α glucosidase (GAA)
 - Deficiency results in glycogen accumulation in lysosomes of various body tissues; especially muscle (cardiac and skeletal)

Pompe disease phenotypes

- Infantile-onset
 - Rapidly progressive with death by 18 months of age
 - Cardiac hypertrophy
 - GAA activity 0-1%
- Juvenile onset
 - Onset after 12 months of age
 - Younger age at onset is generally associated with worse prognosis
 - GAA activity 1-10%
- Adult onset
 - Slowly progressive proximal muscle weakness
 - Survival measured in years to decades
 - GAA activity 10-40%

Pompe Disease Treatment

- Supportive Care
 - Palliative care only until 2006
- Alglucosidase alfa
 - 160L and 2000L production scales manufactured by Genzyme
 - 2000L scale approved in > 40 other countries
 - Only 160L scale (Myozyme®) approved in US

Regulatory History of 2000L product

- July, 2005: Genzyme seeks approval of both 160L and 2000L production scales
 - Data from clinical trial in classic infantile-onset patients (n=18)
 - Untreated, age-matched historical control
 - Only 160L product used
- Inclusion criteria
 - Diagnosis of Pompe disease prior to 6 months of age
 - Treatment initiated by 7 months of age
 - Cardiac hypertrophy
 - Not receiving invasive ventilatory support
- Primary efficacy endpoint
 - Ventilator-free survival at 18 months of age
 - 83% ventilator-free survival at 18 months of age

Regulatory History of 2000L product

- Fall, 2005: FDA review uncovers issues
 - 160L and 2000L products not comparable
- December, 2005: Genzyme withdraws 2000L product from BLA application
- April, 2006: 160L product approved in US for treatment of Pompe disease

Approved Indication for 160L product

“MYOZYME (alglucosidase alfa) is indicated for use in patients with Pompe disease (GAA deficiency). MYOZYME has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use of MYOZYME in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy”

Regulatory History of 2000L product

- First quarter, 2007: Genzyme reports 160L drug shortage
 - Genzyme agrees to provide 2000L product on a case-by-case basis to patients >18 years of age through Myozyme Temporary Access Program (MTAP)
 - reserves 160L product for patients < 18 years of age
- October, 2007: Genzyme seeks approval of 2000L product
 - Concerns regarding product differences leading to differences in biologic effect between 160L and 2000L product
 - Review found insufficient clinical data to establish comparability between 160L and 2000L products

Original 2000L Review

- October, 2007 submission: No head-to-head studies available
- Relies on clinical comparison of 160L and 2000L products
 - Four small, prospective studies in which infants treated with 2000L product were reviewed
 - Patients matched to criteria for infants in 160L trial
 - Seven 2000L treatment-naïve patients available for comparison

Efficacy comparison 160L and 2000L

October, 2007 submission

	160 L product (N=18)	2000 L product (N=7)
18 month ventilator free survival	83%	71%
“Median ventilator free survival”	~ 32 months of age	~ 20-25 months of age

- 2000 L product showed a concerning trend for less efficacy
- Clinical efficacy comparability could not be established between the two products
- Patient group analyzed is too small to draw a definitive conclusion

Regulatory History of 2000L product

- April, 2008: FDA requested that Genzyme submit new application
 - with clinical data to support separate licensure of 2000L product as a new drug
- MTAP closes to new patients
 - At least 53 adult-onset Pompe patients around the US cannot obtain access to drug currently

Current 2000L submission

- May, 2008: Genzyme submitted new 2000L product application
 - For the treatment of late-onset Pompe disease
 - Late-onset includes both juvenile-onset and adult-onset disease
- Efficacy and Safety data rely on AGLU02704, Late Onset Treatment Study (LOTS)
 - double-blind, placebo-controlled study in 90 late-onset patients

LOTS Study Design

- Study Design
 - Multicenter, multinational, double-blind, randomized, placebo-controlled study in patients 8-70 years with diagnosis of Pompe disease who have not previously received enzyme replacement therapy
 - Assigned 2:1 to receive 2000L:Placebo by a minimization algorithm
 - Originally planned for treatment period of 52 weeks
 - 2000L, 20mg/kg/dose, every other week, IV vs. Placebo

LOTS Major Study Objectives

- Study Objectives
 - Evaluate effect of 2000L product on functional endurance as measured by six minute walk test (6MWT)
 - Evaluate effect of 2000L product on respiratory muscle weakness as measured by Forced Vital Capacity (FVC) % predicted in upright position
 - Evaluate safety profile of 2000L product

Primary Efficacy Endpoint: 6MWT

- Measurement of functional endurance
 - Normal ranges: 500-580m for healthy adults
 - Up to 700m for healthy adolescents
 - Used as primary efficacy endpoint in other enzyme replacement therapy (ERT) approvals
- Limitations
 - Does not predict time to ventilator or death
 - Results depend on patient effort and motivation

Primary Efficacy Endpoint: FVC

- Measurement of adequacy of respiratory effort
 - Measures volume of air from deepest inspiration to end of exhalation
 - Abnormal value $< 80\%$ of predicted normal value in healthy population
 - Used as a primary efficacy endpoint in other ERT approvals
- Limitations
 - Does not predict time to ventilator or death
 - Results depend on patient effort and motivation

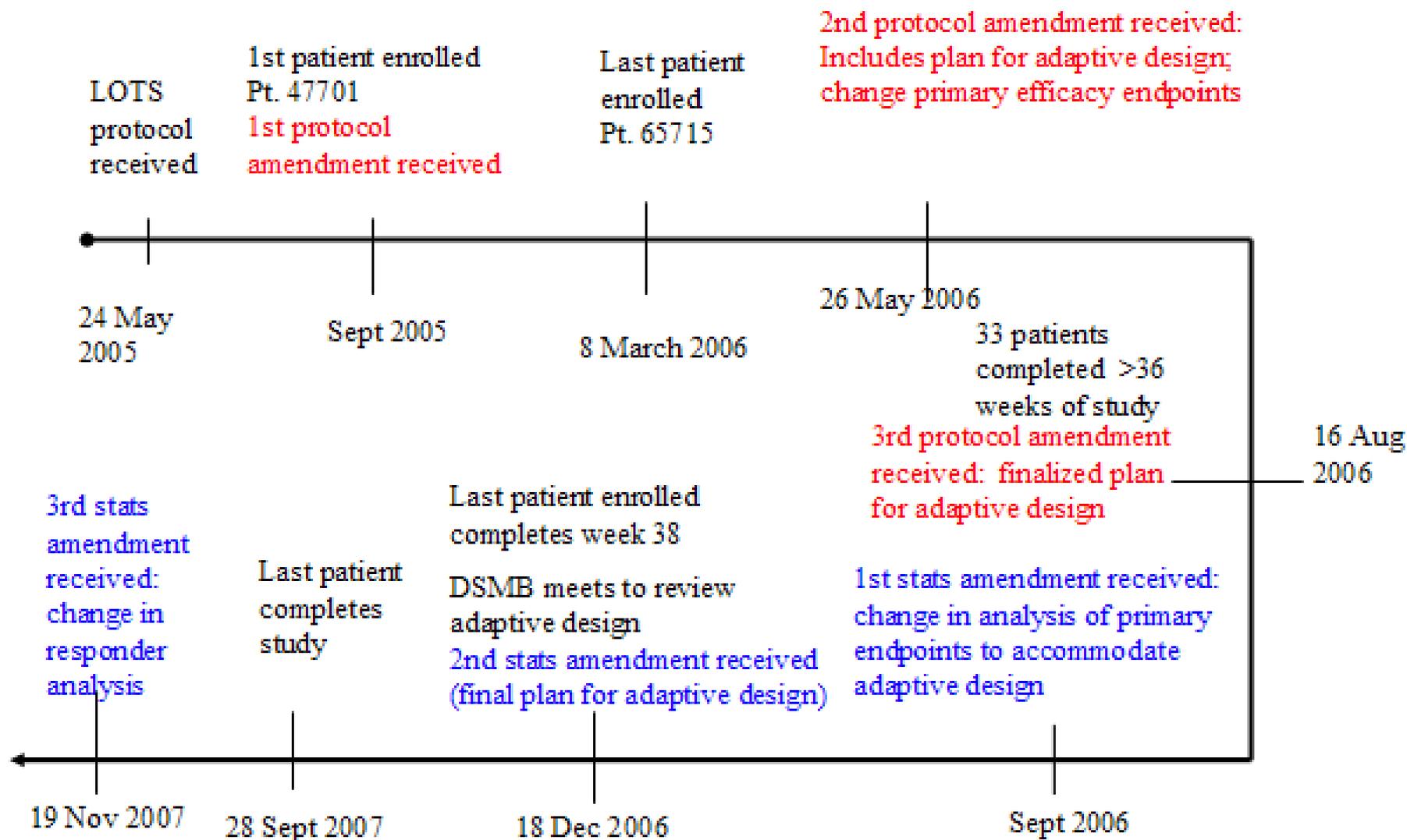
LOTS Patient Population

- Major Inclusion
 - Age \geq 8 years
 - Diagnosis of Pompe disease by GAA activity $<$ 40% in cultured fibroblasts
 - Able to ambulate at least 40m during 6MWT (no maximum distance cutoff)
 - FVC of 30-80% predicted in upright position
 - At least 10% drop in FVC from upright to supine position
- Exclusion criteria
 - No invasive ventilatory support
 - No history of ERT use for GAA in the past
 - No restriction on concomitant medication use

LOTS Original Protocol

- Original Primary Efficacy Endpoints
 - Measurement of meters walked during 6MWT at 52 weeks, adjusted for baseline
 - Measurement of upright FVC (% predicted) at 52 weeks, adjust for baseline
- Numerous secondary, tertiary and exploratory efficacy endpoints
- Original Statistical Analysis
 - Repeated measures analysis of difference in 6MWT at 52 weeks adjusted for baseline differences
 - FVC not to be reviewed if 6MWT was not statistically significant

Time line of protocol and statistical analysis submissions and amendments BLA 125291



In all, 3 protocol amendments and 3 statistical analysis plan amendments ²⁰

Study Design and Statistical Issues

- Changes to study design
- Changes in endpoint
 - Study ongoing
 - After data analyzed
- Changes in statistical methods
 - Study ongoing
 - After data analyzed
- Allocation of subjects – minimization algorithm
- Re-randomization tests

Changed to Adaptive Strategy

- Study was on-going
- Changed from 52-weeks fixed duration
- Rationale
 - Determine optimal duration of study
 - *Comparisons over the entire time-course*
- Necessitated changes to endpoint and analysis

Adaptive Strategy: New Endpoint and Analysis

- Prespecified Endpoint
 - Original: 6MWT at 52 weeks
 - New: Slope (linear rate of change) over entire study
- Prespecified Analysis
 - Original: Repeated measures
 - New: Linear mixed effect model, model-based variance-covariance

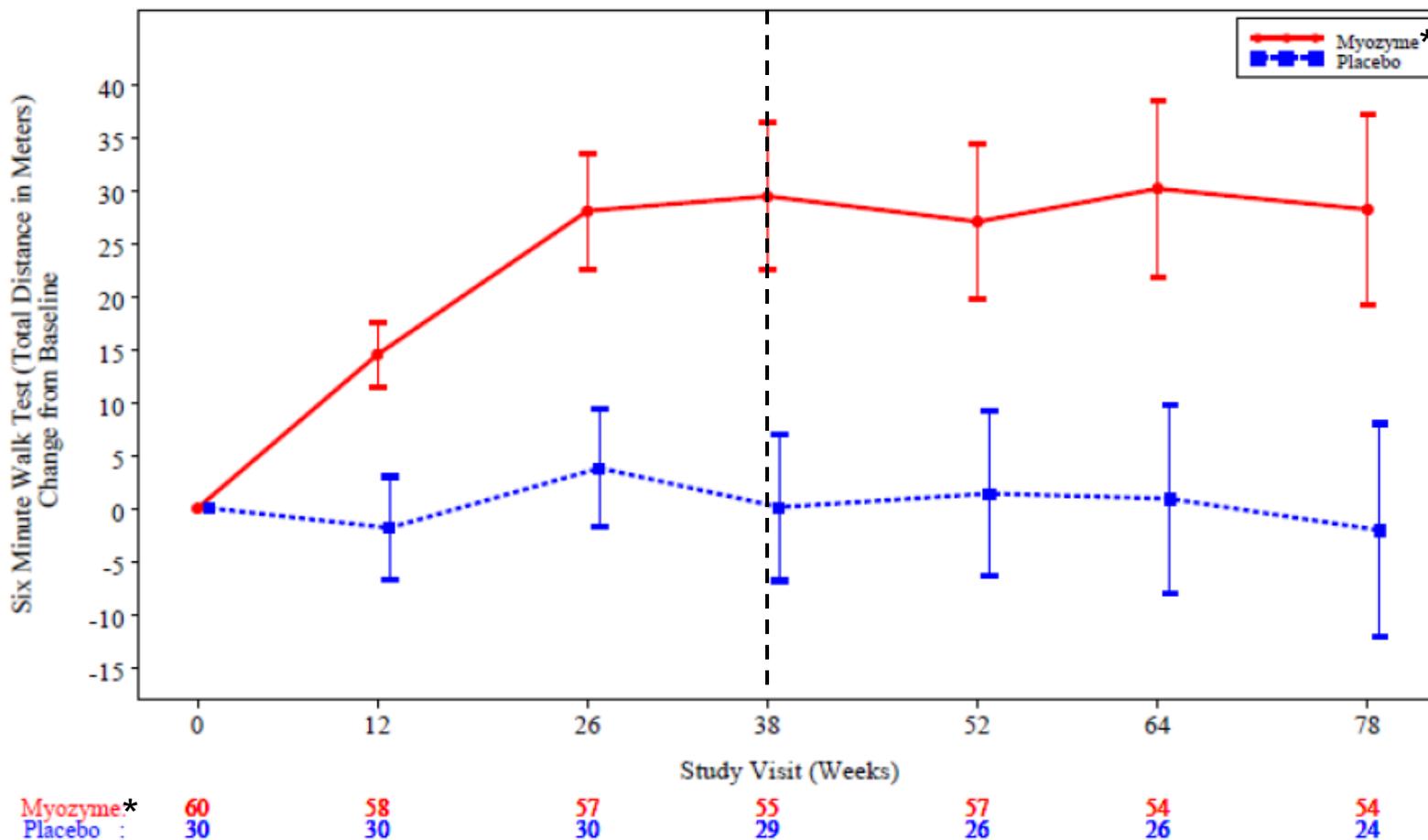
What was the adaptive strategy?

- Approach
 - Compare the rate of change in meters walked relative to meters walked at baseline
 - Use a longitudinal model to assess changes
- Interim analysis
 - After all subjects complete 38 weeks
 - Extend study by 0, 13 or 26 weeks

What was the adaptive strategy?

- Advantages stated by applicant
 - Longitudinal approach uses all data
 - Gain in efficiency
 - Use interim data to determine correct time for stopping trial
- Important to interpretation of study results

Change from Baseline 6MWT 2000L vs. Placebo



*Myozyme = 2000L product

6MWT Efficacy Analysis – Summary Statistics for Distance Walked (meters)

	2000 L N=60	Placebo N=30	Difference
Mean (\pm SD) baseline	332.1 (128)	314.1 (131.4)	
Mean (\pm SD) change from baseline to last observation	26.1 (64)	-4.9 (45)	31
Median change from baseline to last observation	16	-7.5	23

6MWT Efficacy Analysis- Prespecified Primary Analysis

2000 L N=60	Placebo N=30	Diff	P-value	
			Applicant	Re-randomization
<i>Prespecified – LME, model-based variance, in meters/month</i>				
1.2	-0.06	1.3	0.09	n/a
<i>Modified analysis, after analyzing unblinded data – LME, robust variance, in meters/month</i>				
1.2	-0.06	1.3	0.05	0.15

6MWT Efficacy Analysis- Supportive Analysis - ANCOVA

2000 L N=60	Placebo N=30	Diff	P-value	
			Applicant	Re-randomization
<i>Mean (\pm SE) change from baseline to last observation in distance walked</i>				
25.1 (8)	-3.0 (11)	28.1 (13)	0.04	0.06

adjusted for baseline 6MWT stratification, baseline FVC stratification, their interaction and baseline 6MWT

Notes:

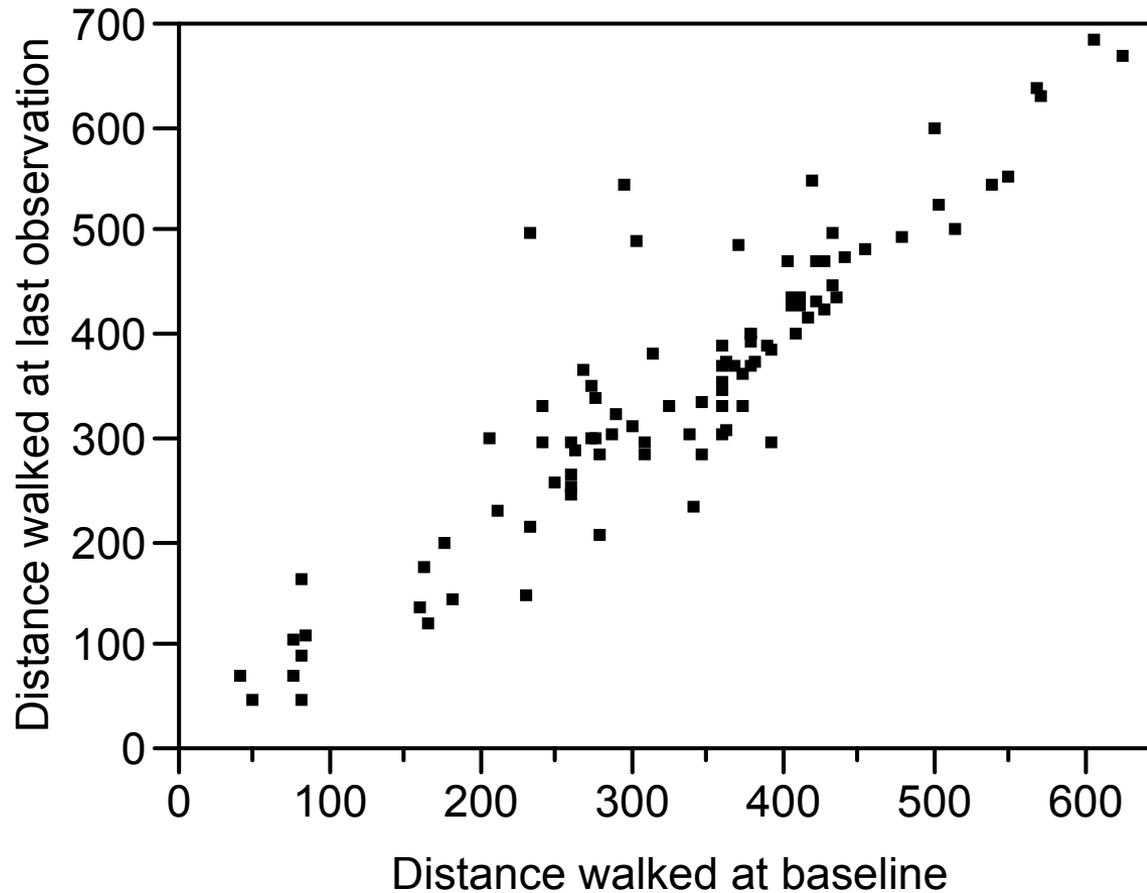
- **Not used in adaptive strategy**
- **Not consistent with rationale for using slopes (pre-specified primary endpoint) and LME (pre-specified analysis)**

ANCOVA – Supportive Analysis

- PROS
 - Fewer assumptions than LME
 - Addresses clinical question of interest
 - Ignores data between baseline and last observation
- CONS
 - Not the basis for adaptive strategy
 - Contradicts applicant's rationale for using LME and slopes
 - Missing data issues: Last observation carried forward (LOCF)

Stratification: Variables correlated to outcome

Example: 6MWT



Stratification

Two schools of thought

1. Stratified Randomization

- Assign at random within strata
- Each subject has same chance of receiving 2000L – 2/3, regardless of previous treatment assignments
- Site, baseline 6MWT, baseline FVC (% predicted)
- Classical analyses: t-tests, F-tests, chi-square tests, etc.

Stratification

Two schools of thought

2. Minimization algorithm – used for LOTS

- Goal: maintain 2:1 balance of 2000L to Placebo
- Subject's chance of 2000L depends on imbalance in covariates
- Probabilities of assignment to 2000L: 1.0, 0.9, 0.5, 0.1, 0.0
- Complicates analysis – not all assignments are equally likely

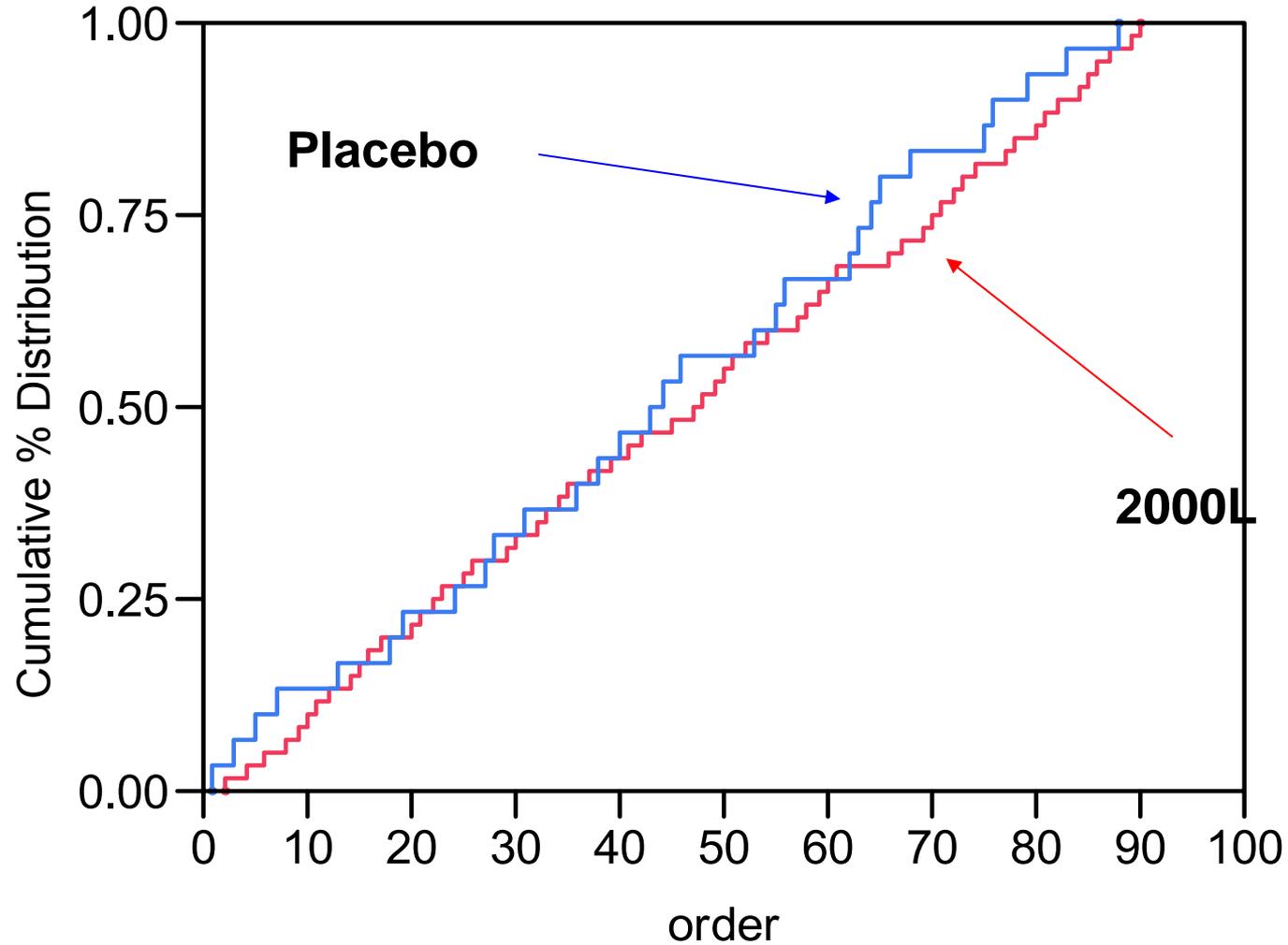
Re-randomization tests

- Idea: Recreate experiment (clinical trial)
- Re-randomize subjects with same constraints, including order of study entry
- Re-randomize 10,000 times
- Example: Fisher's exact test
- Simple when using complete randomization
- More complex when probability of assignment changes
- Computer power now available

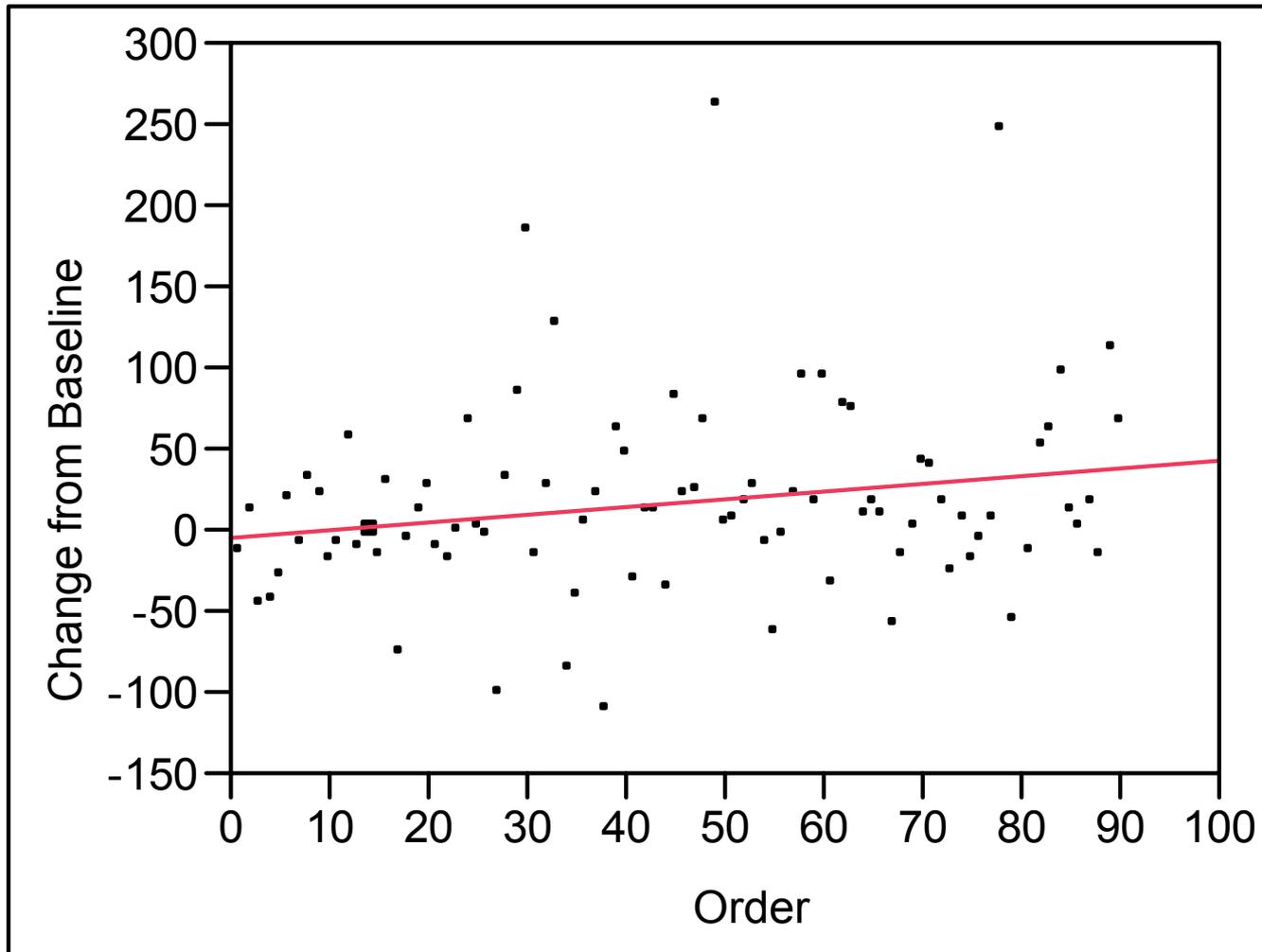
FDA Analysis: Re-randomization

- Accounts for patient arrival
- Accounts of changing probabilities of assignment
- Why do methods give different results?
 - Allocation procedure started with first patient
 - Alternative: assign initial patients without constraints
 - Order of arrival matters – can't ignore

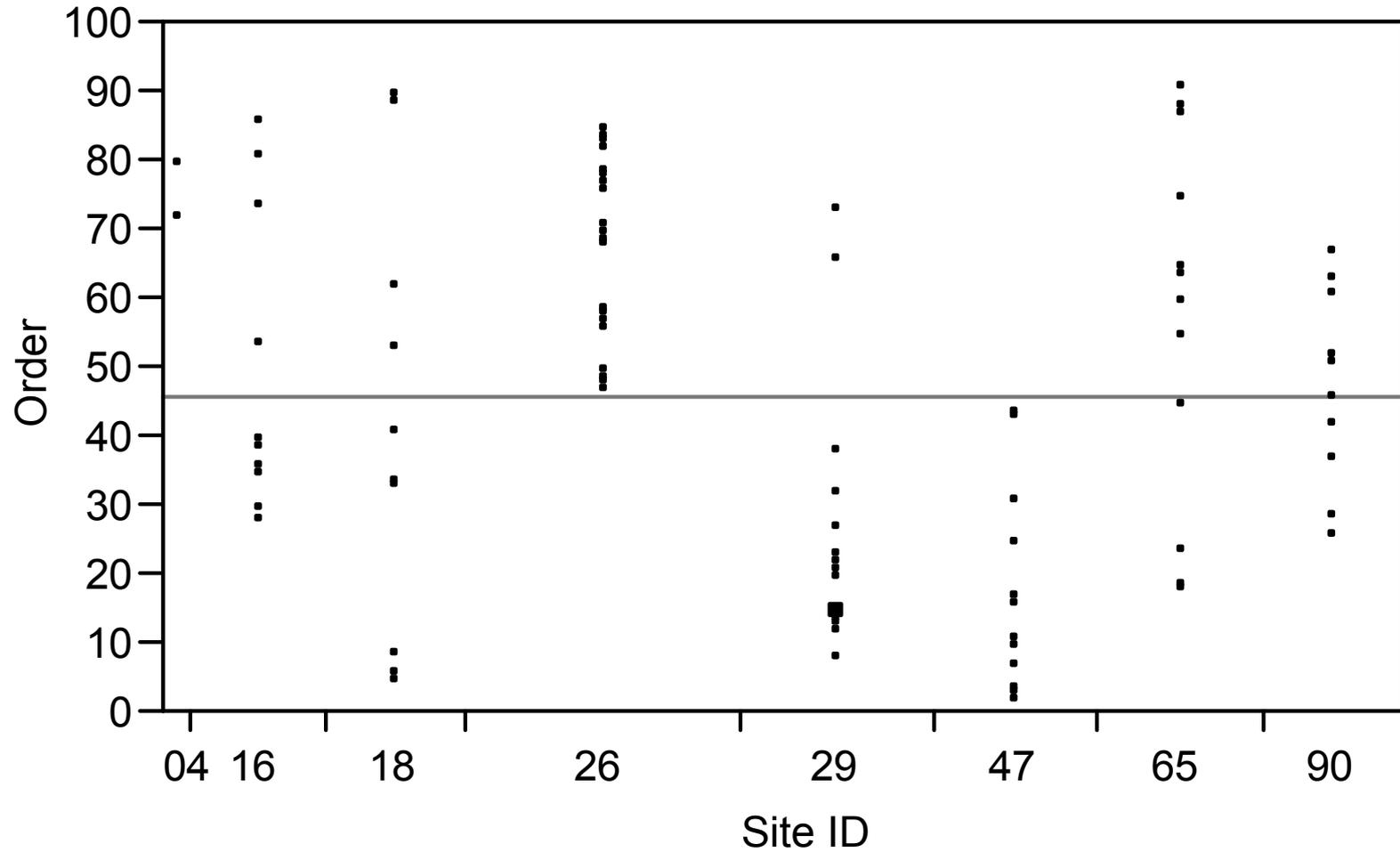
Assignment to Treatment vs Order of Entry



6MWT – change from baseline vs Order of entry



Order of Entry, by Study Site



FVC upright (% predicted) Efficacy Analysis

	2000 L N=60	Placebo N=30	Difference
<i>Summary statistics:</i>			
Mean (\pm SD) FVC at baseline	55.6 (14)	53.4 (15)	
Mean (\pm SD) change from baseline to last observation in FVC	1.4 (5)	-2.3 (4)	3.6
<i>Results of ANCOVA*:</i>			
Mean (\pm SE) change from baseline to last observation in FVC, adjusted for baseline 6MWT stratification, FVC stratification, their interaction and baseline FVC	1.2 (0.7)	-2.2 (1)	3.4 (1) p=0.004

Summary

1. Numerous Changes

- Study design – adaptive strategy
- Analyses
 - Study ongoing: From repeated measures to linear mixed effects
 - After unblinding and initial analysis:
 - Robust variance estimator
 - Emphasis on ANCOVA

Summary

1. Numerous Changes (continued)

- Endpoints
 - Study ongoing: From 52-weeks to slope
 - After unblinding and initial analysis: From slope to change from baseline to last observation

Summary

- Re-randomization tests
 - Are always correct
 - Recreate clinical trial, including patient order
- Prespecified analysis is non-significant
 - Model assumptions violated
 - Still measures the average rate of change
- Changed prespecified analysis after initial analysis of unblinded data

Summary

2. ANCOVA

- May be more appropriate given issues with LME model assumptions
 - Addresses clinical question of interest
 - Fewer assumptions
- However
 - Not the endpoint used in adaptive strategy
 - Contradicts applicant's rationale for using linear models and for using slope
 - Missing data issues – Last Observation Carried Forward

Subgroup Analyses

- Effect of Age and baseline GAA activity
- Effect of Immunogenicity
- Exploratory and Responder Analysis

Age Group Comparisons

Age at First Infusion	Number in 2000 L treatment group (% of total)	Number in Placebo group (%)
< 18 years	2 (3.3)	2 (6.6)
18-30 years	3 (5)	1 (3.3)
30-40 years	12 (20)	7 (23.3)
40-50 years	20 (33.3)	12 (40)
50-60 years	17 (28.3)	7 (23.3)
60-70 years	6 (10)	1 (3.3)
Total	60 (100)	30 (100)

- Only 4 patients enrolled in the study < 18 years of age
- 5/60 (8%) of patients in 2000L group < 30 years of age
- 3/30 (10%) of patients in placebo group < 30 years of age
- Patients over age 30 generally have more attenuated disease

Juvenile-onset patients

- Juvenile-onset population is of interest
- Definition of juvenile-onset population
 - Age at diagnosis
 - Age at first symptoms
- Diagnosis under age 18 years
 - 11 patients total
 - 2 patients were excluded from this group
 - 9 total patients diagnosed under age 18 years

Age at first symptoms

- 14 patients reported symptoms before the age of 18 but were not diagnosed until after age 18
 - 8 were over age 40 at time of enrollment and 3 were over age 50
 - 9 were over age 25 at the time of diagnosis
 - This group does not appear to represent the juvenile-onset population
- Practical definition of juvenile-onset disease
 - Patients who developed symptoms AND were diagnosed with Pompe disease < 18 years of age.
 - 9 patients studied in LOTS with this definition

Efficacy of 2000L in Juvenile-onset patients

Visit	6MWT (M)		% predicted FVC	
	2000 L (n=6)	Placebo (n=3)	2000 L (n=6)	Placebo (n=3)
Screening/Baseline				
Week 12	1.4	-18.0	0	0
Week 26	15.0	7.0	1.8	-0.5
Week 38	-2.3	19.0	2.3	-3.0
Week 52	-3.2	18.0	0.2	-4.0
Week 64	15.6	26.0	-4.6	-3.0
Week 78/Early Termination	-0.8	-20.3	-1.5	-1.0

- Juvenile-onset patients in both treatment groups worsened
- Treatment effect of 19 meters
- Younger patients appear to have more rapid progression of disease

GAA activity

- GAA activity roughly correlates with age of onset
 - Younger patients have lower GAA activity
- 10 patients in LOTS with GAA activity $<1\%$
 - 6/10 randomized to 2000L treatment group
 - 4/10 randomized to placebo treatment group
- These patients tend to be younger
 - 5/10 under age 18 at time of diagnosis

Efficacy of 2000L/GAA activity < 1%

	2000 L (n=6)	Placebo (n=4)
Mean Change 6MWT	-1.0	-13.1
Mean Change % predicted FVC	-1.4	-2.1

- Patients with GAA activity <1% in both treatment groups worsened
- Treatment effect of 12 meters
- Supports earlier finding that younger patients appear to have more rapid progression of disease

Summary of Juvenile-onset Patients

- Generally have worse prognosis
- GAA activity generally lower
- Insufficient efficacy data from LOTS for juvenile-onset patients
- Efficacy data available suggest trend toward decrease effectiveness of 2000L treatment in younger patients and patients with low GAA activity

Immunogenicity of 2000L Product

- Anti-rhGAA IgG antibody
 - May lead to decreases in efficacy and increases in safety concerns
 - Infantile-onset patients may be more likely to develop immune responses than adult-onset
- Inhibitory antibody
 - Inhibitory antibody formation should lead to decrease in efficacy

Immunogenicity

- 160L product clinical trials
 - 89% developed anti-rhGAA IgG antibody formation
 - 10% of patients developed inhibitory antibody
- LOTS
 - All late-onset patients treated with 2000L product developed anti-rhGAA antibodies (100%)
 - 30% (18/60) patients developed inhibitory antibody
- 2000L product may be more immunogenic than 160L

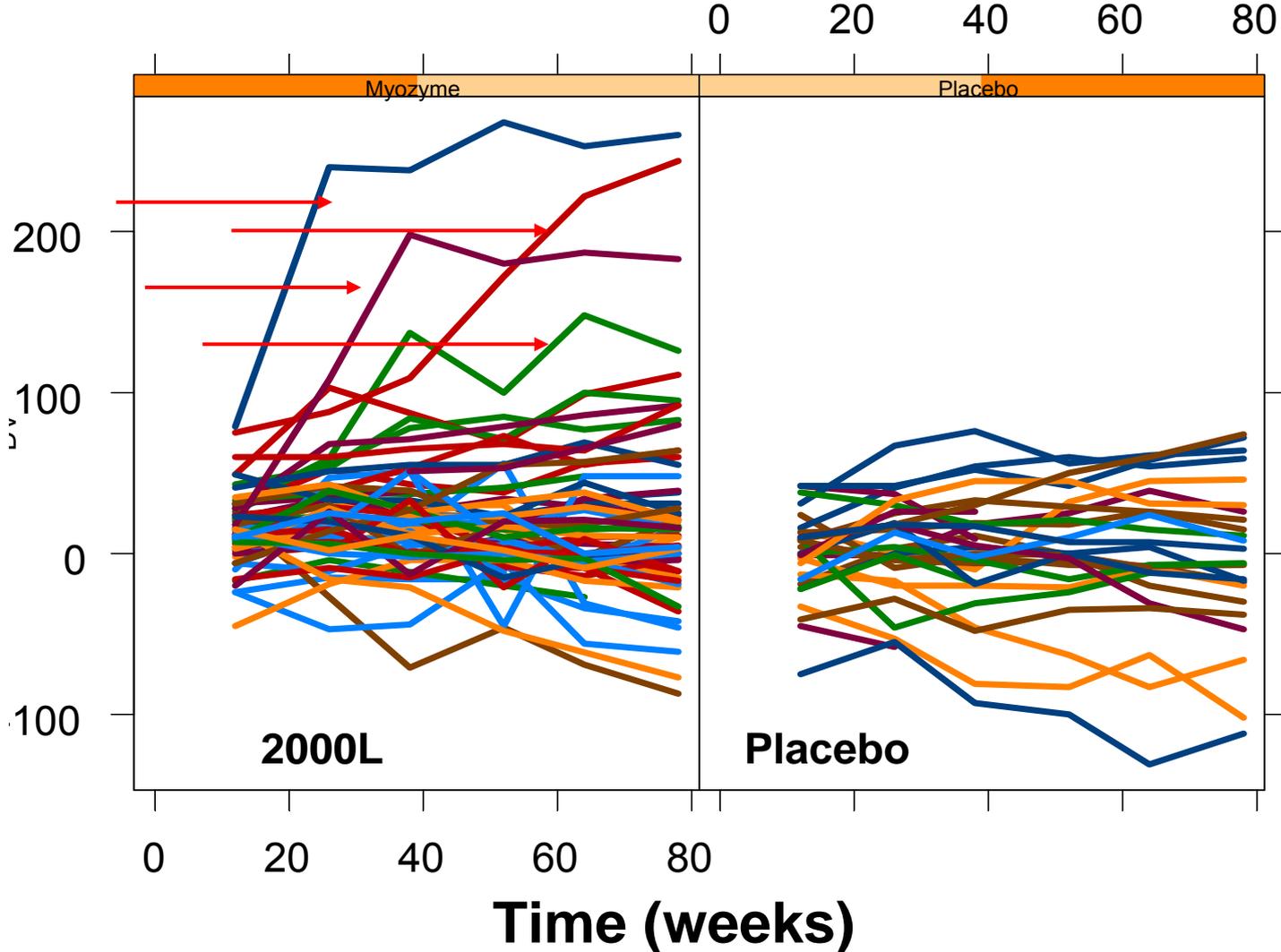
Effect of Inhibitory Antibody on Efficacy

- Subgroup of patients (n=4)
 - All had persistently rising rh-GAA IgG titer and presence of inhibitory antibody at 78 weeks
 - Overall change from baseline 6MWT worse than placebo

Change in 6MWT (M)	Mean
Screening/Baseline	
Week 12	6.0
Week 26	16.3
Week 38	11.8
Week 52	23.3
Week 64	-7.0
Week 78/Early Termination	-8.8

6-Minute Walk Test

Change in Distance Walked
During 6-Minute Walk Test (m)



High Performers and Inhibitory Antibody

- “High performers”
 - Subgroup of patients (n=4)
- 3 out of 4 of these patients developed inhibitory antibodies to rh-GAA
 - Average improvement in 6MWT of 194 meters
 - All had decreasing anti-rhGAA IgG titers
 - Inhibitory antibody may act as “carrier protein” leading to less mistargeting of the enzyme

Responder analysis

- Practical definition of responder
 - Stabilization of disease
 - Prevention of decline in a progressive disorder
- Clinically meaningful as defined by Applicant
 - Originally defined responder as a patient with improvement of at least 54m in 6MWT and 15% FVC upright % predicted over baseline
 - Response thresholds lowered in 3rd statistical amendment
 - These definitions derived from non-Pompe disease populations and may not be applicable

Responder Analysis

- Responders based on Original criteria
 - 2 patients in 2000L group
 - 0 patients in placebo group
- Clinical conclusions difficult to make based on lack of information about the endpoint thresholds in Pompe disease

Background of Safety Analysis

- Major safety issues for ERTS relate to immunogenicity of the product
 - Anaphylaxis
 - Infusion Reactions
 - Chronic Immune Reactions
- Overall safety of 2000L product
 - Comparable to 160L product
 - Differences will be presented

Safety Analysis

- 27 Serious adverse events (SAEs)
 - 1 patient death (2000L treatment group)
 - 2000L group: 19 events in 12 patients
 - Placebo group: 7 events in 5 patients
 - Most SAEs were not related to treatment with 2000L product
- Anaphylaxis occurred in 2000L group, but not in placebo group

Anaphylaxis

- 4/60 = 6.7% Anaphylaxis
 - 2 of these patients withdrew from the study due to this complication
- Incidence is compared with
 - None in placebo group
 - 160L product clinical trials 2/39 (5%)
- The Applicant does not agree with the reviewers classification of patients who developed anaphylaxis
- Definition based on consensus conference convened by NIAID*

* Sampson, H.A., et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium J Allergy Clin Immunol Feb 2006 p391-397

Infusion Reactions (IRs)

	2000L (% of total)	Placebo (% of total)	Total
AEs occurring during or within 2 hours of completion of infusion	232 (78.1)	65 (21.9)	297
Number of patients experiencing	29	15	44

- Defined as a reaction likely related to the medication that occurs during or within 2 hours of completion after completion of infusion or by discretion of the investigator
- Infusion reactions in each group were different
 - 2000L group: IRs included dyspnea, chest pain, urticaria, rash, headache, fever, oral pruritis, lip swelling, and throat tightness
 - Placebo group: Most common IRs included headache, and nausea; no hypersensitivity reactions

Delayed-Onset Infusion Reactions

- AEs that occurred from 2 to 48 hours after completion of infusion that may be related to study drug
- Placebo group had more late infusion reactions
- Types of delayed-onset infusion reactions differed by treatment group

	2000L (N)	Placebo (N)
Total	66	86
 Anaphylaxis	1	0
 Urticaria	2*	0
Headache	19	40
Dysgeusia	0	11

Chronic Immunogenicity Concerns

- Skin
 - 88 episodes occurred in 2000L treatment group compared with 10 episodes in placebo group
 - Angioneurotic edema and urticaria reported in 2000L treatment group only
 - Immune complex mediated skin reactions uncovered in postmarketing surveillance of 160L product
- Urinary Abnormalities
 - Hematuria and/or proteinuria reported in 7 patients treated with 2000L product and 2 placebo treated patients
 - Immune complex mediated glomerulonephritis reported with an earlier form of rh-GAA
 - Longer term follow-up needed to identify potential AEs associated with chronic treatment

Study Design and Statistical Issues

- Changes to study design and statistical analysis made
 - Study ongoing
 - After data analyzed
- Allocation of subjects – minimization algorithm
- Re-randomization tests
- Concern regarding robustness of study conclusions that can be made

Summary

- 28.1m (p=0.06, ANCOVA) difference in 6MWT between 2000L group and placebo group at 78 weeks
 - p-value of 0.06 is based on re-randomization inference
- Pre-specified analysis: 1.2 m/month (p=0.09, LME with model based variance)
 - No re-randomization inference performed for this analysis

Summary FVC findings

- 3.4% ($p=0.004$) difference in upright FVC between 2000L group and placebo group at 78 weeks
 - All analyses of FVC were statistically significant
- FVC may be considered a surrogate endpoint but must be verified with further clinical study

Summary

- Insufficient number of juvenile-onset patients enrolled in LOTS to evaluate efficacy of 2000L product in this group
- Low GAA activity (<1%) appears to be associated with younger patients, and possible attenuated response to 2000L product
- No controlled clinical trials to date evaluating 160L or 2000L product in juvenile-onset Pompe disease patients

Summary

- Immunogenicity of 2000L product appears to be greater than 160L product
- Increased immunogenicity may lead to increases in anaphylaxis and infusion reactions in 2000L product compared with 160L

Summary

- Delayed-onset anaphylaxis, which has not been described previously with 160L product appears to be present with 2000L product
- Chronic exposure to 2000L product has not been adequately studied and patients may be at increased risk for development of immune-mediated skin and kidney reactions with chronic exposure

What is a REMS?

- A Risk Evaluation and Mitigation Strategy
 - A risk management plan that utilizes tools beyond routine labeling to ensure that the benefits of a drug outweigh its risks.
 - Designed to meet specific goals in minimizing product risks
 - Essentially the same as a RiskMAP except that REMS are required and enforceable
 - FDA may determine a REMS is needed at the time of approval to ensure that the benefits of the drug outweigh the risks

REMS Elements

- A REMS can include
 - Medication Guides and/or PPI for patients
 - Communication plan for healthcare professionals
 - Elements to assure safe use
 - Required training or certification of prescribers
 - Certified dispensers
 - Administration of the drug in certain health care settings
 - Documentation of safe use prior to dispensing
 - Each patient using the drug is subject to certain monitoring
 - Each patient using the drug is enrolled in a registry

When Should a REMS be Considered?

- Products with important benefits should be considered for a REMS in one or more of the following situations:
 - Risks are serious and preventable
 - Safe and effective use may call for specialized healthcare skills or settings
 - When benefits justify the risks in only a limited patient population
 - Product is in a class of products with similar risks that require a REMS

Why a REMS is needed for alglucosidase alfa 2000L

- Prevent medication errors - high risk of medication errors with availability of 2000L product*
 - Established name (alglucosidase alfa) of 160L and 2000L products is the same
 - Dose is the same for both products
- Prevent use in high-risk patients - target use of 2000L to intended population
 - 2000L product is potentially more immunogenic than 160L product
 - Patients with infantile and juvenile-onset Pompe Disease have increased risk for immune-mediated adverse events

* FDA does not consider the 2000L and 160L products to be comparable

Sponsor's Proposed Distribution Plan for 160L Product

- Training and Communication
 - In-service and training to staff who treat infantile-onset patients
 - Training of preferred distributors
 - Notify parents of infantile-onset patients
- Annual recertification of infantile-onset staff
- Disclosure statement from sites administering to both populations
- 160L product packaged with intended patients name on package
- Clear labeling

Potential Issues with Sponsor's Proposal

- Proposal focuses on distribution of 160L to only infantile-onset patients
- Proposal does not focus on preventing 2000L product from being used in infantile or juvenile-onset patients

Additional Possible REMS Considerations

- Communication to all healthcare professionals that treat all forms of Pompe Disease
- Enrollment, training, and certification of all prescribers and facilities that administer 2000L product
 - Distribution of 2000L product to only certified facilities
- Enrollment of all patients being treated with 2000L product

Additional Possible REMS Considerations

- Both 2000L and 160L product packaged specifically for the intended patient
- Verification by the certified site that the patient is enrolled in the REMS program
- Verification by the certified site that either product is administered to the intended patient

REMS proposal relies on fail-safe system at point of manufacturing and packaging by company

Remaining Issue

- The intended population requires clear criteria.
 - A definition of patients that are eligible and ***not*** eligible for alglucosidase alfa 2000L is needed

Questions for the Advisory Committee

- Do you believe LOTS has established the effectiveness of the 2000L product? (Vote: Yes or No)
 - If not, should an additional study be conducted to determine whether the 2000L product is effective in treating late-onset Pompe Disease? (Discuss)
 - If additional study is recommended, should a head-to-head study vs. the 160L product be conducted, or an alternate study design? (Discuss)

- Please consider the following decisional options for the 2000L product and state which option, based on the evidence presented, is most appropriate: (Choose a, b, or c)
 - Not approved. If no approval is recommended, then the 2000L product can be made available to adult-onset patients under a treatment IND, whereby the Applicant may charge for product as part of the conduct of an additional study or studies. These studies would be conducted to further evaluate the 2000L product. (Discuss)
 - Approval under Accelerated Approval (Subpart E), whereby the 2000L product can be approved using the FVC as a surrogate endpoint reasonably likely to predict clinical benefit, and a verification study to demonstrate clinical benefit of the 2000L product would be required of the Applicant during the post-marketing period. If you believe this is the most appropriate decision, please recommend a study design for the verification study, such as a head-to-head comparison vs. the 160L product. (Discuss)
 - Regular Approval based on the 6MWT findings in LOTS. (Discuss)

- If an Accelerated Approval or a regular Approval (2.b. or 2.c.) is recommended, please consider the following:
 - The LOTS trial enrolled an inadequate number of patients with juvenile-onset Pompe disease. Only four patients were under 18 years of age at the time of enrollment in the study, one of whom was exposed to 2000L product (one patient aged 16 years). Only nine patients in LOTS developed symptoms and were diagnosed with Pompe disease under the age of 18, six of whom were exposed to 2000L product. Should the indication for the 2000L product be restricted to the adult-onset population only (i.e., patients who were diagnosed and had symptom onset over 18 years of age)? (Vote: Yes or No)
 - If you recommend approval for a restricted age group (e.g., adults only), what safeguards should be implemented to avoid use of the 2000L product in patients less than 18 years of age, such as communication plans or restricted distribution? See attached REMS template. (Discuss)
 - Should additional studies be required as post-marketing commitments to assess efficacy? (Vote: Yes or No)
 - If yes, please describe the design of the study(ies). (Discuss)
 - Should additional studies be required as post-marketing requirements to assess safety? (Vote: Yes or No)
 - If yes, please describe the design of the study(ies). (Discuss)