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RARE DISEASE WORKSHOP SERIES

Improving the Clinical Development Process

Section 2: Multivariate or Multiple Domain Methods

Aldurazyme Responder Index

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Key Problem: Clinical Variability

- **MPS I**

- Rare, slowly progressive, multisystem disorder
- Reversible and irreversible components
- Patient-to-patient heterogeneity
- Limited natural history data

- **Endpoint**

- Challenge to demonstrate a clinically and statistically significant change in a single endpoint across patients in a small, short study



Heterogeneity in Hurler-Scheie

Severe joint disease
Tracheostomy for airway dx
Modest liver enlargement



Severe joint disease
No sleep apnea
Moderate liver enlargement



Milder joint disease
Severe sleep apnea, on CPAP
Massive liver enlargement





Aldurazyme for MPS I

- **MPS I** - lysosomal storage disorder caused by a deficiency of α -L-iduronidase, leading to GAG accumulation, secondary changes, and multisystem disease
 - Severe (Hurler) and attenuated (Hurler-Scheie, Scheie)
 - Corneal clouding, coarse facies, cardiac disease, respiratory insufficiency, hepatomegaly, carpal tunnel, joint contractures, short stature, neurodegeneration
- **Laronidase** - recombinant human α -L-iduronidase made in CHO cells (enzyme replacement therapy)
 - Dosed 0.5 mg/kg IV weekly over 3-4 hrs



Aldurazyme for MPS I

- **Phase 3 Study Design**

- 45 patients, multi-center, multi-national, randomized, double-blind, placebo-controlled, 26-week study followed by 3.5 year extension
- **Co-Primary Endpoints:** Changes in Percent Predicted FVC (Absolute), 6-Minute Walk Test (meters)
- **Secondary Endpoints:** Changes in Liver Volume (%), AHI (Events/Hr), Shoulder Flexion (Degrees), uGAG (%)
- **Tertiary Endpoints:** Changes in Percent Predicted FEV₁, TLC, Shoulder Extension, Knee Flexion and Extension, Growth, Acuity, ADL, QoL



Caveats, Challenges, Issues with Study

- **Patient Population**

- Small study (N=45)
- Mostly Hurler-Scheie (intermediate) with long-standing disease
- Broad age range (6-43 yr), but none < 5 yr
- Perform functional endpoints (FVC, 6-MWT)

- **Study Logistics**

- Multiple countries, languages, and regulations
- Complex, expensive, weekly travel
- Placebo arm – study duration, ethics, and PK

- **Analysis**

- Two co-primary endpoints (FVC, 6-MWT)
- Practical to enroll patients only with abnormal FVC, but not 6-MWT
- Percent predicted FVC affected by release of joint contractures
- Conservative primary analysis (Wilcoxon rank sum test)



Phase 3 Study Endpoints

- **Percent Predicted FVC**

- Patient's FVC / Predicted FVC x 100
- Spirometry per American Thoracic Society guidelines
- Predicted FVC calculated using Polgar (5-7 yr) or Hankinson (>7 yr) formula with current height (to account for growth) or baseline height only (to account for postural changes)
- Baseline value was the last of 3 assessments during screening
- Performed at Wks 0, 4, 8, 12, 16, 20, 26; then q 3 mo

- **6-MWT**

- Patient walks back and forth along the same 15-meter path for 6 min and the distance walked is recorded in meters
- Timed using same calibrated stopwatch
- Standardized instructions, no assistance, rest at any time
- Baseline value was the last of 3 assessments during screening
- Performed at Wks 0, 4, 8, 12, 16, 20, 26; then q 3 mo



Phase 3 Study Analysis

- **Primary Analysis Method**

- Between-group differences for percent predicted FVC and 6-MWT were assessed in the ITT population from Baseline to Week 26 using the Wilcoxon rank sum test
- $P \leq 0.05$ considered statistically significant

- **Secondary Analysis Method**

- Pre-specified ANCOVA to adjust for disease heterogeneity and baseline differences
 - FVC – study center, baseline FVC, AHI, TLC, liver volume, uGAG
 - 6-MWT – study center, baseline 6-MWT, sex, standing height, liver volume



Aldurazyme Label

Table 1: Primary Efficacy Outcomes

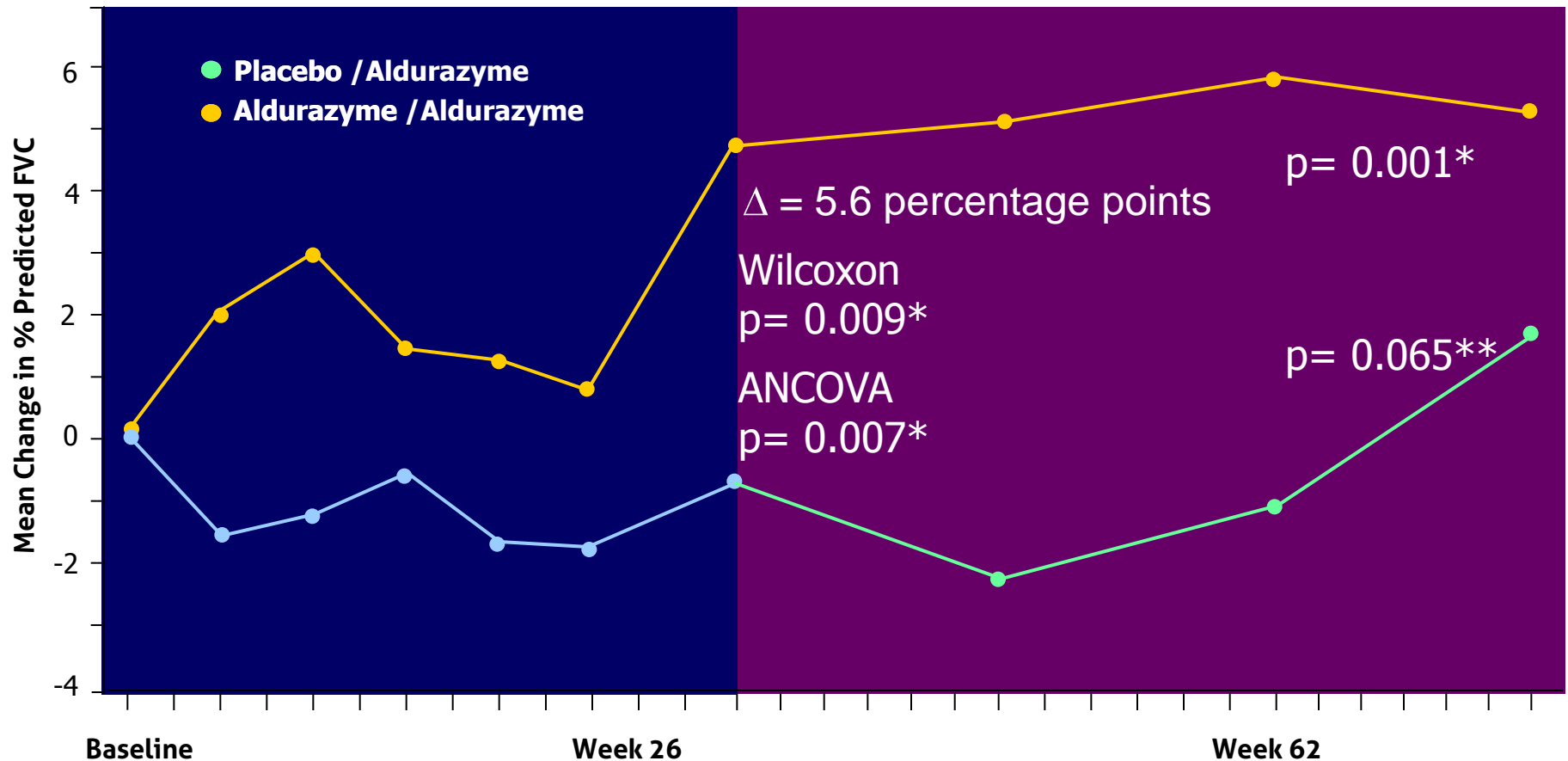
		ALDURAZYME N = 22	Placebo N = 23
Forced Vital Capacity (percent of predicted normal)			
Baseline	Mean \pm s.d.	48 \pm 15	54 \pm 16
Week 26	Mean \pm s.d.	50 \pm 17	51 \pm 13
Change from baseline to week 26	Mean \pm s.d.	1 \pm 7	-3 \pm 7
	Median	1	-1
Difference between groups	Mean	4	
	Median (95% CI)	2 (0.4, 7) p=0.02*	
6-Minute Walk Distance (meters)			
Baseline	Mean \pm s.d.	319 \pm 131	367 \pm 114
Week 26	Mean \pm s.d.	330 \pm 127	348 \pm 129
Change from baseline to week 26	Mean \pm s.d.	20 \pm 69	-18 \pm 67
	Median	28	-11
Difference between groups	Mean	38	
	Median (95% CI)	39 (-2, 79) p=0.07*	

*By Wilcoxon Rank Sum Test

Phase 3 Study: Percent Predicted FVC

Double-Blind

Open-Label Extension

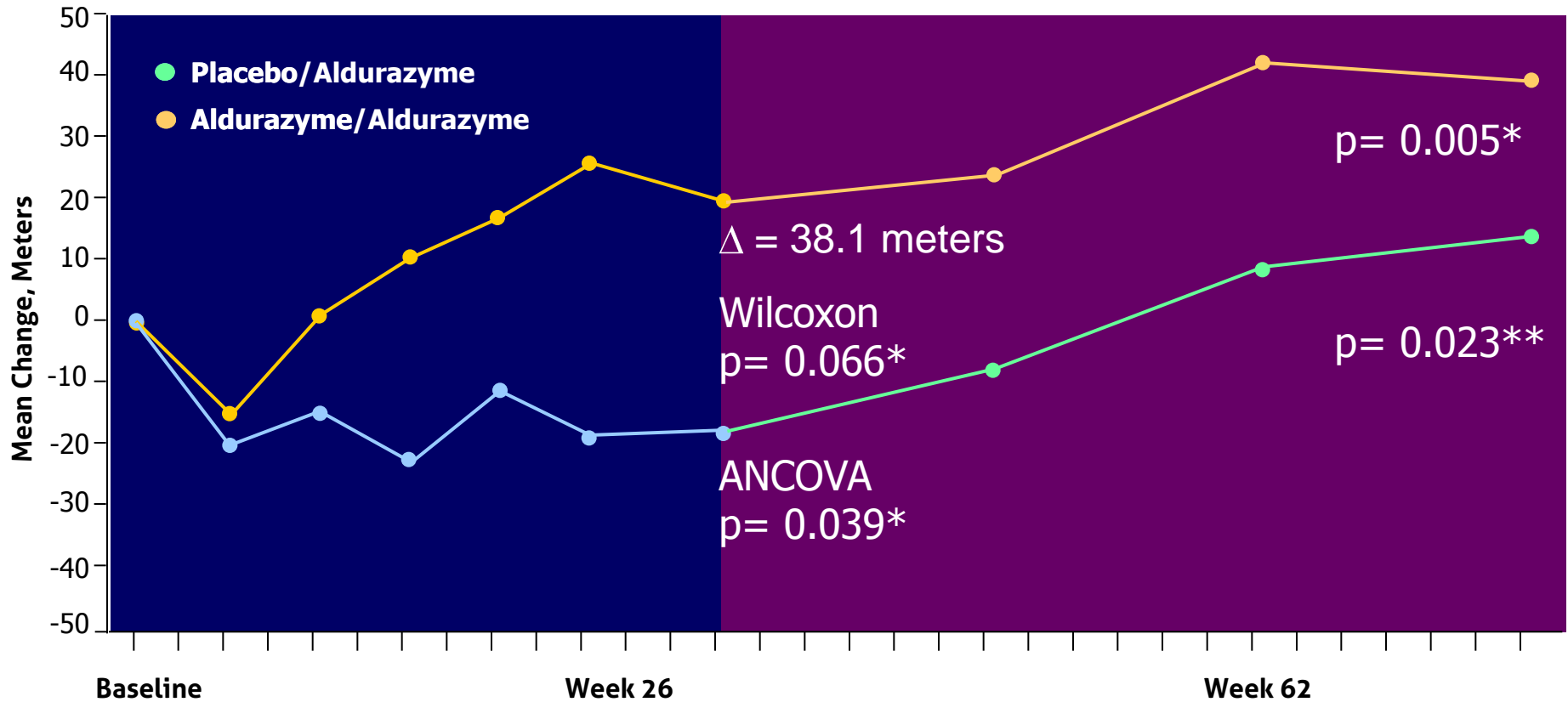


* Change from Baseline ** Change from Week 26
Median difference 3.0
All calculations used baseline height

Phase 3 Study: 6-MWT Distance

Double-Blind

Open-Label Extension



* Change from Baseline

** Change from Week 26



Phase 3 Study Primary Results

- Percent Predicted FVC
 - 4 percentage point mean difference (5.6*)
 - 11.3% relative change* vs. 11% MCID
 - 42% Aldurazyme vs. 9% placebo achieved MCID (p=0.017)*
 - Similar to spirometry effects for approved CF and asthma drugs
- 6-MWT
 - 38 m mean difference vs. 54 m MCID (95% CI 37-71m)
 - 42% Aldurazyme vs. 13% placebo achieved MCID (p=0.047)
 - Similar to changes seen for approved pulmonary HTN drugs

* Using baseline height for 26 weeks



Key Problem

- Patients with heterogeneous, multisystem diseases may show different therapeutic responses that are not adequately captured by a single organ endpoint
- Treatment effect becomes “diluted out” by calculating mean change across each endpoint separately
- “Responder” depends on the endpoint



Potential Solution

- **Traditional endpoint** approach assesses mean change across multiple patients in one endpoint and if patient is a “responder”
- **Composite endpoint** approach assesses change across multiple endpoints within a single patient to determine the extent of response and if patient is a “responder”



Composite Endpoint Approach

- Accommodates patient heterogeneity
- More comprehensive view of patient response
- More sensitive than single organ endpoint
- Define domains with thresholds of clinically significant change (+1 improve, 0 unchanged, -1 decline)
- Endpoints
 - Responders
 - Proportion of patients with net improvement
 - Net Change
 - Improvements minus declines per patient



Phase 3 Study: Composite Endpoint

Domains

Clinically Significant Thresholds

-
- FVC $\pm 11\%$
 - 6MWT ± 54 meters
 - Apnea-Hypopnea Index ± 10 events/hour
 - Shoulder Flexion ± 20 degrees
 - Visual Acuity ± 2 lines on eye chart



Phase 3 Study: Composite Endpoint

Placebo

Patient	FVC	6MWT	SHFLEX	AHI	ACUITY
	11%	54m	20 deg	10 ev/hr	2-lines
1			Decline		
2					
3		Decline			
4	Decline		Improve		
5		Decline	Not Available		
6		Decline	Improve	Decline	
7		Improve			
8				Not Available	
9	Improve			Improve	
10	Decline			Not Available	
11				Improve	
12		Decline			
13		Decline			
14		Improve			
15	Decline		Decline		
16		Improve			
17			Decline	Decline	
18			Decline		
19			Decline		
20		Decline			
21	Improve			Decline	
22					
23			Decline		

Aldurazyme

Patient	FVC	6MWT	SHFLEX	AHI	ACUITY
	11%	54m	20 deg	10 ev/hr	2-lines
24	Improve		Decline		
25	Improve	Improve			Improve
26		Decline			
27		Decline			
28		Improve	Improve		Improve
29				Improve	
30	Decline	Improve	Improve	Not Available	Improve
31	Improve		Improve		
32	Improve				Improve
33		Improve	Improve		
34			Decline		
35	Improve	Improve	Improve		Improve
36	Improve	Improve			
37			Not Available	Improve	
38	Improve		Decline		
39	Improve	Improve	Decline	Improve	
40		Decline	Decline		
41					
42			Not Available	Not Available	
43		Decline			
44	Improve		Not Available		
45				Improve	

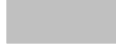
Clinically Significant Changes



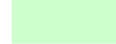
Improve



Decline



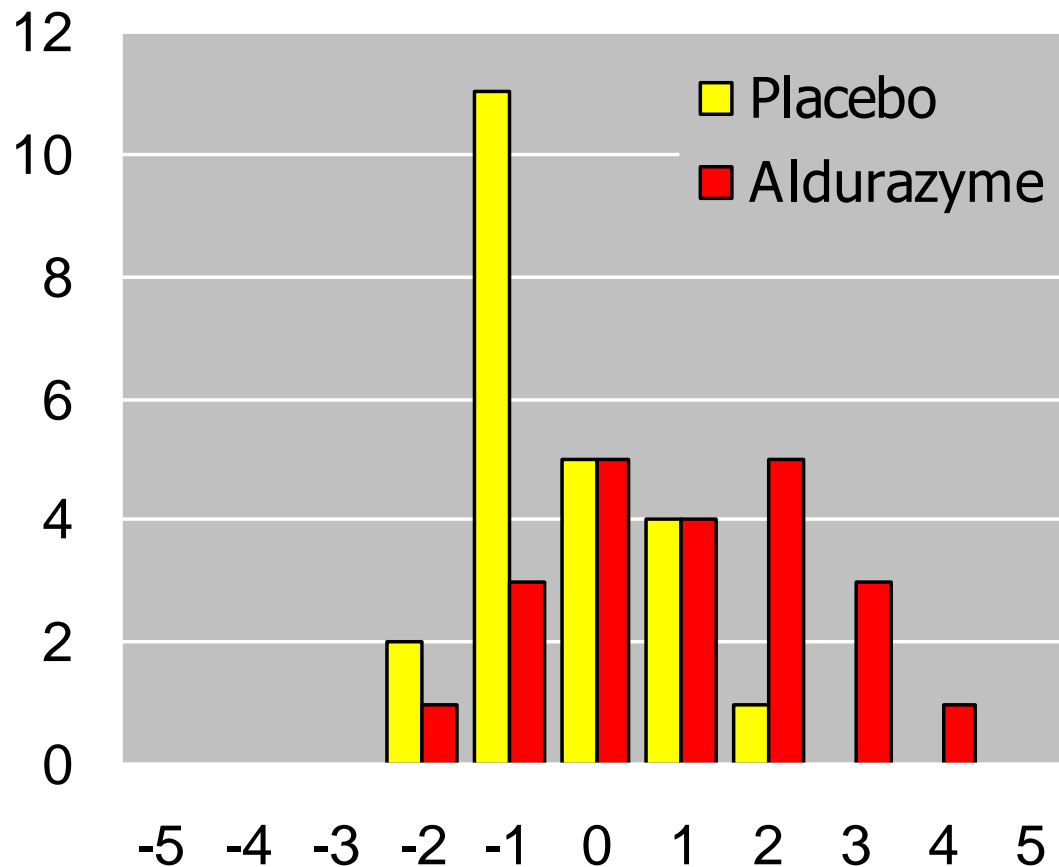
No Change



Not Available



Phase 3 Study: Responders and Net Change



Responders

59% Aldurazyme
22% Placebo
($p=0.016$)

Mean Net Change

1.0 Aldurazyme
-0.4 Placebo
($p=0.003$)



Summary of Recommendation

- Consider novel composite endpoints with broader view of “overall benefit” and “responder” for clinical treatment trials of multisystem diseases, especially those that are rare and clinically heterogeneous
- Obtain buy-in from regulatory agencies and validation by experts
 - Agree upon domains, weighting, clinically significant change thresholds, scoring system, definition of “responder”, and statistical analysis