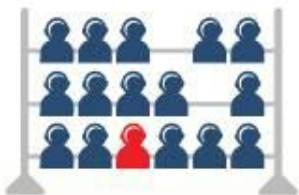




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RARE DISEASE WORKSHOP SERIES

Improving the Clinical Development Process

Workshop 1: Optimizing the Choice of Statistical Analysis
and Study Design for Ultra Rare Diseases

November 8, 2010 8:00 a.m. – 3:00 p.m.

Bethesda Marriott, 5151 Pooks Hill Road, Bethesda, MD
Congressional Ballroom - Salons I-II

Welcome

Emil D. Kakkis, M.D., Ph.D.

President

Kakkis EveryLife Foundation



EveryLife Foundation Goals

Transform the development of rare disease therapeutics

- Establish a new Office of Drug Evaluation specifically for biochemical and genetic diseases
- Create new qualification criteria for surrogate endpoints to improve access to Accel. Approval
- Evaluate and establish best and new alternative study analysis and design strategies for pivotal studies of rare disease therapeutics





RARE DISEASE WORKSHOP SERIES
Improving the Clinical Development Process

Our foundation effort is formally endorsed by **165** disease organizations



Education. Support. Hope.



NORD
National Organization for Rare Disorders





The Rare Disease Workshop Series

Working workshops looking for new ideas and best in class strategies

Goals

- Improving the clinical development for rare diseases
 - Find ways to improve study design, endpoints and stats
- Develop the data to support the best accepted and novel approaches for both statistical analyses and study designs
 - Advance the *applied* science of statistical analyses
 - Evaluate new study designs in small studies
- Evaluate ways to qualify surrogate, biomarkers and other endpoints for pivotal studies of rare disease treatments
- Produce guidances, publications or policy documents



Series of 5 Workshops Planned

- Workshops 1 & 2:
Optimizing the Choice of Statistical Analysis and Study Design for Rare Diseases
 - Workshop 1: November 8, 2009
 - Workshop 2: TBD, Likely Jan/Feb.
- Workshops 3 & 4:
Improving Access to the Accelerated Approval Process by Creating Qualification Criteria for the Use of Surrogate and other Endpoints for Rare Diseases
- Workshop 5:
Draft Proposed Guidance Documents and Policy Recommendations for Rare Diseases

**All workshops will be completed by September 2011*



Brownback-Brown Amendment for Rare Disease Regulation Review

- 2010 FDA Approp. Bill Section 740
 - Establishes review group
 - Report to Congress due in March 2011
 - Implementation by September 2011
- 2011 FDA Approp. Section 741 specifies areas
 - Guidances on development, studies, surrogate endpoints

Nov 2010
EveryLife
Foundation
Workshop

Dec 2010
Draft FDA
Rare Disease
Committee
Report

Feb 2011
Rare
Disease
Day

May/June 2011
FDA FY 12
Appropriations
introduced

Sept 2011
Implement
report

Oct 2010
IOM
Report

Dec 2010
HS/OMB
finalizes
2012 FDA
Budget

Jan 2011
FDA RD
Committee
Public
Meeting

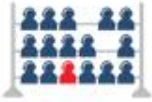
Mar 2011
FDA Rare
Disease
Committee
Report



Aldurazyme (laronidase) for MPS I

- Mucopolysaccharidoses
 - Enzyme deficiencies resulting in glycosaminoglycan (GAG) accumulation in lysosomes, affecting tissues and organs to varying degrees
- Double-blind, placebo-controlled, randomized 1:1, 26-week study
- 45 patients, ages ≥ 5
- Coprimary endpoints variables:
 - 6-minute walk test (6MWT) distance
 - Wilcoxon Rank Sum Test
 - % of predicted normal forced vital capacity (FVC)
 - ANCOVA

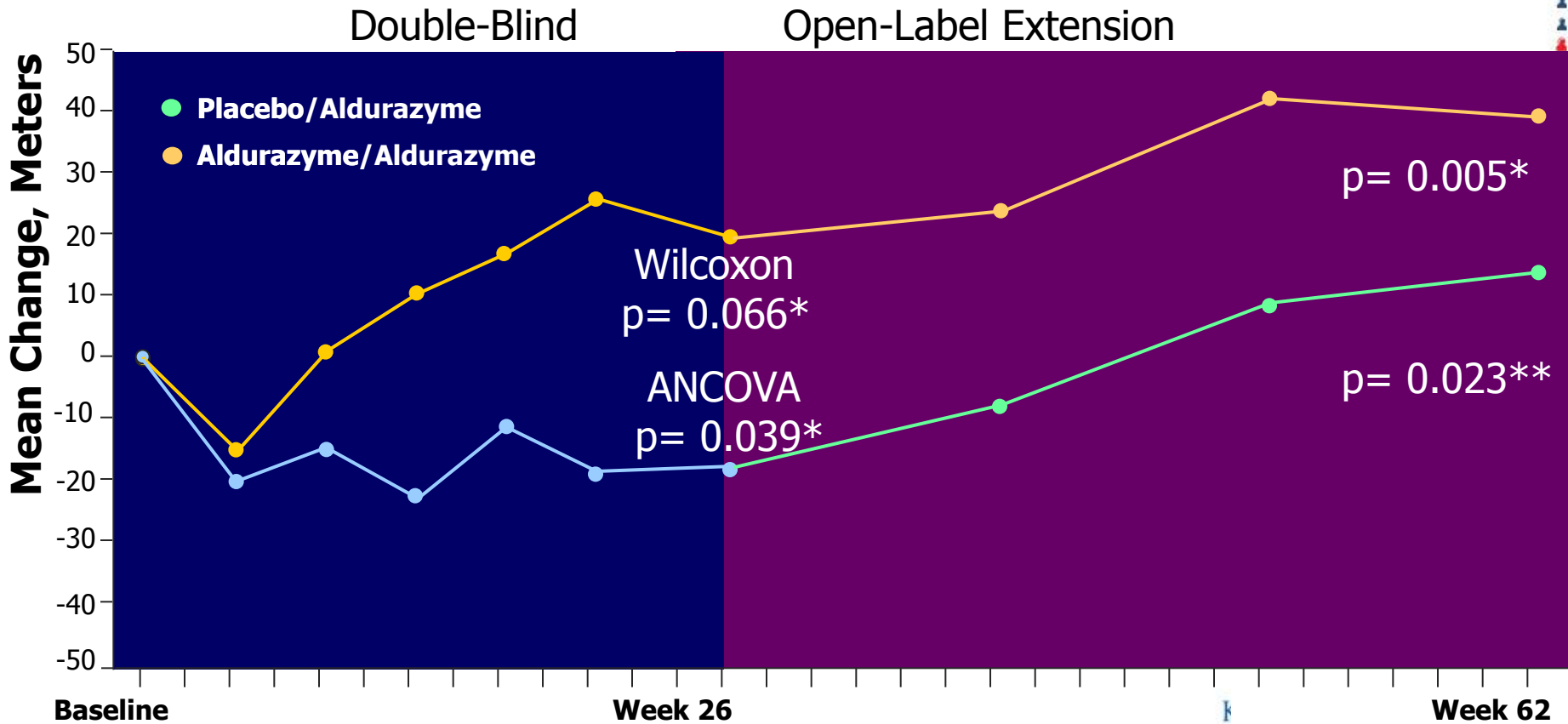




Phase 3 Study: Aldurazyme increases 6MWT

No entry criteria for selection for 6MWT baseline

Excess patient heterogeneity complicates data



* Change from Baseline

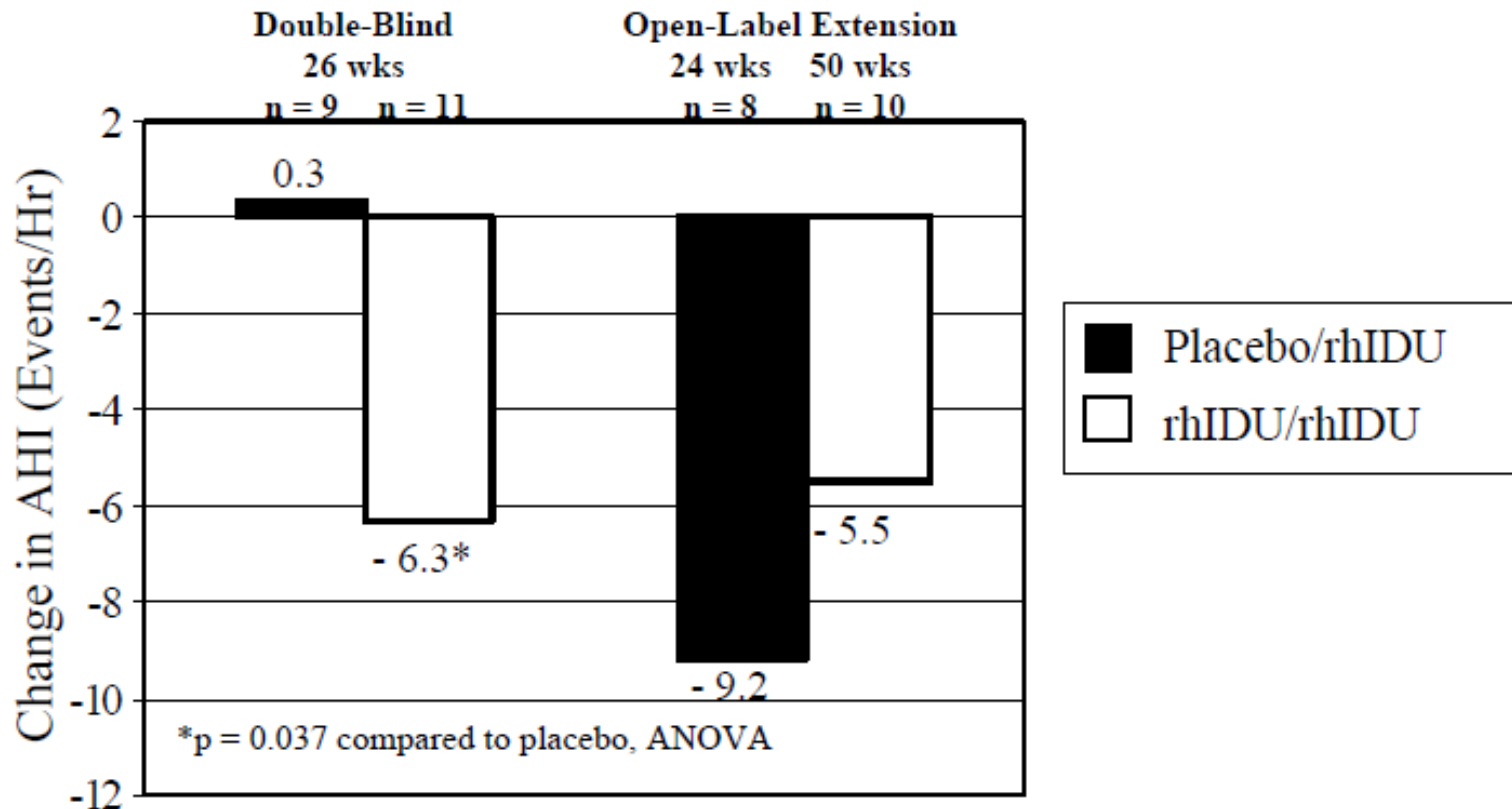
** Change from Week 26



Heterogeneity cannot always be controlled by patient selection

Success only in subsets who are affected with the problem, sleep apnea

Figure 10: rhIDU Reduces AHI

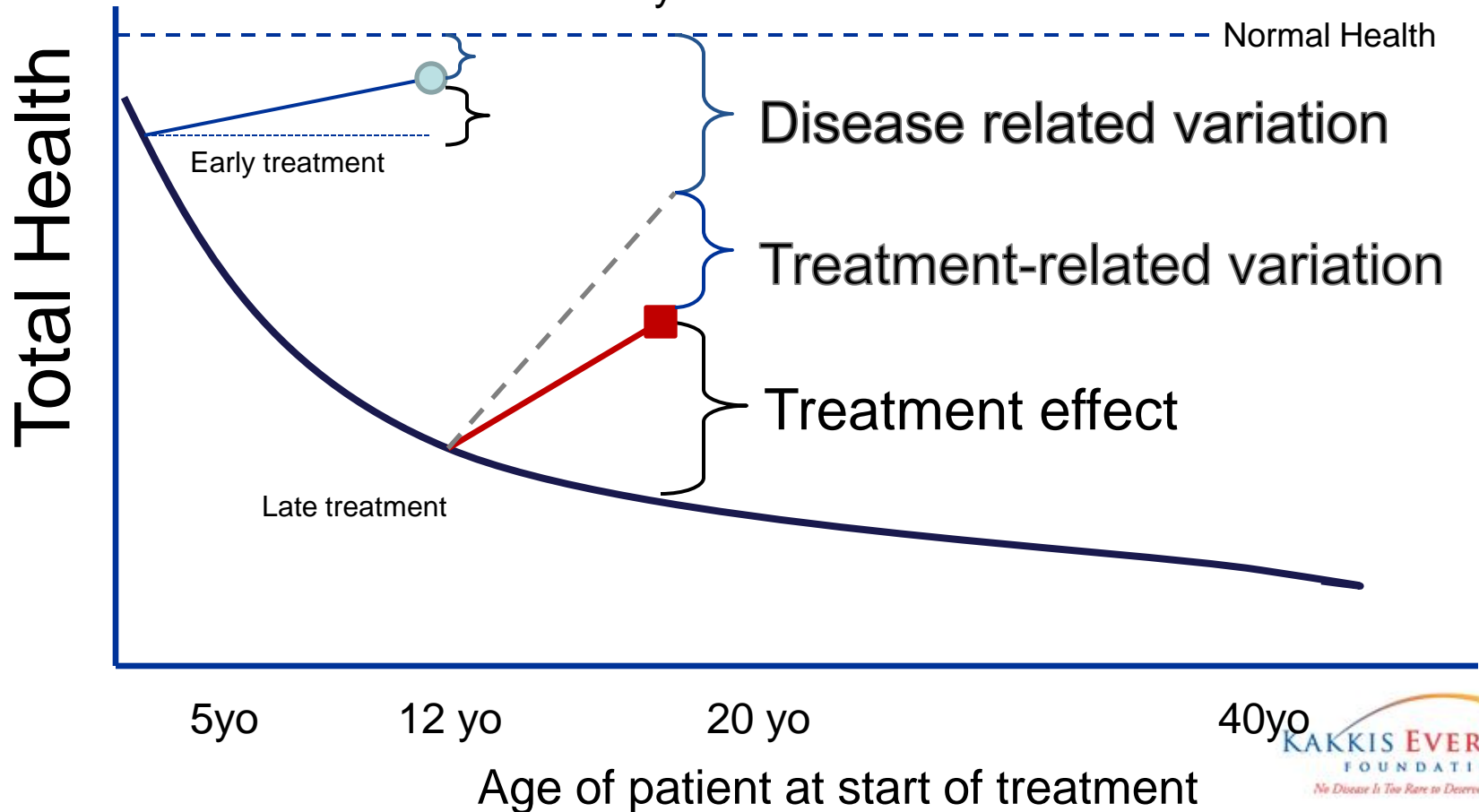




Disease severity and progression variation complicates clinical endpoints

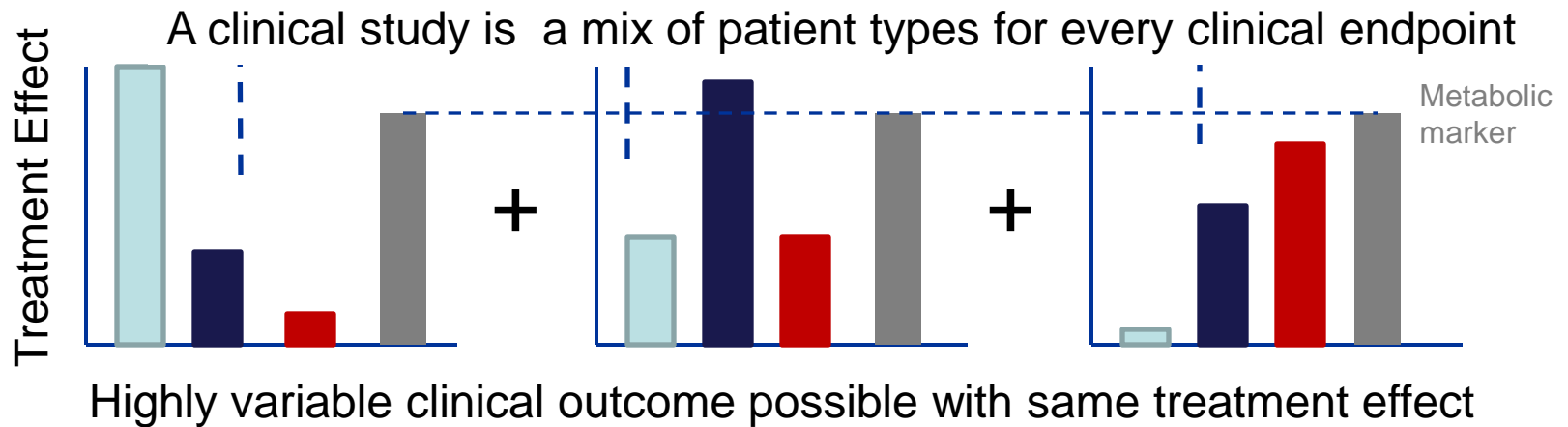
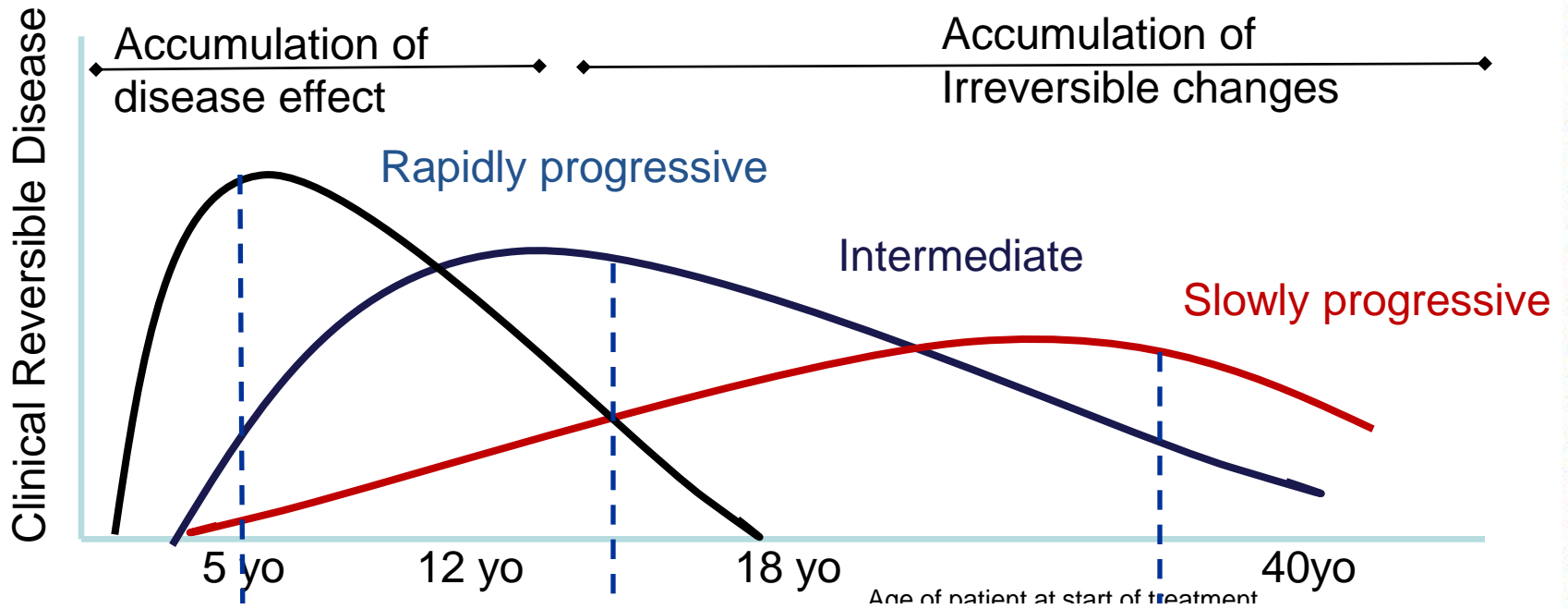
- Variable degrees of secondary irreversible changes alter outcomes

Natural History Course for an IEM Patient





Clinical endpoints: complicated in rare diseases

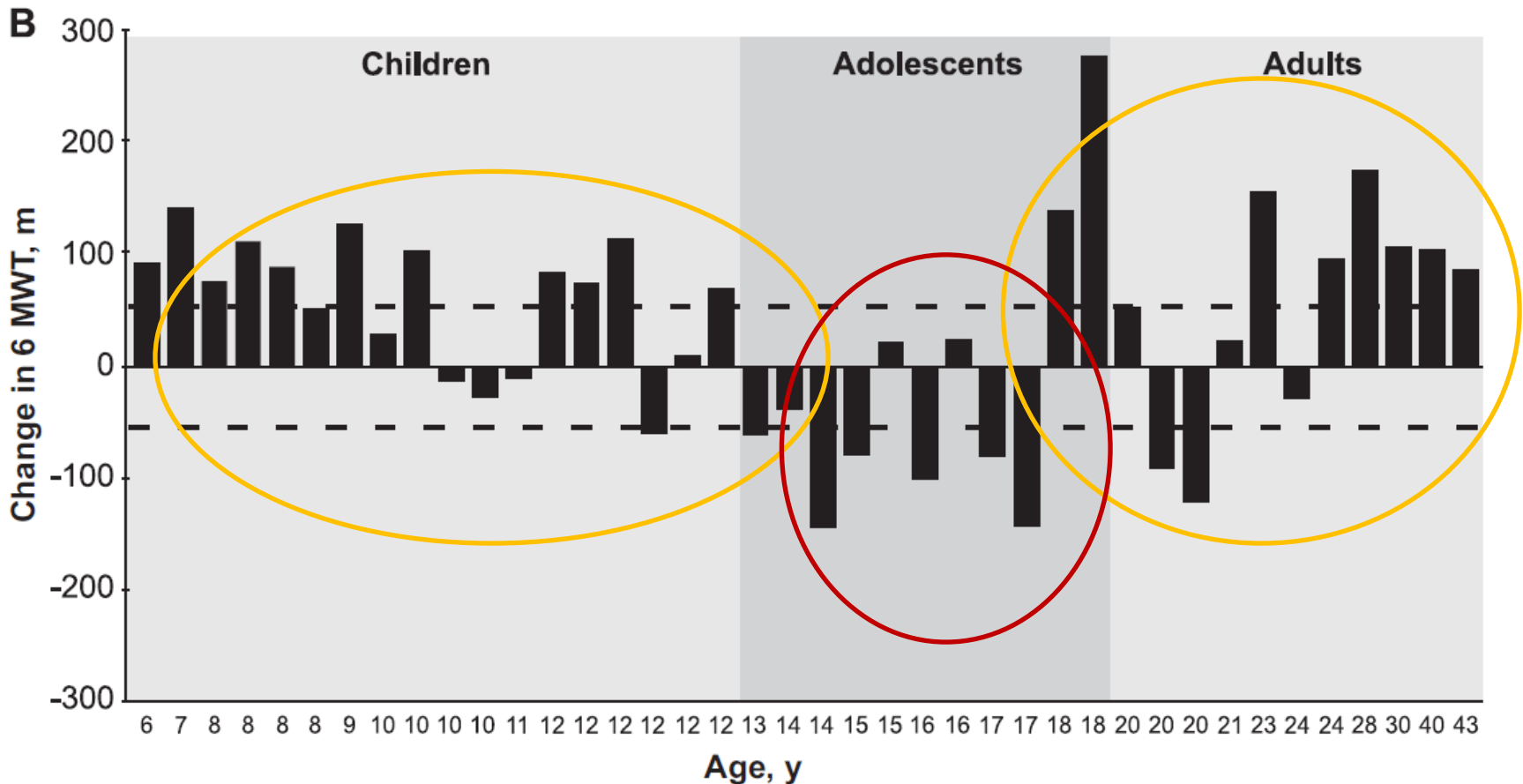




Complexity in Disease

Different body systems, Different progression

Laronidase Change in 6 MWT over 3.5 yrs



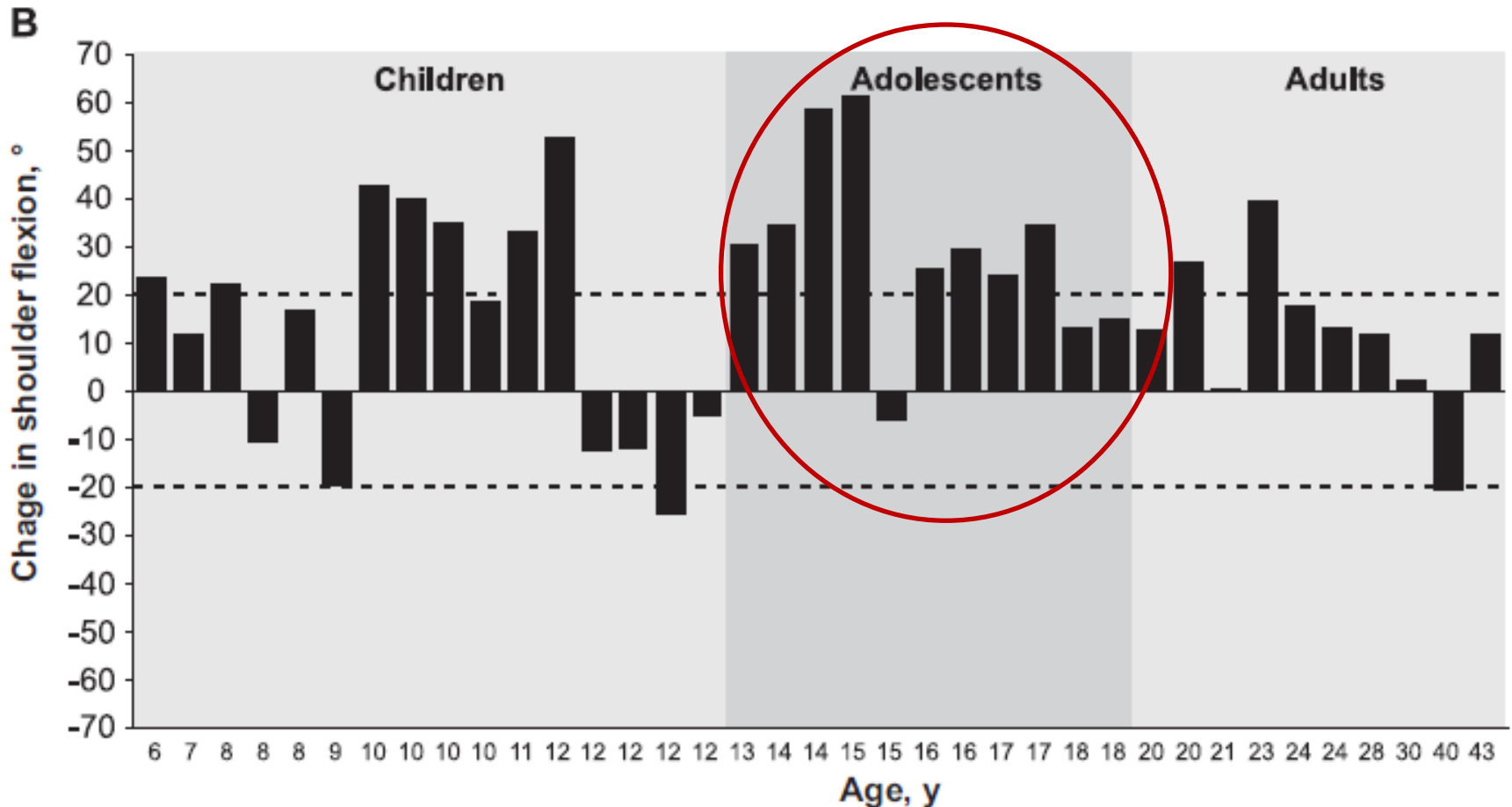
* Clarke et al 2009: 4 yr F/U Ph 3 Study



Shoulder Flexion

Long-term effects of rhIDU in MPS I

Clarke et al 2009: 4 yr F/U Ph 3 Study





Deconstructing Rare Disease Studies

Working backward, step by step

- We normally design studies going forward
- Breaking down the challenges might need to be different

Disease

Treatment Strategy

Measures of Disease
Endpoint variables

Design a Study

Statistical Analysis

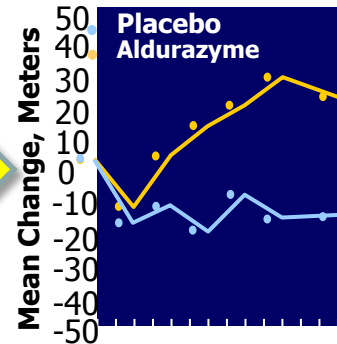
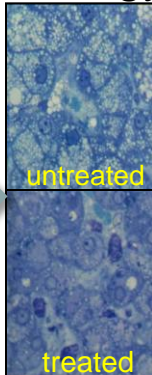


Table II. Primary efficacy outcomes

		Laronidase group (n = 22)	Placebo group (n = 23)
P/C (% of predicted normal)	Baseline	Mean ± SD 48.4 ± 14.5	54.2 ± 16.0
	Week 26	Mean ± SD 53.3 ± 18.5	53.5 ± 14.2
	Change from baseline to week 26	Mean ± SD 4.9 ± 8.7	-0.7 ± 5.9
Difference between groups	Median	3.0	0.0
	Mean		5.6
	Median (95% CI)		3.0 (0.5, 8.6)
	Wilcoxon rank sum ANCOVA*		P = .009†
6-minute walk test distance (meters)	Baseline	Mean ± SD 319.1 ± 131.4	366.7 ± 113.7
	Week 26	Mean ± SD 338.8 ± 127.1	348.3 ± 128.8
	Change from baseline to week 26	Mean ± SD 19.7 ± 68.6	-18.4 ± 67.5
Difference between groups	Median	27.5	-11.0
	Mean		38.1
	Median (95% CI)		38.5 (-2.0, 79.0)
	Wilcoxon rank sum ANCOVA*		P = .066†

Are the endpoint variables optimal?

Could design Be improved?

What works & what fails and why?



Key statistical challenges for rare disease studies

- Minimal historical clinical study information regarding acceptable endpoints or effect of treatment
- Large clinical heterogeneity despite single gene defects
 - Variability in severity, progression and irreversibility
 - Disease severity relative to irreversibility can be complex
- Complex multi-system disorders must be reduced to a single primary endpoint, failing to capture overall treatment benefit
 - What does “substantial clinical benefit” really mean?



RARE DISEASE WORKSHOP SERIES
Improving the Clinical Development Process

Agenda:

- 7:30 am Registration and Continental Breakfast
- 8:00 am Welcome
Emil Kakkis, M.D., Ph.D.
President & Founder, Kakkis EveryLife Foundation
- 8:15 am Keynote Presentation
Thomas Fleming, Ph.D.
Professor of Biostatistics, University of Washington

Ultra rare disease case study presentations:

Section 1: Single Variable Methods

- 9:00 am Pompe Late Onset Treatment Trial
L.J. Wei, Ph.D.
Professor, Harvard University
- 9:20 am Post Marketing Fabry Trial
P.K. Tandon, Ph.D.
Senior Vice President Global Biomedical Data Sciences & Informatics, Genzyme Corporation
- 9:40 am Naglazyme Phase III
Emil Kakkis, M.D., Ph.D.
Former CMO, BioMarin Pharmaceutical Inc.
- 10:00 am Discussion of Single Variable Methods
- 10:15 am Break



RARE DISEASE WORKSHOP SERIES
Improving the Clinical Development Process

Section 2: Multivariate or Multiple Domain Methods

- 10:30 am Aldurazyme Responder Index
Gerry Cox, M.D., Ph.D.
Vice President, Clinical Research, Genzyme Corporation
- 10:50 am Multivariate Methods and Characterization of Clinical Effect of Complex Diseases
Brent A. Blumenstein, Ph.D.
Lead Statistician, Trial Architecture Consulting
- 11:10 am Hunter Phase III O'Brien analysis, issues with Elaprase
David A. Amato, Ph.D.,
Director of Biostatistics, Shire Human Genetic Therapies
- 11:30 am Discussion of Multivariate or Multiple Domain Methods

Strategies on Improving the Treatment Development Process

- 11:45 am FDA Perspective
Yuqun Luo, Ph.D.
Mathematical Statistician, FDA\CBER
Estelle Russek-Cohen, Ph.D.
Deputy Director, Division of Biostatistics, FDA\CBER
- 12:05 pm Critical Path Institute Strategies
Marc Cantillon, M.D.
Director of Coalition Against Major Disease (CAMD), Critical Path Institute
- 12:25 am Lunch



Planned statistical analysis on endpoints for approved ultra rare drugs

1:10 pm Overview on Analysis of Ultra Rare Drugs Data

Emil Kakkis, M.D., Ph.D.

1:20 pm Explanation of Analysis on Endpoints for Approved Treatments & Findings

Mei Sheng Duh, MPH, ScD

Managing Principal, Analysis Group, Inc.

James Signorovitch, Ph.D.

Manager, Analysis Group

Discussion on Additional Analyses and Modification of Analysis

- Methods to control variation
- Multivariate methods
- Alternative study designs for rare disease studies
- Proposals for rare disease double-blind, placebo-controlled data sets to obtain for analysis

3:15 pm Workshop Summary

3:30 pm Workshop Adjourns



Thank you to our sponsors and supporters for the workshop

- Majority funded by the EveryLife Foundation
- Series Sponsor George Weiss
- Series Supporters
 - Corporate sponsors, data and financial support
 - BioMarin, Shire, Genzyme
- Thank you to The Analysis Group team
 - Stepped up to complete first segment of analyses
- Scientific Advisory Committee
 - LJ Wei, B. Blumenstein, T. Lachenbruch, L. Friedman
 - J. Wittes for early work on the project