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The Challenges of Managing Heterogeneity in Rare Diseases

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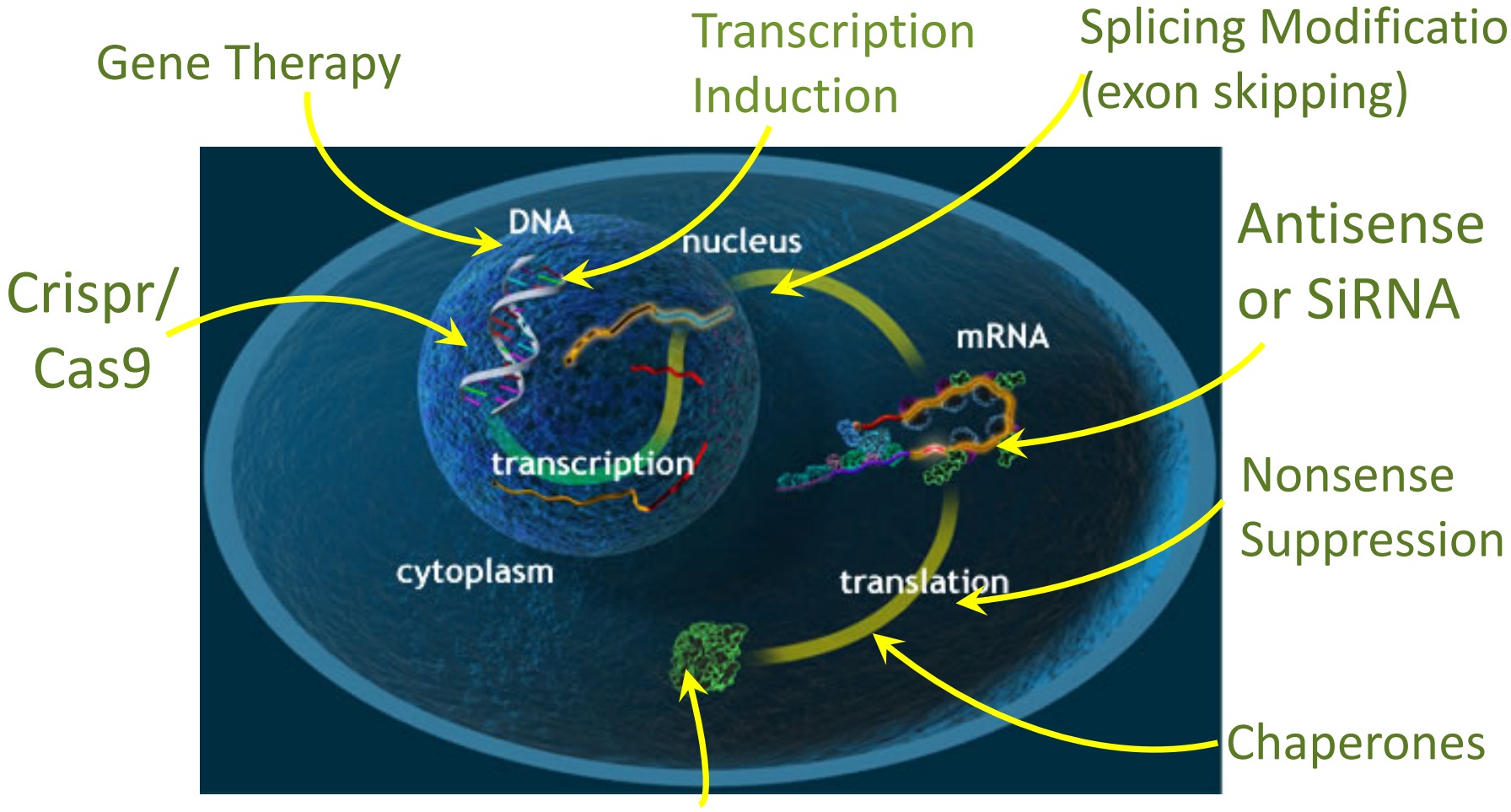
We are now in the Golden Age for Rare Disease Treatments

Treating Genetics Disorders in Golden Age

The last 10 years have greatly changed the available modalities



Expertise and Experience is Rare in Rare

- Development is distinctly different
- Complexity of diseases and lack of knowledge
- No prior history of drug development
- New biomarkers and measures
- Statistics and analyses are difficult in small populations

A specialized Center of Excellence group at FDA with specific insight and experience could be of great benefit to review divisions struggling with rare disease drugs

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What is the largest problem in translating rare disease treatments into approvals?

Heterogeneity

Heterogeneity distinguishes and uniquely complicates rare disease development

- Diagnosis, Age, Genetics, null and missense
- Disease severity
- Distribution of disease within a single patient
- Progression/irreversibility in different symptoms
- History of treatment, specific or palliative
- **Small numbers of patients**

The Development Paradigm for Phase 3

- Single population
- Single primary endpoint
- Randomized 1:1 study
- Single analysis, ITT-based
- Multiplicity adjustments for other endpoints

The paradigm leads to a crafted simplistic and at times uninformed study for rare diseases that fails to capture disease variation and efficacy

The Development Paradigm Is Not Adapted to Highly Heterogeneous Small Populations

- Cannot screen and select study patients efficiently
- Cannot over-power variation with large “n”
- Difficult to craft a single endpoint answer
- Statistics are hard to manage/adequate power
- Variation is often 10 fold larger than a clinical meaningful treatment effect size
- Multiplicity adjustments crush any hope and oversimplify results

Heterogeneity Topics for Concern in the Paradigm

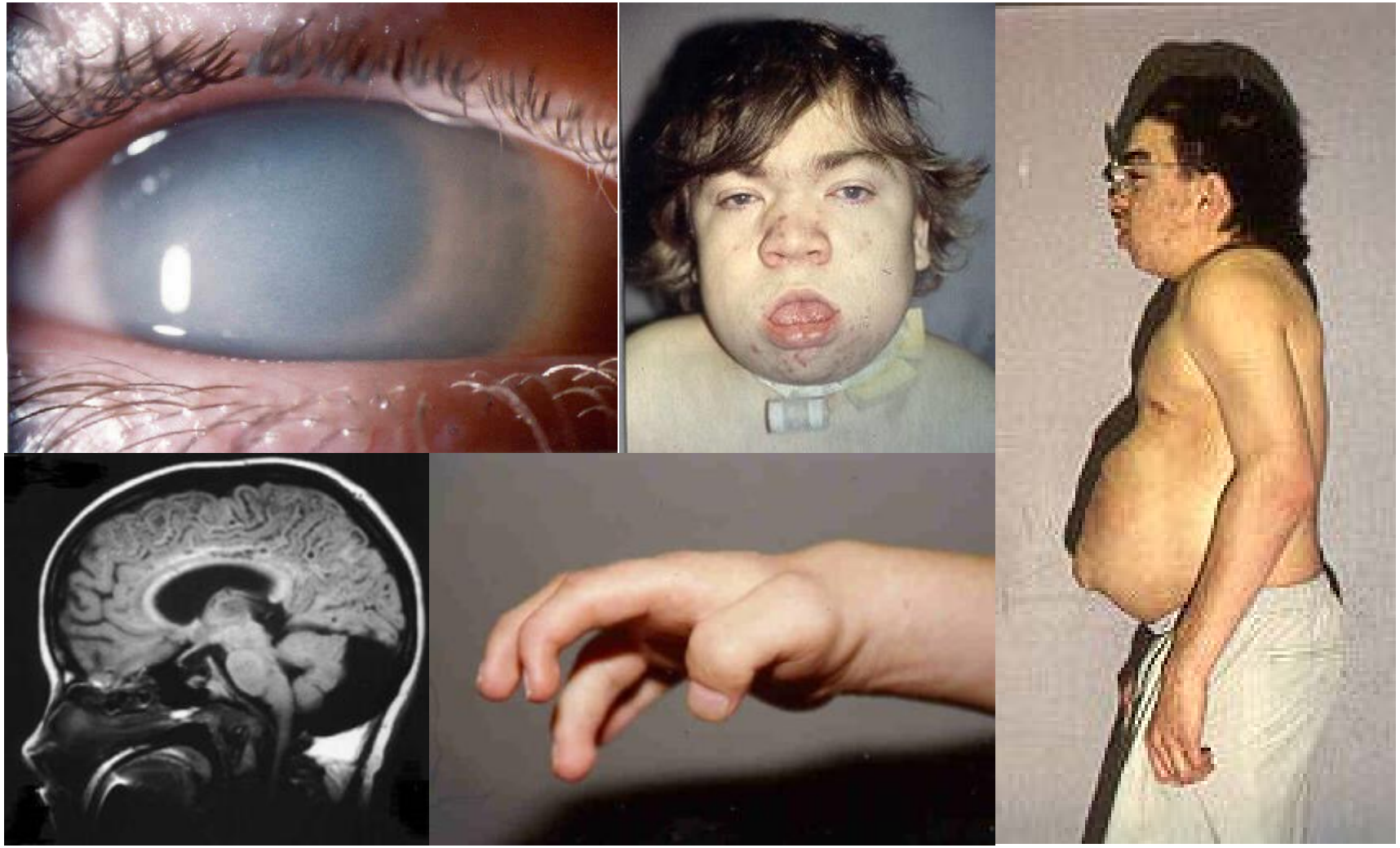
- Selection of Populations for Study
  - Intent to Treat (ITT) analysis and its negative impact on understanding
- Single endpoints to assess a complex disease
  - Missed opportunities to learn more
- Multiplicity adjustments that violate scientific analysis and insight
  - Current approach reduces accuracy of decisions by limiting the meaning of supportive data

Selection of Patients For Study

All of these patients have the same MPS I Disease

Heterogeneity Within a Patient

Mucopolysaccharidosis Type I



Aldurazyme Phase 3 Study*: Heterogeneity Across Disease

- Respiratory Complications
  - Respiratory infections 51%
  - Sleep apnea 47%
  - Reactive airway/asthma 24%
- Interventions
  - Tonsillectomy/ Adenoidectomy 67%
  - CPAP 9%
  - Nebulizer 7%
- Musculoskeletal Disease
  - Joint stiffness 76%
  - Joint contractures 51%
  - Joint pain 29%
  - Spinal deformity 27%
- Outcomes
  - Physical therapy 31%
  - Wheelchair 30%
  - Walker 7%

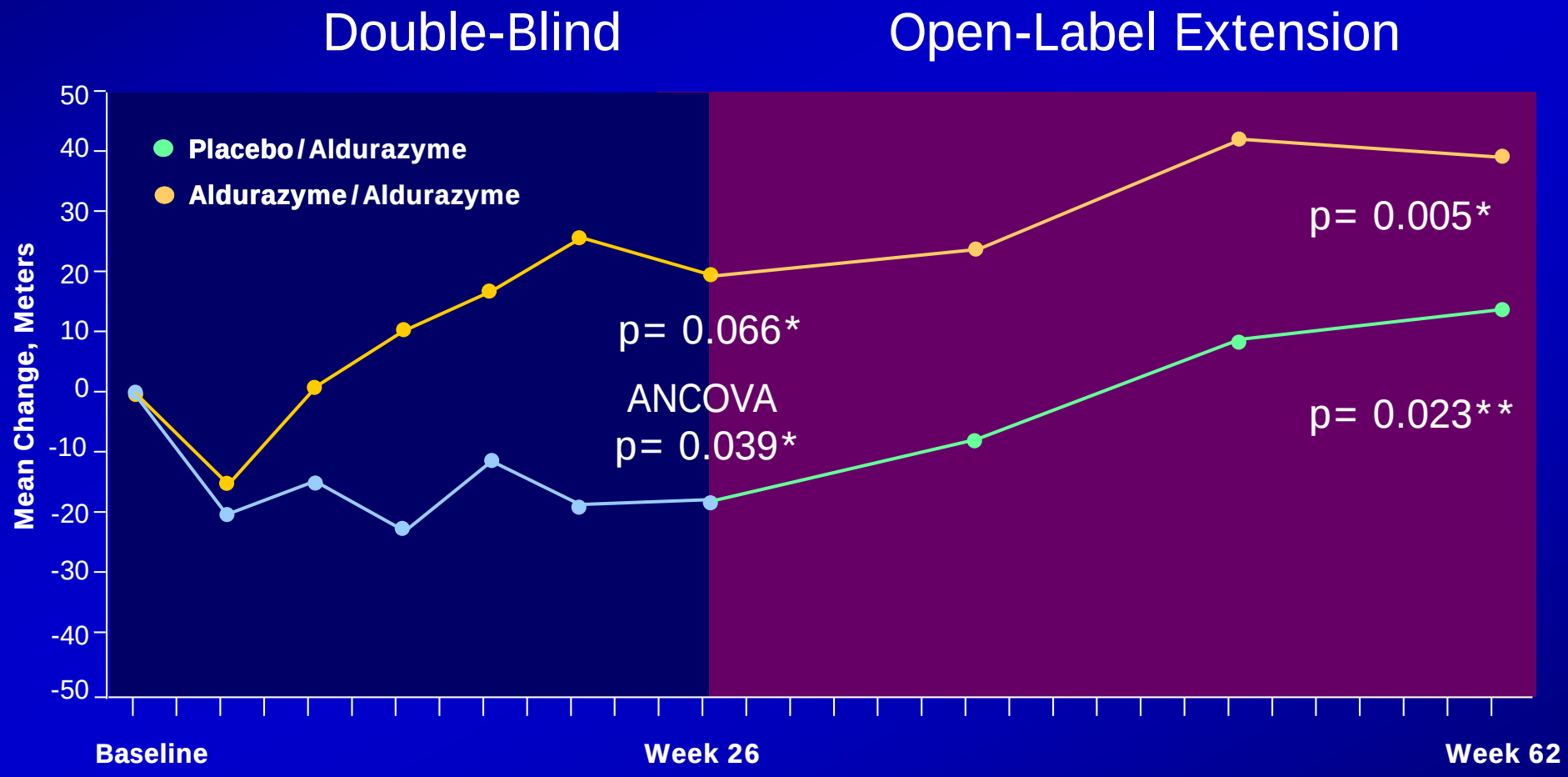
*Information derived from slides at the Aldurazyme AdCom Jan 2003

Phase 3 Study: Baseline 6MWT Patient Characteristics

	Placebo (n=23)	Aldurazyme (n=22)
6MWT (meters)		
Median	360.0	348.5
Range	60 - 571	14 - 591
Age Mean (Range)	15.4 (6,39)	15.6 (7,43)

Range is 10X the MID of 54 meters Used!

Phase 3 Study: The Miracle 1º Endpoint Aldurazyme Increases 6MWT Distance



* Change from Baseline ** Change from Week 26

Heterogeneity Complications

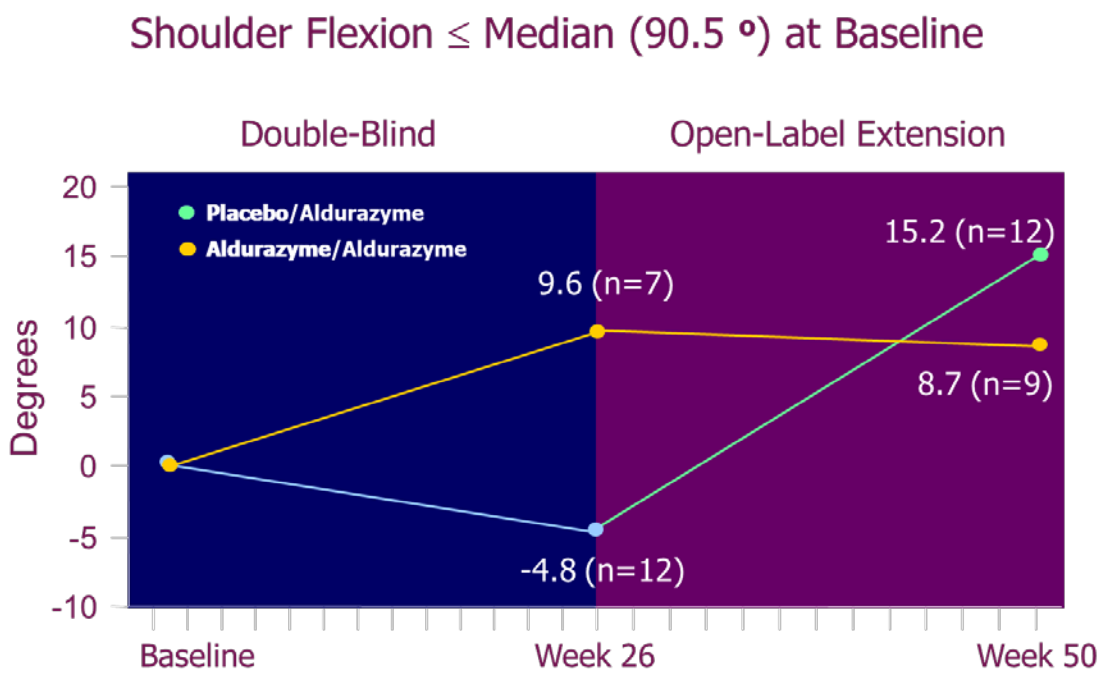
- Ages 6 to 43 years in one study
- Range of baseline walking 14m to 591m
- Could not select for impaired walkers (ITT)
  - Subset <300m baselines was stat significant
- +42m difference (p=0.066 Wilcoxon)
  - With ANCOVA for age and baseline p=0.039*

Conclusion made then: Endpoint missed

*Prespecified exploratory analysis of the primary endpoint

ITT driven analyses and inadvertent impact on secondary endpoints

- Shoulder flexion 2nd endpoint missed for ITT analysis
  - Subset **with** restriction at baseline was positive



- Sleep apnea 2nd endpoint also missed
  - Subset **with** Sleep apnea at baseline positive

What could be improved in the analytical approach?

- Statistical non-parametric method
  - Use of covariables help reduce impact of variation: ANCOVA positive
- Use of ITT as the only valued approach
  - Misguided application in rare diseases
- Time Course/Time integration not assessed
  - Multiple assessments verify a biologic pattern and cross over impact
- Other endpoints showed same pattern confirm the effect is biological and not random
  - Anti-multiplicity-mindset fails to recognition overall pattern of response that contributes to likely true effect

Another way to capture effect on multiple domains

Multi-Domain Responder Index (MDRI)

Captures large important changes in both directions and combine

- Large (>MID) Change in individual patients
- Accommodates patient heterogeneity
- Several domains with thresholds of clinically significant change (+1, 0, -1)
- 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	± 11%
6MWT	± 54m
AHI	± 10 events/hour
Shoulder Flexion	± 20 degrees
Visual Acuity	± 2 lines on eye chart

Phase 3 Study: MDRI

Clinically Significant Changes

Improvement | Decline | No Change | Not Available

Placebo

Patient	FVC	6MWT	SHFLEX	AHI	ACUITY
	11%	54m	20 deg	10 ev/hr	2-lines
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					

Aldurazyme

Patient	FVC	6MWT	SHFLEX	AHI	ACUITY
	11%	54m	20 deg	10 ev/hr	2-lines
24					
25					
26					
27					
28					
29					
30					
31					
32					
33					
34					
35					
36					
37					
38					
39					
40					
41					
42					
43					
44					
45					

Learning from Aldurazyme and Managing Heterogeneity: rhGUS enzyme for MPS VII

- Reduce randomization bias
- Enhance power by measuring all

BLIND START STUDY DESIGN

- BioMarker measured in all

URINE GAG SHOWS BIOLOGIC EFFECT

- Captures multiple domains and avoid multiplicity issue

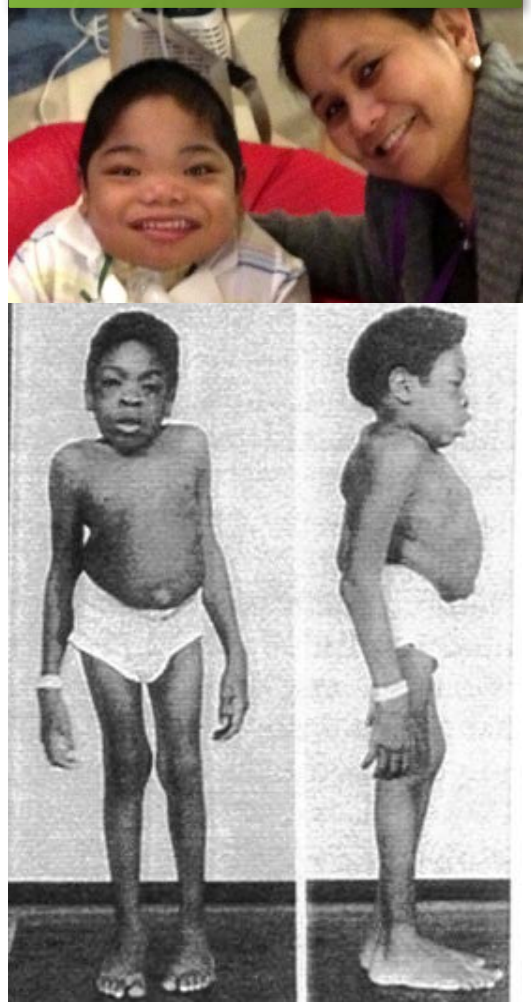
MDRI ANALYSIS

Managing Heterogeneity rhGUS ERT in MPS 7

Combining New Study Design with MDRI

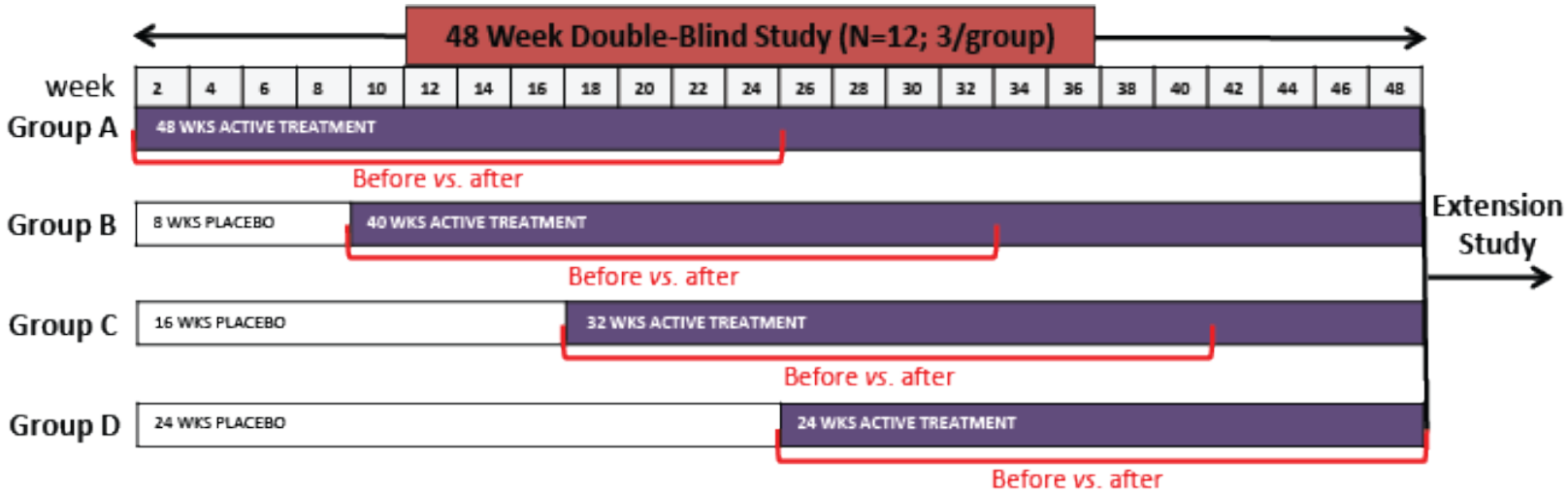
- **MPS 7:** Glycosaminoglycans (GAG) storage caused by enzyme deficiency
- Key symptoms/prognosis
  - Large liver/spleen, airway/pulmonary disease, joint stiffness, etc.
  - Death: teens-30s; hydrops[1] < 1 year
- **Treatment:** No approved drug therapy
- **Prevalence:** **~200 patients worldwide**
- **Status:**
  - Positive Phase 3 data presented 2016
  - Pre-filing meetings held with FDA and EMA
  - Plan to submit US & EU regulatory filings 1H17

Sly Syndrome



[1]Non-immune hydrops fetalis, a very severe neonatal condition

Managing Heterogeneity During Randomization
Blind Start Design: 5X more powerful



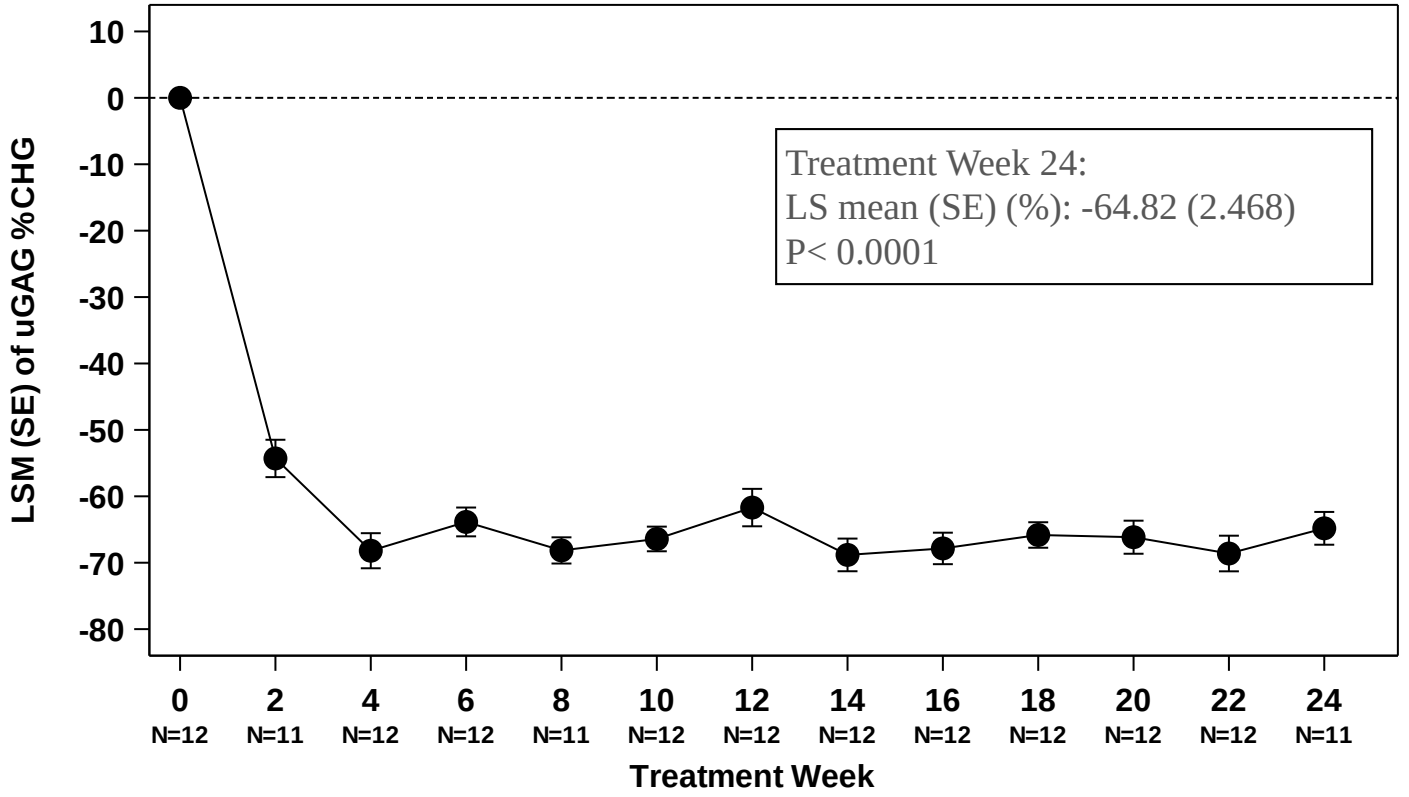
- 12 Patients enrolled with no disease entry criterion, “All Comers”
- Primary efficacy endpoint (in EU): Percentage change in urinary GAG excretion from baseline after 24 weeks of treatment
  - BioMarker is assessable in all subjects
- Key Secondary: Multi-domain Responder Index (MDRI) score
  - Assessing six different domains as one endpoint

Enzyme therapy in MPS 7: Managing heterogeneity

Rapid and Sustained BioMarker (uGAG) Reduction

64.8 percent reduction at 24 weeks in 12 patients, Blind Start Design

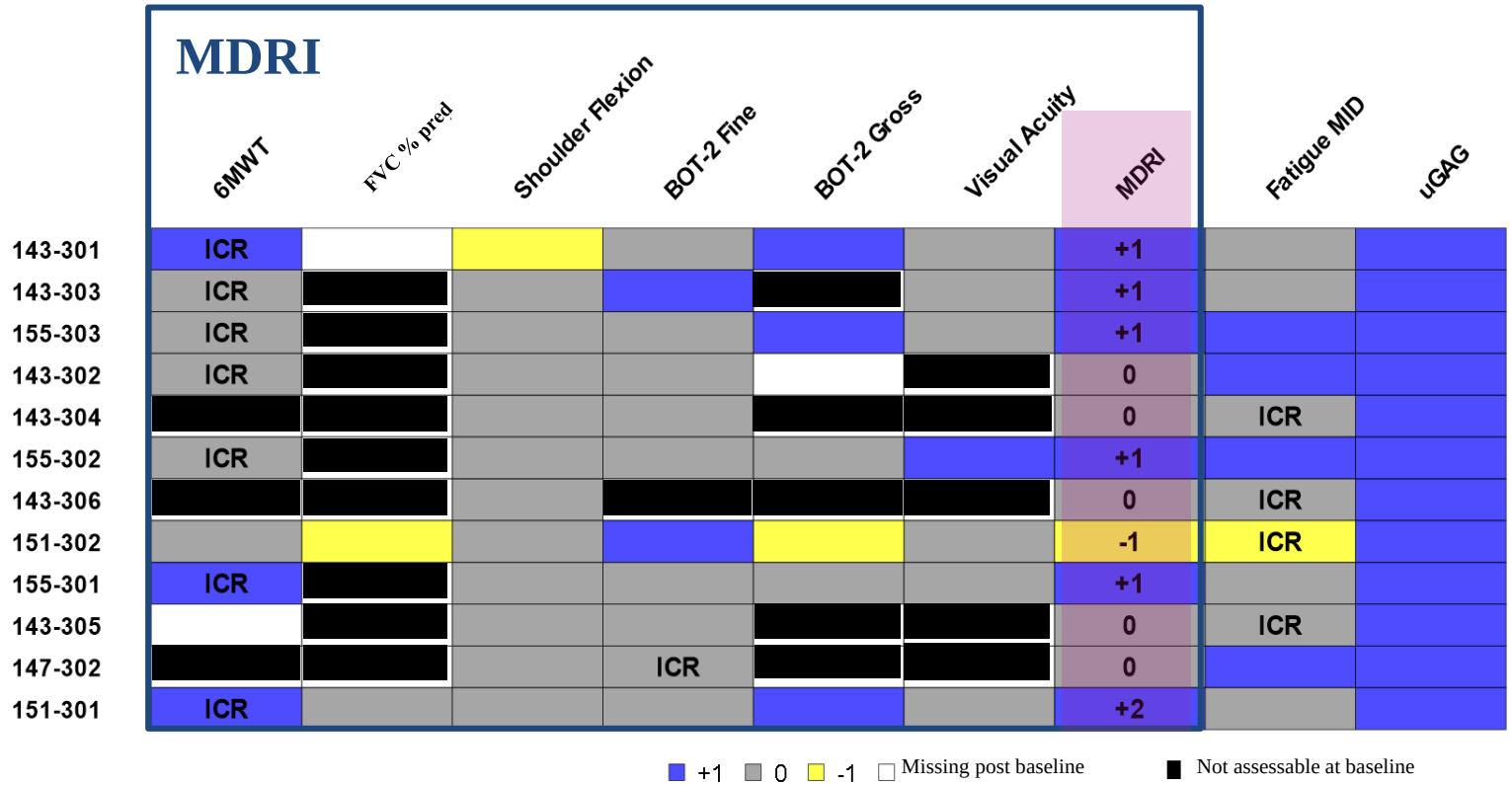
PERCENT CHANGE FROM BASELINE IN UGAG (DERMATAN SULFATE) EXCRETION



MDRI Shows Signs of Clinical Improvement

Mean improvement of + 0.5 domains (p=0.0527)

Shift toward improved with 3:1 ratio of improved to worse domains



- 6/12 patients: MDRI score improvement of +1 or more
- 5/12 patients: No worsening of this progressive disease
- 1/12 patient: Worsening with MDRI score of -1

MDRI Advantages in Heterogeneity

- Study effective in unselected populations
  - Assess what is assessable
  - No dilution of effect size for unaffected or unassessed
- Multiple domains evaluated
  - Broader view of efficacy across the population
- ITT is irrelevant as no impact on outcome
  - No disease manifestation does not dilute result
  - If not assessable, also does not impact the result
- The guesswork of endpoint choice is reduced
- Randomization bias and negative impact removed

Multiplicity Adjustments in Rare Diseases

- Designed to avoid fishing expeditions for positives
- Often used incorrectly in wrong situations
- Anti-multiplicity attitude fails to appreciate the insight from secondary and other endpoints
- Need to have better insights when it is appropriate

Statistical Purity ⟷ **Getting The Science Correct**

Extreme example for misuse of multiplicity testing in science

- Nine Tissues Tested with a Student “t” test, all p<0.02

Tissue GAG levels (μg/mg dry weight) MPS I canines receiving i.v. rhIDU

			0.58 mg/kg/wk		
Tissue	**Normal (*n* = 6)**	**Untreated MPS I (*n* = 3)**	**Nontolerant[A] (*n* = 9)**	**Tolerant[A] (*n* = 9)**	**Further storage reduction**
Liver	1.87 ± 0.555	28.6 ± 6.81	4.61 ± 1.43	2.37[B] ± 0.566	49%
Spleen	2.01 ± 0.374	23.4 ± 4.21	3.90 ± 1.40	2.33[B] ± 0.800	40%
Lymph node	4.30 ± 2.85	40.9 ± 20.4	13.4 ± 4.63	5.18[B] ± 2.51	61%
Renal cortex	3.55 ± 0.145	35.8 ± 2.55	18.5 ± 6.52	7.02[B] ± 3.96	62%
Renal medulla	6.93 ± 2.99	36.0 ± 20.4	23.8 ± 7.96	13.7[B] ± 5.21	42%
Lung	4.23 ± 1.53	17.9 ± 6.75	9.39 ± 2.79	5.12[B] ± 2.50	45%
Heart valve	7.72 ± 2.34	81.1 ± 28.1	77.5 ± 11.3	59.0 ± 24.4	24%
Myocardium	0.305 ± 0.477	3.14 ± 0.435	1.53 ± 0.570	0.902 ± 0.802	41%
Synovium	ND	14.8 ± 3.51	6.73 ± 3.80	4.36 ± 2.97	35%
Mean change	–	–	–	–	44%

All tissues p<0.02

- Reviewer requested Bonferroni multiplicity adjustment,
  - Claimed that with 9 tests, that none would remain positive
- So doing fewer tissues gives us more truth?

Multiplicity and Heterogeneity in Icatibant Phase 3

- Phase 3 primary endpoint failed and FDA did not approve
- Multiplicity did not allow the review of secondaries

Table 7 – Comparison of Key Efficacy Results: JE049 #2102 and JE049 #2103 EMA review page 33

	JE049 #2102			JE049 #2103		
Efficacy endpoint	**Icatibant**	**Tranexamic acid**	**p-value**	**Icatibant**	**Placebo**	**p-value**
Number of subjects in ITT population	36	38		27	29	
Median time to onset of symptom relief (h)[1]						
All attacks	2.0	12.0	<0.001	2.5	4.6	0.142
Cutaneous attacks	2.5	18.2	<0.001	3.4	10.0	0.221
Abdominal attacks	1.6	3.5	0.026	2.0	3.0	0.159
Median time to onset of symptom relief including all symptoms (h)[2]						
Cutaneous swelling	2.6	18.1	<0.001	3.1	10.2	0.039
Cutaneous pain	1.5	12.0	0.003	1.6		0.007
Abdominal pain	1.6	3.5	0.026	2.0	3.3	0.056
Nausea	1.3	1.5	0.550	1.1	2.3	0.080

1º

2º

Extensive positive results throughout the studies
Supportive data demonstrate efficacy

Table 7 – Comparison of Key Efficacy Results: JE049 #2102 and JE049 #2103

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Abdominal pain	1.6	3.5	0.026	2.0	3.3	0.056
Nausea	1.3	1.5	0.550	1.1	2.3	0.080
Response rate 4 h after start of treatment (%)	80.0	30.6	<0.001	66.7	46.4	0.176
Median time to relief of each symptom present in the pre-dose VAS other than the primary symptom						
Cutaneous swelling	2.0	7.5	0.220	3.5	10.0	0.053
Cutaneous pain	1.5	12.0	0.018	1.6	23.9	0.018
Abdominal pain	-[3]	-[3]	-[3]	2.1	10.0	0.046
Nausea	1.3	1.5	0.550	1.1	2.3	0.080
Median time to almost complete symptom relief (h)	10.0	51.0	<0.001	8.5	23.3	0.069
Median time to regression of symptoms according to the patient (h)	0.8	7.9	<0.001	0.8	16.9	<0.001
Median time to regression of visible symptoms according to the physician (h)	1.7	8.0	<0.001	6.5	14.0	0.240
Median time to overall patient improvement according to the physician (h)	1.5	6.9	<0.001	1.0	5.7	<0.001

p<.05

p<.10

P<.001 Patient View

P<.001 Doctor view

What was the impact?

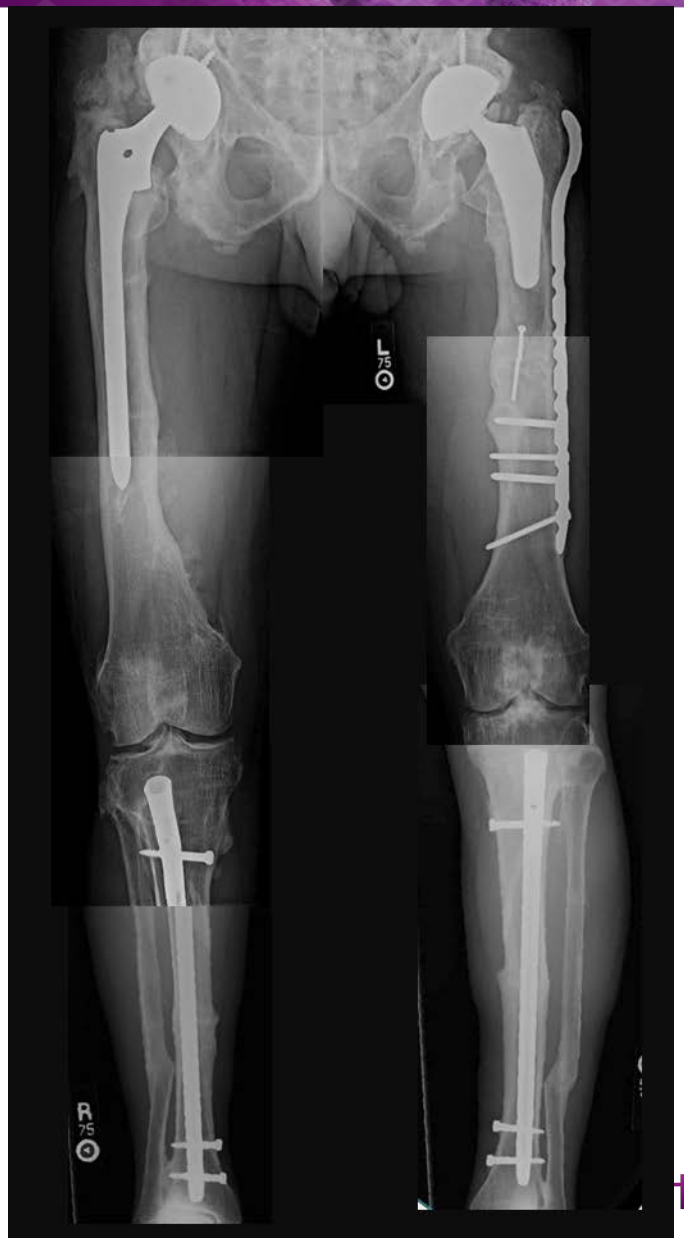
- Approved by EMA in 2008
- Second Phase 3 conducted and positive: approved in the US ~3 years later in 2011

- But what else happened?
  - Jerini stock collapsed on failure to get US approval
  - Company put into play and eventually sold to Shire
  - Assets divided up and product retained
  - Technology and effective team lost
    - Peptide modeling technology developed by Jerini and its team lost as well as essentially their company

Burosumab MAb Against FGF23 for XLH

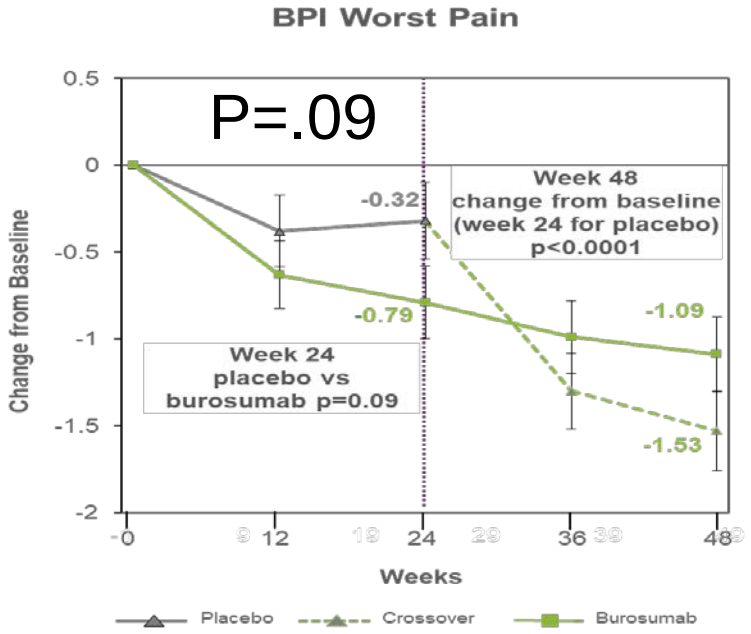
Increased low serum phosphate associated with bone disease

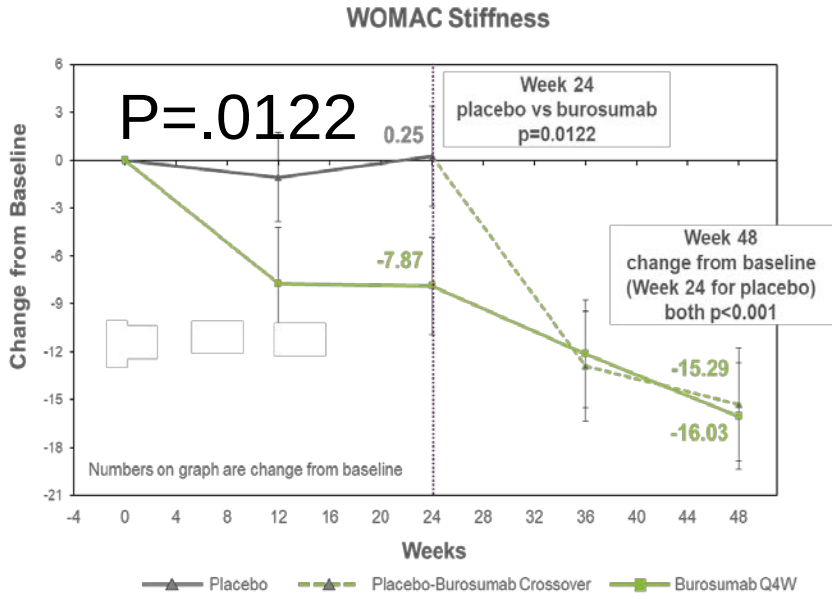
- **XLH:** Excess FGF23[1] causes excess renal phosphate loss
- **Key symptoms:** Rickets, deformity, short stature, fractures, pain, osteomalacia, stiffness
- **Standard of care:** Oral phosphate + Vitamin D (nephrocalcinosis risk)
- **US prevalence:** ~12,000
- **Regulatory Review Status:**
  - EU: Positive CHMP opinion 12/2017
    - EC decision expected early 2018
  - US: PDUFA date: April 17, 2018



[1]Fibroblast growth factor 23

Secondary Endpoints: Crysvita
Multiplicity Adjustment: What does it mean?

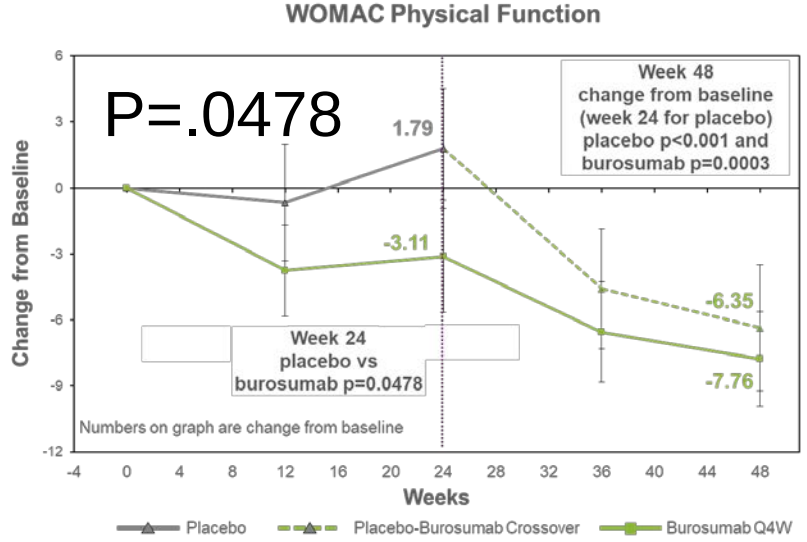




WEEK 24: Only Stiffness Positive

WEEK 48: All Three Positive

<u>Exploratory Endpoint:</u>
Fracture Healing p <.001, OR 17



Value of a Rare Disease Center of Excellence (COE) at FDA

- Centralized support for new methodology and endorsement of innovation in dev programs
- Support for individual divisions less familiar with new methods or management of rare diseases
- A driving force for innovation in studies and analyses to enhance the discovery of truth
- Assures rigor in how approaches are taken in details beyond expertise of review divisions
- **Heterogeneity issues for rare diseases can be addressed and managed optimally**

The Golden Age of Rare Disease Treatments

- Exciting times for rare diseases
- More diseases, more technologies
- Opportunity to change the future for all time
- Time for all of us to do our best in assuring we get the right answers for patients

Managing Heterogeneity Is Key