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RARE DISEASE WORKSHOP SERIES
Improving the *Clinical Development Process*

Urinary GAG as a biomarker in MPS disorders

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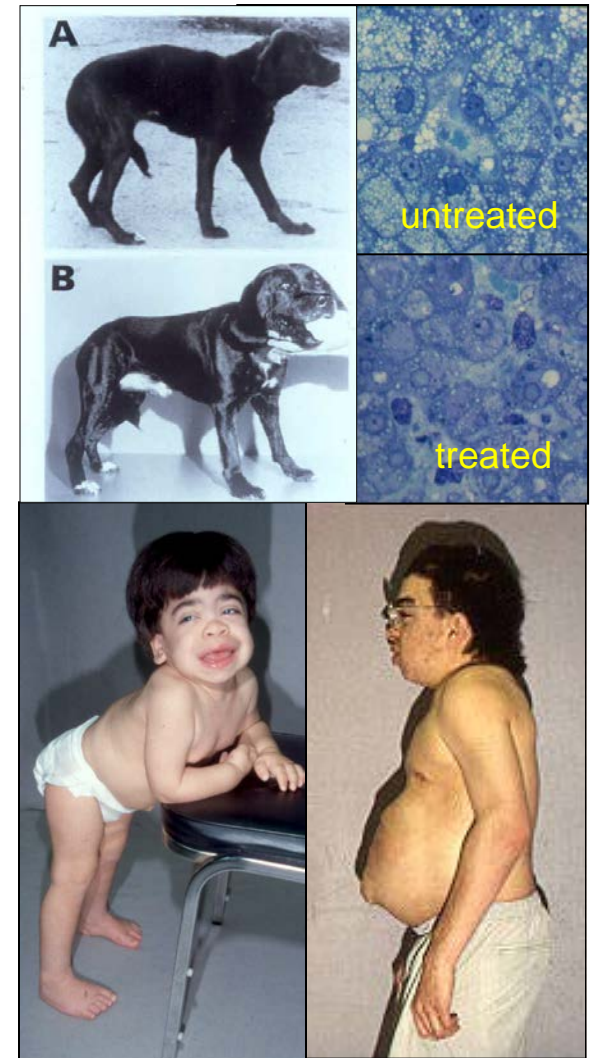
November 8, 2011



Development of Enzyme replacement therapy (ERT) for Mucopolysaccharidosis I

Aldurazyme® (laronidase)

- Deficiency of Iduronidase
- Multi-system lysosomal storage disease
- Canine model of MPS I
- ERT therapy reverse deficiency
- Surrogate measures of Storage
 - Liver/spleen size by MRI
 - Urinary GAG (urGAG) by chemical assay



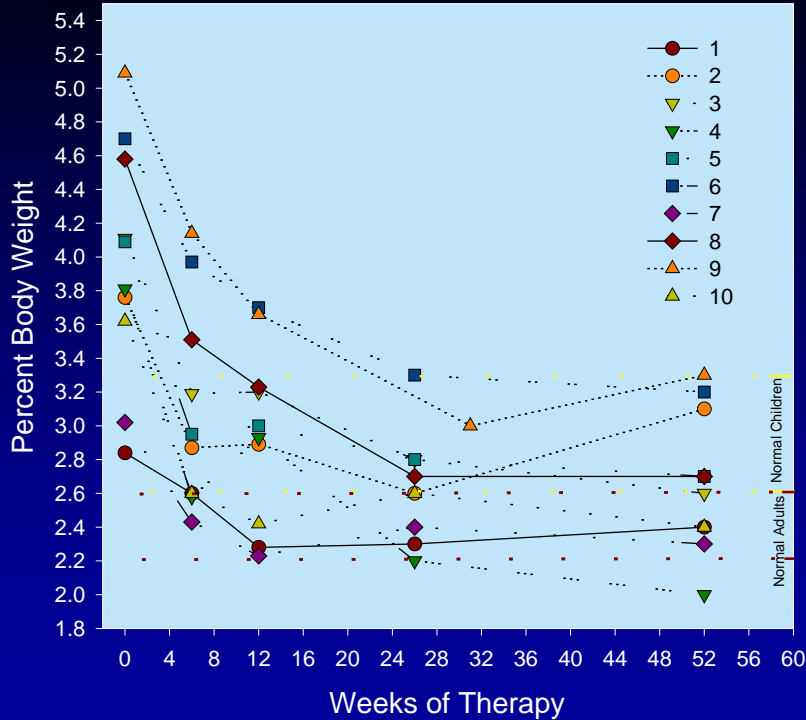


Aldurazyme[®] (laronidase) Phase 1/2 Study Storage-related surrogate endpoints

Liver Size

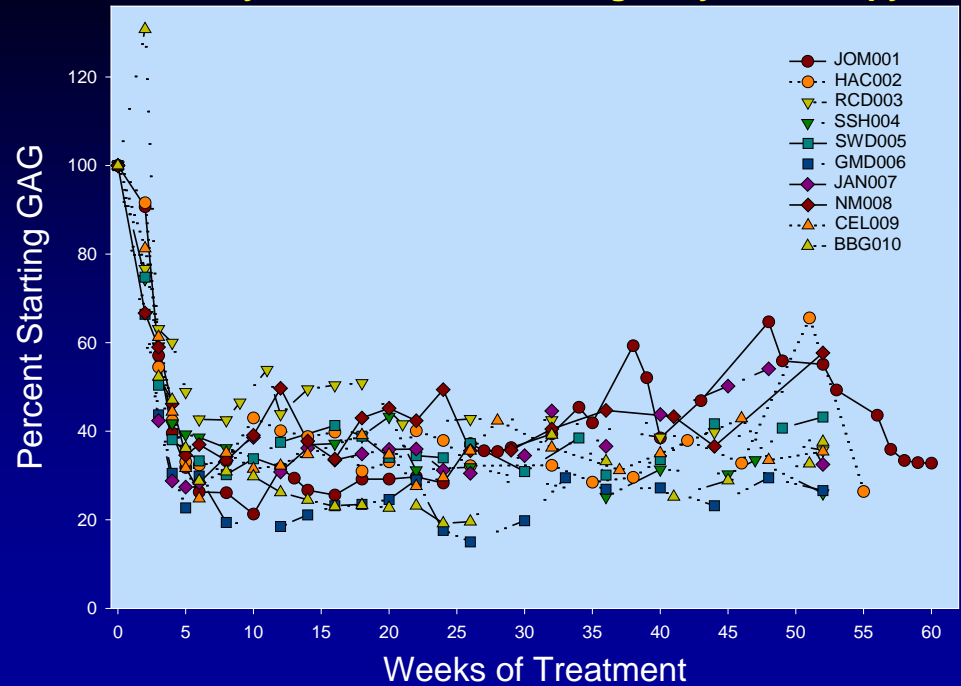
Urine GAG

Reduction in Liver Volume During Enzyme Therapy



P<0.001

Urinary GAG Excretion During Enzyme Therapy

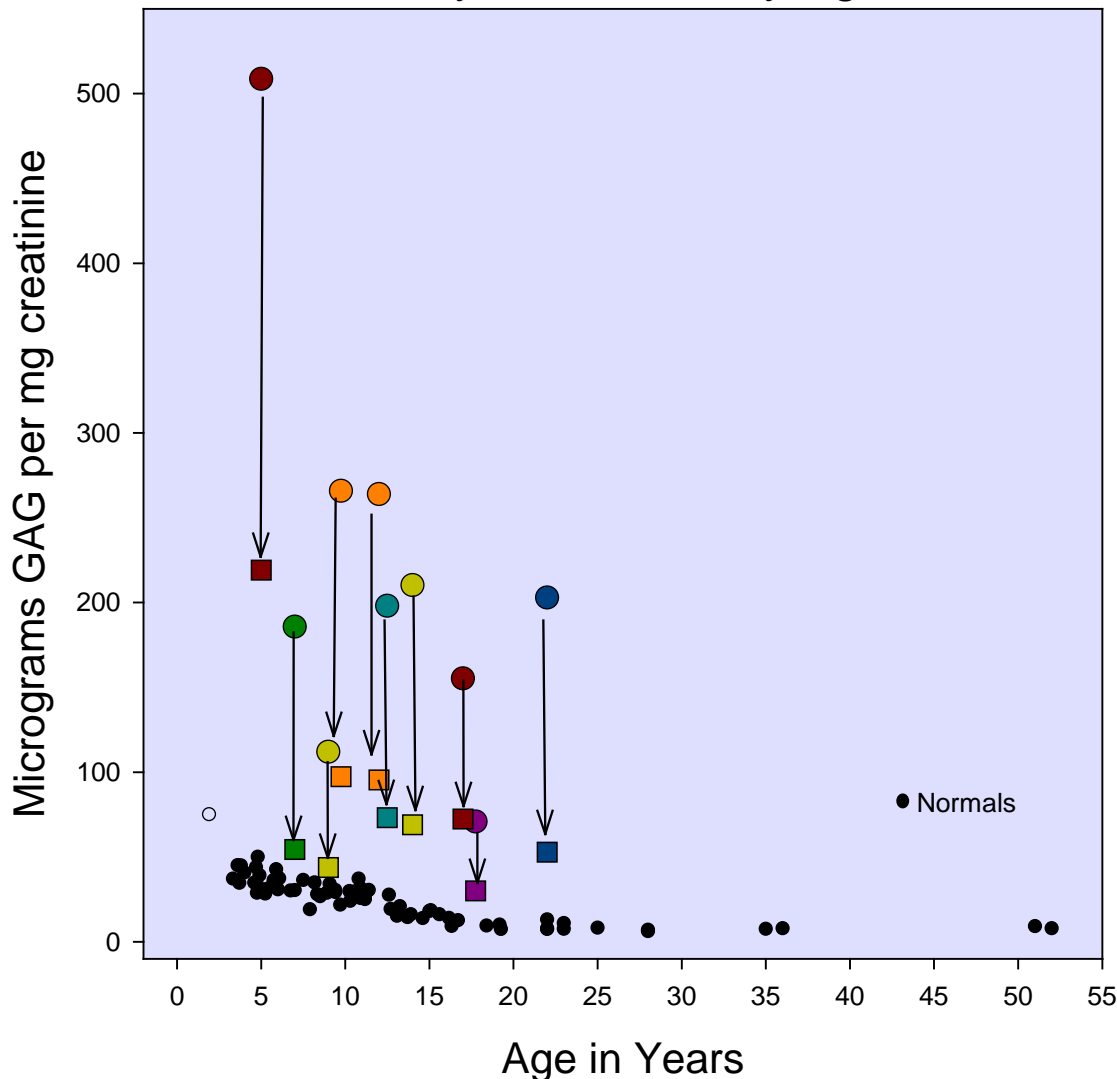


P<0.001



Urinary GAG decreases 80% of the amount above the 95%ile for urGAG

Urinary Total GAG By Age



Substantial near normalization in Urinary GAG

How much change is enough?

Calibration of Change relative to potential clinical efficacy is a challenge.



What does change in urinary GAG really mean clinically?

- Is urinary GAG predictive of clinical effect?
- How much GAG reduction is enough?:
“Calibration question”
- How can urine reflect other tissues with disease?



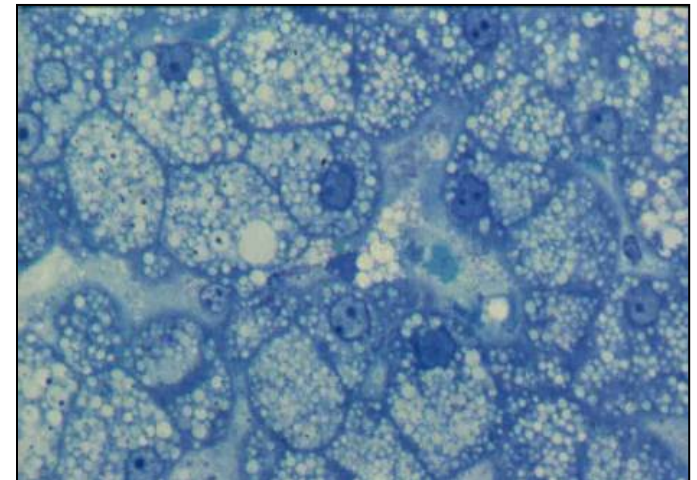
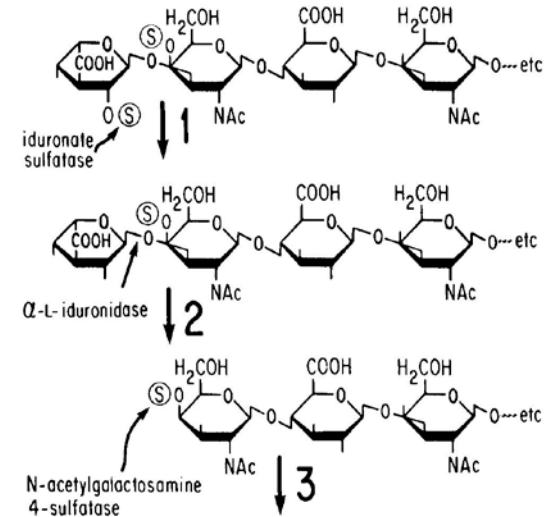
Clinical experience in MPS Diseases now is extensive with urGAG

- Aldurazyme in MPS I
- Naglazyme in MPS VI
- Elaprase in MPS II
- Galsulfase in MPS IVA
- Plus animal model work
 - MPS VII mouse
 - MPS I dog and mouse



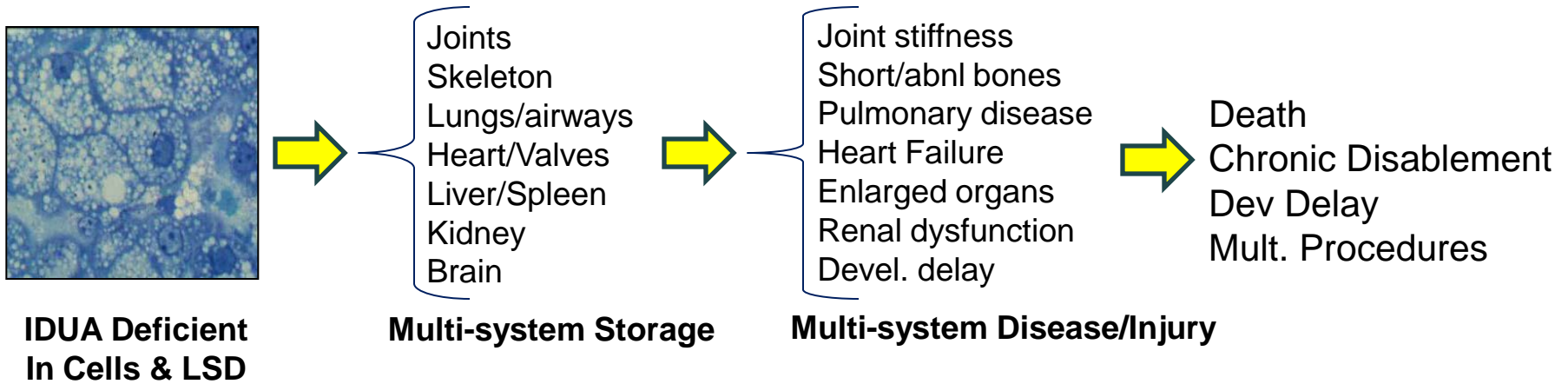
Urinary Glycosaminoglycans (urGAG) Measured as total Alcian Blue binding GAG

- Primarily Dermatan Sulfate, some Heparan
- Accumulate in cells, and then are dumped out with cell lysis
- Large molecular weight anionic sugars derived cellular sources
 - Renal tubular cells
 - Some systemic filtration
- Assay sensitive and specific with large dynamic range
- Levels elevated 5 -30 fold over normal

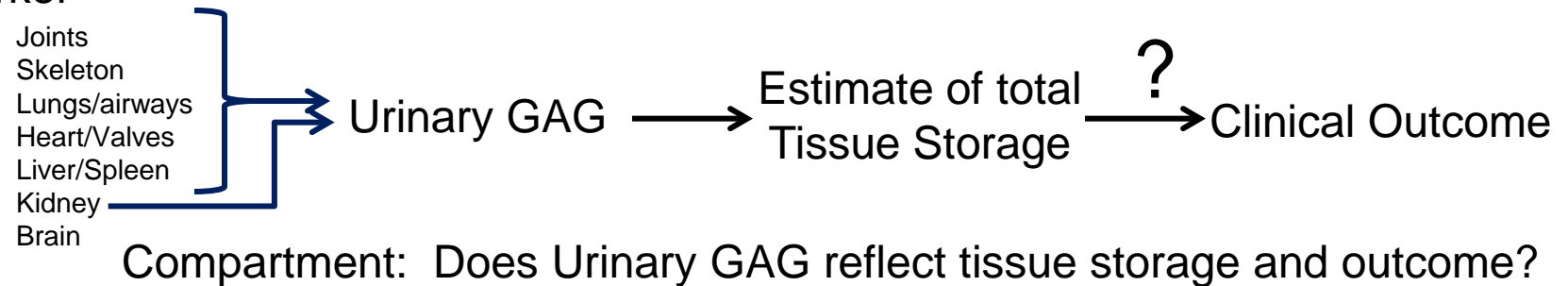




Pathophysiologic Map of MPS I & urGAG



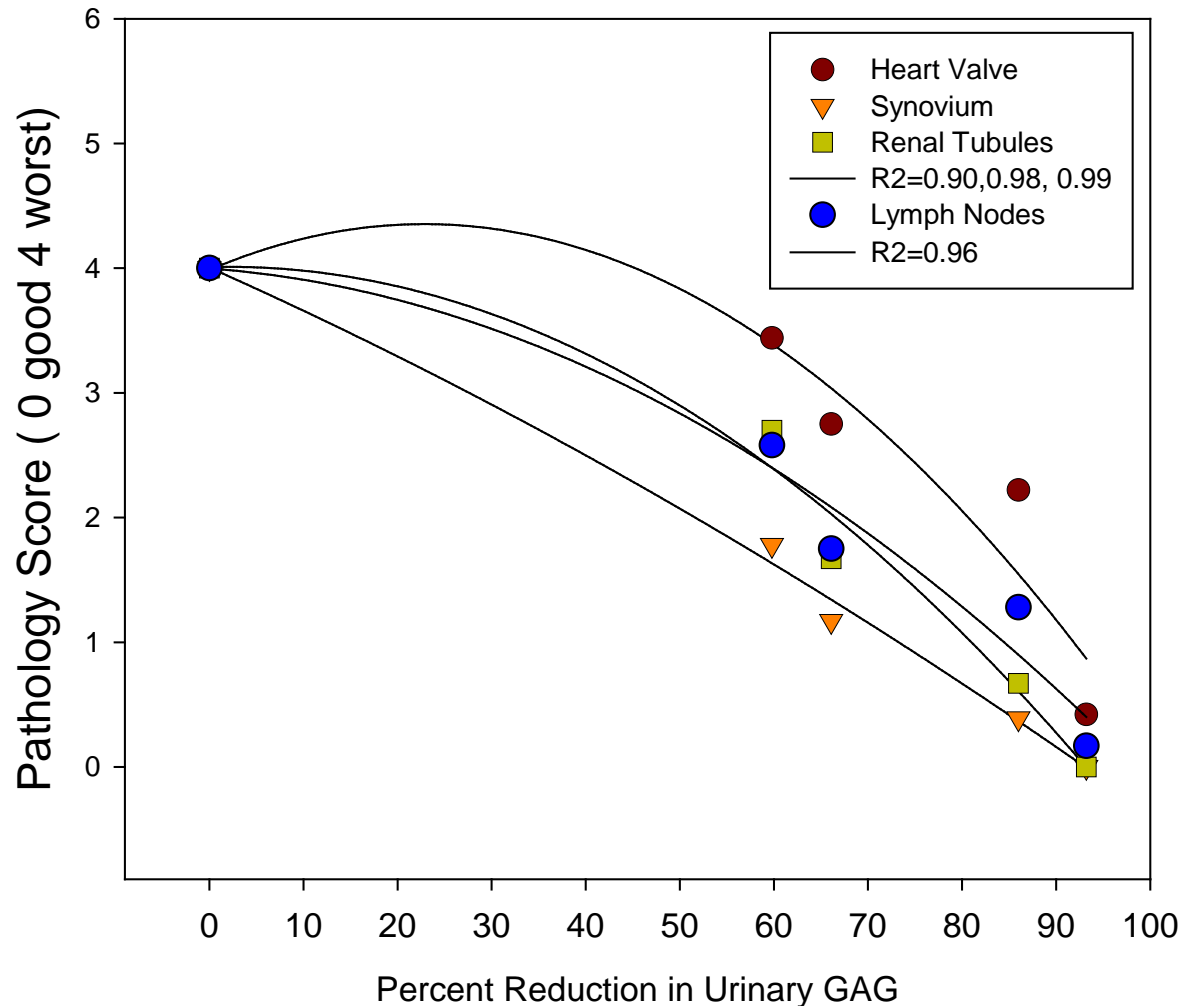
Biomarker





Blinded pathologic scoring correlates in diverse tissues with reduction in urinary GAG in canines

Pathologic Scoring in Key Tissues

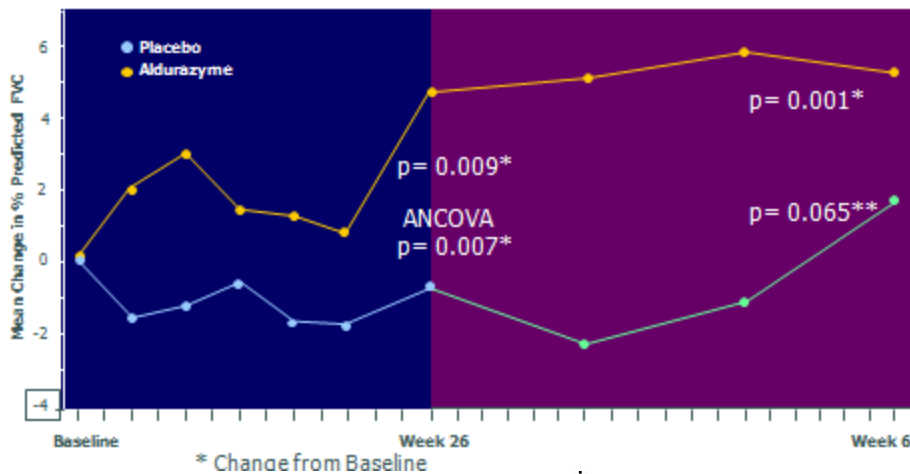




Phase 3 RDBPC Study in 45 MPS I Patients Positive Was urGAG predictive of outcome?

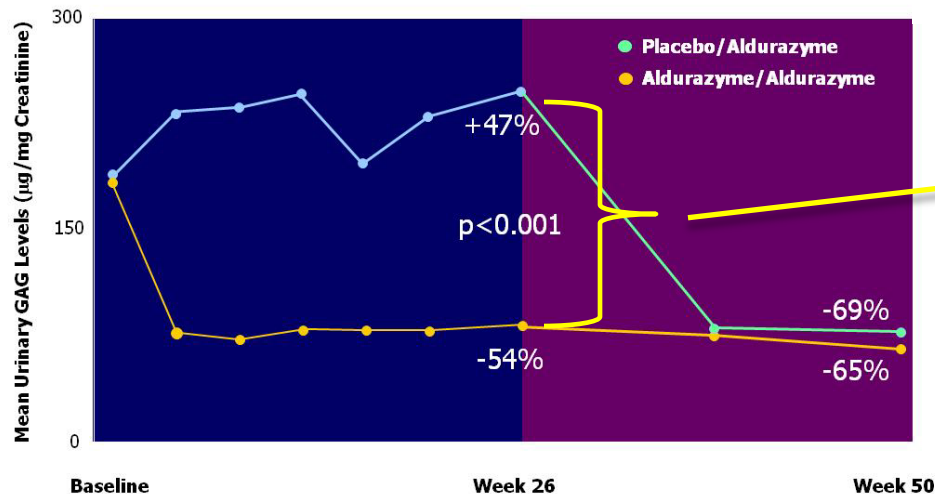
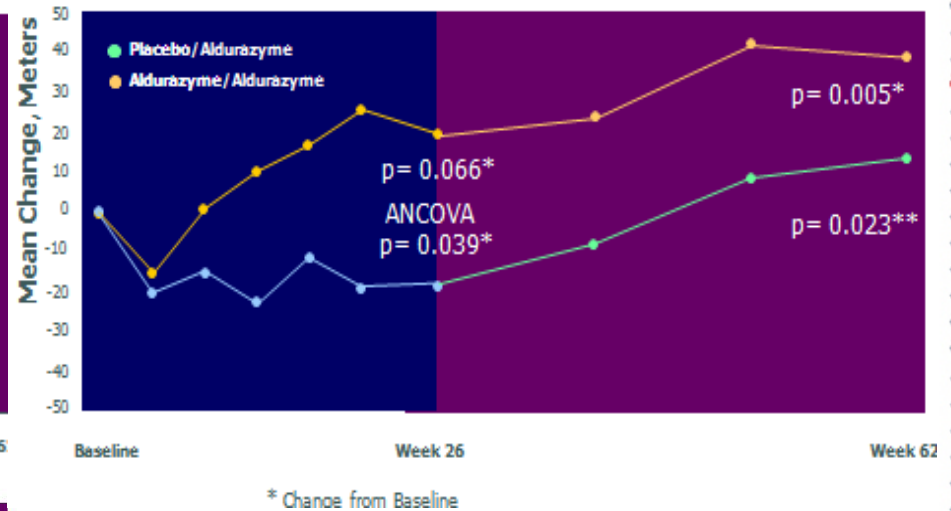
FVC (Patients selected for <80%)

Double-Blind Open-Label Extension



6MWT (No patient selection)

Double-Blind Open-Label Extension



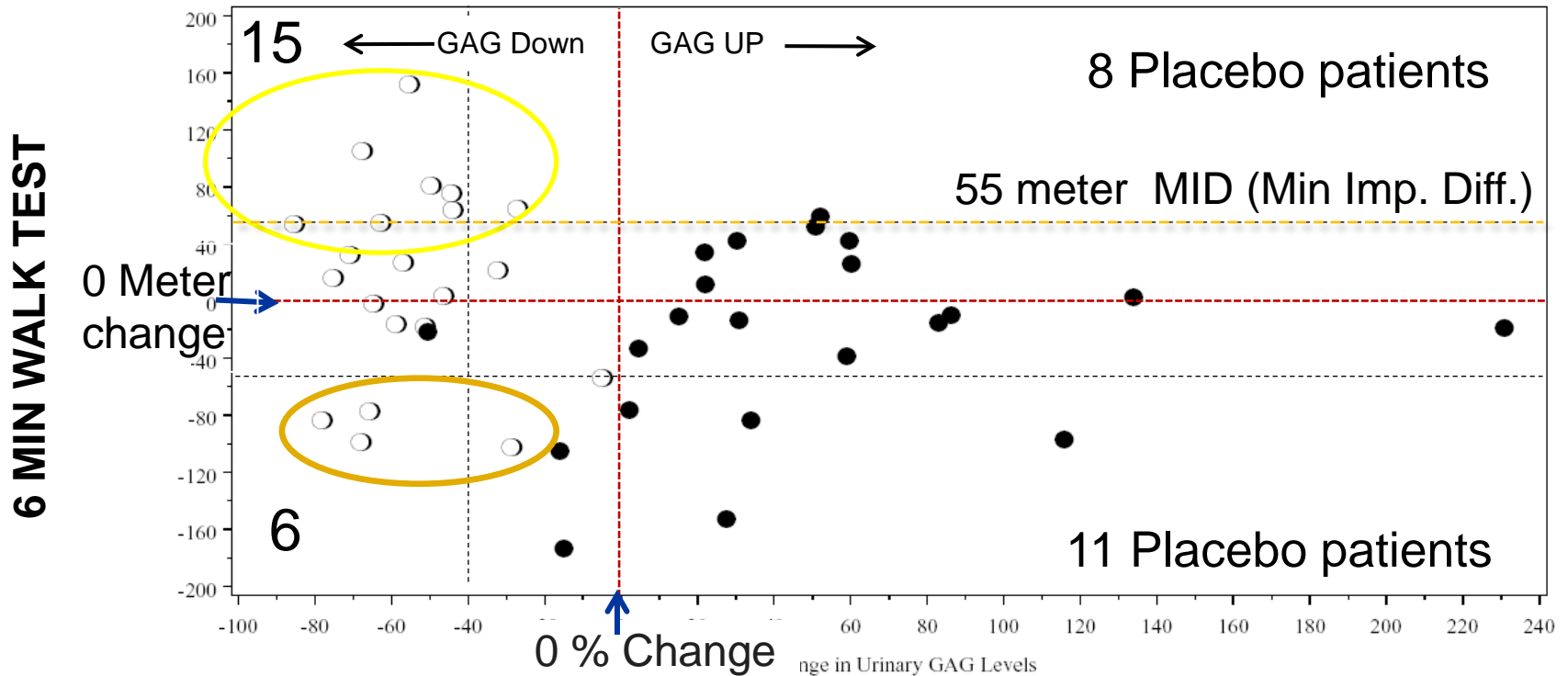
Urine GAG

Difference between
Placebo and treated



Urine GAG Reduction has Weak Linear Correlation to 6MWT *But does segregate those that improve significantly* 45 MPS I patients RDBPC treated with laronidase for 6 months

Change from Baseline to Week 26 in Six-Minute Walk (m) versus % Change from Baseline to Week 26 in Urinary GAG Level (ug/mg Creatinine)
Intention to Treat Population



Placebo ●
rhIDUA ○

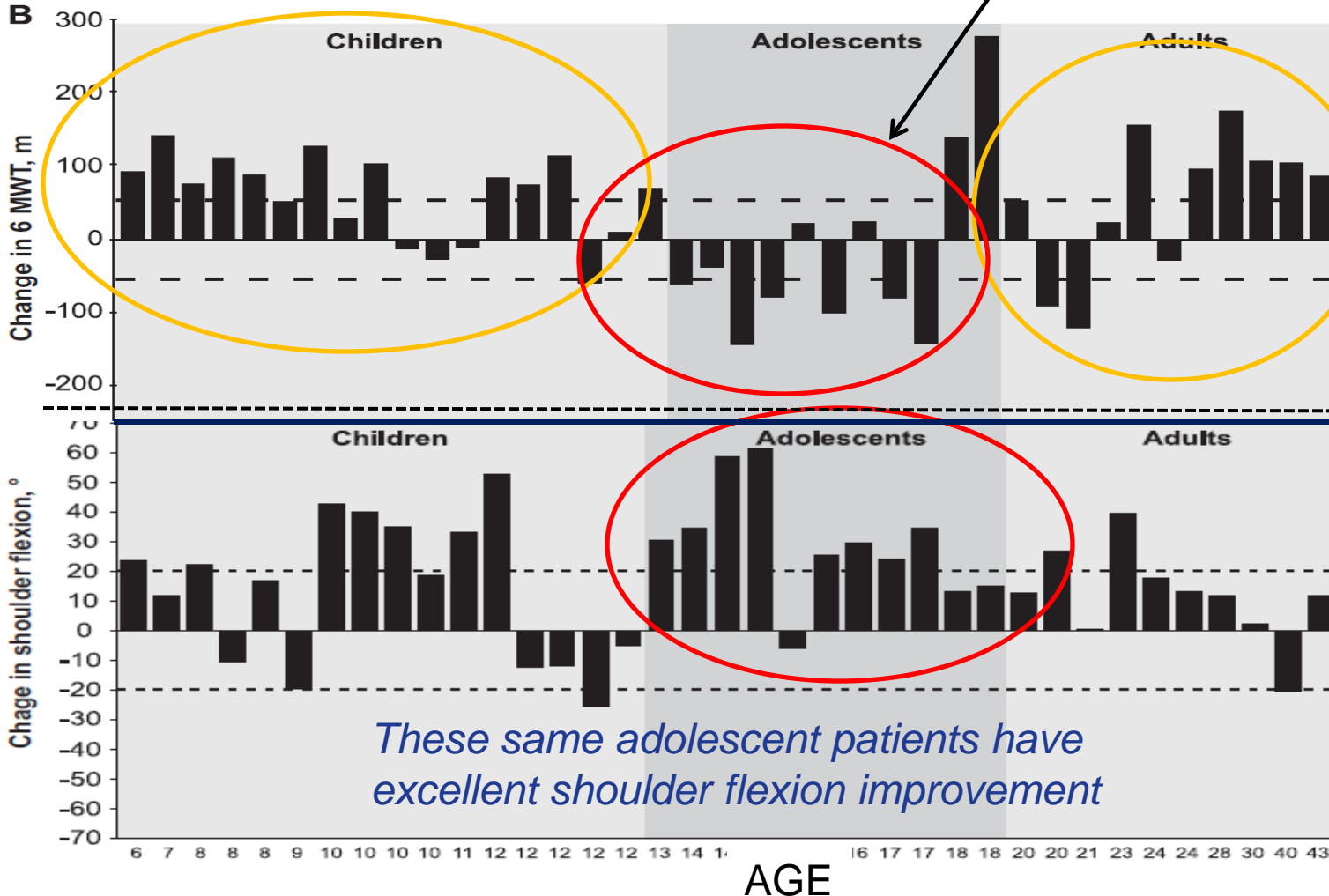
URINE GAG PERCENT CHANGE



MPS I Patients on Laronidase Change in 6 MWT over 3.5 Years

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

Cervical spinal cord compression in some advanced Hurler-Scheie patients



SHOULDER FLEXION: 6 MIN WALK TEST



Single clinical endpoints may not reflect patient outcome completely Correlations of clinical endpoints with CHAQ/HAQ

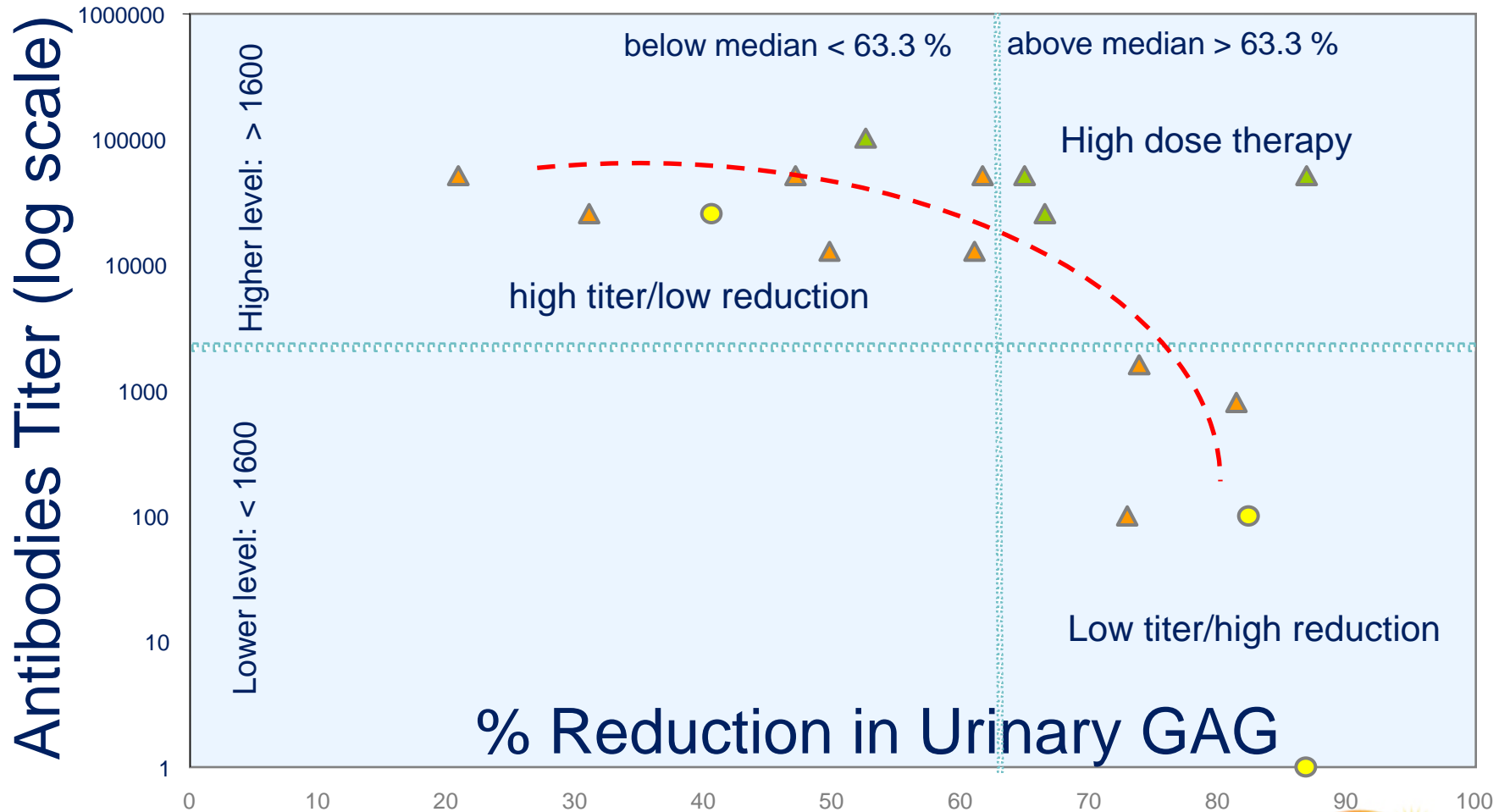
- In combined outcomes from 3 MPS Phase 3 studies, the composite score was more strongly correlated with disability than the individual scores

Objective assessment	Pearson Correlation with CHAQ/HAQ*	P-Value
Continuous scores		
6MWT	-0.24	0.032
FVC	-0.19	0.091
Shoulder	-0.23	0.051
O'Brien rank score (6MWT, FVC, Shoulder)	-0.50	<0.001

*Patient-assessments pooled from treatment and placebo arms (n=76); Higher CHAQ/HAQ scores indicate greater impairment .



Immune response and urinary GAG excretion in young MPS I

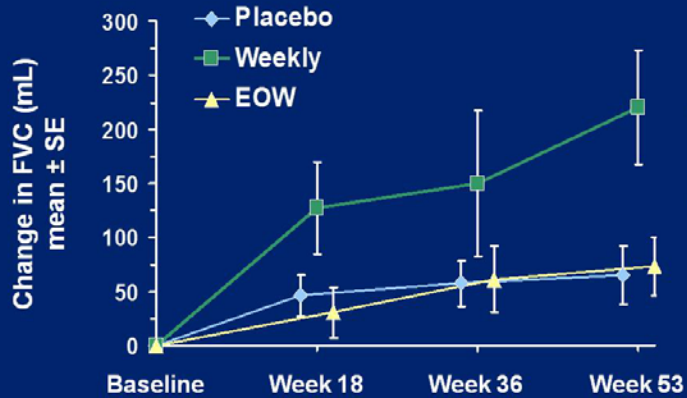


● 100 U/kg, MPS I HS ▲ 100 U/kg, MPS I/H ▲ 200 U/kg, MPS I/H



Urinary GAG Predicts Clinical Effects in Elaprased Ph 3 Effects

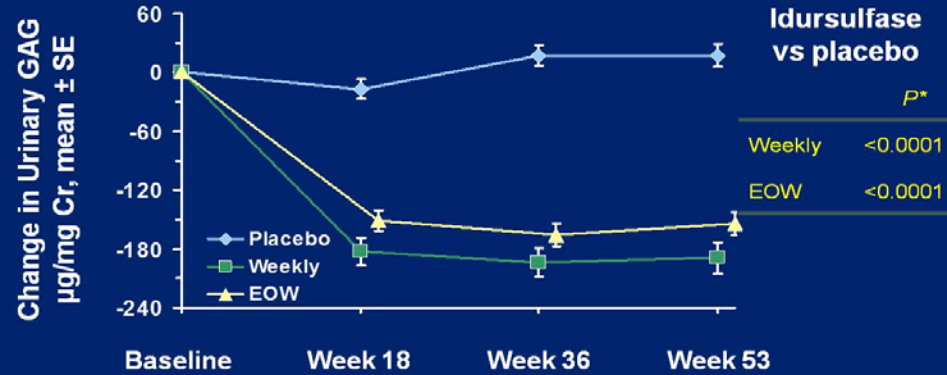
FVC



Idursulfase vs placebo

	<i>P</i> *
Weekly	0.0011
EOW	0.3735

urGAG



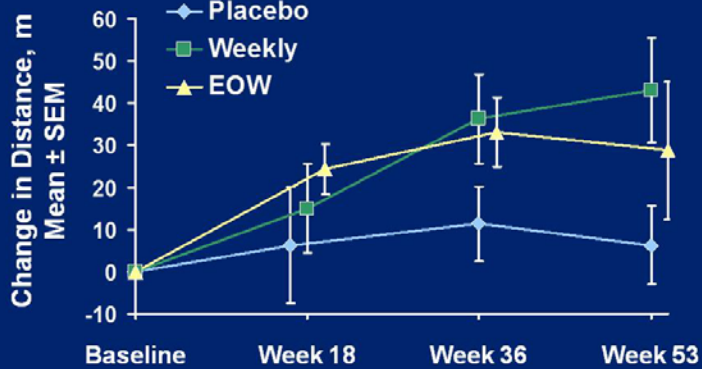
Idursulfase vs placebo

	<i>P</i> *
Weekly	<0.0001
EOW	<0.0001

Idursulfase Weekly vs EOW, *P** = 0.0176
**P* based on ANCOVA at Week 53

**P* based on ANCOVA at Week 53

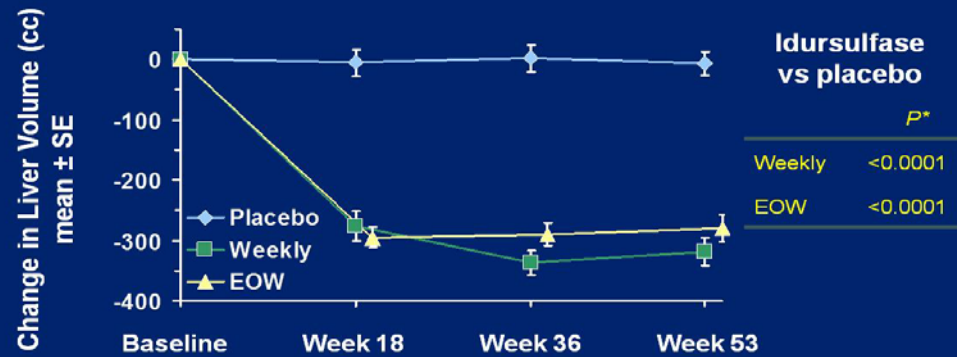
6MWT



Idursulfase vs placebo

	<i>P</i> *
Weekly	0.0131
EOW	0.0732

Liver



Idursulfase vs placebo

	<i>P</i> *
Weekly	<0.0001
EOW	<0.0001

Idursulfase Weekly vs EOW, *P** = 0.3963
**P* based on ANCOVA at Week 53

**P* based on ANCOVA of % change at Week 53



Qualifying Urinary GAG for ERT in MPS Diseases

1) Disease Criteria

- Cause of disease clearly understood
- Pathophysiology mechanisms reasonably understood

2) Drug Criteria

- Drug mechanism of action is direct and known
- Drug pharmacokinetics, pharmacodynamics and metabolism are relevant to the disease process being treated

3) Biomarker Criteria

- Biomarker has direct relationship to important disease process
- Biomarker assay is sensitive and specific with a sufficient dynamic range and able to calibrate change with change in pathology
- Sampling compartment predicts disease compartment/tissue

4) Preclinical Model Data Criteria

- Preclinical treatment studies show dynamic dose-response relationship on pathophysiology
- Preclinical studies show a clinical effect but cannot be required to show a clinical effect since models not clinically the same
- Survey of human disease show a relationship to biomarker