



# Disclaimer:

Presentation slides from the Rare Disease Workshop Series are posted by the EveryLife Foundation for Rare Diseases for educational purposes only. They are for use by drug development professionals and statisticians, and are not to be used to guide the prescribing or use of any of the drugs mentioned in the slides. To obtain information on a particular drug, refer to the drug labeling. Do not reproduce or distribute the slides (full set or any portion of) without the permission of the author.



**RARE DISEASE WORKSHOP SERIES**  
Improving the *Clinical Development Process*

# Spinal Fluid Substrate Markers in MPS I

Agnes Chen, MD

8 November 2011

Los Angeles Biomedical Research Institute at Harbor-  
UCLA Medical Center



# Glycosaminoglycans as a biomarker for mucopolysaccharidoses

- Glycosaminoglycans are the direct substrate for the enzymes deficient in the mucopolysaccharidoses.
- Published assays of glycosaminoglycans
  - Dye-based (e.g. Alcian Blue, dimethylmethylene blue)
  - Mass spectrometry



# Questions

- Is there a substrate assay (e.g. GAG for MPS) that is sensitive and specific enough to distinguish normal from abnormal?
- Is the assay responsive to treatment changes?
- Does the sampling compartment (e.g. CSF) represent the clinically relevant compartment (brain)?

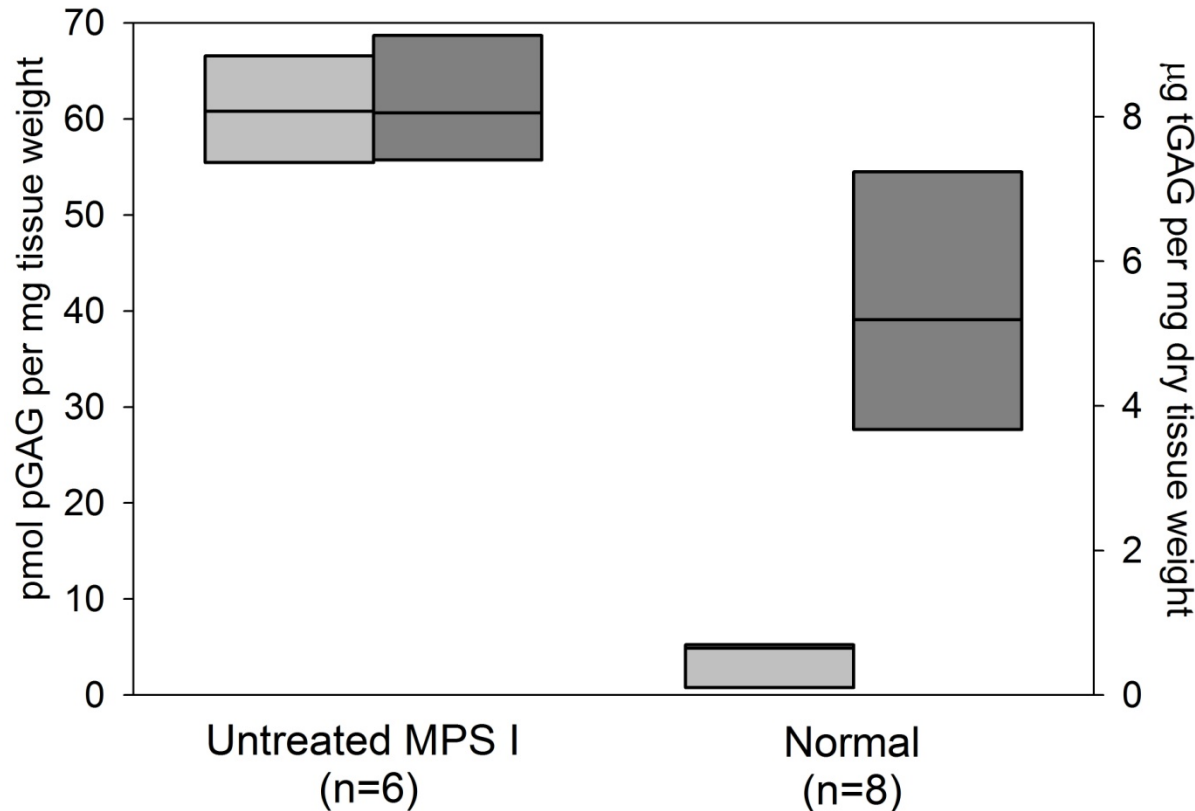


## **Sensi Pro NRE: New assay to measure only substrate accumulating due to deficient enzyme (pathologic GAG)**

- Quantifies the non-reducing ends from the GAG fragments that accumulate in MPS patients
- Large dynamic range
- MPS class specific



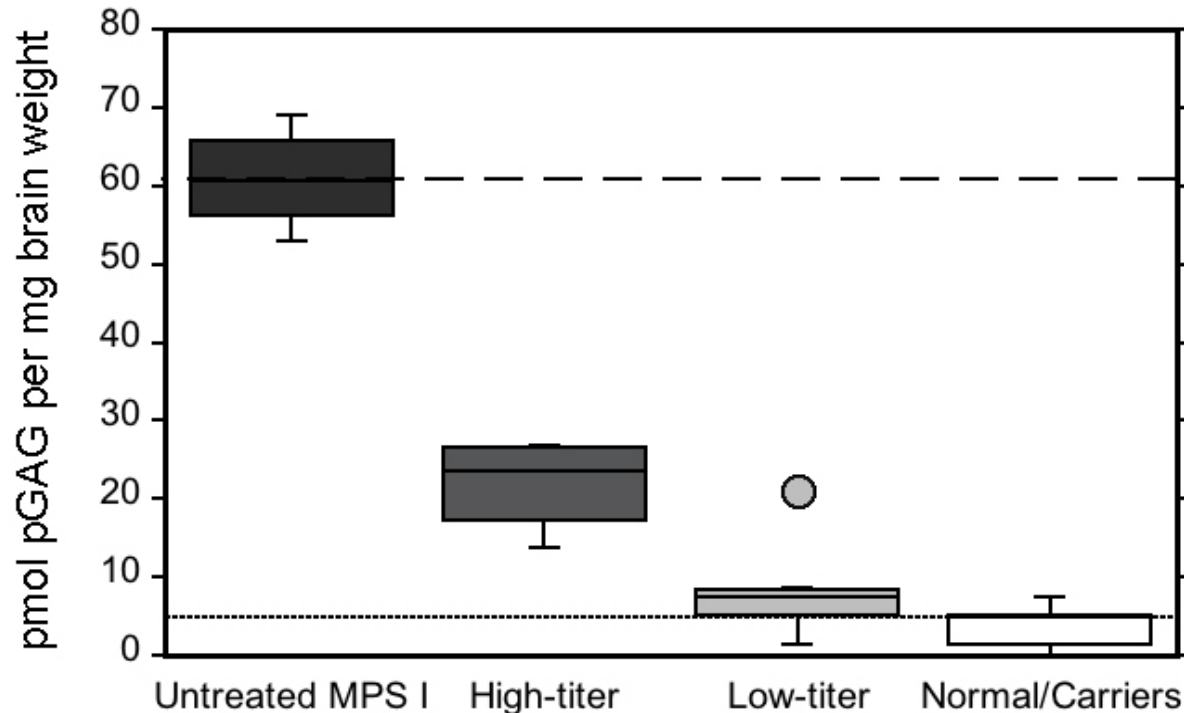
# GAG in brain: Pathologic GAG (light gray) vs. Total GAG (dark gray)



Median value represented by horizontal line.

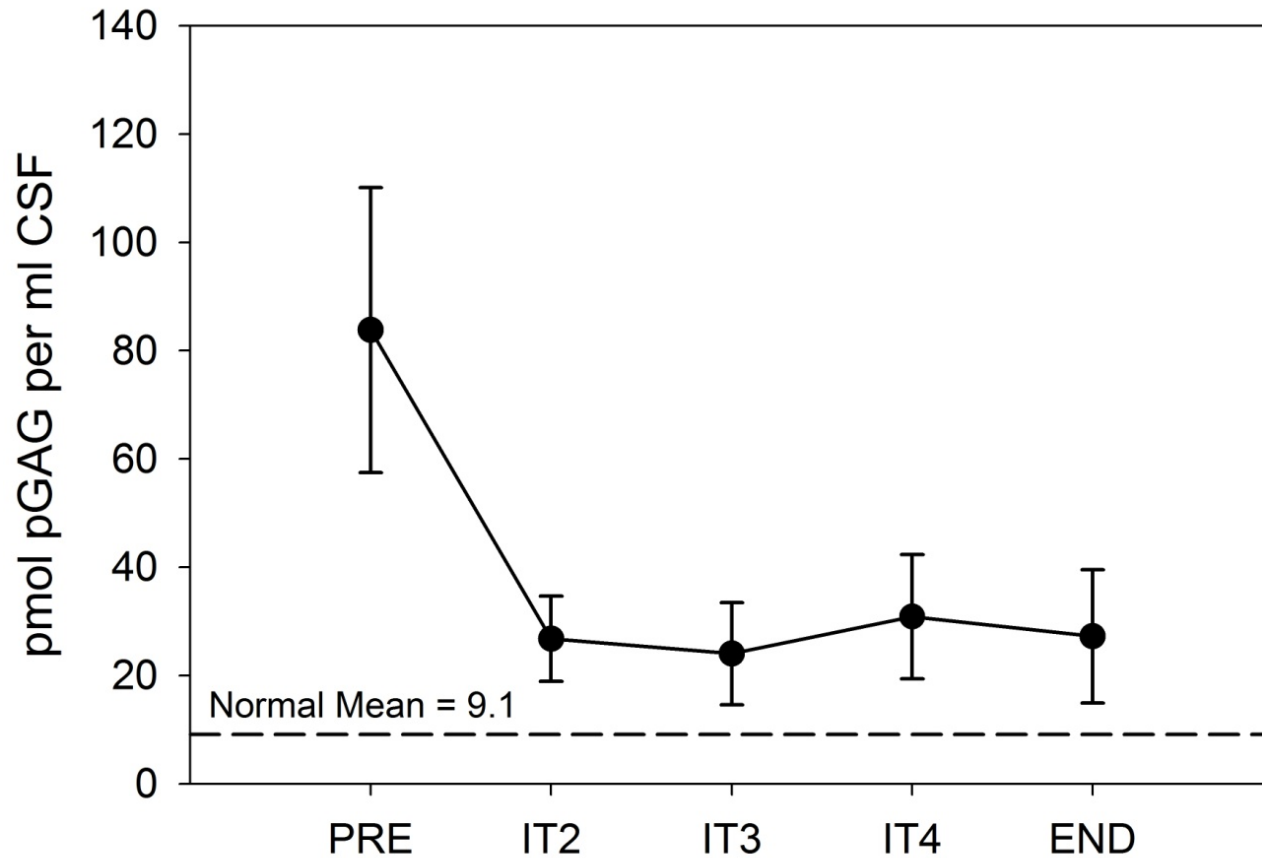


# Pathologic GAG in the brains normal and MPS I dogs (treated dogs are separated by tolerance status)





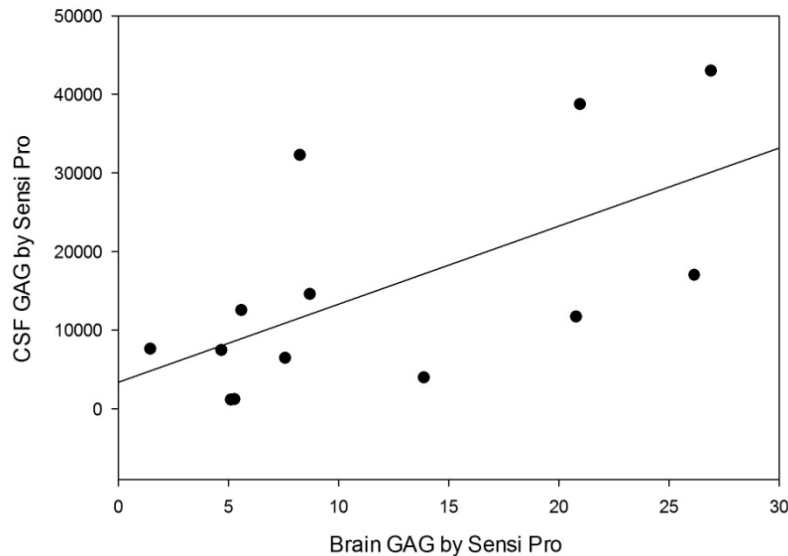
# CSF pGAG before and after treatment



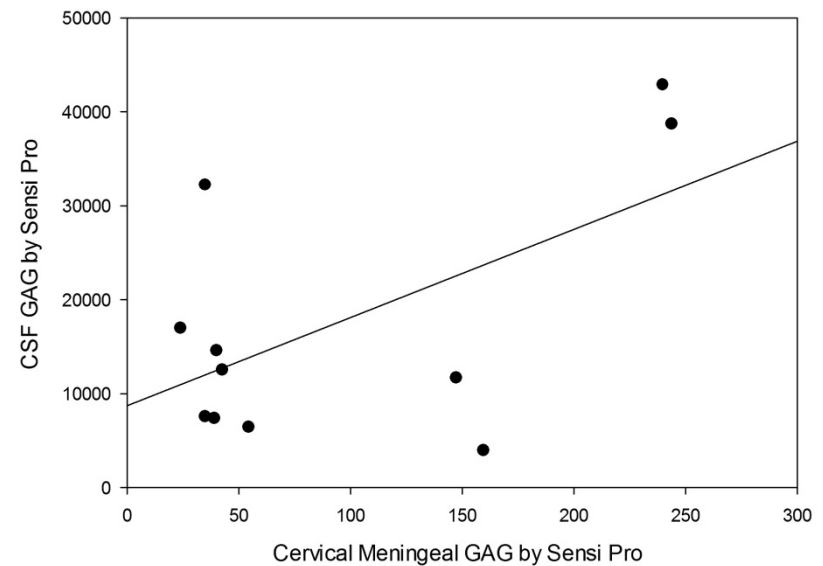


# CSF pGAG is more closely correlated to brain than the meninges

**CSF and brain:  $r=0.66$**

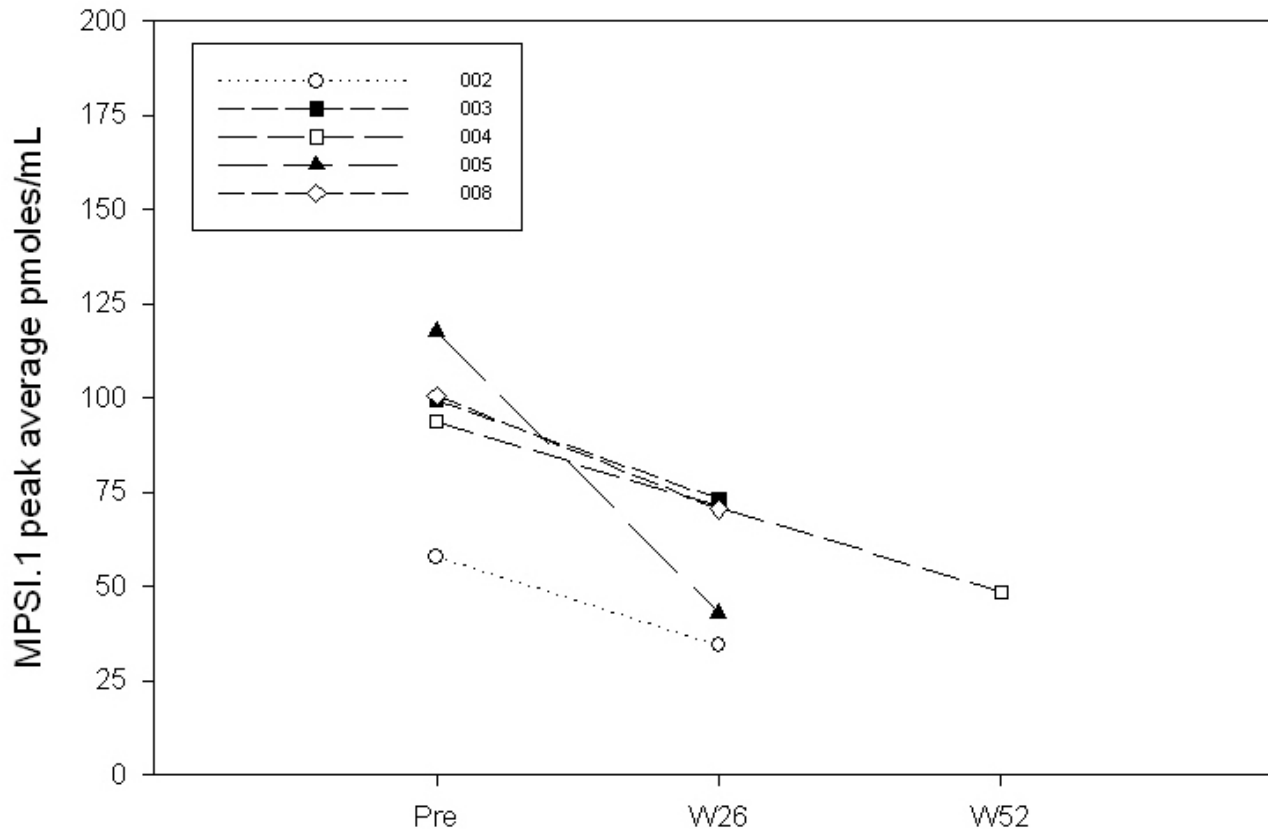


**CSF and meninges:  $r=0.39$**



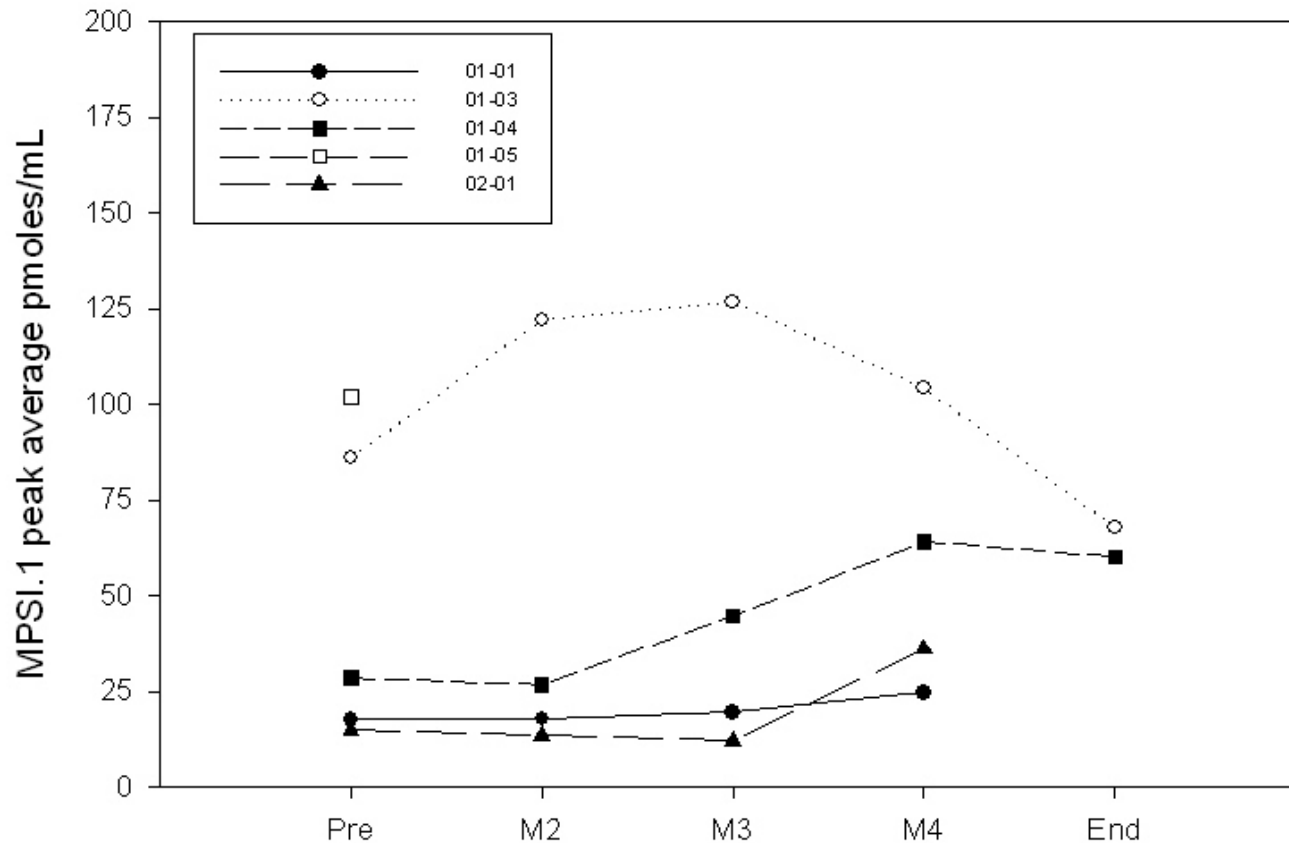


# CSF GAG from phase I/II clinical trial





# CSF GAG in MPS I spinal cord compression trial





# Questions

- Is there a substrate assay (e.g. GAG for MPS) that is sensitive and specific enough to distinguish normal from abnormal?
- Is the assay responsive to treatment changes?
  - The Sensi-Pro assay detected substantial differences between normal, abnormal, and treated animals.
- Does the sampling compartment (e.g. CSF) represent the clinically relevant compartment (brain)?
  - Need more correlation data. Can we demonstrate that incremental changes in the biomarker correlate with incremental changes in the brain?



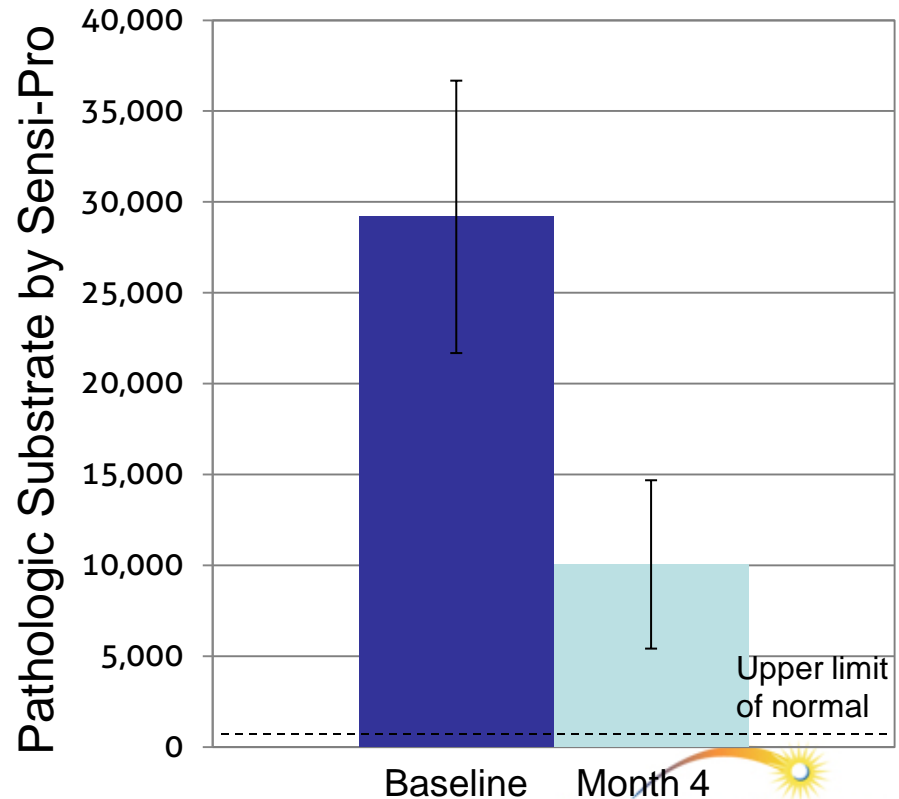
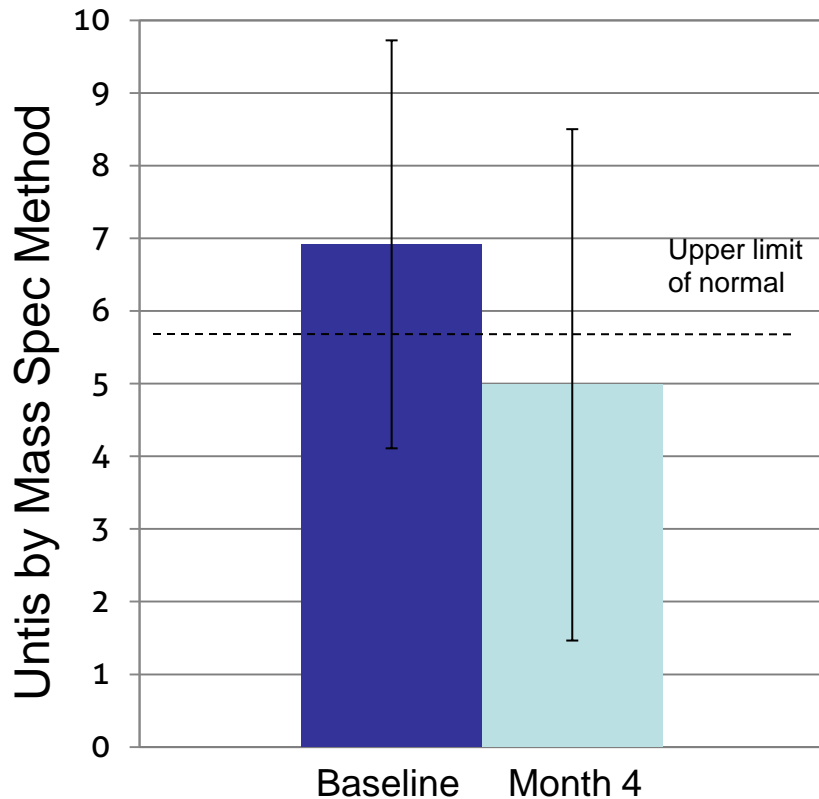
# EXTRA SLIDES



# Comparison of Mass Spectrometry Assay and Sensi-Pro Assay

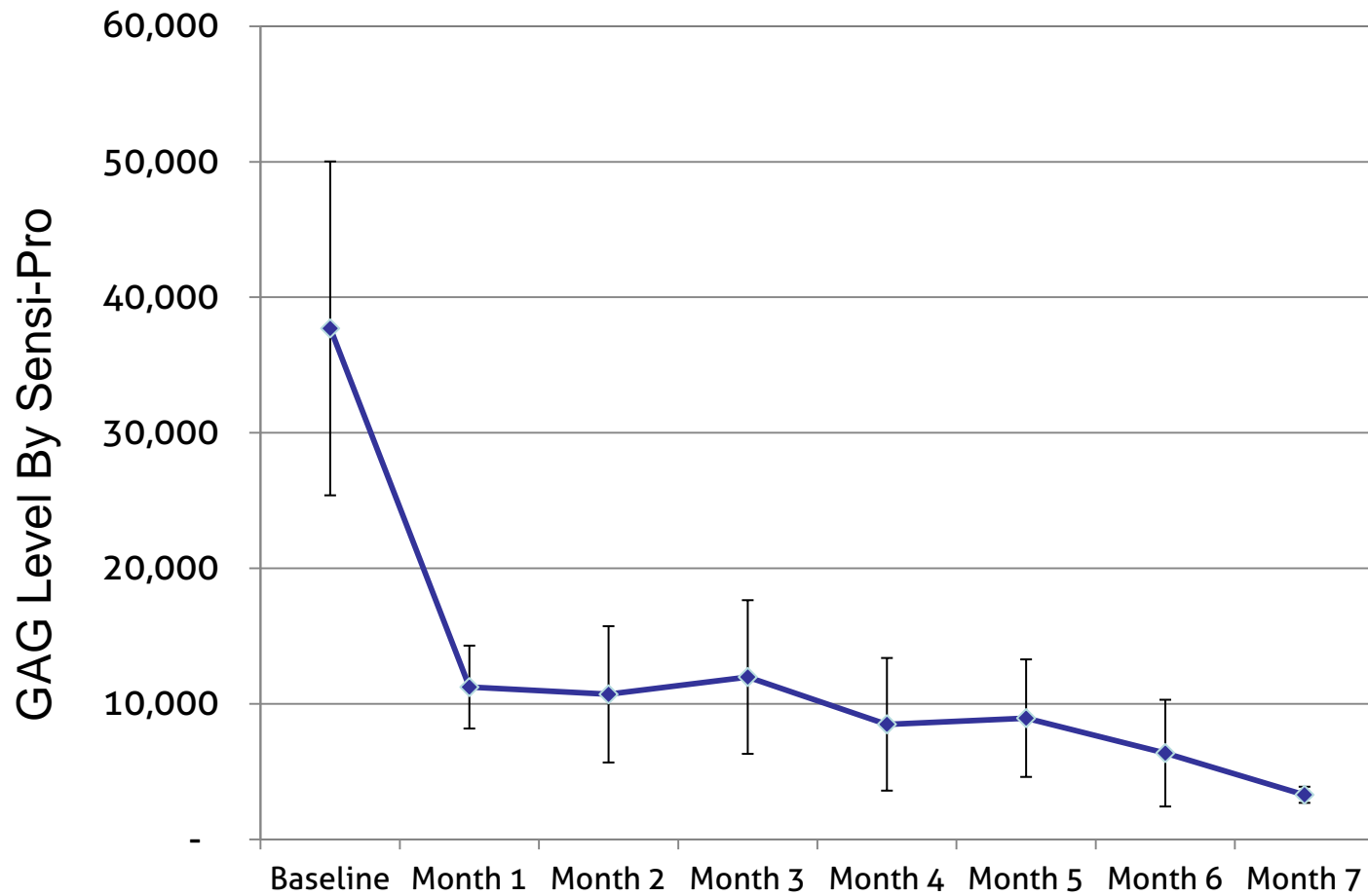
## Mass Spectrometry Assay

## Sensi-Pro NRE Assay





## Serum GAG Levels as Measured by Sensi-Pro (MPS I Dogs Treated with IV / IT rhIDU)



### Notes

- Serum GAGs in wild type dogs were ~ zero (n=2)
- Error bars are standard deviation