Enzyme replacement therapy (ERT) for mucopolysaccharidosis VII (MPS VII; Sly's Syndrome) reduces lysosomal storage in a 36-week Phase 1/2 clinical study

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Disclosure Information

WORLD Symposium™ 2015

(Emil Kakkis)

I have the following financial relationships to disclose:

Employee and Stockholder of Ultragenyx Pharmaceutical Inc.

- and -

I will discuss the following off label use and/or investigational use in my presentation:

UX003 (recombinant human beta-glucuronidase; rhGUS) for MPS VII

rhGUS for MPS VII Clinical Development Plan

Phase 1/2 open-label study
Assessing the safety, efficacy and dose of UX003
Ongoing

Phase 3 Pivotal Study
Randomized, Placebo-controlled, blind-start, single-crossover study to assess the safety and efficacy of UX003
Enrolling

Long-term efficacy and safety study
All subjects on UX003 (Extension study)
Planned

Under 5 and Infant Study
Open-label in patients < 5 years of age, including those with Hydrops Fetalis
Planned for 2015

Phase 1/2 Study rhGUS Objectives

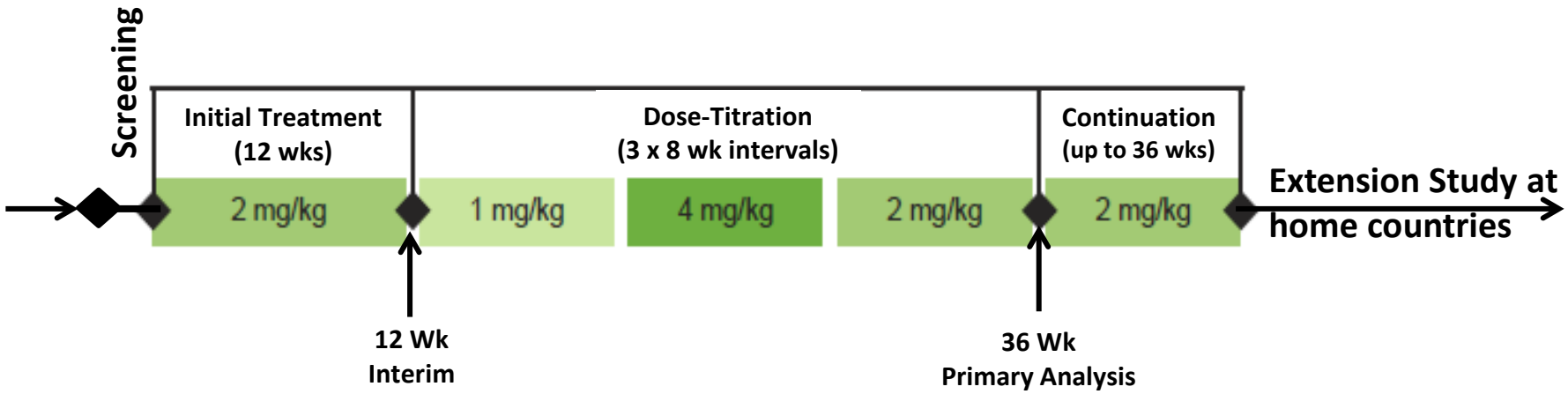
- Primary objectives
  1) Safety and tolerability
  2) Evaluate impact on lysosomal storage
  3) Establish the dose for rhGUS

- Secondary objectives
  - Pulmonary function
  - Shoulder range of motion
  - Physical function including walking and stair climbing capacity
  - Patient reported outcomes
  - Height and weight growth velocity

- Key other objectives
  - Liver and spleen size
  - Pharmacokinetics (PK)

Study is not powered to assess clinical endpoints

rhGUS Phase 1/2 Study Overview



- N = 3
  - Confirmed Dx (enzyme assay/genetic test)
  - 5 – 30 years old inclusive
  - uGAG excretion >2-fold over normal
  - No history of successful BMT
- Dosing every 2 weeks (QOW)
- Single central site in Manchester, UK

rhGUS Phase 1/2 Study Status

- Study started with FPI in Dec 2013
- 3 subjects enrolled and enrolment ended
- All subjects received 19 infusions
  - No missed infusions
- Key data available
  - Clinical, Safety, PK/PD up to 36 weeks
- All subjects currently in Continuation Phase
  - 2 mg/kg QOW

Phase 1/2 Subject Demographics and Baseline Characteristics

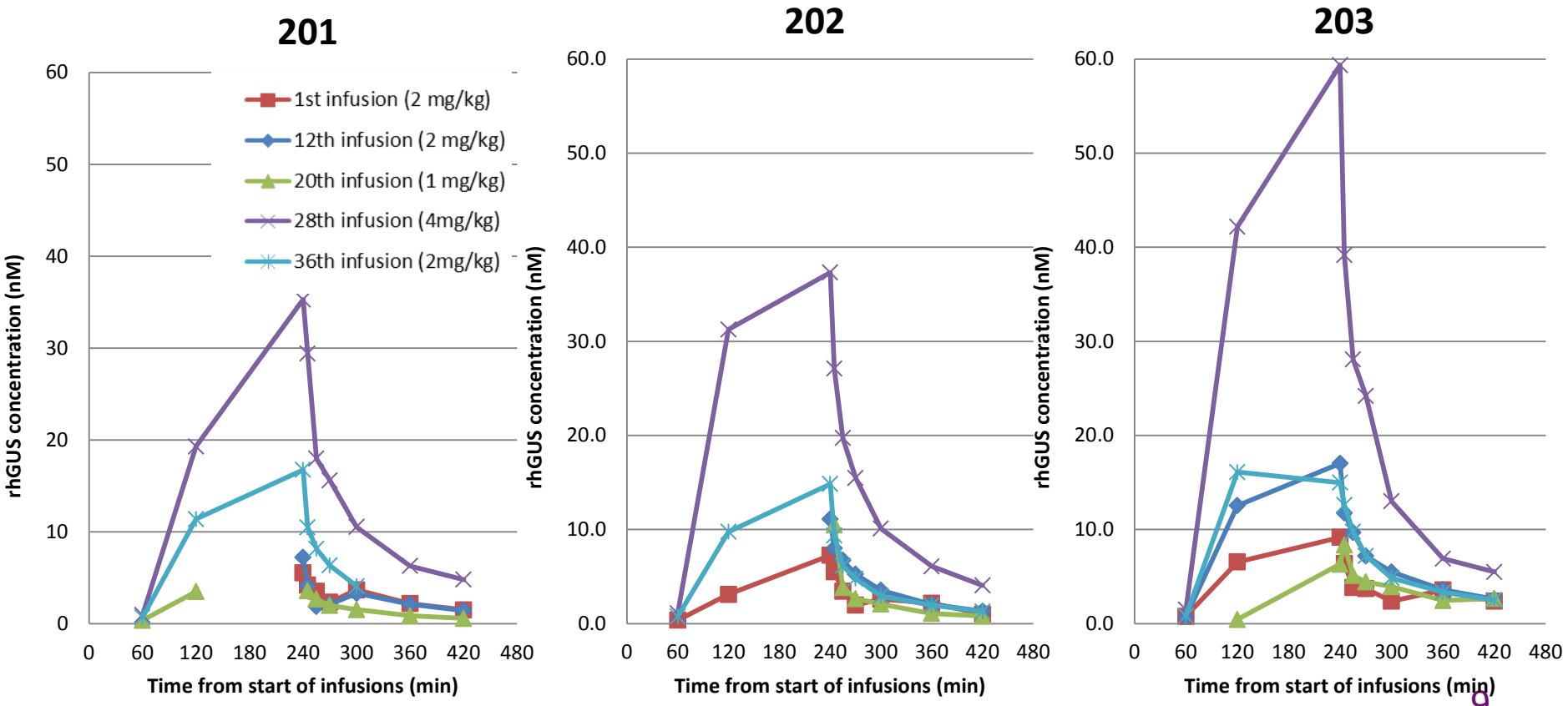
Subject:	111-201	111-202	111-203
Sex	Male	Female	Male
History of Hydrops Fetalis	Yes	Yes	No
Age at diagnosis	1.1 yrs	< 1 mos	5.5 yrs
Age at start of ERT (years)	5.5	9.4	25.1
Race	White	White	Asian
Standing height (cm)	102.5	123.9	157.3
Weight (kg)	20.6	34.6	78.8
Diagnosis	Leukocyte enzyme activity	Leukocyte enzyme activity	Leukocyte enzyme activity

Key Findings: Safety and Tolerability
rhGUS infusions appear safe and well tolerated

- No SAEs up to 36 wks
- No drug-related or hypersensitivity infusion associated reactions (IARs)
- Complement levels normal at week 12
- All AEs were Grade 1 (mild) except one Grade 2 (moderate) event of hip arthralgia (unrelated)
- AEs consistent with symptoms of MPS VII or related to IV catheterization
  - Most Common AEs: Respiratory disorders, infections, arthralgia, infusion site extravasation
- No AEs were considered to be drug-related

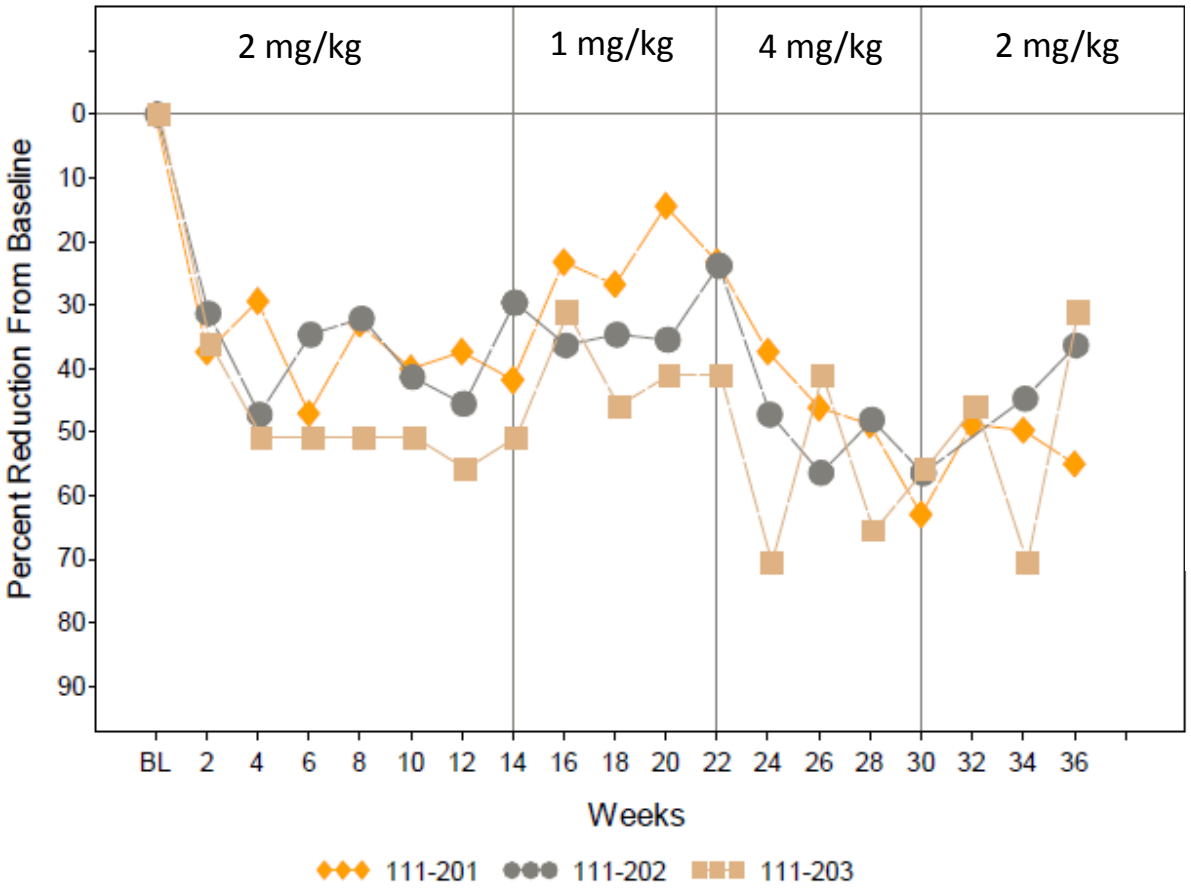
PK: Subject Profiles Show Dose-Dependence

- [rhGUS] is well above K_{uptake} for 7 hours+
- PK is dose-dependent, non-linear from 2 to 4 mg/kg dose

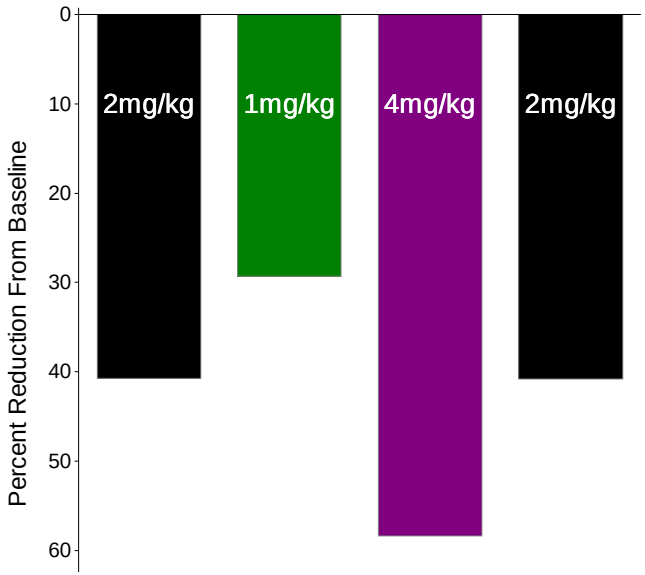


Rapid and Sustained Dose-Dependent Reduction in uGAG: 4 > 2 > 1 mg/kg

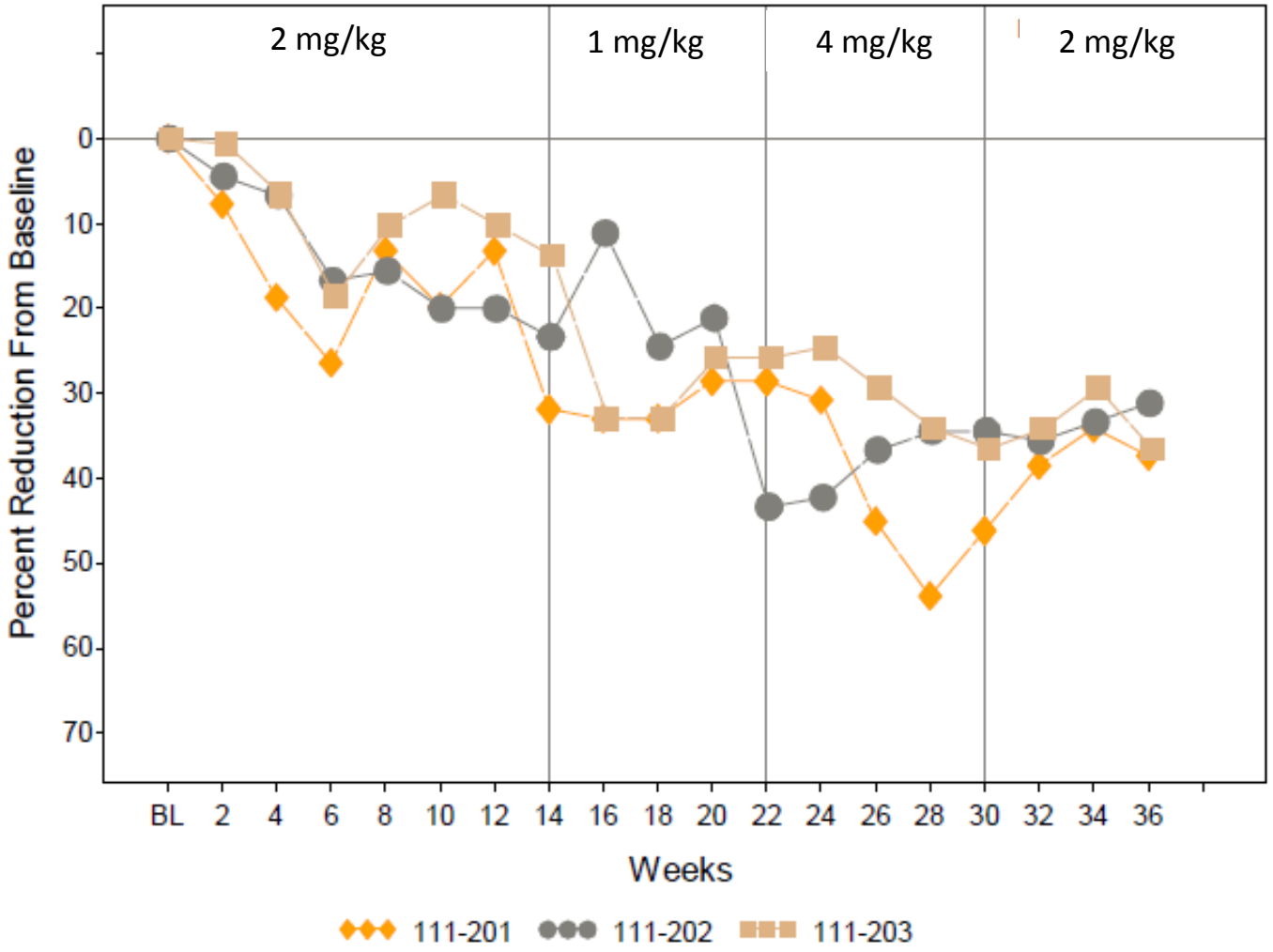
Time course of uGAG reduction



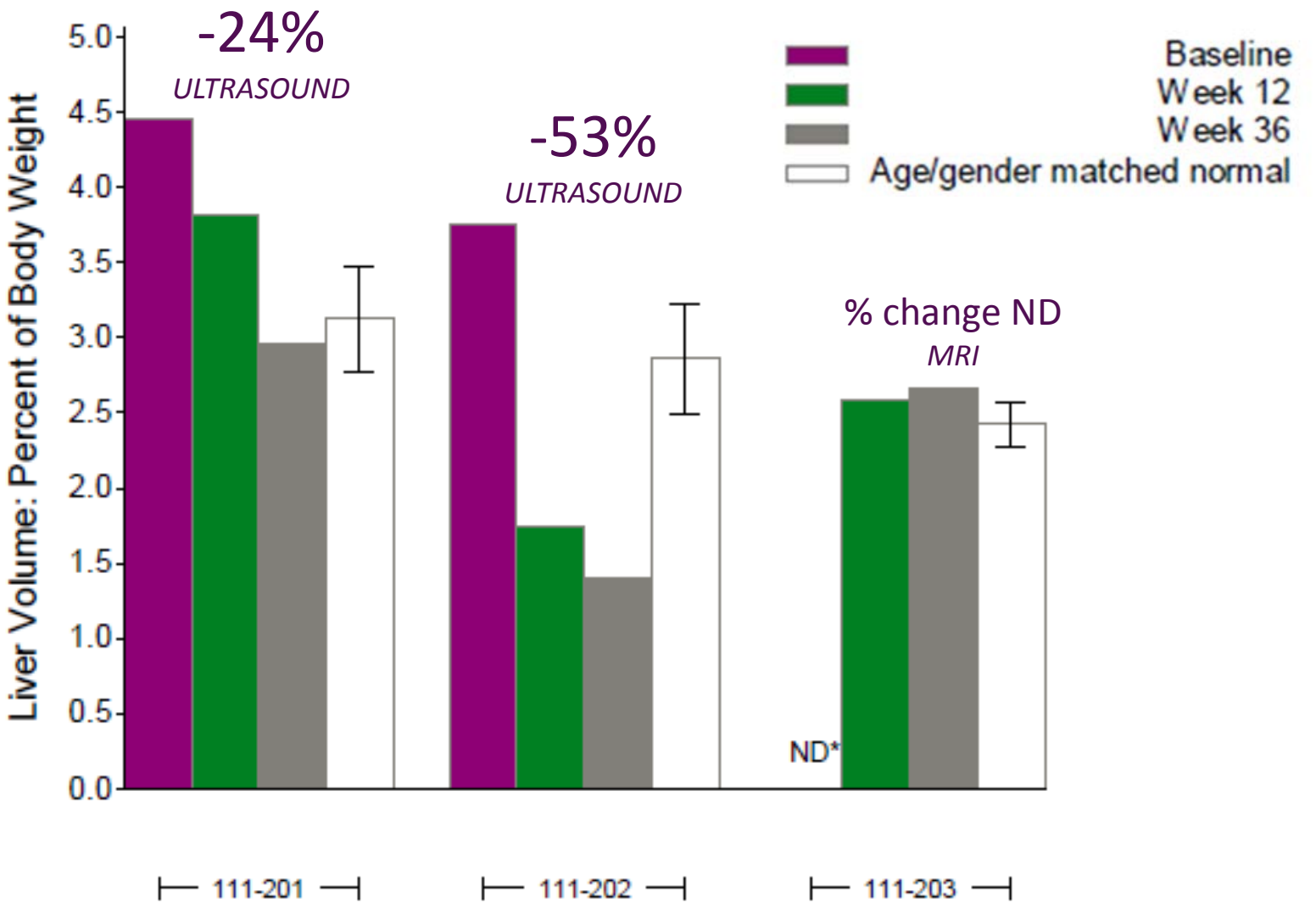
Mean uGAG reduction at end of each dosing interval



Progressive Reduction in Serum GAG



Significant Reduction in Enlarged Liver Size



*Baseline scan was not determined (ND); subjectively radiologist reports no change at BL vs. week 12

Clinical Evaluations: Pulmonary Function

- Only 1 subject (203) was able to perform the tests
- Subject 203 had improved pulmonary function
  - **FVC increased 13.4%** from baseline at week 30
  - **MVV1 increased 14.9%** from baseline at week 30
  - FEV was comparable to screening

203 Assessments	dose	FVC (L)	FEV1	MVV1
Screening		2.91	2.26	77.13
Week 6	2 mg/kg	3.04	2.07	87.1
Week 12	2 mg/kg	2.99	2.04	85.68
Week 22	1 mg/kg	2.78	2.07	86.88
Week 30	4 mg/kg	3.3	2.31	88.61
Week 36	2 mg/kg	3.21	2.24	84.08

Shoulder Flexion and Motor Abilities

- Goniometry: shoulder range of motion
  - Normal shoulder flexion (n=2) and extension (n=3) measures at baseline
  - 1 subject with limited passive ROM in shoulder flexion at screening AND baseline resolved at Week 6 and maintained within normal range at subsequent visits
- BOT-2: assesses fine and gross motor abilities
  - 2 subjects could not complete all assessments: age or cognitive ability
  - Subject 111-203 was cooperative and attentive
    - Gross motor tests difficult to assess due to persistent hip pain
    - Manual dexterity results suggest improved function following treatment, no change in fine motor precision
- 6MWT/Stair Climb: difficult to interpret
  - Variable due to cooperation of 5 and 9 year olds & hip pain in adult
    - 201 showed fluctuations up and down in 6MWT; 202 had high baseline 6MWT and modest changes

Other Clinical Assessments

- 2 of 3 subjects showed substantial weight gain
  - 1 physician assessment of improved appetite
- No significant improvement in standing height
- MPS health assessment questionnaire (HAQ) and physician global impression of change (PGIC) indicate subjective improvements in the patients
  - All 3 subjects showed improvement in fatigue/ lack of energy on PGIC
  - MPS HAQ Caregiver and Mobility scores, but not Self Care score improved for 2 of 3 subjects
  - Not a blinded study

Summary of Phase 1/2 Key Findings

- **Safety of every other week infusions of rhGUS**
  - rhGUS appears safe and well tolerated and no SAE's
  - No infusion associated reactions in 57 infusions
- **Lysosomal storage is substantially reduced**
  - Rapid reduction in uGAG and in liver size
- **Clinical Evaluation is still preliminary**
  - Heterogeneous subjects and only 3 total
  - Some evidence of clinical benefit
    - Increased PFT's in one patient, HAQ and PGIC scores
- **Dose data supports 4 mg/kg QOW dosing**
  - rhGUS is 4x MW of other MPS enzymes

Acknowledgements

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