

# **Rare Disease Forum Meeting #1**

**Case Study: Mepsevii™**

**Qais Abu Ali, MD, FACMG**

*Ultragenyx Pharmaceutical Inc.  
Novato, CA*

# Disclosures

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- Qais Abu Ali, MD is an employee of Ultragenyx Pharmaceutical Inc.

# Outline

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- Background
- Challenges
- Pivotal study design
- Requests by FDA
- Discussion
- Conclusions

# Background

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- Mucopolysaccharidosis (MPS) VII (Sly Syndrome)
- An ultra-rare, chronically debilitating, life-threatening, and progressive lysosomal disorder
- Deficiency of beta-glucuronidase (GUS) enzyme
- Tissue accumulation of dermatan, chondroitin, and heparan sulfate glycosaminoglycans (GAGs)

# Background

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- **Clinical (phenotypic) heterogeneity**
  - Hydrops fetalis
  
  - Enlarged liver and spleen, cardiac and pulmonary involvement, joint and bone abnormalities, cognitive impairment, corneal clouding, short stature
- Most patients die before second or third decade of life due to heart disease or pulmonary failure<sup>1</sup>

# Background

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- Development of enzyme replacement therapy (ERT)
- Vestronidase alfa (recombinant human GUS)

# Challenges

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- Disease-related
- Drug development-related

# Challenges: Disease-related

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- Ultra-rare
  - Estimated prevalence  $<1/1,000,000^1$
  - Fewer than 100 living patients worldwide (internal estimate)
- Pan-ethnic
- Life threatening
- Significant heterogeneity in disease manifestations
- No therapy available upon initiation of clinical studies



# Challenges: Drug development-related

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- Disease-related issues hampered our ability to design and execute a traditional development program
  - Randomized designs
  - Placebo-control
  - Sufficient statistical power
  - Identification of a single primary efficacy endpoint

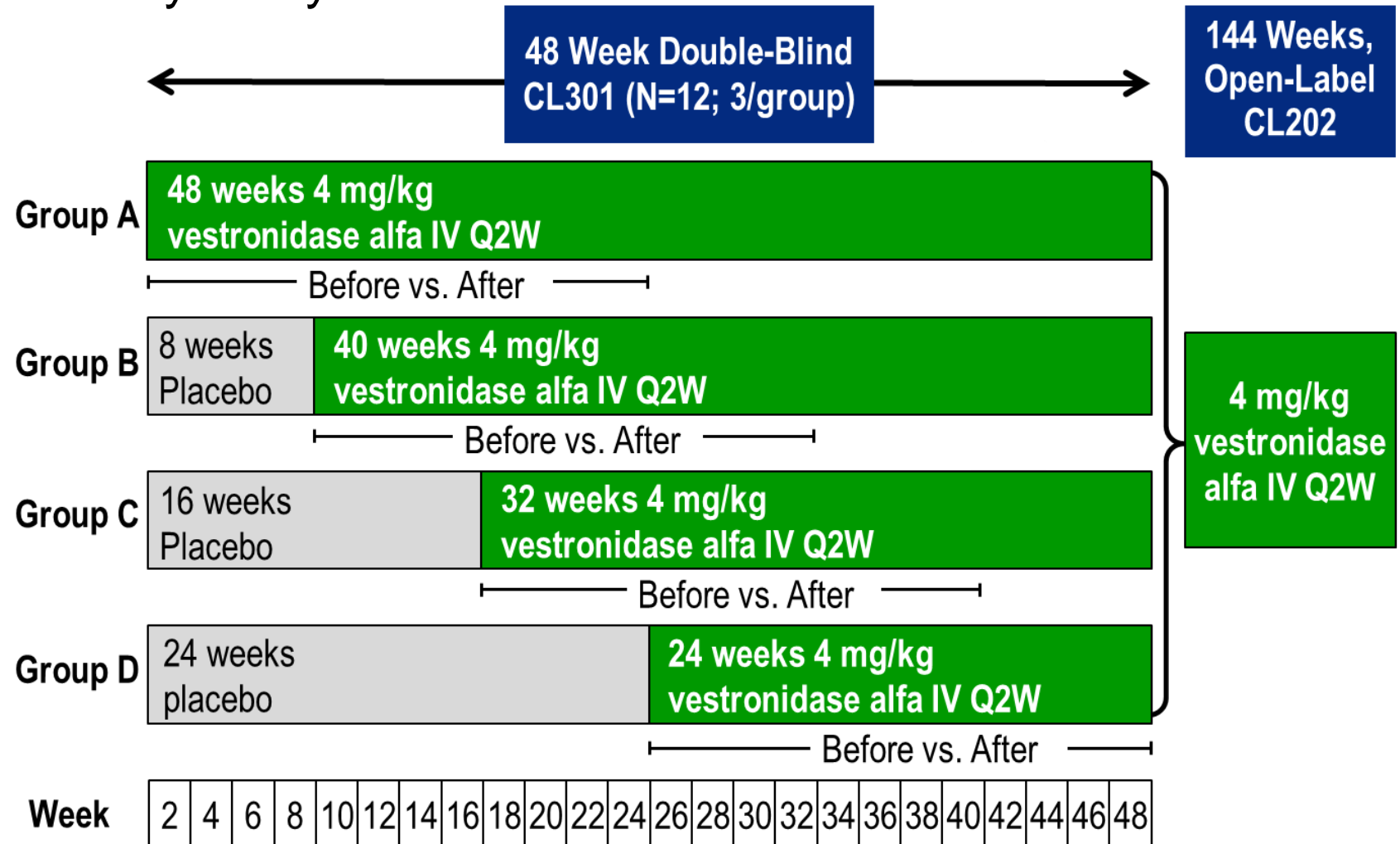
# Pivotal Study Design

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- **All-comer enrollment strategy**
- **Randomized; Placebo-controlled; Single crossover**
- **Utilized blind start design**
- **No primary efficacy endpoint in the US**
  - **Urinary GAG (uGAG) as a primary efficacy endpoint by EMA**
- **Multi-domain responder index (MDRI)**

# Blind Start Study Design

## Primary analyses



# Multi-Domain Responder Index (MDRI)

- Novel approach
- Six clinical domains
  - 6-minute Walk Test (6MWT)
  - Forced Vital Capacity (FVC)
  - Shoulder flexion
  - Visual acuity
  - Bruininks-Oseretsky Test of Motor Proficiency (BOT-2)  
(fine motor and gross motor)
  - Domain responses were scored on a pre-specified minimal important difference (MID) for each endpoint

# Multi-Domain Responder Index (MDRI)

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- Combination of responses across different domains allowed assessment of vestronidase alfa effectiveness more broadly
- Not all subjects needed to complete all tests and could successfully be assessed on only some tests
- Non assessable data did not hinder the results

# MDRI and MID

Domain	MID
6MWT	<ul style="list-style-type: none"><li>• 23 meters <i>and</i> 10% change from baseline</li></ul>
FVC <sub>%pred</sub>	<ul style="list-style-type: none"><li>• 5% absolute change <i>or</i></li><li>• 10% relative change from baseline</li></ul>
Shoulder flexion	<ul style="list-style-type: none"><li>• 20-degree change in passive shoulder range of motion</li></ul>
Visual acuity	<ul style="list-style-type: none"><li>• 3 lines (corrected, both eyes)</li></ul>
BOT-2 fine motor	<ul style="list-style-type: none"><li>• Fine Motor Precision: change of 0.72</li><li>• Manual Dexterity: change of 1.47</li></ul>
BOT-2 gross motor	<ul style="list-style-type: none"><li>• Balance: 0.57</li><li>• Running speed and agility: 0.59</li></ul>

## MDRI Score



# Requests by FDA

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- Biomarker (uGAG) accepted a secondary efficacy endpoint
- MDRI critical for demonstration of clinical benefit
- Accepted additional inclusion of specific efficacy endpoint results in the prescribing information (label)
  - 6MWT
  - Liver and spleen size

# Discussion

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- ERT development for MPS VII languished for nearly 20 years
- Extreme rarity and heterogeneous clinical presentation stymied drug development using traditional study design approaches
- Incorporating several innovative elements to be able to efficiently and safely evaluate the small number of subjects



# Conclusions

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- Phase 3 study leveraged existing data from previously approved ERTs
- Great efforts between Ultragenyx and FDA were also focused on understanding each party's perspective and learning/explaining the various novel aspects of this pivotal study



**Thank You**

# Placeholder

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- Slides to be added by Dina Zand, MD (FDA)