Rare Disease Forum Meeting #1

Case Study: Mepsevii™

Qais Abu Ali, MD, FACMG

Ultragenyx Pharmaceutical Inc.
Novato, CA

Disclosures

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

Outline

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

Background

- 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

- **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[1]

1. Montaño AM et al. *J Med Genet* 2016;0:1-16

Background

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

Challenges

- Disease-related
- Drug development-related

Challenges: Disease-related

- 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

1.Orphanet, Prevalence and Incidence of Rare Diseases: Bibliographic Data, Orphanet Report Series, Rare Disease Collection, 2016

Challenges: Drug development-related

- 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

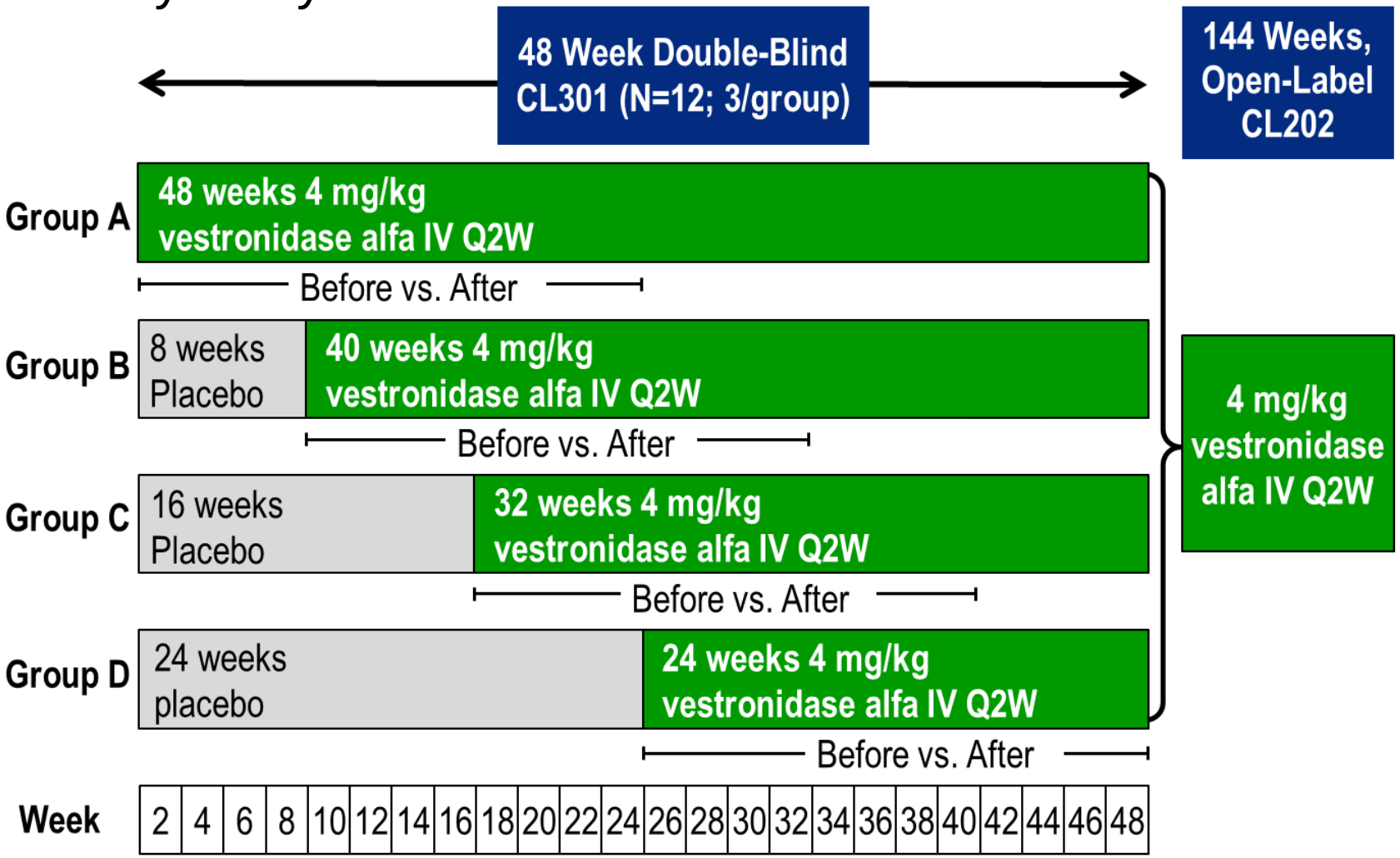
Pivotal Study Design

- **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)**

Harmatz, Whitley, Wang, Bauer, Song, Haller, Kakkis. A novel Blind Start study design to investigate vestronidase alfa for mucopolysaccharidosis VII, an ultra-rare genetic disease. Molecular Genetics and Metabolism. Academic Press; 2018 Apr;123(4):488-494.

Blind Start Study Design

Primary analyses



2Harmatz, Whitley, Wang, Bauer, Song, Haller, Kakkis. A novel Blind Start study design to investigate vestronidase alfa for mucopolysaccharidosis VII, an ultra-rare genetic disease. Molecular Genetics and Metabolism. Academic Press; 2018 Apr;123(4):488-494.

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

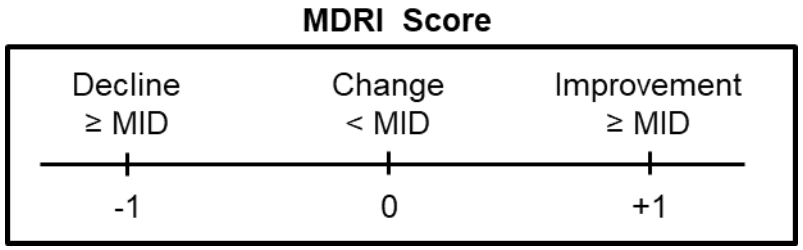
Signorovitch, J. 2011. Statistical analysis for Multi-domain Outcomes. Everylife Foundation Rare Disease Workshop #2 Presentation. In Clinical Evaluation of Rare Disease Treatments. Boston, Massachusetts.

Multi-Domain Responder Index (MDRI)

- 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	• 23 meters *and* 10% change from baseline
$FVC_{\%pred}$	• 5% absolute change *or* • 10% relative change from baseline
Shoulder flexion	• 20-degree change in passive shoulder range of motion
Visual acuity	• 3 lines (corrected, both eyes)
BOT-2 fine motor	• Fine Motor Precision: change of 0.72 • Manual Dexterity: change of 1.47
BOT-2 gross motor	• Balance: 0.57 • Running speed and agility: 0.59



Requests by FDA

- 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

- 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

- 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

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