Application of Current FDA Statute to Rare Disease Drug Development: A Fabry Case Study

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This presentation is being provided in response to EveryLife Foundation for Rare Diseases request during its Scientific workshop.
Amicus Today

**Galafold** (migalastat)

**AT-GAA**
Pompe Completed Phase 1/2

**PRECLINICAL PIPELINE**
of products for rare metabolic diseases

**BIOLOGICS PLATFORM**
Protein Engineering & Glycobiology

**CHART**
Chaperone-Advanced Replacement Therapy

**SMALL MOLECULE**
Pharmacological Chaperones

~400 EMPLOYEES globally

~$550M Cash (6/30/18)

GLOBAL FOOTPRINT in 27 countries

*AT-GAA, also known as ATB200/AT2221*

Current FDA Statues in Rare Disease Drug Development: A Fabry Case Study (Galafold)
Fabry Disease Overview

- Rare, devastating, X-linked deficiency of lysosomal enzyme alpha-galactosidase A ($\alpha$-Gal A) leading to accumulation of globotriaosylceramide (GL-3) and Lyso-Gb$_3$ resulting in morbidity and premature death

- Multi-systemic
  - Morbidity: Gastrointestinal, pain, hearing loss
  - Mortality: Renal failure, cardiac failure, sudden death, stroke

- Orphan disease: 1:117,000 – 1:40,000 diagnosed world wide

- Evolution of understanding Fabry disease (2001 – Current)
  - Classic vs late onset
  - Males vs females
  - Genotype vs phenotype
  - Missense/amenable mutations

- Approved treatments include intravenous (IV) enzyme replacement therapies Fabrazyme® and Replagal® (outside the US) and the oral pharmacological chaperone Galafold®
Galafold Mechanism of Action

**GL-3 Accumulation**

Stabilized Mutant α-Gal A

Endoplasmic Reticulum → Golgi Apparatus → Lysosomes

Migalastat

Active Site

Mutational

Reduced ER Retention

Enhanced Trafficking

Decreased Substrate

GL-3 Accumulation
Galafold Development Program and Exposure

• Largest development program in Fabry disease comprised of 20 clinical studies
  – Mean Duration of Exposure: 3.6 years; Maximum Duration of Exposure: 11.0 years
  – 591 unique patients & healthy volunteers; 402 subjects exposed to migalastat
  – 51 amenable variants studied

• 21 patients treated in global expanded access programs

• Post marketing: >450 patients

• Two Pivotal studies
  • Study 011: Migalastat vs placebo
    – Primary endpoint: Reduction of KIC GL-3
  • Study 012: Migalastat vs ERT
    – Primary endpoint: Annualized rate of change in GFR

• Treatment with migalastat was found to be generally safe and well tolerated
• Majority of TEAEs were mild to moderate in severity
• No signals of safety concern have emerged from post marketing experience
# Galafold Submissions and Approvals

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Key Examples of FDA Advancing Regulatory Landscape

• Use of the *in vitro* HEK assay to identify target population
  – Defined criteria to determine amenability
  – Determination of treatment eligibility based on knowledge of genotype

• Generalizability of amenable variants in labeling demonstrates precision medicine
  – Application of FDA Guidance: *Developing Targeted Therapies in Low Frequency Molecular Subsets of a Disease (December 2017)*
  – 51 amenable variants studied in clinical trials, 348 approved in label
Opportunities for Further Innovation

• Global Harmonization of clinical trials and use of endpoints
  – Basis of approval vastly different between U.S. and rest of world
  – Time to approval in major geographies can be synchronized through harmonization of endpoints and clinical trial design

• Application of regulatory framework should be flexible allowing for key data in pivotal studies to be reflected in label
  – Minimal data from pivotal Study 012 included in US label
  – Divergence in global labeling on clinical data

• Use of innovative and novel approaches to communicate pertinent labeling information
  – Novel tools for conveying information to HCPs adopted in all regions outside the U.S.
Recommendations to Expedite Drug Development for Rare Diseases

- **Streamlined global development**
  - Collaboration and open communication among regulators
  - Harmonization of clinical trial design and endpoint selection
  - Guidance *General Principles for Planning and Design of Multiregional Clinical Trials* (July 2018)

- **Alignment within FDA on how guidances and regulations should be implemented in special cases**

- **Non-competitive information sharing**
  - Information obtained from Natural history and disease registries important for rare diseases
  - Evolution of thinking that may impact development

- **Implementation of new guidances**
  - *Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics* (April 2018)
  - Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) – Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases (April 2018)
THANK YOU