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

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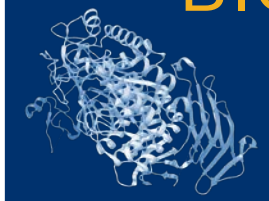
This presentation is being provided in response to EveryLife Foundation for Rare Diseases request during its Scientific workshop.

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

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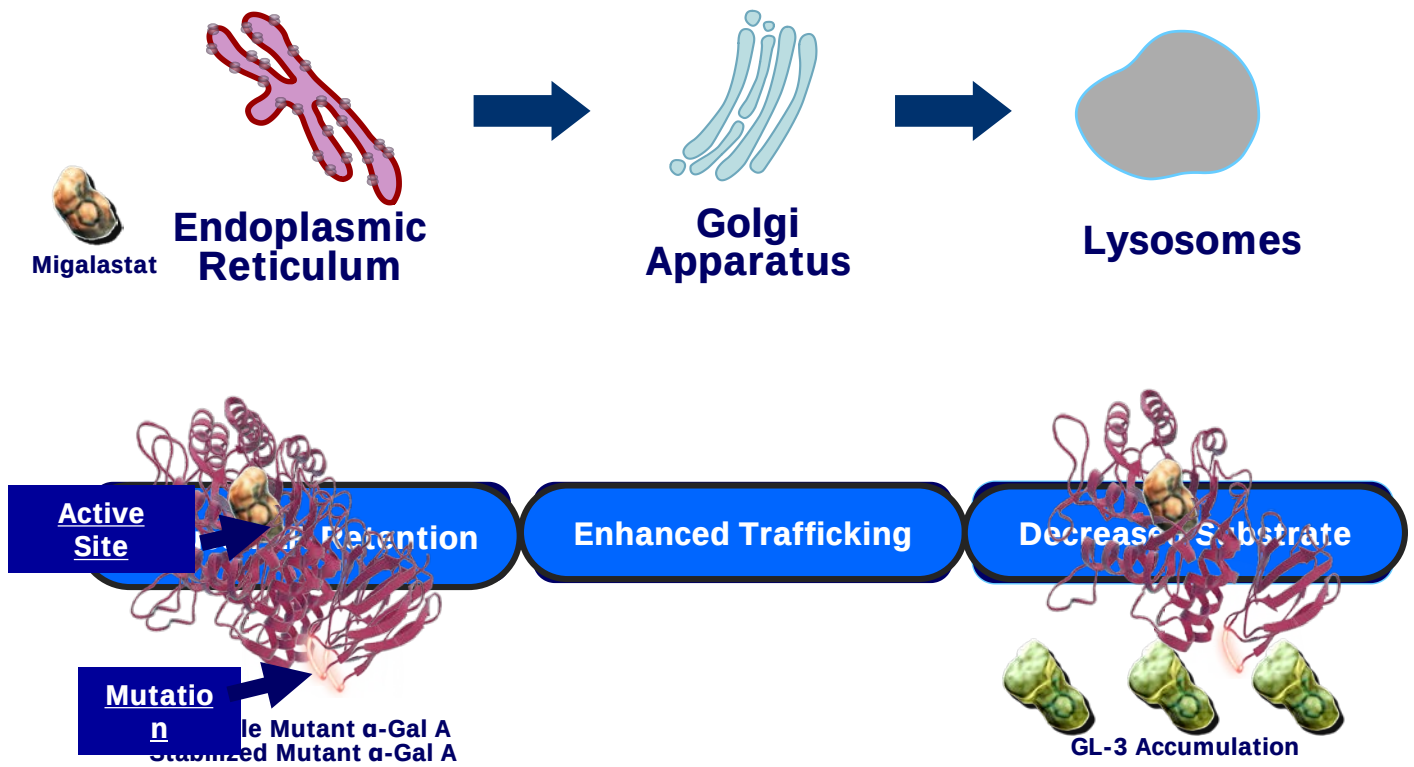
Fabry Disease Overview

- Rare, devastating, X-linked deficiency of lysosomal enzyme alpha-galactosidase A (α-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



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

Country	Status	Original submission date	Approval date	Basis of Approval
European Union	Approved	3 June 2015	26 May 2016	ERT Controlled Study
Norway	Approved	3 June 2015	26 May 2016	ERT Controlled Study
Iceland	Approved	3 June 2015	26 May 2016	ERT Controlled Study
Switzerland	Approved	10 May 2016	28 October 2016	ERT Controlled Study
Liechtenstein	Approved	3 June 2015	17 November 2016	ERT Controlled Study
Israel	Approved	8 August 2016	29 June 2017	ERT Controlled Study
Australia	Approved	3 June 2016	9 August 2017	ERT Controlled Study
Canada	Approved	8 July 2016	5 September 2017	ERT Controlled Study
Korea	Approved	30 September 2016	20 December 2017	ERT Controlled Study
Japan	Approved	28 June 2017	23 March 2018	ERT Controlled Study
United States	Approved	13 December 2017	10 August 2018	Placebo Controlled Study
Taiwan	Submitted	31 August 2016	TBD	ERT Controlled Study

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

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