FABRY DISEASE:

• Phenotypic Spectrum
• Genotype/Phenotype Correlations
• Enzyme Replacement Therapy (ERT)

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FABRY DISEASE

“AN X-LINKED LYSOSOMAL STORAGE DISEASE”

α-Galactosidase A
Xq22.1

Human X Chromosome
FABRY DISEASE: X-LINKED INHERITANCE

If Father Is Affected
All Daughters Heterozygotes
All Sons Unaffected

If Mother Is Heterozygotes
50% Daughters Heterozygotes
50% Sons Unaffected
METABOLIC DEFECT IN FABRY DISEASE

Globotriaosylceramide (GL-3, Gb3)

\[
\text{Gal} \quad \alpha \quad \text{Gal} \quad \beta \quad \text{Glu} \quad \beta \quad \text{Ceramide}
\]

\[\alpha\text{-Galactosidase A (}\alpha\text{-Gal A)}\]

\[
\text{Gal} \quad + \quad \text{Gal} \quad \rightarrow \quad \text{Glu} \quad \rightarrow \quad \text{Ceramide}
\]

Lactosylceramide (GL-2, Gb2)
PHENOTYPIC SPECTRUM OF FABRY DISEASE

Affected Males

Later-Onset Phenotypes:

- **Cardiac Subtype**
- **Renal Subtype**

**Classic Phenotype**

<1% Increasing α-Gal A Activity

Classic Phenotype (Severe Disease)

Later-Onset Phenotype

Years

0 10 20 30 40 50 60 70 80 90 100
MAJOR EARLY SITES OF GL-3 ACCUMULATION

- **Micro-Vascular Endothelium & Smooth Muscle:**
  - Ischemia & Occlusion: Acroparesthesias, Hypohidrosis, GI Pain, Angiokeratoma

- **Cardiomyocytes:** Early Diastolic Dysfunction > LVH & Mitral Insufficiency in Adolescents; Arrhythmias Later

- **Renal Endothelial, Podocytes & Tubular Cells:**
  - Microalbuminuria > Proteinuria; Isothexanuria, Sediment Inclusions
## MANIFESTATIONS IN ADOLESCENTS & ADULTS

<table>
<thead>
<tr>
<th>Vascular Glycolipid Deposition</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Angiokeratoma</td>
</tr>
<tr>
<td>Peripheral Nerves</td>
<td>Acroparesthesias; Excruciating Pain</td>
</tr>
<tr>
<td>Sweat Glands</td>
<td>Hypohidrosis</td>
</tr>
<tr>
<td>Intestine</td>
<td>Abdominal Pain/Diarrhea</td>
</tr>
<tr>
<td>Heart</td>
<td>LVH, Myopathy, Arrhythmias</td>
</tr>
<tr>
<td>Brain</td>
<td>TIAs, Strokes</td>
</tr>
<tr>
<td>Kidney</td>
<td>Renal Failure</td>
</tr>
</tbody>
</table>

**Average Age at Death**: ~40 Years
FABRY DISEASE: AGE AT DIALYSIS

Thadhani et al., *Kidney Int.* 61:249, 2002

13% Females

![Age at Dialysis Graph](image-url)
FABRY DISEASE: SURVIVAL ON DIALYSIS (USRSD 1985-1993)

Thadhani et al., *Kid. Int.* 61:249, 2002

![Graph showing survival distribution function for Fabry Disease and controls.](image-url)
FABRY DISEASE: SURVIVAL AFTER RENAL TRANSPLANTATION

Oto et al., Transplantation 69: 2337-2339, 2000

Matched Control (n = 186)

Matched Control (n = 186)

Fabry Disease (n = 93)

Percent of Patients Alive

Months Post-Transplant
KIDNEY DAMAGE STARTS IN FABRY CHILDREN EVEN BEFORE PROTEINURIA

KIDNEY DAMAGE STARTS IN FABRY CHILDREN EVEN BEFORE PROTEINURIA


ELECTRON MICROGRAPH OF A GLOMERULUS FROM AN 11 YEAR OLD BOY WITH FABRY DISEASE

The Patient Had Normal Glomerular Filtration Rate (GFR) and a Urine Protein/Creatinine Ratio of ~ 40 mg/g at Biopsy
Later-Onset Phenotypes:
• Residual (>1%) α-Gal A Activity;
• Missense Some Splicing Mutations; CRIM-Positive
• Most Lack Pain, Skin Lesions, Hypohidrosis, Eye Changes

Cardiac Subtype:
• No Vascular Endothelial GL-3 Accumulation
• Late-Onset: LVH, Myopathy, Arrhythmias, Proteinuria, Normal Renal Function for Age

Renal Subtype:
• Variable, but Late-Onset Renal Failure at 50-80s
RENAL PATHOLOGY


**Classic Phenotype**  
p.R227X

**75 y/o Cardiac Later-Onset Phenotype**  
p.N215S
ENZYMATIC DIAGNOSIS

α-Galactosidase A Activity

α-Gal Activity in Plasma

α-Gal Activity in Leukocytes
Safety and Efficacy of Recombinant Human α-Galactosidase A Replacement Therapy in Fabry Disease

The International Fabry Disease Study Group


- Multinational, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study: 8 Sites in 4 Countries
- 58 Classical Affected Patients: 56 M; 2 F
  - Average Age: 30 yrs
- Dose: 1 mg/kg q 2 wk x11 Doses of Human α-Gal A
  - Produced in CHO Cells by Genzyme
PRIMARY ENDPOINT RESULTS

Renal Histology: Capillary Endothelium Clearance

**Double Blind**

- Placebo: 0/29 (0%)
- Fabrazyme: 20/29 (69%)

P < 0.001 (2x2 Chi Square)

**Extension Study**

- Placebo Fabrazyme (PL / FZ): 24/24 (100%)
- Fabrazyme / Fabrazyme (FZ / FZ): 23/25 (92%)

Week 20*

+ 6 Months*

*As Treated Population, Considered Equivalent to Intent-To-Treat
Long Term Safety and Efficacy of Enzyme Replacement Therapy for Fabry Disease


The International Fabry Disease Study Group

- All 58 Patients from Phase 3 Continued in Extension Study
- Dose: 1 mg/kg q 2 wk of Fabrazyme
- After 30 to 36 Months of ERT:
  - Sustained Capillary Endothelial GL-3 Clearance
  - Plasma GL-3 Remained Normal
  - Mean Serum Creatinine and Estimated GFR Remained Stable
  - Infusion Associated Reactions Continued to Decreased with Time
Sustained, Long-Term Renal Stabilization After 54 Months of Agalsidase Beta Therapy in Patients with Fabry Disease


The International Fabry Disease Study Group
Agalsidase-Beta Therapy for Advanced Fabry Disease: A Randomized Trial.


PHASE 4 CLINICAL TRIAL

- Largest Randomized, Double-Blind, Placebo-Controlled Trial in Fabry Disease (n = 82)
- Narrow Inclusion Criteria: Mid to Moderate Renal Disease:
  - Serum Creatinine ≥ 1.2 mg/dl to < 3.0 mg/dl
  - Resulted in High Screening Failure (67&%)
- 252 Patients Screened at 41 Eligible Sites in 9 Countries
PRIMARY ENDPOINT - PROBABILITY OF AN EVENT

Kaplan-Meier Analysis of Time to the First Occurrence of a Composite Event

Risk Reduction 61%  \( (p=0.034) \)

Placebo
44% Events
12/27 Patients

Fabrazyme
28% Events
13/47 Patients

Percent

Time in Study (Months)
SUMMARY: PHASE 4 CLINICAL TRIAL

ERT IN ADVANCED DISEASE SLOWS CLINICAL PROGRESSION

- Fabrazyme Therapy Slowed the Rate of Clinical Progression as Manifested by Renal, Cardiac, and Cerebrovascular Outcomes in Patients with Advance Disease

- There was a 61% Risk Reduction for Events in Patients Treated with Fabrazyme ($p = 0.034$)

- Indicated Importance of Reducing Proteinuria with ACEi & ARBs

- Most Pronounced Effects Observed in Patients Who Had Less Advanced Disease, Emphasizing the Importance of Early Treatment
EFFECTS OF EARLY ERT & DOSE ON FABRY RENAL DISEASE & REVERSIBILITY


• Compared α-Gal A Dose & Cumulative Dose on Renal Biopsy Morphology Before & After 5 Yrs of ERT in 12 Patients (1F) from 7-33 Yrs (9<18 Yrs)
  – 7 Patients on 0.2 mg/kg EOW, 2 on Varying Dose & 3 on 1 mg/kg EOW

• All Doses Cleared Glomerular Endothelial & Mesangial Cell Inclusions

• Podocyte GL-3 Clearance Was Highly Correlated with Cumulative Dose (p =0.002)
  – There Was Essentially No GL3 Podocyte Clearance at 0.2 mg/kg EOW (7 Patients)
  – Patients on 1 mg/kg EOW Cleared Podocyte & Tubular GL-3

• Podocyte Clearance & Decreased Albumin/Creatinine Were Highly Correlated (p = 0.0001)

“ The Current Study…. Suggests Early Initiation of Treatment & the Use of Sufficiently High Enzyme Dose to Achieve Maximal Clearance of Kidney Cells”
## APPROVAL OF FABRAZYME FOR ENZYME REPLACEMENT THERAPY FOR FABRY DISEASE

<table>
<thead>
<tr>
<th>Country</th>
<th>Dose (mg/kg)</th>
<th>Date</th>
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<tbody>
<tr>
<td>European Union</td>
<td>1.0</td>
<td>August, 2001</td>
</tr>
<tr>
<td>United States</td>
<td>1.0</td>
<td>April, 2003</td>
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Approved in Over 50 Countries