

Fabry Disease

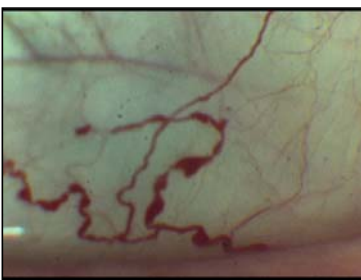
Recognition, Diagnosis, and Treatment of Fabry disease



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Fabry Disease

Conjunctival Vessels in Fabry




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Fabrazyme<sup>®</sup> agalsidase beta

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Fabry Disease

Conjunctival Involvement



- Note the sausage-like and markedly dilated vessels.

From R.J. Desnick, PhD, MD



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Corneal Whorl in Fabry Disease



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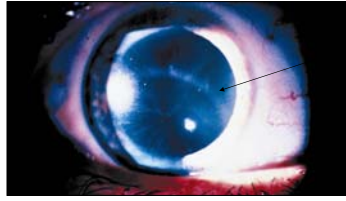
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Courtesy of Massimo Sola, MD

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Corneal Opacity



Note "spoke-like" pattern on cornea, visible through slit-lamp ophthalmoscopy

With permission, from R.J. Desnick, PhD, MD

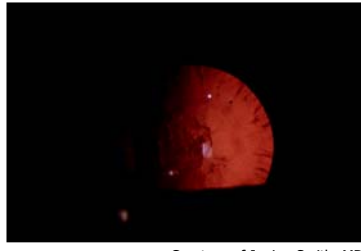


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Anterior Cataract in Fabry



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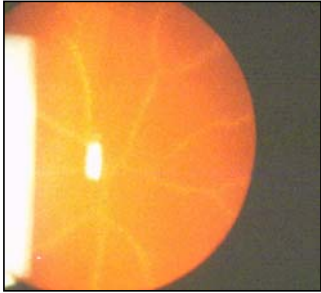
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Courtesy of Janine Smith, MD

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## Fabry Cataract



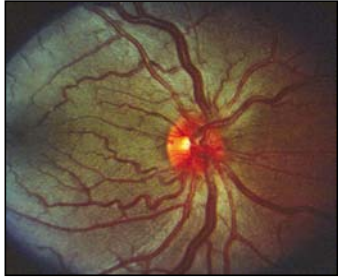
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## Retinal Vessel Tortuosity in Fabry Disease



Courtesy of Dr. E. Traboulsie

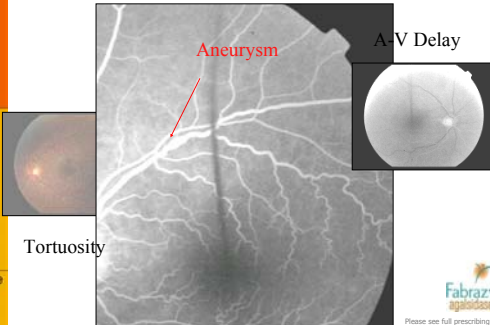
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## Retinal Vascular Changes in Fabry Disease



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Fabry Disease

## Overview

- Disease background
- Inheritance
- Signs and symptoms
- Clinical presentation to specialists
- Diagnosis
- Symptom management
- Enzyme replacement therapy
- Fabrazyme<sup>®</sup> clinical trials
- Fabrazyme<sup>®</sup> safety information
- Fabry Registry
- Fabry disease resources

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Fabry Disease

## Fabry Disease Background

- Under-recognized, genetic (X-linked) lysosomal storage disorder
- Progressive, often life-threatening
- Characterized by deficiency of the lysosomal enzyme alpha-galactosidase A ( $\alpha$ -GAL)
- Enzyme deficiency leads to progressive cellular accumulation of glycosphingolipids (fatty substances), particularly globotriaosylceramide (GL-3), in many body tissues
- Progressive, pathologic changes result in end-organ damage in most classic Fabry cases

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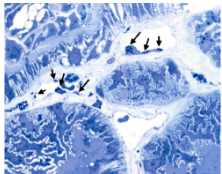
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Fabry Disease

## Fabry Disease Background

- Clinical manifestations include:
  - Renal failure
  - Cardiomyopathy
  - Cerebrovascular accidents
- GL-3 accumulates in tissues throughout the body
- GL-3 accumulation in renal endothelial cells may play a role in renal failure
- Average life expectancy is 50 years<sup>1</sup>



Light microscopy of the renal capillary endothelium. Note areas of GL-3 accumulation.

1. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *J Med Genet* 2001;38:750-60.

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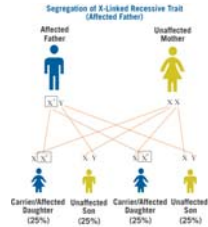
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## Inheritance

### Affected Father

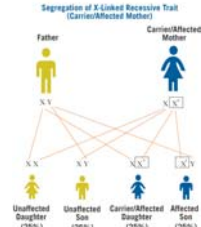
- No male-to-male transmission
- Will pass defective gene to all daughters, but no sons



## Inheritance

### Carrier/Affected Mother

- 50% risk of passing defective gene to both sons and daughters
- Sons who inherit gene will have Fabry disease
- Daughters will be carriers who may have disease manifestations to varying degrees



## Females with Fabry Disease

- X-linked disease but females can exhibit signs and symptoms to varying degrees
  - Due to random X-chromosomal inactivation (Lyonization)
- Disease manifestations in females more common than previously supposed<sup>1,2,3</sup>
- Two women were enrolled in the clinical studies with Fabrazyme®. Therefore, no determination can be made whether symptomatic women respond to Fabrazyme® differently than men.

- MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet* 2001;38:769-807.
- Wendrich K, Whybra C, Ries M, Gal A, Beck M. Neurological manifestation of Fabry disease in females. *Contrib Nephrol* 2001;136:241-4.
- Whybra C, Wendrich K, Ries M, Gal A, Beck M. Clinical manifestation in female Fabry disease patients. *Contrib Nephrol* 2001;136:245-50.

## Fabry Disease Early Manifestations

- Intermittent paresthesia and acroparesthesia
  - Chronic burning, tingling pain
  - Usually in the extremities
- Episodic "Fabry crises" of agonizing, incapacitating pain
  - Can last minutes to days
  - Can disappear or worsen in adulthood
  - Experienced by 80%-90% of patients
- Recurrent fever
  - Accompanying pain

## Fabry Disease Early Manifestations (cont.)

- Angiokeratomas (see figure)
  - "Bathing trunk" distribution
  - Non-blanching lesions
  - Dark red to blue-black color
  - Appear in adolescence
  - Worsen in adulthood
- Hypohidrosis or anhidrosis
  - Reduced or absence of sweating
- Heat or cold intolerance
- Exercise intolerance



Photo from R.J. Desnick, PhD, MD

## Fabry Disease Early Manifestations (cont.)

- Corneal and lenticular opacities (see figure)
- Whorl-like corneal rays
  - Only visible by slit-lamp
  - Usually does not affect vision
  - Useful diagnostic indicator
  - Found almost universally among males, and in approximately 70% of females with Fabry disease

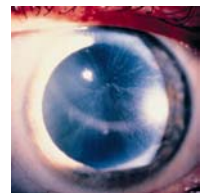


Photo from R.J. Desnick, PhD, MD

### Fabry Disease Early Manifestations (cont.)

- Mild proteinuria
- Gastrointestinal problems
  - Abdominal pain
  - Diarrhea
  - Vomiting
  - Nausea
- Psychological problems
  - Depression
  - Denial of symptoms
- While the safety and effectiveness of Fabrazyme® in pediatric patients have not been established, clinical studies in children are ongoing.

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### Fabry Disease Later Manifestations

- Renal dysfunction
  - Leading to uremia and hypertension
  - Progressing to end-stage renal disease
- Cardiovascular dysfunction
  - Myocardial infarction
  - Left ventricular hypertrophy
  - Valvular abnormalities
  - Arrhythmias

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### Fabry Disease Later Manifestations (cont.)

- Cerebrovascular complications
  - Risk of early stroke
  - Hemiplegia
  - Hemianesthesia
  - Transient ischemic attacks
- Neurological complications
  - Vertigo
  - Tinnitus
  - Hearing loss
  - Nystagmus
  - Diplopia

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### Clinical Presentation to a Range of Specialists

- Nephrologists
- Cardiologists
- Neurologists
- Pediatricians
- Primary Care Physicians
- Ophthalmologists
- Dermatologists

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### Clinical Presentation to Nephrologist

#### Patients may present with:

- Early renal failure
- Abnormal urinalysis
  - Proteinuria
  - Hematuria
  - Lipiduria
- Elevated serum creatinine
- Tubular dysfunction (polyuria, polydipsia)
- Symptoms suggesting Fanconi's syndrome
- Progressive renal insufficiency of unknown etiology
- Family history of renal problems

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### Clinical Presentation to Cardiologist

#### Patients may present with:

- Left ventricular hypertrophy
- Mitral valve prolapse and/or regurgitation
- Premature coronary artery disease
- Angina
- Myocardial infarction
- Arrhythmia

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## Clinical Presentation to Neurologist

**Patients may present with:**

- Acroparesthesia
- Early stroke
- Transient ischemic attacks
- Muscle weakness
- Vertigo/dizziness
- Tinnitus
- Hyperacusis
- Nystagmus
- Head pain
- Hemiataxia/ataxia of gait


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## Clinical Presentation to Pediatrician

**Patients may present with:**

- Pain in the hands and feet
- Angiokeratomas
- Hypohidrosis/anhidrosis
- Fever with elevated erythrocyte sedimentation rate
- Exercise intolerance
- Heat/cold intolerance
- Family history of renal or cardiac problems, or early stroke
- Gastrointestinal problems
- While the safety and effectiveness of Fabrazyme® in pediatric patients have not been established, clinical studies in children are ongoing.


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## Clinical Presentation to Primary Care Physician

**Patients may present with:**

- Acute and chronic pain
- Fatigue
- Weakness
- Heat/cold intolerance
- Hypohidrosis
- Fever
- Angiokeratomas
- Gastrointestinal problems
- Depression
- Family history of renal or cardiac problems, or early stroke


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Fabry Disease

## Potential Misdiagnoses<sup>1,2,3,4,5,6</sup>

MISLEADING SYMPTOMS	DISEASE
Pain in the joints, elevated erythrocyte sedimentation rate	Rheumatoid or juvenile arthritis
Pain accompanied by fever and an elevated erythrocyte sedimentation rate	Rheumatic fever
Acute pain in the extremities	Erythromelalgia
Acute pain with no apparent cause	Neurosis
Pain and temperature sensitivity in the extremities	Raynaud's syndrome
Stroke-like events in brainstem structures	Multiple sclerosis
Angiokeratomas	Lupus
Severe abdominal pain	Acute appendicitis
Unexplained pain in extremities	"Growing pains"
Angiokeratomas	Petechiae


1. Daniels RJ, Sgarbi MA, King SM, et al. Galactosidase A deficiency: Fabry disease. In: The Metabolic and Molecular Basis of Inherited Disease. New York: McGraw-Hill, 2001; 2730-34.  
2. Whalen C, Weisbach K, Kim M, Gal A, Beck H. Clinical manifestation in female Fabry disease patients. *Corrich Nephrol* 2001; 136:245-50.  
3. Zlotnik H, Kemp C. Fabry disease. *Ann Intern Med* 2002; 137:39-44.  
4. Palani PP, Sommer A, Nimmakuri A, Charan EC, Zhu TL. Fabry's disease: a multisystemic disorder. *Postgrad Med J* 1997; 73:710-2.  
5. Kolditz RW. Fabry disease. In: *Neurogenetics*. J. Collins, L. eds. Stroke Syndromes. New York: Cambridge University Press, 1995; 453-9.  
6. Morgan SJ, Crawford WA. Anderson Fabry disease. *BMJ* 1988; 297:872-3.

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Fabry Disease

## Diagnosis

- Disease usually presents in childhood, yet disease often goes unrecognized until adulthood<sup>1,2</sup>
  - Underlying pathology is advanced
- Median age of diagnosis is 28.6 years<sup>3</sup>
- Delayed diagnosis may be due to under-recognition of early signs and symptoms
- Symptoms of Fabry disease similar to those of other more common disorders
- Early diagnosis is important
  - Disease is progressive

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1. Shalby ED, Shalby WB, Korczynski TK. Painful fingers, heat intolerance, and interdigital ulcers of the ear: easily ignored childhood signs of Fabry disease. *Pediatr Dermatol* 1995; 12:215-9.  
2. Hinkley DJ, Chhab TS, Sauer KR. Fabry's disease presenting as syncope, angiodermatosis, and spoke-like cataracts in a young man: discussion of the differential diagnosis. *MO Med* 1997; 162:773-6.  
3. Hinkle JT, Hopwood JJ, Cogan AG, Carey MP. Prevalence of lysosomal storage disorders. *JAMA* 1999; 281:249-54.

Fabry Disease

## Diagnosis (cont.)

**Clinical diagnosis based on:**

- Family history
- History of childhood fevers in association with pain in the extremities
- Characteristic skin lesions (angiokeratomas)
- Characteristic "whorled" corneal opacity
- Observation of other signs and symptoms

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## Diagnosis (cont.)

### Confirmatory diagnosis

- Enzyme assay
  - Blood test to evaluate enzyme levels
  - Males with classical Fabry disease usually have less than 1% of normal enzyme levels
  - Females can have 0-100% of normal enzyme levels
    - Normal enzyme levels in females does NOT preclude affected/carrier status
- Genetic testing to identify females
  - Mutation analysis when family mutation is known
  - Linkage analysis when the family mutation is not known

## Genetic Counseling



- Important service to offer patients
- Can help identify other family members, including extended family
  - Potentially avoid delayed diagnoses in these family members
- Can help patients understand risk of transmitting disease to offspring
- While the safety and effectiveness of Fabrazyme® in pediatric patients have not been established, clinical studies in children are ongoing.

## Treatment and Management

- Symptom management
- Enzyme replacement therapy
- Team approach to treatment
  - Coordination among many medical specialties since disease is multisystemic

## Symptom Management

- Frequent and severe pain
  - Prophylactic therapy with certain medications, including narcotics<sup>1</sup>
- Gastrointestinal symptoms
  - Pancrelipase or metoclopramide<sup>2</sup>
- Patients vulnerable to stroke
  - Prophylactic therapy with anticoagulant medication<sup>1</sup>
- Emotional support and family counseling
  - Contact with others who have Fabry disease can be important, due to rarity of disease

## Symptom Management (cont.)

### Non-specific medical interventions

- Lifestyle changes
  - Avoidance of stimuli that cause pain
  - Increased fluid intake
- Interventions for advanced Fabry disease
  - Dialysis or kidney transplantation for renal complications
  - Pacemaker, antiarrhythmic medications, coronary bypass, angioplasty, as appropriate, for cardiac complications

## Fabrazyme® Enzyme Replacement Therapy

- Addresses enzyme deficiency by providing exogenous source of the deficient  $\alpha$ -GAL enzyme
- Enzyme replacement therapy indicated for use in patients with Fabry disease. Fabrazyme® reduces globotriaosylceramide (GL-3) deposition in the capillary endothelium of the kidney and certain other cell types.
- The reduction of GL-3 inclusions suggests that Fabrazyme® may ameliorate disease expression; however, the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established.

## Fabrazyme®

- Evaluated in several clinical trials
- In studies completed to date:
  - Treatment results in significant GL-3 reduction from the vascular endothelium of the kidney, heart, and skin and from certain other renal cell types
  - GL-3 deposition still present in vascular smooth muscle cells, tubular epithelium and podocytes, at variably reduced levels
- Studies are ongoing to further evaluate safety and efficacy



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## Clinical Data Background

- Fabrazyme® was filed with the FDA under an accelerated approval mechanism
  - Fabry disease is serious, often life-threatening, with a slow progression of organ failure
- Under accelerated approval, marketing approval may be granted on the basis of adequate and well-controlled clinical trials
  - Trials are designed to establish that the product has an effect upon a surrogate endpoint that is reasonably likely to predict clinical benefit
  - Approval under these regulations requires that the applicant study the product further to verify the clinical benefit.

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## Clinical Data Background (cont.)

- Genzyme chose GL-3 reduction in renal interstitial capillary cells as the surrogate marker
  - It is believed that reduction of this lipid will likely predict benefit to the patient
- Post-marketing studies are being conducted to evaluate clinical benefit to patients

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## Preclinical Studies

- Performed in several animal models
  - Including the  $\alpha$ -GAL knockout mouse (Fabry mouse)
- Studies assessed safety and pharmacodynamics of agalsidase beta and pattern of GL-3 removal
- Dose-finding study in Fabry mouse<sup>1</sup>
  - Demonstrated GL-3 depletion in a dose-dependent manner
  - Depletion in plasma, liver, heart, and kidneys of enzyme-treated animals
- Results provided rationale and dosing strategy for a phase 1/2 trial in humans

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1. Sauerby VA, Zidek KM, Gordon RE, Denrick RJ. Fabry disease: preclinical studies demonstrate the effectiveness of  $\alpha$ -galactosidase A replacement in enzyme-deficient mice. *Am J Hum Genet* 2001; 68:1425.

## Phase 1/2 Study<sup>1</sup>

- Single-center, open-label, dose-ranging study
- Involved 15 male patients with classical Fabry disease
  - Plasma  $\alpha$ -GAL activity <1.5 nmol/hr/mL
- Patients received one of five dosing regimens for a total of 5 infusions
  - 0.3, 1.0, or 3.0 mg/kg every 2 weeks; or
  - 1.0 or 3.0 mg/kg every 48 hours
- Conducted to evaluate safety and pharmacokinetics
- Results from this small study provided preliminary data on safety, pharmacokinetics, and in vivo activity of Fabrazyme®

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1. Eng CH, Bankajaram H, Gordon RE, Goldman H, Phelps K, Kim L, Guse A, Winton S, Falton JF, Broder S, Stacy CB, Melito D, Paronzo K, Becker K, Cologan M, Denrick RJ. A Phase 1/2 clinical trial of enzyme replacement in Fabry disease: pharmacokinetics, adverse events, and safety studies. *Am J Hum Genet* 2003; 73:713-22.

## Phase 3 Placebo-Controlled Study<sup>1</sup>

- Double-blind, randomized, placebo-controlled
- Conducted in 8 centers in the United States and Europe
- 58 participants
  - 56 men and 2 women
  - All had Fabry disease with below normal  $\alpha$ -GAL activity (<1.5 nmol/hr/mL in plasma, and <4 nmol/hr/mg in leukocytes)
- Participants ranged in age from 16 to 61 years
  - average age approximately 30 years

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1. Eng CH, Guffon N, Wilson WK, Germann DP, Lee P, Wulfsberg S, Caplan L, Leshford SE, Denrick RJ. Safety and efficacy of recombinant human  $\alpha$ -galactosidase A replacement therapy in Fabry's disease. *N Engl J Med* 2003; 349:9-16.

**Fabry Disease**

### Phase 3 Placebo-Controlled Study (cont.)

- Patients randomized to receive infusion of Fabrazyme® (n=29) or placebo (n=29) every 2 weeks for 20 weeks
  - 11 doses
- No statistically significant differences in baseline characteristics between placebo and Fabrazyme® groups
  - Including age, height, weight, gender, and race
- Patients continued on any prophylactic drugs or analgesics for pain for trial duration
- All patients were pretreated with acetaminophen and an antihistamine

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### Phase 3 Placebo-Controlled Study (cont.)

**Primary efficacy endpoint:**

- Reduction of GL-3 inclusions in renal interstitial capillary endothelial cells
  - Renal failure is common, devastating feature of Fabry disease
  - GL-3 in renal endothelial cells may play a role in renal failure
- Assessed by light examination of tissue biopsy samples
- Samples were assigned a score of 0 (normal or near normal) to 3 (severe vessel inclusions)
- Treatment success defined as score of 0 at week 20

**Other endpoints:**

- GL-3 reduction in vascular endothelium of heart and skin
- Pain reduction
  - As determined by McGill Pain Questionnaire (Short Form)
- Reduction of GL-3 in plasma
- Maintenance of mean serum creatinine levels

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**Fabry Disease**

### Phase 3 Placebo-Controlled Study (cont.)

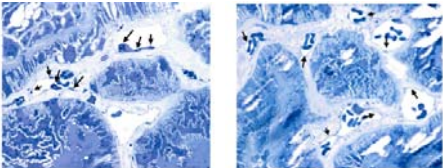
**Phase 3 study results:**

- Statistically significant ( $p < 0.001$ ) reduction to normal or near normal levels of GL-3 from renal capillary endothelium
- 20 of 29 Fabrazyme®-treated patients (69%) achieved a score of 0 (no or trace vessel inclusions) at 20 weeks
- 8 of 29 Fabrazyme®-treated patients had a score of 1
  - Including 5 who improved and 3 who had a score of 1 at baseline
- 1 patient had a missing biopsy and was assigned a score of 3
- 0 of 29 patients placebo-treated had a 0 score ( $p < 0.001$ )
- The reduction of GL-3 inclusions suggests that Fabrazyme® may ameliorate disease expression; however, the relationship of GL-3 inclusion reduction to specific clinical manifestations has not been established
- No differences between groups in symptoms or renal function were observed during this 5 month study.

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### Phase 3 Study Results (cont.): Primary Endpoint



Light microscopy of the renal capillary endothelium before and after Fabrazyme®

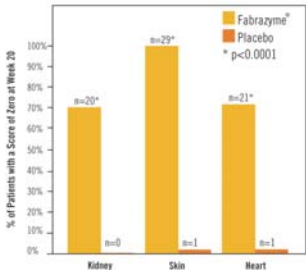
Before Fabrazyme® Score = 3

After Fabrazyme® Score = 0

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### Phase 3 Study Results (cont.): Response Rates for GL-3 Reduction



Site	Fabrazyme® (n=29)	Placebo (n=1)
Kidney	~70% (n=20)	0% (n=0)
Skin	~100% (n=29)	~2% (n=1)
Heart	~70% (n=21)	~2% (n=1)

\* p < 0.0001

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### Phase 3 Study Results (cont.)

- Pain scores
  - Improved from Baseline to Week 20 in both treatment groups
  - Since there was no statistically significant difference between the groups, an actual effect cannot be separated from a placebo effect.

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### Phase 3 Study Safety

- A statistically significant difference was observed for three adverse events that were reported more frequently in patients treated with Fabrazyme® compared to placebo.
- These adverse experiences were:
  - Rigors (15/29 [52%] vs. 4/29 [14%])
  - Fever (14/29 [48%] vs. 5/29 [17%])
  - Skeletal pain (6/29 [21%] vs. 0/29 [0%])
- Skeletal pain reported during this study represents isolated musculoskeletal events and is most likely not due to the infusion of Fabrazyme®.

### Phase 3 Study Safety (cont.)

- Rigors and fever represent primarily infusion-associated reactions. The initial presentation of these most often coincided with IgG seroconversion, which occurred in 83% of patients treated with Fabrazyme®.
- When rigors and fever occurred, they were generally mild to moderate in nature and were successfully managed by a temporary reduction in infusion rate, and treatment with acetaminophen and diphenhydramine.

### Phase 3 Study Safety (cont.)

Incidence (%) of adverse events and selected laboratory abnormalities that occurred during the phase 3 placebo-controlled study in at least 2 patients more in the Fabrazyme® group compared to placebo (continued on next slide)

Adverse Event	Placebo (n=29)	Fabrazyme® (n=29)
<b>Body as a Whole</b>		
Chest pain	3 (10)	5 (17)
Fever	5 (17)	14 (48)
Pain	3 (10)	6 (21)
Pallor	1 (3)	4 (14)
Rigors	4 (14)	15 (52)
Temperature changed sensation	1 (3)	5 (17)
<b>Cardiovascular</b>		
Cardiomegaly	1 (3)	3 (10)
Hypertension	0	3 (10)
Hypotension	2 (7)	4 (14)
Edema dependent	1 (3)	6 (21)

### Phase 3 Study Safety (cont.)

Incidence (%) of adverse events and selected laboratory abnormalities that occurred during the phase 3 placebo-controlled study in at least 2 patients more in the Fabrazyme® group compared to placebo (continued on next slide)

Adverse Event	Placebo (n=29)	Fabrazyme® (n=29)
<b>Central and Peripheral Nervous System</b>		
Dizziness	2 (7)	4 (14)
Headache	11 (38)	13 (45)
Paresthesia	2 (7)	4 (14)
<b>Gastrointestinal System</b>		
Dyspepsia	1 (3)	3 (10)
Nausea	4 (14)	8 (28)
<b>Musculo-Skeletal System</b>		
Arthrosis	0	3 (10)
Skeletal pain	0	6 (21)

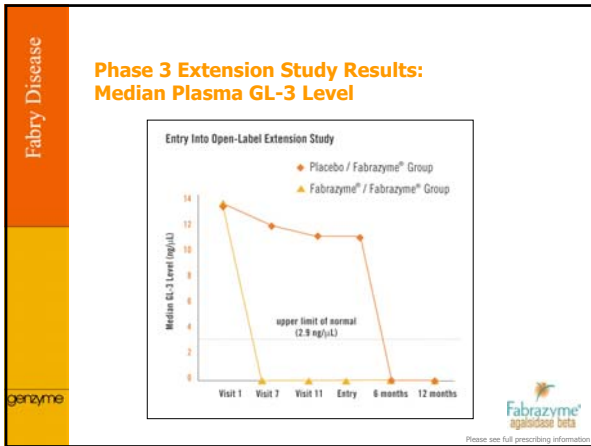
### Phase 3 Study Safety (cont.)

Incidence (%) of adverse events and selected laboratory abnormalities that occurred during the phase 3 placebo-controlled study in at least 2 patients more in the Fabrazyme® group compared to placebo (continued from previous 2 slides)

Adverse Event	Placebo (n=29)	Fabrazyme® (n=29)
<b>Psychiatric</b>		
Anxiety	5 (17)	8 (28)
Depression	1 (3)	3 (10)
<b>Reproductive, Male</b>		
Testicular pain	0	2 (7)
<b>Respiratory System</b>		
Bronchitis	1 (3)	3 (10)
Bronchospasm	0	2 (7)
Laryngitis	0	2 (7)
Pharyngitis	2 (7)	8 (28)
Rhinitis	7 (24)	11 (38)
Sinusitis	0	2 (7)

### Phase 3 Extension Study

- All 58 patients from the phase 3 study chose to enroll in an open-label extension
- After 6 months of open-label treatment, all 22 former placebo patients with available biopsies attained a score of 0 for renal vasculature
- Overall (after 6 or 12 months of Fabrazyme®)<sup>1</sup>:
  - 47 of 49 (96%) biopsied patients had a histologic score of 0 for renal vasculature
  - 32 of 40 (80%) had a score of 0 in the heart vasculature
  - 51 of 53 (96%) had a score of 0 in the skin vasculature
- GL-3 reduction was maintained in the superficial and deep vessel skin capillary endothelium up to 36 months of treatment.



**Phase 3 Extension Study Results (cont.)**

- Mean serum creatinine values (mg per dL)
  - Continued to remain normal from baseline with treatment up to 30 months<sup>1</sup>

Treatment Group	Phase 3 Placebo-Controlled Study			Phase 3 Extension Study		
	Baseline	Week 20	6 Months	12 Months	18 Months	24 months
Placebo/Fabrazyme*	0.8 ± 0.2 (n = 29)	0.8 ± 0.3 (n = 29)	0.8 ± 0.3 (n = 26)	0.8 ± 0.3 (n = 28)	0.9 ± 0.3 (n = 27)	0.8 ± 0.4 (n = 25)
Fabrazyme*/Fabrazyme*	0.9 ± 0.2 (n = 29)	0.9 ± 0.2 (n = 29)	0.9 ± 0.2 (n = 28)	0.9 ± 0.3 (n = 28)	0.9 ± 0.3 (n = 28)	0.9 ± 0.4 (n = 25)

1. Data on file, Genzyme Corporation.

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- Extension Study Safety**
- After 24-30 months, the most common treatment-related adverse events occurring on the day of infusion were:
    - Rigors, somnolence, temperature change sensation, fever, rhinitis, nausea, and headache
  - Successfully managed using standard medical practices
  - All patients were pretreated with antipyretics with/without an antihistamine
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- Extension Study Safety (cont.)**
- Infusion reactions occurred in some patients after receiving antipyretics, antihistamines, and oral steroids
  - Infusion reactions declined in frequency with continued use of Fabrazyme®, however, serious infusion reactions occurred after extended durations of treatment
  - Fifty-two out of 58 (89%) patients developed anti-Fabrazyme® IgG antibodies
    - After 24-30 months of treatment, antibody titers decreased in approximately half of all seroconverted patients
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- Extension Study Safety (cont.)**
- Seven patients have tested IgG negative upon repeat antibody testing
    - They will continue to be monitored long-term to assess tolerization
    - The clinical relevance of a decrease in antibody titers is unknown
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- Extension Study Safety (cont.)**
- Some patients developed IgE or skin test reactivity specific to Fabrazyme®
    - Some were successfully reinfused after developing these reactions
  - Physicians should consider testing for IgE in patients who experienced suspected allergic reactions and consider the risks and benefits of continued treatment in patients with anti-Fabrazyme® IgE.
  - There are no marketed tests for antibodies against Fabrazyme®. If testing is warranted, contact your local Genzyme representative or Genzyme Corporation toll-free at 800-745-4447.
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### Consensus Panel Recommendations<sup>1</sup>

- In a 2003 publication, a consensus panel of physicians with expertise in treating Fabry disease recommended that Fabry patients with disease manifestations receive enzyme replacement therapy as early as possible.<sup>1</sup>
- With availability of Fabrazyme®, greater awareness of Fabry disease is essential so that diagnosis is no longer overlooked or delayed, and treatment can be promptly initiated.

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1. Denckwajtis R, Brady RO, Barranger J, Collins AJ, Gorman DP, Goldman M, Girosi F, Glickman S, Wilson WF. Fabry Disease, An Under-Recognized Hemolytic Disorder: Expert Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy. *Ann Intern Med* 2003; 138:238-46.



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### Fabrazyme® Indication

- Fabrazyme® is indicated for use in patients with Fabry disease. Fabrazyme® reduces GL-3 deposition in the capillary endothelium of the kidney and certain other cell types.
- The reduction of GL-3 inclusions suggests that Fabrazyme® may ameliorate disease expression; however, the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established.

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### Fabrazyme® Dosage

- The recommended dosage of Fabrazyme® for adults and adolescents 16 years of age and older is 1.0 mg/kg body weight infused every 2 weeks as an IV infusion.
- The initial IV infusion rate should be no more than 0.25 mg/min (15 mg/hr). The infusion rate may be slowed in the event of infusion-associated reactions.
- After patient tolerance to the infusion is well established, the infusion rate may be increased in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hr) each subsequent infusion.
- Thirty-one of 58 (53%) patients have received infusion at rates  $\geq$  33 mg/hr.

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### Fabrazyme® Safety Information

- Patients should be given antipyretics prior to infusion. If an infusion reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of additional antipyretics, antihistamines and/or steroids may ameliorate the symptoms.
- Because of the potential for severe infusion reactions, appropriate medical support measures should be readily available when Fabrazyme® is administered.

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### Fabrazyme® Safety Information (cont.)

- Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion reactions. Patients with compromised cardiac function should be monitored closely if the decision is made to administer Fabrazyme®.
- Other reported serious adverse events included stroke, pain, ataxia, bradycardia, cardiac arrhythmia, cardiac arrest, decreased cardiac output, vertigo, hypoacusia, and nephrotic syndrome. These adverse events also occur as manifestations of Fabry disease; an alteration in frequency or severity cannot be determined from the small numbers of patients studied.

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### Fabrazyme® Safety Information (cont.)

- Two women were enrolled in the clinical studies with Fabrazyme®. Therefore, no determination can be made whether symptomatic women respond to Fabrazyme® differently than men. There is also insufficient information to determine whether the relationship between cellular histologic evaluations of biopsies and clinical manifestations differ between women and men.
- The safety and effectiveness of Fabrazyme® in pediatric patients have not been established, although clinical trials are ongoing.

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## Fabry Registry

- Established in order to better understand the variability and progression of Fabry disease in the population as a whole and in women, and to monitor and evaluate long-term treatment effects of Fabrazyme®.
- The Registry will also monitor the effect of Fabrazyme® on pregnant women, and their offspring, and determine if Fabrazyme® is excreted in breast milk.
- Patients should be encouraged to participate and advised that their participation is voluntary and may involve long-term follow-up.



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## Fabry Registry (cont.)

- Physicians can monitor their patients' disease status
  - Utilizing patient-specific reports
  - Exchanging non-identifiable clinical data among physicians to facilitate clinical decision-making
  - Accessing information on current treatment guidelines and practice patterns
- Patient- and physician-identifiable information submitted to Fabry Registry maintained as confidential



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## Fabry Registry (cont.)

- Open database
- Helps optimize patient outcomes and increase understanding of Fabry disease by:
  - Providing individualized patient reports and informative clinical summaries
  - Encouraging physician collaboration and shared expertise
  - Facilitating important publications
- Physicians may publish their own data or publish analyses on aggregate Fabry Registry data



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## Fabry Registry (cont.)

- Led by independent Board of Advisors
  - Physicians with extensive experience in managing patients with Fabry disease
- Registry integrity maintained
  - Commitment to privacy and confidentiality
  - Quality of data
  - Comprehensive data collection
    - Registry open to all patients with Fabry disease, regardless of treatment modality



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## Fabry Registry (cont.)

- Important resource to the Fabry medical and patient communities
- Fabry Registry treatment guidelines and publications may contribute to:
  - Earlier disease recognition and diagnosis
  - Earlier intervention
  - Enhanced clinical evaluation and monitoring
  - Improved quality of care
  - Optimal patient outcomes



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## Fabry Registry Enrollment

- Enrollment open to any physician managing a patient with Fabry disease
- Call Fabry Registry toll-free at 800-745-4447, ext. 15500
- Visit Fabry Registry online at [www.fabryregistry.com](http://www.fabryregistry.com)



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## Fabry Disease Resources

### LysoSolutions® network of programs and services

- Designed to support people living with lysosomal storage disorders and those who care for them
  - Research and development
  - Clinical trial programs
  - Disease registries
  - Network of medical specialists
  - Disease information and education
  - Information on diagnostic testing
  - Patient resources and advocacy
  - Health insurance and reimbursement information

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## Fabry Disease Resources

### Genzyme Medical Information Toll-Free 800-745-4447

- Diagnostic testing information
- Information on treatment centers with expertise in treating Fabry disease
- Pharmacovigilance/safety information
- Antibody/plasma GL-3 testing information
- Literature and other presentations on Fabry disease

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## Fabry Disease Resources

### Genzyme Treatment Support Toll-Free 800-745-4447

- Assistance with health insurance issues
- Staffed by healthcare professionals with expertise in:
  - Reimbursement
  - Health insurance
  - Case management
  - Healthcare delivery system

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## Fabry Disease Online Resources

### Genzyme-sponsored resources:

- Fabry Community [www.fabrycommunity.com](http://www.fabrycommunity.com)
- Fabrazyme® [www.fabrazyme.com](http://www.fabrazyme.com)
- Genzyme [www.genzyme.com](http://www.genzyme.com)
- Fabry Registry [www.fabryregistry.com](http://www.fabryregistry.com)

### Non Genzyme-sponsored resources:

- Fabry Support & Information Group [www.fabry.org](http://www.fabry.org)
- National Organization for Rare Disorders [www.rarediseases.org](http://www.rarediseases.org)

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With the exception of its own websites, Genzyme does not endorse any particular organization or the content contained on their website.



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## Future Directions

- Genzyme investigating other disease-specific therapies for Fabry disease
  - Gene therapy
  - Use of small molecules as possible monotherapy or adjunct to enzyme replacement therapy
- Genzyme has a continued commitment to making a major positive impact on the lives of people with serious diseases

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