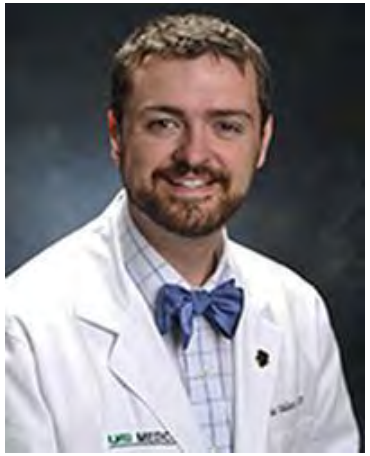
Fabry Disease Research Highlights



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Fabry Disease

- Rare heterogenous X-linked lysosomal disorder caused by mutations in the GLA gene, leading to deficiency in enzyme α-galactosidase A (α-Gal-A).
- Reduced or absent α-Gal-A activity leads to accumulation of glycosphingolipids (Gb3) in organs, which may progress to multisystemic organ failure.
- Characteristic features of Fabry Disease include:
  - Acroparesthesias
  - Proteinuria and Kidney disease
  - Early onset stroke
  - Hypertrophic cardiomyopathy and arrythmias
  - Gastrointestinal problems
  - Angiokeratomas
  - Hypohidrosis
  - Corneal opacity
  - Tinnitus
  - Hearing loss

Germain DP et al. An expert consensus on practical clinical recommendations and guidance for patients with classic Fabry disease. *Mol Genet Metab.* 2022; 137(1-2): 49-61.
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Fabry Knowledge

Knowledge of Fabry Disease Among Healthcare Professionals

Category	Findings
Participants (N=84)	General practitioners: 35 Anaesthetists: 17 Neurologists: 17 Opticians: 15
Awareness & Knowledge	32% unaware of Fabry disease 10% reported good knowledge
Symptom Recognition	Most recognized: Fatigue/lethargy Least recognized: Dermatological issues
Exposure to Fabry Patients	89% had never encountered a Fabry patient
Training & Education	9% received education in medical school 14% received specialty training
Interest in Learning	80% eager to learn more about Fabry disease
Preferred Knowledge Sources	Medical school: 93% Specialized training, key opinion leaders, and conferences: 87%

- **Objective:** Assess the awareness, knowledge, and recognition ability of non-Fabry HCPs regarding Fabry disease in the UK.
- **Design:** Phase 2 of a research project; online survey conducted with 84 non-Fabry HCPs, including general practitioners, anesthetists, neurologists, and opticians.
- **Conclusion:** Awareness and knowledge of Fabry disease among non-specialist HCPs remain low, highlighting the need for improved education and targeted training to enhance early recognition and diagnosis.

Kenny T et al. Awareness of Fabry disease among non-Fabry specialists: Opportunities for education. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

Clinical Trials

ERT: Pegunigalsidase Alfa

Endpoint	Evaluated Pts	Outcome
Safety	29	51 PA-related treatment-emergent adverse events (TEAEs) in 13 pts (44.8%); none severe/serious
Infusion-Related Reactions (IRRs)	9	43 IRRs (2.4 events/100 infusions); most (62.8%) occurred in year 1; 5/9 pts with IRRs had baseline ADAs
Antidrug Antibodies (ADAs)	9	5 seroreverted, 3 titer-boosted, 1 stable
eGFR Slope (mL/min/1.73m²/year)	29	Varied: Males, -2.4; Females, -1.8; ADA−, -1.8; ADA+, -2.6
Plasma Lyso-Gb3	29	Stable in females; non-clinically significant increase in males
Pain & Quality-of-Life	29	Stable over ≥3 years
Dose Adjustment to 1 mg/kg E2W	3	Due to deteriorating kidney function (n=1) or pain crises (n=2)

- **Objective**: Assess long-term safety and efficacy of pegunigalsidase alfa at 2 mg/kg every 4 weeks in patients with Fabry disease previously treated with another ERT.
- **Design**: BRIGHT51 (NCT03614234) 5-year extension study of BRIGHT trial participants with clinically stable Fabry disease (eGFR slope > -2 mL/min/1.73m²/year).
- **Conclusion**: Pegunigalsidase alfa 2 mg/kg every 4 weeks was well tolerated over ≥3 years, with stable plasma lyso-Gb3, pain, and quality-of-life measures. eGFR slope remained stable in ADA-negative (ADA−) males and females but was more negative in ADA-positive (ADA+) males, requiring further investigation.

Bernat JA et al. Extending the interval between pegunigalsidase alfa infusions in patients with Fabry disease: Five-year interim results from the ongoing BRIGHT51 study. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

AAV Gene Therapy: 4D-310

Endpoint	Follow-up Duration	Outcome
Peak VO2 (Exercise Capacity)	12-24 months	Increased
Global Longitudinal Strain (GLS)	12-36 months	Improved
KCCQ (Cardiac QoL)	12-36 months	Improved or stable
Safety	20-41 months	No new 4D-310-related adverse events

- **Objective:** Evaluate the safety and efficacy of 4D-310, a cardiotropic AAV gene therapy, in improving cardiac function and quality of life in adults with Fabry disease.
- **Design:** Ongoing Phase 1/2 trials (INGLAXA-1, INGLAXA-2) with a single IV dose (1E13 vg/kg) in 6 participants, follow-up ranging from 20 to 41 months.
- **Conclusion:** Interim results show sustained improvements in peak VO2, GLS, and KCCQ scores for up to 3 years, with no new treatment-related adverse events reported.

Thomas M et al. Phase 1/2 clinical trial evaluating 4D-310 in adults with Fabry disease cardiomyopathy: Interim analysis of cardiac and safety outcomes in patients with 21-42 months of follow up. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

AAV Gene Therapy: ST-920

Endpoint	Evaluated Participants	Outcome
Safety	31	No withdrawals, no deaths, no Grade 4 AEs Most common AEs: pyrexia, headache, fatigue
α-Gal-A Activity	26 of 31	Physiological or supraphysiological levels reached, longest observation: 1100 days
ERT Withdrawal	All ERT patients	Successfully discontinued ERT by Sept 2024
Lyso-Gb3 Reduction	All patients	Substantial drop in naïve/pseudo-naïve, slight reduction in ERT-treated before stabilizing
Immunogenicity	All patients	Marked decrease in anti-drug antibodies (ADA) post-treatment
Quality of Life	18 with ≥12 months	Significant improvements in pain, vitality, physical/general health, and GI symptoms

- **Objective:** Assess the safety, efficacy, and immunogenicity of ST-920, an AAV2/6-based gene therapy, in adults with symptomatic Fabry disease.
- **Design:** Ongoing Phase 1/2 STAAR trial (NCT04046224) with 31 participants (18 with ≥12-month follow-up) receiving ST-920 at doses up to 2.63×10^{13} vg/kg.
- **Conclusion:** ST-920 is well-tolerated, increases α-Gal-A activity, reduces lyso-Gb3, enables ERT withdrawal, lowers anti-drug antibodies, and improves quality of life, including pain reduction and gastrointestinal symptoms.

Hughes D et al. Isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease: Updated results from an ongoing phase 1/2 study (STAAR). Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

Lentivirus Gene Therapy: LV-GLA

- **Objective:** Assess long-term safety, enzyme activity, and durability of LV-GLA, a lentivirus-transduced autologous stem cell therapy, in Fabry disease.
- **Design:** Phase 1 FACTS trial; 5 males with classical Fabry received single LV-GLA infusion after non-myeloablative conditioning, with 5-year follow-up.
- **Conclusion:** LV-GLA was well-tolerated, sustained α-Gal-A production, enabled ERT discontinuation, stabilized cardiac/kidney function, reduced lyso-Gb3 in most, and maintained safety over 5 years.

Endpoint	Evaluated Participants	Outcome
Safety	5	No severe adverse events after initial transplant period; all pts remain healthy
α-Gal-A Enzyme Activity	5	Increased leukocyte and plasma enzyme levels with detectable vector copy levels at 5 years
ERT Discontinuation	5	All eligible to stop ERT; 3 pts elected to discontinue and did not restart
Cardiac Outcomes	5	Stable left-ventricular mass index and cardiac fibrosis, even in pts with baseline hypertrophic cardiomyopathy
Renal Function (eGFR Slope Change)	5	Varied impact: 3 pts showed mild decline, 2 had a similar slope to baseline
Proteinuria	2 (with baseline proteinuria)	Decreased and sustained in 1 pt at 2.5 years, in another at 3 years
Plasma Lyso-Gb3 Levels	4	Reduced in 4 pts
Immunogenicity	5	No elevated anti-agalsidase antibody titres at 5 years

Khan A et al. Lentiviral gene therapy for Fabry disease - 5 year end of study analysis for the FACTS trial. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

SRT: AL01211

- **Objective:** Assess safety, pharmacodynamics, and preliminary efficacy of substrate reduction therapy (SRT), AL01211, in treatment-naïve male patients with Fabry disease [N=16].
- **Design:** Phase 2 open-label, multicenter, dose-finding study with 26 weeks of daily AL01211 treatment (30 mg or 60 mg).
- **Conclusion:** AL01211 appears to be safe and well-tolerated, and demonstrates significant reductions in GL1, GL3, and Lyso-GL3, with clinical improvements in kidney function, pain, and quality of life.

Dose (mg/day)	GL1 Reduction (%)	GL3 Reduction (%)	Lyso-GL3 Trend	Safety	Clinical Outcomes (6M, 30 mg)
30 mg	70%	~50%	Gradual reduction	Safe, well-tolerated	Stabilized kidney function, reduced pain, improved QoL
60 mg	83%	Greater reduction, faster	Faster reduction	Safe, well-tolerated	Ongoing assessment

Ouyang Y et al. Interim results from a phase 2 trial of the GCS inhibitor AL01211 in treatment naïve, classic male Fabry dise ase patients. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

Real-World Studies

Accelerated Infusion of Agalsidase Beta in Fabry Disease

Characteristic	Details
Patient Demographics	3 females, 2 non-classic males, 3 classic males
Baseline Infusion Duration	90-222 minutes
Infusion Acceleration	Reduced by 20-30 minutes per session
Current Infusion Duration	6 patients at 20 min, 2 classic males at 40 min (ongoing reductions)
Safety	No infusion-associated reactions (IARs)
Plasma lyso-GL3	Stable and low
Antidrug Antibodies (ADAs)	Negative in most; 1 non-classic male with low-titer ADAs (1:400-800)

- **Objective:** Evaluate safety and tolerability of faster agalsidase beta (1 mg/kg biweekly) infusions with reduced total volume.
- **Study Design:** Ongoing Phase 4, open-label, single-arm study (NCT06019728) enrolling 14 participants (ages 2-65).
- **Conclusion:** Agalsidase beta infusions as short as 20 minutes appear safe in ERT-experienced patients, supporting potential protocol adjustments to reduce treatment burden.

Banikazemi M et al. A phase 4 study to evaluate the safety and tolerability of higher infusion rates of agalsidase beta to shorten infusion duration in Fabry disease - interim analysis. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

Patient-Reported Outcomes in followME Fabry Pathfinders Registry

- **Objective:** Evaluate real-world PROs in patients with Fabry disease receiving migalastat using the followME Fabry Pathfinders registry.
- **Design:** Prospective observational study analyzing PROs (BPI, FABPRO-GI, TSQM) in patients treated with migalastat for ≥2 years, with at least two ePRO measurements over ≥2 years.
- **Conclusion:** Pain, gastrointestinal symptoms, and treatment satisfaction remained stable over 36 months, with increased effectiveness and global satisfaction scores in the true baseline subgroup.

Population	Median Migalastat Duration	Key PRO Findings
Overall (N=86)	4.0 years (IQR: 3.4–4.3)	**BPI:** Pain and pain interference remained low and stable **FABPRO-GI:** Bowel movement patterns stable **TSQM:** Stable treatment satisfaction
True Baseline (N=25)	3.8 years (IQR: 3.5–4.3)	**BPI:** Pain and pain interference remained low and stable **FABPRO-GI:** Bowel movement patterns stable **TSQM:** Increased effectiveness and global satisfaction; convenience remained stable

Feldt-Rasmussen U et al. FollowME Fabry Pathfinders Registry: Patient-reported outcomes in a cohort of patients on migalastat treatment for median 4 years. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

Tolerability and IRRs in Patients Switching to Pegunigalsidase Alfa

Patient Group	Prior AB Experience	Outcomes After Switching to PA
Female (n=1)	Worsening fatigue before infusions	Stable energy between infusions, tolerated 60-min infusions without premedication
Males (n=3)	Frequent IRRs, extensive premedication, prolonged infusions (150-270 min)	Reduced/discontinued premedications, no corticosteroids, 2/3 shortened infusions (60-90 min), only 1 mild IRR
Adverse Events	2 males tested positive for neutralizing antidrug antibodies before EAP	No PA-related serious adverse events; 1 patient with prior cardiac history experienced MI during EAP

- **Objective:** Assess tolerability and infusion-related reactions (IRRs) in patients with Fabry disease switching from agalsidase beta to pegunigalsidase alfa in the US Expanded Access Program (EAP).
- **Design:** Retrospective medical record review of 4 patients with Fabry disease (3 male, 1 female) with >5 years of prior ERT who switched from agalsidase beta to pegunigalsidase alfa due to low agalsidase beta tolerability.
- **Conclusion:** Patients switching to pegunigalsidase alfa experienced fewer IRRs, reduced premedication use, and shorter infusion times, suggesting improved tolerability compared to agalsidase beta.

Holida MD et al. Improved tolerability following enzyme replacement therapy switch to pegunigalsidase alfa: A case series from two centers of the expanded access program. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

Disease Severity Outcomes in Pegunigalsidase Alfa-Treated Patients

Patient Group	Baseline MSSI Severity	Change at 12 Months	Change at 24 Months
ERT-Naïve (n=16)	Mild: 50% (8/16) Moderate: 50% (8/16)	Mild increased to 81% (13/16)	Mean MSSI Change: -7.5 (Improvement)
ERT-Switch (n=71)	Mild: 44% (31/71) Moderate: 51% (36/71) Severe: 5% (4/71)	Mild stable at 48% (31/64)	Mean MSSI Change: -1.9 (Stability with trend toward improvement)
Overall MSSI Change (n=80 at 12M, n=56 at 24M)	39 mild, 44 moderate, 4 severe	Mean Change: -1.7	Improvement in all MSSI domains as early as 6 months
Severity Category Change	14% (11/80) had a shift	9 improved (8 moderate → mild, 1 severe → moderate); 2 worsened (both ADA-positive males)	-

- **Objective:** Evaluate 24-month changes in disease severity using the Mainz Severity Score Index (MSSI) in patients with Fabry disease treated with pegunigalsidase alfa.
- **Design:** Analysis of MSSI changes in 87 PA-treated patients (ERT-naïve and ERT-switch) from 3 clinical trials (F01/F02, F20, F30) and 1 extension study (F03).
- **Conclusion:** ERT-naïve patients showed a reduction in disease severity, while ERT-switch patients maintained stable MSSI scores over 12 months with a trend toward improvement at 24 months.

Hughes D et al. Clinical assessment of disease severity in patients with Fabry disease treated with pegunigalsidase alfa: An integrated analysis. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

Cardiology

Stroke Risk Reduction with Agalsidase Beta Treatment

Population	Median Follow-Up	Stroke Incidence	Stroke Type	Stroke Risk
Treated (N=1868)	5.8 yrs	70 (5.55 per 1000 person-years)	72.7% ischemic (125/172 strokes)	0.36 (lower risk)
Untreated (N=1868)	3.3 yrs	102 (11.18 per 1000 person-years)		-

- **Objective**: Assess stroke incidence in patients with Fabry disease treated with agalsidase beta versus untreated patients in the Fabry Registry.
- **Design**: Matched cohort analysis (1:1) of 1868 pairs (52.4% males, 68.3% classic phenotype) to estimate stroke risk
- **Conclusion**: Agalsidase beta treatment may lower stroke risk in patients with Fabry disease, with findings consistent across multiple adjustments.

Burlina A et al. Reduced incidence of stroke in patients with Fabry disease treated with agalsidase beta: A matched analysis from the Fabry Registry. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

Quality of Life

Gender Disparities in Fabry Disease Care

- **Objective**: Assess the experiences, healthcare perceptions, and challenges faced by females living with Fabry disease across North America and Japan.
- **Design:** Patient-developed surveys completed by 138 female respondents from the US, Canada, and Japan.
- **Conclusion:** Female patients with Fabry disease report disparities in healthcare support, lack of HCP understanding, and significant mental health and family planning concerns, highlighting the need for improved HCP education and gender-equitable care.

Key Topic	US (n=53)	Canada (n=39)	Japan (n=47)
Perceived difference in healthcare vs males	80%	44%	51%
HCPs understand unique challenges in females (Disagreed)	73%	77%	41%
Most stressful life stage (family planning)	67%	72%	60%
Fabry disease affects mental health	85%	80%	77%
Top concern	Symptoms (83%)	Symptoms (87%)	Disease inheritance (89%)

Alton J et al. Exploring the lived experiences and care perceptions of females living with Fabry disease in the US, Canada, and Japan. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

Long-Term Impact of Migalastat on QoL in Adolescents with Fabry

- **Objective**: Assess the long-term impact of migalastat on quality of life in adolescents with Fabry disease and amenable GLA variants.
- **Design**: Phase 3b, two-stage, open-label, multicenter study (NCT03500094) with an ongoing open-label extension (NCT04049760); PROs measured using the Pediatric Health and Pain Questionnaire (FPHPQ).
- **Conclusion**: Migalastat treatment led to improvements in gastrointestinal symptoms, paresthesia, and overall QoL, with positive trends observed regardless of prior ERT status.

Category	Findings
Participants	22 enrolled (mean age: 14.6 years) 21 treated (10 males, 11 females) 11 ERT-experienced
Study Progression	19 completed primary study (12 months) 16 entered the open-label extension (OLE)
Baseline Symptoms	GI symptoms: 76.2% (9/10 males, 7/11 females) Paresthesia: 61.9% (6/10 males, 7/11 females)
Patient-Reported Outcomes (PROs)	1-point improvement in FPHPQ scores (n=18): - Pain - Dizziness - Tiredness in hot environments
Quality of Life (QoL) Trends	Positive trends in QoL improvements observed, regardless of prior ERT treatment history

Hopkin RJ et al. Quality of life of migalastat-treated adolescents with Fabry disease: Results from the ASPIRE study and open-label extension. Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

Assessment of Clinical Depression in Patients with LSDs

Category	Patients (N=44)	Key Findings
LSD Types	54% Fabry Disease 27% Gaucher Disease 18% MPS 1% Other	—
On Disease-Modifying Therapies	66% (29 patients)	ERT: 24 Chaperone: 3 Substrate reduction: 1 Bone marrow transplant: 1
Clinical Depression Reported	77% (34 patients)	10 patients on antidepressants (5 on ≥2 antidepressants)
Common Symptoms	Feeling sad: 44% Lack of enjoyment: 50% Suicidal ideation: 14% Fatigue: 52% Sleep issues: 45%	
BDI-II Scores	Minimal: 33 patients (Median: 2.5) Mild: 1 patient (Score: 1) Moderate: 5 patients (Median: 23) Severe: 5 patients (Median: 34)	Significant depression burden detected, often not identified in consultations

- **Objective**: Evaluate the presence and severity of clinical depression in patients with lysosomal storage disorders (LSDs) using the Beck's Depression Inventory-II (BDI-II).
- **Design**: Cross-sectional study of 44 LSD patients (21 females) completing BDI-II during routine clinic visits between March and June 2024.
- **Conclusion**: Clinical depression is prevalent among LSD patients, often undetected in face-to-face consultations, highlighting the need for routine psychological assessments using validated tools like BDI-II.

Joseph DP et al. Clinical depression and impact on patients with lysosomal diseases (LDs): Service evaluation from a specialist centre using the Beck's Depression Inventory (BDI-II). Presented at WORLD*Symposium;* Feb 3-7, 2025; San Diego, CA.

Clinical Pearls

Clinical Pearls

Clinical Trial Data:

- **AL01211**: Safe and well-tolerated, with significant reductions in GL1, GL3, and Lyso-GL3, alongside improvements in kidney function, pain, and quality of life.
- **4D-310 Gene Therapy**: Shows sustained improvements in peak VO_2, GLS, and KCCQ scores for up to 3 years with no new treatment-related adverse events.
- **ST-920:** Well-tolerated, increases α-Gal-A activity, reduces lyso-Gb3, enables ERT withdrawal, lowers anti-drug antibodies, and improves quality of life, including pain and gastrointestinal symptoms.
- **LV-GLA:** Well-tolerated with sustained α-Gal-A production, stabilized cardiac and kidney function, reduced lyso-Gb3 in most patients, and maintained safety over 5 years.
- **Pegunigalsidase Alfa:** Well-tolerated over ≥3 years with stable lyso-Gb3 levels, pain, and quality of life. Further investigation needed to understand impact on eGFR in ADA+ males.

Clinical Pearls

Real World Data:

- **Agalsidase Beta:**
  - Infusions as short as 20 minutes appear safe in ERT-experienced patients, supporting potential protocol adjustments to reduce treatment burden.
- **Migalastat:**
  - Pain, gastrointestinal symptoms, and treatment satisfaction remained stable over 36 months, with increased effectiveness and satisfaction scores in patients who started at baseline.
- **Pegunigalsidase Alfa:**
  - Fewer IRRs, reduced premedication use, and shorter infusion times compared to agalsidase beta, suggesting improved tolerability.
  - ERT-naïve patients showed reduced disease severity, while ERT-switch patients maintained stable MSSI scores over 12 months, trending toward improvement at 24 months.

Clinical Pearls

Comorbidities:

- **Agalsidase Beta:**
  - Reduces CKD progression, improves survival, and lowers overall costs, with earlier treatment initiation enhancing both economic and clinical outcomes.
  - Significantly lowers stroke risk in Fabry disease patients, with consistent findings across various adjustments.

QoL:

- **Female Fabry Disease Patients:** Report disparities in healthcare support, lack of HCP understanding, and challenges related to mental health and family planning, underscoring the need for improved HCP education and gender-equitable care.
- **Depression:** Clinical depression is common and often undetected in routine consultations, highlighting the importance of psychological assessments using validated tools like the BDI-II.

Awareness:

- Awareness and knowledge of Fabry disease remain low among non-specialist HCPs, emphasizing the need for improved education and targeted training to enhance early recognition and diagnosis.