



Disappointment and/or a glimmer of hope? - When biochemical efficacy does not translate into (primary) clinical benefit

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Fabry disease [Online Mendelian Inheritance in Man (OMIM) #301500; ORPHAcode:324] is a rare, X-linked lysosomal storage disorder^[1]. Pathogenic variants in the *GLA* gene (OMIM #300644; gene locus Xq22.1) result in reduced alpha-galactosidase A [Enzyme Commission (EC) number 3.2.1.22.] activity and accumulation of glycosphingolipids, primarily globotriaosylceramide (Gb3) and lyso-globotriaosylsphingosine (lyso-Gb3)^[1]. Multiorgan involvement mainly affects the kidneys, heart, and nervous system and reduces life expectancy^[1]. Individuals may present with a classical phenotype, typically observed in hemizygous men, or late-onset phenotypes predominantly involving the kidneys or heart^[1]. Women with heterozygous pathogenic *GLA* variants show highly variable disease courses from asymptomatic or mild involvement to severe manifestations^[1].

Current disease-specific therapies include intravenous enzyme replacement therapy (ERT) and oral chaperone therapy with migalastat, which stabilizes misfolded endogenous enzyme but is restricted to patients with amenable missense *GLA* variants, although *in vitro* amenability may not necessarily implicate a clinical treatment response^[2-4]. ERT lowers substrate levels and improves organ outcomes but is associated with more adverse effects and the development of neutralizing anti-drug antibodies, which might impair treatment efficacy^[4]. More recently, pegunigalsidase alfa has emerged as an alternative ERT with lower immunogenic potential^[4]. Sadly, the clinical manifestations continue to progress to end-stage kidney and cardiovascular disease despite these specific therapies^[5]. Therefore, new and more effective treatment options are sorely needed.

One novel therapeutic concept relies on inhibition of glycosphingolipid biosynthesis [substrate reduction therapy (SRT)]^[4]. By blocking ceramide glucosyltransferase (glucosylceramide synthase; EC number 2.4.1.80), small molecules such as lucerastat reduce synthesis of glucosylceramide, a precursor of Gb3 and lyso-Gb3, independent of the underlying *GLA* variant^[4].



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Nordbeck and colleagues recently reported the results of the phase 3 MODIFY trial and its open-label extension (OLE) evaluating lucerastat in Fabry disease^[6]. MODIFY (NCT03425539) was a randomized, double-blind, placebo-controlled trial evaluating oral lucerastat in patients with moderate-to-severe neuropathic pain^[6]. Drug dosing was 1,000 mg twice daily, with dose reduction according to kidney function^[6,7].

The primary endpoint was change in average neuropathic pain from baseline to six months, assessed daily using the Brief Pain Inventory short form (BPI-SF3) for worst pain during the preceding 24 h (range 0–10), with values averaged over the four weeks preceding each study visit. The BPI-SF3 was previously used to examine the effect of ERT^[8]. A sample size of 99 participants (2:1 randomization) was calculated to detect a ≥ 2 -point between-group difference in BPI-SF3. MODIFY randomized 118 participants {lucerastat [$n = 80$]; placebo [$n = 38$]}, of whom 109 completed the primary study. The mean age was 39.3 ± 14.1 years, 53% were female, 83% had a classical Fabry phenotype, 17% had migalastat-amenable and 66% had non-amenable *GLA* variants, and 17% were not tested. Mean estimated glomerular filtration rate (eGFR) was 98.2 ± 25.2 mL/min/1.73m², median urinary albumin-creatinine ratio (UACR) was 23.0 (12.0–114.8) mg/g, and 62% were ERT-naïve. The baseline characteristics were balanced between groups. 107 individuals entered the OLE, 79 were included in the interim analysis.

After this novel therapeutic approach has been shown to be effective in Gaucher disease^[9], this long-anticipated report sheds important, albeit sobering, light on the efficacy for Fabry disease^[6]. There was no difference in the primary endpoint after six months of treatment {Least squares mean (LSM) difference: -0.4 [95% confidence interval (CI): -1.2, 0.4], $P = 0.32$ } with either lucerastat ($n = 80$) or placebo ($n = 37$), despite lower plasma Gb3 levels with lucerastat (LSM change from baseline to month 6: -673 vs. +201 ng/mL [placebo group]; difference: -874 ng/mL [95%CI -1098, -650], $P < 0.0001$; measured by a central laboratory for all participants)^[6]. Because the primary endpoint was not met, this secondary endpoint could not be considered significant under the hierarchical testing strategy^[6]. Plasma lyso-Gb3 levels were stable with lucerastat, but increased with placebo, largely driven by ERT discontinuation^[6]. Abdominal pain, diarrhea, and cardiac safety outcomes (e.g. left ventricular mass) did not differ between treatment groups.

Kidney function did not differ significantly between lucerastat and placebo overall. The effect on eGFR slope was 0.2 mL/min/1.73m²/year {[95%CI: -0.4, 0.8]; $P = 0.53$ }, while UACR was similar between groups {LSM: 16% [95%CI: -24, 77]; $P = 0.49$ }. In an exploratory subgroup with eGFR < 90 mL/min/1.73m², eGFR increased by 3.8 mL/min/1.73m² with lucerastat compared with a reduction of -1.6 mL/min/1.73m² with placebo. Notably, the < 90 mL/min/1.73m² eGFR threshold was used because few participants met the initially prespecified cut-off value of < 60 mL/min/1.73m². Whether albuminuria was associated with eGFR slopes was not specified.

An unplanned interim analysis from the OLE was performed after ongoing participants had received lucerastat for at least 12 months. Although pain-related outcomes were collected during the OLE, corresponding results were not reported, while suppression of Fabry disease biomarkers was maintained. With a median lucerastat exposure of 23.0 months, the median eGFR slope changed from -3.5 mL/min/1.73m²/year (95%CI: -5.0, -2.0) before randomization to -1.5 mL/min/1.73m²/year (95%CI: -2.6, -0.3) thereafter. This effect was most pronounced among individuals with eGFR < 90 mL/min/1.73m² {LSM: -6.2 mL/min/1.73m²/year [95%CI -8.7, -3.7] and -1.9 mL/min/1.73m²/year [95%CI -4.0, 0.3] before and after randomization}, and those classified as “deteriorating” or “fast deteriorating” {LSM: -9.8 mL/min/1.73m²/year [95%CI -15.8, -4.1] and -1.2 mL/min/1.73m²/year [95%CI -6.8, 4.4] before and after randomization}, whereas no apparent effect was observed in participants without kidney disease, those who received ERT until screening, or those receiving renin angiotensin system (RAS) inhibition at baseline.

Although lucerastat had no significant effect on the primary pain endpoint, the OLE may provide preliminary evidence for renal benefit. Given the limitations inherent to its non-randomized design, the results remain hypothesis-generating but warrant further investigation of whether SRT may be a therapeutic strategy for Fabry disease with renal involvement.

Evidence from other SRTs provides important parallels. Although an earlier phase 2 trial demonstrated progressive reductions in circulating biomarkers and skin capillary endothelial Gb3 inclusions, the randomized, controlled Patient Experience in Fabry Disease On VenglustaT (PERIDOT) trial (NCT05206773) evaluating venglustat did not meet its pain-related endpoint^[10,11]. A similar dissociation between biochemical substrate reduction and clinical efficacy was observed in GM2 gangliosidosis, in which venglustat reduced cerebrospinal fluid GM2 without improvement in clinical endpoints^[12]. Migalastat provides a further example for the complex relationship of biomarkers and organ outcomes: treatment has been associated with preservation of eGFR and reductions in left ventricular mass, whereas treatment-induced changes in lyso-Gb3 levels did not correlate with changes in kidney function, cardiac involvement, or pain^[13].

This discordance highlights the limitations of circulating glycosphingolipids as surrogate measures of treatment efficacy. Although circulating concentrations are associated with certain Fabry phenotypes and manifestations^[14], treatment-associated changes have shown inconsistent relationships with clinical outcomes^[6,10,13]. Experimental studies have reported particularly high lyso-Gb3 in the liver, although hepatic contribution to circulating levels remains uncertain^[14,15]. Preclinical evidence further suggests that total tissue Gb3 and lyso-Gb3 burden alone may not explain small-fiber neuropathy, as glycosphingolipid accumulation differs between neuronal populations and may not directly correspond to neuropathic dysfunction^[16]. Thus, reduction of circulating biomarkers demonstrates substrate reduction but should not itself be interpreted as reversal of manifest tissue injury or clinical benefit^[13].

From a mechanistic point of view, SRT differs fundamentally from chaperone therapy. Unlike migalastat, SRT is not restricted to amenable *GLA* variants and therefore could offer an oral treatment option across genotypes. However, patient selection may be important. MODIFY was enriched for classic Fabry phenotype compared with registry populations, likely mirroring the restriction to neuropathic pain, while women represented approximately half of the cohort^[6,17]. Neuropathic pain tends to occur later in women with Fabry disease, and neither age at pain onset, pain duration, nor sex-specific treatment effects were reported^[6,18]. Residual enzyme activity, phenotype, disease stage, and duration of manifest neuropathy therefore remain potential modifiers of response to SRT and cohorts' heterogeneity may have limited the ability to identify subgroup-specific treatment effects^[6]. Recruitment and drug development for rare diseases may additionally be complicated by concurrent clinical trials competing for a limited pool of eligible participants, as exemplified by the lucerastat OLE and PERIDOT.

SRT programs therefore generate several testable hypotheses. In particular, SRT may exert organ-specific effects that are not captured by pain-related endpoints, with potential benefit in kidney disease. Potential effects on cardiac structure will be addressed in the phase 3 CARDiac AssessmentT in Fabry patients on venglustat trial (NCT05280548). Patient selection may also be relevant, raising the question whether SRT alone is enough to modulate disease burden, or whether a certain threshold of residual alpha-galactosidase activity is required for clinical benefit. In the context of enzyme activity, gene therapies which can induce supraphysiologic levels of alpha-galactosidase are emerging^[4].

Taken together, lucerastat may augment the therapeutic landscape in Fabry disease, but MODIFY illustrates the challenges between biomarker reduction and clinical benefit. This discrepancy underscores the need for complementary endpoints of small-fiber neuropathy like intraepidermal nerve fiber density or quantitative

sensory testing^[19]. The renal findings from the OLE remain hypothesis-generating and require confirmation in adequately powered randomized, controlled trials, with appropriate stratification by genotype, phenotype and residual enzyme activity, and evaluation of interactions with concomitant standard-of-care therapies like RAS inhibitors, given their central role in chronic kidney disease management.

DECLARATIONS

Authors' contributions

Wrote the first draft of the manuscript: Paschen C, Sunder-Plassmann G
Critically revised the manuscript and provided feedback: Allmer DM, Schmidt A
All authors read and approved the final version of the manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool OpenAI ChatGPT (version 5.5, released 2026-05-05) was used solely for language editing. The tool did not influence the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

Schmidt A and Sunder-Plassmann G served as investigators in the MODIFY trial. Paschen C reports speaker honoraria from Amicus Therapeutics, consulting fees from Sanofi, and non-financial support (including travel, accommodation, and conference fees) from Amicus Therapeutics, Chiesi Farmaceutici, and STADA Arzneimittel AG, outside the submitted work. Schmidt A received speaker honoraria from and participated in meetings sponsored by Amicus and Sanofi-Genzyme. Sunder-Plassmann G received honoraria and research funding from Amicus, Chiesi Farmaceutici, Freeline, and Sanofi-Genzyme. Allmer DM has no conflicts of interest to declare.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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