Media Release
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Clear route to registration positions lucerastat as the potential first oral therapy for all patients with Fabry disease

Allschwil, Switzerland – February 06, 2026
Idorsia Ltd (SIX: IDIA) announces the design of its FDA-agreed Phase 3 registration program for lucerastat in Fabry disease. Building on the robust biomarker and renal findings from the MODIFY Phase 3 trial and its long-term open-label extension (OLE), the program focuses on lucerastat's impact on renal pathology – a central driver of morbidity and mortality in Fabry disease – with the goal of securing market authorization.

Fabry disease is a rare, X-linked lysosomal storage disorder caused by mutations in the *GLA* gene that lead to deficient α-galactosidase A (α-GalA) activity and progressive accumulation of globotriaosylceramide (Gb3). Over time, Gb3 accumulation drives multisystem organ damage, primarily impacting the kidneys, heart, and nervous system. According to DelveInsight, approximately 16,000 patients were diagnosed with Fabry disease across the seven major markets (US, EU4, UK, Japan) in 2020, a number expected to increase to roughly 21,000 by 2034. The Fabry disease market is projected to reach around USD 4 billion by 2034, underscoring the continued demand for innovative, patient-focused therapies.

Srishti Gupta, MD, CEO of Idorsia commented:
"This is an important step forward for Idorsia and for the Fabry community. Fabry disease is a serious, progressive condition with a clear need for effective, convenient therapies that address the underlying biology across the full patient population. The strength of our long-term data and a clearly defined regulatory pathway position lucerastat as a uniquely differentiated oral approach. Drug development in Fabry disease is challenging, and meaningful innovation requires both scientific rigor and persistence. With its mutation-independent mechanism and growing body of long-term evidence, we believe lucerastat has the potential to make a real difference for patients."

Registration program agreed with health authorities
Idorsia has aligned with the US FDA on a streamlined registration strategy comprising two complementary clinical trials designed to definitively characterize lucerastat's renal effects. This program is also in line with the feedback received from European Medicines Agency.

Pivotal kidney biopsy study (n=16)
- Adult males with Fabry disease, treatment-naïve or pseudo-naïve;
- Designed to show a decrease from baseline in renal Gb3 burden after 18 months of treatment.

Renal function comparative study (n ≈ 74)
- Adult patients with Fabry disease;
- Assessment of lucerastat versus established enzyme replacement therapies (agalsidase beta, pegunigalsidase alfa);
- Designed to reinforce lucerastat as the first oral therapy suitable for all patients with Fabry disease, irrespective of their mutation type.

The program is expected to support a potential regulatory filing as early as 2029.

Alberto Gimona MD, Head of Global Clinical Development at Idorsia, commented:
"The body of evidence we have generated to date shows that long-term treatment with lucerastat consistently reduces the glycosphingolipid substrates that accumulate in Fabry disease. We also observe a slower decline in kidney function compared with patients' prior historical trajectories. Importantly, kidney biopsy data from long-term treated patients demonstrate low-to-no levels of characteristic lysosomal deposits. Following constructive discussions with health authorities, we have agreed on the trials that will form the basis for establishing substantial evidence of effectiveness in support of a future NDA and MAA. The agreed program includes a pivotal baseline-controlled biopsy study and a second study which will then show that an oral treatment can potentially achieve a similar effect to today's cumbersome standard-of-care."

About the MODIFY study (NCT03425539) and OLE (NCT03737214)
MODIFY was a multicenter, double-blind, randomized, placebo-controlled, Phase 3 study evaluating lucerastat as an oral monotherapy for adults with Fabry disease. A total of 118 patients from 14 countries were randomized 2:1 to lucerastat or placebo. Upon completion of the double-blind period, 107 patients entered a long-term OLE assessing safety, tolerability, and renal outcomes.

Primary results from MODIFY and the 12-month interim OLE analysis have been published in *Nature Communications*, ("Lucerastat, an oral therapy for Fabry disease: Results from a pivotal phase 3 study and its open-label extension", January 2026).

While the MODIFY study did not meet its primary endpoint of reducing neuropathic pain over six months, lucerastat demonstrated a robust pharmacodynamic effect, significantly reducing plasma and urinary Gb3 levels compared to placebo. These reductions were sustained over time in the OLE, with patients switching from placebo to lucerastat showing similar biomarker reductions.

More importantly, as presented at **WORLD*Symposium*™ 2026**, an interim analysis of the OLE, where ongoing patients had been treated with lucerastat for at least 42 months – some exceeding six years of continuous therapy – revealed a notable shift in renal function trajectory. Treatment with lucerastat was associated with a reduction in the rate of eGFR decline as compared to eGFR slope observed in the 2 years preceding their enrollment in MODIFY (eGFR slope, historical: -3.50; Lucerastat: -1.64). Lucerastat treatment was also associated with a particularly marked attenuation of kidney function loss in patients with severe disease course, such as classic males with Fabry disease (historical: -4.32; Lucerastat: -2.05), patients with impaired renal function at baseline (eGFR <90 mL/min/1.73m^2) (historical: -6.18; Lucerastat: -2.49), Anti-Drug Antibody (ADA+) positive patients (historical: -7.75; Lucerastat: -3.43). The effect was independent of the gene variants' amenability to migalastat. Lucerastat also led to a 51% decrease in plasma Gb3 levels and was well-tolerated with long-term treatment.

In addition, the positive impact on kidney function was supported by a kidney biopsy sub-study of six male adult patients with classic Fabry disease who had received lucerastat monotherapy for a median treatment period of 56 months. The study evaluated the number of kidney Gb3 inclusions using established quantitative (Barisoni Lipid Inclusion Scoring System (BLISS)) and semi-quantitative (Fabrazyme Scoring System (FSS)) methodologies. At enrollment in MODIFY, 4 participants were ERT naïve or pseudo-naïve and 2 switched from ERT. Median kidney Gb3 BLISS score was 1.7 (range: 0.7–4.5; mean (SD): 2.41 (1.59)). Mean FSS scores were 0 indicative of "no or trace" accumulation (5/6 participants) or 1 indicative of mild accumulation (1/6). The 2 patients who switched from ERT had BLISS scores of 1.6-1.8 and a FSS score of 0. The results indicate that long-term treatment with lucerastat monotherapy was associated with low-to-no levels of kidney Gb3 inclusions.

Notes to the editor

About Fabry disease

Fabry disease is a rare, X-linked lysosomal storage disorder caused by mutations in the *GLA* gene that results in the absence or markedly reduced activity of the enzyme α-galactosidase A (α-GalA). α-GalA normally breaks down a fatty product known as globotriaosylceramide (Gb3) in the cells of the body. Deficiency over time results in an accumulation of Gb3 deposits throughout the body, leading to multisystem disease, mainly affecting the kidneys, heart, and nervous system.

The disease manifests in two main phenotypes: classic Fabry disease, typically presenting in childhood with severe, multisystemic involvement, and late-onset Fabry disease, which may emerge in adulthood with predominant cardiac or renal symptoms. Fabry disease affect a patient's life expectancy and quality of life. Due to its variable presentation and non-specific symptoms, Fabry disease is frequently underdiagnosed or misdiagnosed, leading to delays in treatment and increased risk of irreversible organ damage.

As the gene responsible for Fabry disease is found on the X chromosome (of which males have one, and females two), males with deleterious mutations have little or no residual alpha-GalA activity. Therefore, these male patients with Fabry disease experience a wider spectrum of symptoms, and in some cases, a greater severity. It is now widely accepted that women with Fabry disease are heterogeneous with respect to disease severity and may sometimes also develop life threatening complications of the disorder. Up to 70% of female carriers develop Fabry related symptoms at some point in their life.

Current treatment options include enzyme replacement therapies (ERTs) and oral chaperone therapy for patients with amenable mutations. However, these therapies have limitations, including intravenous administration, immunogenicity, and mutation-specific efficacy. There remains a significant unmet need for a well-tolerated, oral, disease-modifying therapy that can be used regardless of genotype or prior treatment history.

Lucerastat in Fabry disease

Lucerastat is an investigational, oral substrate reduction therapy designed to treat Fabry disease independently of α-Gal A activity, *GLA* mutation status, or prior enzyme replacement therapy (ERT). It acts by inhibiting glucosylceramide synthase, thereby reducing the synthesis of glycosphingolipids, including globotriaosylceramide (Gb3), which accumulate due to deficient α-galactosidase A activity in Fabry disease.

Preclinical studies demonstrated that lucerastat is a highly soluble and bioavailable small molecule capable of penetrating key tissues affected by Fabry disease – including the kidneys, liver, and dorsal root ganglia – where it effectively reduces substrate accumulation. Clinical pharmacology studies confirmed lucerastat's favorable pharmacokinetic profile, characterized by rapid absorption, predictable elimination, and no evidence of saturation, supporting consistent exposure across dosing regimens.

Across Phase 1 studies, lucerastat was well tolerated at doses up to 4000 mg, with no dose-limiting toxicities and a safety profile unaffected by concomitant medications. In a 12-week exploratory study in adult Fabry patients receiving ERT, lucerastat 1000 mg twice daily led to a rapid and sustained reduction in plasma Gb3 and related biomarkers, confirming its mechanism of action and potential for fast-onset substrate reduction.

The recently published Phase 3 MODIFY study and its long-term extension further support lucerastat's disease-modifying potential. While the primary endpoint of neuropathic pain reduction was not met, lucerastat demonstrated robust and sustained biomarker reductions and a promising renal signal, with a slower rate of eGFR decline in patients with impaired kidney function. These findings suggest lucerastat may offer long-term organ protection and broaden therapeutic options for Fabry patients, especially those underserved by current treatments.

Key Literature

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About Idorsia

The purpose of Idorsia is to challenge accepted medical paradigms, answering the questions that matter most. To achieve this, we will discover, develop, and commercialize transformative medicines – either with in-house capabilities or together with partners – and evolve Idorsia into a leading biopharmaceutical company, with a strong scientific core.

Headquartered near Basel, Switzerland – a European biotech hub – Idorsia has a highly experienced team of dedicated professionals, covering all disciplines from bench to bedside; QUVIVIQ™ (daridorexant), a different kind of insomnia treatment with the potential to revolutionize this mounting public health concern; strong partners to maximize the value of our portfolio; a promising in-house development pipeline; and a specialized drug discovery engine focused on small-molecule drugs that can change the treatment paradigm for many patients. Idorsia is listed on the SIX Swiss Exchange (ticker symbol: IDIA).

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