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Nature Communications reports promising effect of Idorsia's lucerastat on kidney function in Fabry disease

- In patients with impaired renal function or fast-deteriorating eGFR at baseline, lucerastat was associated with a marked attenuation of kidney function loss, suggesting a potential disease-modifying effect
- The company is working with health authorities to find the optimal pathway to approval

Allschwil, Switzerland – January 12, 2026
Idorsia Ltd (SIX: IDIA) announces the publication of results from the pivotal Phase 3 MODIFY study and its open-label extension (OLE) evaluating lucerastat, an oral substrate reduction therapy, in adults with Fabry disease. The data, published in *Nature Communications*, titled "Lucerastat, an oral therapy for Fabry disease: Results from a pivotal phase 3 study and its open-label extension", reinforce lucerastat's potential to address key unmet needs in Fabry disease, particularly in patients with renal impairment.

About the MODIFY study (NCT03425539) and its open label extension (NCT03737214)
MODIFY was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of lucerastat as an oral monotherapy in adult patients with Fabry disease. 118 patients were randomized in a 2:1 ratio to either lucerastat or placebo. At the end of the double-blind period, 107 patients entered an open label extension study, to determine the long-term safety and tolerability of lucerastat oral therapy and to further evaluate its clinical efficacy on renal function, in adult patients with Fabry disease.

The MODIFY study in Fabry disease enrolled a diverse population of 118 patients across 14 countries. As announced in an earlier press release, while the 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, an interim analysis of the OLE, where ongoing patients had been treated with lucerastat for at least 12 months, revealed a notable shift in renal function trajectory, with a reduction in the rate of eGFR decline among patients treated with lucerastat as compared to eGFR slope observed in the 2 years preceding their enrollment in MODIFY. In patients with impaired renal function or fast-deteriorating eGFR at baseline, lucerastat was associated with a marked attenuation of kidney function loss, suggesting a potential disease-modifying effect. In addition, there was a stabilization of cardiac function, with no worsening over time of the echocardiography left ventricular mass index (see this press release for more details).

Professor Derralynn Hughes, University College London, Royal Free London NHS Foundation Trust, London, UK, Chief Investigator in MODIFY commented:
"Stability or the reduction of loss of kidney function is a therapeutic goal for patients with Fabry disease. This can only be seen with long-term treatment. The renal signal observed in the long-term evaluations is encouraging and warrants further investigation. Lucerastat's oral administration, tolerability, and mechanism make it an important candidate for broader Fabry disease populations."

Beyond the reported interim analysis, the OLE has now collected data from patients who continued treatment with lucerastat for at least 42 months, with some treated with lucerastat for over 6 years. Lucerastat was well tolerated, with no treatment-related serious adverse events. In addition, Idorsia has conducted a kidney biopsy sub-study belonging to the OLE of the Phase 3 study. This sub-study enrolled male participants with classic Fabry disease who had been treated for more than 3 years with lucerastat monotherapy. The main objective of the sub-study was to evaluate the number of Gb3 inclusions in certain types of kidney cells using established methods of quantification.

The data collected in such a small population are very encouraging, support further investigation for patients with Fabry disease, and have been instrumental in the design of a new Phase 3 program. The company is working with the US FDA to design the optimal program to ensure the regulatory pathway to approval.

As the next steps for lucerastat are being planned, the OLE study will be concluded. To ensure continuity of care for participants still receiving lucerastat at study closure, a post-trial access program is being established.

Alberto Gimona MD, Head of Global Clinical Development at Idorsia, commented:
"The patients who have taken part in MODIFY and the extension study – some of whom have now been treated with lucerastat for over 6 years – have been true heroes for the Fabry community. Thanks to their participation, we have gained great insight into the benefits of long-term treatment with lucerastat. The data reported in *Nature Communication*, together with the confirmatory results from the longer treatment duration and the kidney biopsy sub-study, are driving us to generate the regulatory data required to bring lucerastat to patients. We remain committed to advancing this innovative treatment for patients living with Fabry disease."

Notes to the editor

About Fabry disease

Fabry disease is a rare, X-linked lysosomal storage disorder caused by mutations in the *GLA* gene, resulting in deficient or absent activity of the enzyme α-galactosidase A (α-Gal A). This enzymatic deficiency leads to the accumulation of globotriaosylceramide (Gb3) and its derivatives in cells throughout the body. Over time, this buildup causes progressive damage across multiple organ systems, including the kidneys, heart, nervous system, skin, eyes, and gastrointestinal tract.

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. 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.

Recent newborn screening programs and high-risk population studies suggest that Fabry disease is more prevalent than previously estimated, with a diagnosed prevalence of more than 21,000 patients expected across the US, EU5, and Japan by 2034, and a higher incidence of late-onset forms. Notably, female patients, once considered carriers, are now recognized as affected individuals with a wide spectrum of disease severity – up to 70% of heterozygous females develop Fabry-related symptoms during their lifetime.

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.

In early clinical trials, 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.

About Prof Derralynn Hughes

Prof Derralynn Hughes is professor of experimental hematology at the University College London, director of research and innovation at the Royal Free London, and co-clinical director of the North Central London Cancer Alliance. Prof Hughes is also chair of the international working group on Gaucher disease. She has clinical responsibilities in the area of hematology and lysosomal storage disorders (LSD) and is chair of the anemia clinical practice group.

Prof Hughes directs the research program in the LSD unit where interests include understanding the pathophysiology of phenotypic heterogeneity in Fabry disease and bone-related pathology in Gaucher disease and malignancy. Prof Hughes is principal investigator of a number of clinical trials examining the efficacy of enzyme, chaperone and gene therapies and other new agents in the treatment of Gaucher, Fabry, Pompe and MPS disorders. A particular interest relates to the clinical and biological effects of bone disease and malignancy in Gaucher disease. She is an author of over 150 papers in the area of macrophage biology and lysosomal storage disorders. Prof Hughes serves as a consultant to Idorsia.

Key scientific literature

- Nordbeck P., et al. Lucerastat, an oral therapy for Fabry disease: Results from a pivotal phase 3 study and its open-label extension. Nature Communications, 10 January 2026 (online ahead of print). https://doi.org/10.1038/s41467-025-68256-5
- Guérard N., et al. Lucerastat, an iminosugar for substrate reduction therapy: tolerability, pharmacodynamics, and pharmacokinetics in patients with Fabry disease on enzyme replacement. Clin Pharmacol Ther. 2018; 103(4):703-11.
- Welford RWD., et al. Glucosylceramide synthase inhibition with lucerastat lowers globotriaosylceramide and lysosome staining in cultured fibroblasts from Fabry patients with different mutation types. Hum Mol Genet 2018; 27(19): 3392-3403
- Germain DP. Fabry disease. Orphanet J Rare Dis. 2010 Nov 22;5:30.

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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