Media Release
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Ad hoc announcement pursuant to Art. 53 LR

Idorsia to further characterize lucerastat for the treatment of Fabry disease by continuing the open-label extension of the Phase 3 MODIFY study

- Idorsia will consult with health authorities and share the data collected so far to define the regulatory pathway for lucerastat in Fabry disease

Allschwil, Switzerland – December 13, 2021
Idorsia Ltd (SIX: IDIA) today announced that after the planned interim analysis of the open-label extension (OLE) of the Phase 3 MODIFY study with lucerastat for the treatment of adult patients with Fabry disease, the study will continue. The company will consult with health authorities in the first half of 2022, and discuss the data collected up until the first interim analysis of the OLE study. The data includes the placebo-controlled 6-month treatment period with 118 patients in MODIFY, as well as the analysis of 107 patients who continued into the OLE, many of whom are treated with lucerastat for one year and some who have received treatment for up to 2 years.

While lucerastat (1000 mg b.i.d) did not meet the primary endpoint of reducing neuropathic pain during 6 months of treatment versus placebo, the company has made observations on renal function and cardiac echocardiography which, if confirmed with longer-term data, would indicate a treatment effect on the main organs affected by the disease.

Lucerastat demonstrated a substantial reduction in levels of the Fabry-disease biomarker **plasma Gb3** after 6 months of treatment. A nominally significant ($p<0.0001$) difference in the change from baseline to month 6 in plasma Gb3 between lucerastat and placebo was observed, with a decrease of approximately 50% observed in plasma Gb3 in the lucerastat treatment group compared to an increase of 12% in the placebo group. Interestingly, a decrease in plasma Gb3 was observed in virtually every patient on treatment with lucerastat. Likewise, a nominally significant ($p=0.02$) difference in the percent change from baseline to month 6 in **plasma lysoGb3** between lucerastat and placebo was also observed. The change in these Fabry-disease biomarkers was maintained or further improved with continued lucerastat treatment in the OLE.

Based on patient historical data, mean **estimated glomerular filtration rate (eGFR)**, a measure of kidney function, was decreasing prior to the study. During the 6 months of the MODIFY study, a slightly higher increase in eGFR was observed in the lucerastat group versus placebo, as measured by the eGFR slope. This potential effect of lucerastat on kidney function over 6 months of treatment was further evaluated at the interim analysis of the extension study. The average eGFR decline was -2.75 mL/min/1.73m^2 per year on treatment overall, while in the two years preceding the study (historical values), the decline was -3.55 mL/min/1.73m^2 per year. In a subgroup of patients with an eGFR value of less than or equal to 90 mL/min/1.73m^2 at baseline, denoting kidney function impairment, a slower decline of eGFR of -3.41 mL/min/1.73^2 per year was observed on treatment versus an historical decrease of -6.29 mL/min/1.73^2 per year.

Also, in several patients treated with lucerastat, especially those with **a high left ventricular mass index (LVMI)** at baseline, a decrease of LVMI with lucerastat was seen. These data need to be further characterized.

In MODIFY, of the 118 patients enrolled, 80 patients were randomized to lucerastat. Lucerastat was well tolerated. No clinically meaningful change in vital signs, ECGs, or marked laboratory abnormalities was observed. Two patients in each group (lucerastat 2.5%; placebo 5.4%) discontinued due to adverse events. Serious adverse events (SAE) were reported in 5 patients (6.3%) and 1 patient (2.7%) in the lucerastat and placebo groups, respectively. No SAE was fatal, and all were considered as not related to study treatment. The interim analysis of the OLE study, which included 114 patients treated for an average duration of 15 months, provided a safety and tolerability profile consistent with that observed during 6-month randomized treatment period.

Jean-Paul Clozel, MD and Chief Executive Officer of Idorsia, commented:
"I have been impressed to consistently see such a substantial decrease in plasma Gb3, in almost every patient treated with lucerastat, even after switching from enzyme replacement therapy. Accumulation of Gb3 is the main cause of organ damage in Fabry disease, therefore it stands to reason to me that decreasing plasma Gb3 should translate into a beneficial effect on the organs effected by Fabry disease. Following the analysis of the 6-month data from MODIFY and now the first interim analysis of the open label extension study, we have an indication that this is indeed the case."

Jean-Paul Clozel, concluded:
"We are in the very fortunate position to have a large cohort of patients on treatment. By now, many have been treated for 1 year and some for up to 2 years. By continuing to collect data we will further characterize the signal we have observed and determine whether lucerastat can offer benefit for the kidneys and the heart. In the meantime, we will discuss our results with health authorities globally to define the regulatory pathway forward for lucerastat in patients with Fabry disease."

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 in an ongoing open label extension study, which aims to determine the long-term safety and tolerability of lucerastat oral therapy and to further evaluate its clinical efficacy on renal and cardiac function, in adult patients with Fabry disease over a period of up to a further 48 months.

About lucerastat in Japan

The efficacy of lucerastat has been evaluated in an open-label Phase 3 study in 22 Japanese patients with Fabry disease. The results of the study are currently in preparation for scientific disclosure in a peer-reviewed publication.

Notes to the editor

About Fabry disease

Fabry disease is a rare, genetic, lysosomal storage disorder that results in reduced or absent α-galactosidase A (alpha-GalA) an enzyme that normally breaks down a fatty product known as globotriaosylceramide (Gb3) in the cells of the body. Over time, this results in an accumulation of Gb3 deposits throughout the body, leading to progressive pathophysiology in the cardiovascular system, and the nervous system as well as in organs, including the kidneys, heart, skin, ears, eyes, and lung. Symptoms of Fabry disease affect a patient's life expectancy and quality of life. Since the symptoms are non-specific, Fabry disease is often undetected or misdiagnosed. As the disease is progressive, early diagnosis is essential to manage the symptoms as soon as possible and reduce the risk of developing serious complications.

According to Delveinsight, the diagnosed prevalence of Fabry disease in 2018 was approximately 7,500 patients in the US and the EU-5 (i.e., France, Germany, Italy, Spain and the UK). Large genetic newborn screening programs have revealed a higher incidence of Fabry disease than that detected in the general population, suggesting an underestimation of the prevalence of Fabry disease. 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.

There is an unmet need for a well-tolerated, disease-modifying, oral treatment that can be used regardless of *GLA* mutation and previous treatment. Current treatment approaches for Fabry disease include enzyme replacement therapy (ERT). ERT is given with frequent intravenous infusions of recombinant human agalsidase α or agalsidase β and may not adequately control symptoms. Migalastat, an oral chaperone therapy enhancing α-galactosidase A activity, is the other therapy that has been granted marketing authorization in the EU, Japan, and the US as an oral monotherapy for the long-term treatment of a subset of patients with Fabry who have an amenable mutation. Other treatments are aimed at alleviating individual symptoms, such as anticonvulsants, antidepressants, and opioids for severe pain. In advanced Fabry disease, hemodialysis and kidney transplantation may be necessary. Currently, treatment options do not adequately control Fabry disease for all patients. Therefore, an effective treatment with convenient administration could significantly change the treatment landscape for patients with Fabry disease.

Lucerastat in Fabry disease

Lucerastat, a small molecule glucosylceramide synthase inhibitor, is in development as a novel, disease-modifying substrate reduction therapy for Fabry disease, regardless of the patient's *GLA* variant. Preclinical studies showed that lucerastat is a soluble, bioavailable inhibitor of glucosylceramide synthase that reduces the accumulation of α-galactosidase A substrates in tissues affected by Fabry disease, including kidneys, liver, and dorsal root ganglia. In clinical pharmacology studies, lucerastat had reproducible pharmacokinetics, characterized by rapid absorption, quick elimination, and no evidence for saturation of absorption or elimination mechanisms. By working on the underlying disease mechanism and reducing the build-up of Gb3, lucerastat has the potential to alleviate symptoms of Fabry disease, independent of both previous ERT treatment and *GLA* mutation. Across Phase 1 studies, lucerastat doses up to 4000 mg were well tolerated and the safety profile was not affected by concomitant treatments.

The safety, tolerability, pharmacodynamics, and pharmacokinetics of oral lucerastat were evaluated in an exploratory study in adult patients with Fabry disease. In this single-center, open-label, randomized study, 10 patients with Fabry disease were randomized to lucerastat for 12 weeks on top of ERT and 4 to ERT only. A rapid decrease in plasma Gb3, a marker of Fabry disease, and its precursors was observed, demonstrating that lucerastat 1000 mg b.i.d. inhibits glucosylceramide synthase and provides alpha-GalA substrate reduction with a fast onset in adult patients with Fabry disease on ERT.

Key Literature

- 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

Idorsia Ltd is reaching out for more – We have more ideas, we see more opportunities and we want to help more patients. In order to achieve this, we will develop Idorsia into a leading biopharmaceutical company, with a strong scientific core.

Headquartered near Basel, Switzerland – a European biotech-hub – Idorsia is specialized in the discovery, development, and commercialization of small molecules to transform the horizon of therapeutic options. Idorsia has a broad portfolio of innovative drugs in the pipeline, an experienced team of professionals covering all disciplines from bench to bedside, state-of-the-art facilities, and a strong balance sheet – the ideal constellation to translate R&D efforts into business success.

Idorsia was listed on the SIX Swiss Exchange (ticker symbol: IDIA) in June 2017 and has over 1000 highly qualified specialists dedicated to realizing our ambitious targets.

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