Media Release
May 16, 2018

Idorsia initiates MODIFY, a Phase 3 registration study to assess lucerastat as a potential new treatment option for patients with Fabry disease

- Idorsia to host an investor webcast to discuss the Phase 3 program today at 14:00hrs CEST

Allschwil, Switzerland – May 16, 2018
Idorsia Ltd (SIX: IDIA) today announced that the first patient has been enrolled in a registration study to investigate the effect of lucerastat, as an oral monotherapy, for the treatment of adult patients with genetically confirmed Fabry disease, irrespective of their genetic mutation type.

MODIFY will recruit over 100 patients from 29 trial sites across 9 countries. Its primary endpoint is a reduction in neuropathic pain, described as feeling like burning, shocks or shooting, stabbing, tingling, and/or pins and needles primarily in the hands and feet. This major symptom is reported by many patients with Fabry disease as significantly impacting their daily activities and quality of life, despite existing treatment.

Dr. Derralynn Hughes, DPhil, FRCP, FRCPath and EU Coordinating Investigator, commented:
"Today's news is an important milestone for the Fabry research and patient communities that have contributed to the development of this study. Pain is a genuine and pressing unmet need of the Fabry patient population. Pain remains a significant burden for many patients, even for some of those who are already being treated with enzyme replacement therapy. Lucerastat represents an exciting potential new oral treatment option to address this."

Fabry disease is a rare, life threatening, inherited lysosomal storage disorder in which a particular lipid, called globotriaosylceramide (Gb3), accumulates in cells of many organs of the body. This build-up results in cellular dysfunction leading to a range of signs and symptoms from neuropathic pain (pain primarily in the hands and feet), stomach, skin and eye problems, to hypertension, progressive kidney damage, cardiomyopathy, and stroke. New treatment options are needed to treat the underlying mechanism of the disease and provide symptomatic relief.

Martine Clozel, MD and Chief Scientific Officer, commented:
"Idorsia's preclinical data indicate that lucerastat has the potential to treat patients with Fabry disease, regardless of their specific gene mutation type. MODIFY will include patients who were never treated with enzyme or patients who stopped enzyme replacement therapy. In parallel to MODIFY, we will also run a pediatric study to assess lucerastat in children aged from 2 to 18 years. Lucerastat is therefore a potential new oral treatment option for a very broad spectrum of patients living with Fabry disease."

Guy Braunstein, MD and Head of Global Clinical Development, added:
"We have worked closely with patients during the development of the MODIFY protocol for lucerastat. We conducted an international patient survey to better understand the symptoms of

patients with Fabry disease, and validated a patient reported outcome instrument to specifically assess Fabry neuropathic pain, in accordance with health authority guidance."

About the MODIFY study

MODIFY is a multicenter, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of lucerastat oral monotherapy in adult patients with Fabry disease. The study aims to determine the effect of study treatment on neuropathic pain during 6 months of treatment, measured with Idorsia's validated Fabry disease pain instrument. At the end of the double-blind period, patients will be given the possibility to enter in an open label extension study. Approximately 108 patients are expected to be enrolled, randomized in a 2:1 ratio to either lucerastat or placebo. The study is expected to run for around 20 months.

Notes to the editor

About Fabry disease

Fabry disease is a rare, life threatening, genetic disorder involving a deficiency or dysfunction of alpha-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 may result in a build-up of Gb3 deposits throughout the body, particularly in the kidneys, heart and nervous system.

The symptoms range from neuropathic pain (primarily pain in the hands and feet), stomach, skin and eye problems, to hypertension, progressive kidney damage, cardiomyopathy and stroke. 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.

The median prevalence of diagnosed Fabry disease is 1.0 per 100,000 in males and 1.9 per 100,000 in females. 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 approaches for Fabry disease include enzyme replacement therapy (ERT). ERT requires intravenous infusions every two weeks to replace the deficient enzyme in the cells with a genetically engineered form. Migalastat is the other therapy that has been granted marketing authorization in the EU and Japan as an oral monotherapy for the long-term treatment of a subset of patients with Fabry disease 16 years and older who have an amenable mutation. Other treatments are aimed at alleviating individual symptoms, such as opioids for severe pain. In advanced Fabry disease, hemodialysis and kidney transplantation may be necessary.

Data supporting lucerastat in Fabry disease

Idorsia preclinical research with a mouse model of Fabry disease has shown that glucosylceramide synthase inhibition with lucerastat reduces the accumulation of Gb3 in kidney and certain nerve endings. Furthermore, Idorsia has shown that lucerastat lowers Gb3 in cultured cells from patients with Fabry disease of both sexes harboring different GLA genetic mutation types.

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 received lucerastat 1000 mg b.i.d. for 12 weeks on top of enzyme replacement therapy and four patients with Fabry disease received 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 GCS and provides alpha-GalA substrate reduction with a fast onset in adult patients with Fabry disease on ERT.

The results of the exploratory clinical study, together with confirmation of a favorable tolerability profile, and the preclinical evidence suggest that lucerastat has the potential to provide safe oral therapy for adult patients with Fabry disease, independent of their mutation or phenotype.

About Dr. Derralynn Hughes DPhil, FRCP, FRCPath

Dr Derralynn Hughes is a senior lecturer in hematology at University College London, UK, and has clinical responsibilities in the area of hematology and lysosomal storage disorders at the Royal Free London NHS Foundation Trust. She directs the research program in the lysosomal storage disorders unit research laboratory and is principal investigator of a number of clinical trials, registries and observational studies. Dr Hughes studied medicine at Oxford University in the UK, and joined the research group in the Sir William Dunn School of Pathology as an MRC training fellow, writing a doctoral thesis in the area of macrophage biology. Her interest in the role of the macrophage in inflammatory and developmental processes has endured and now, she has focused her laboratory research interests towards the role of inflammatory cell interactions in the pathophysiology of the

lysosomal storage disorders Gaucher and Fabry disease. Major laboratory projects are currently aimed at understanding the pathophysiology underlying Gaucher-related bone pathology, increased incidence of malignancy in Gaucher disease and phenotypic variation in Anderson-Fabry disease.

References

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Investor webcast

An investor conference call and webcast will be held to discuss the Phase 3 program. The call will start with presentations by senior management, followed by a Q&A session (live access to the speakers).

Date: Wednesday May 16, 2018
Time: **14:00 CEST | 13:00 BST | 08:00 EDT**

Webcast participants should visit Idorsia's website www.idorsia.com 10-15 minutes before the webcast is due to start. Conference call participants should start calling the number below 10-15 minutes before the conference is due to start.

Dial-in: **CH: +41 44 580 65 22 | UK: +44 203 009 24 70 | US: +1 877 423 08 30**
PIN: 32979293#

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 Europe's leading biopharmaceutical company, with a strong scientific core.

Headquartered in Switzerland - a biotech-hub of Europe - Idorsia is specialized in the discovery and development of small molecules, to transform the horizon of therapeutic options. Idorsia has a broad portfolio of innovative drugs in the pipeline, an experienced team, a fully-functional research center, and a strong balance sheet – the ideal constellation to bringing R&D efforts to business success.

Idorsia was listed on the SIX Swiss Exchange (ticker symbol: IDIA) in June 2017 and has over 600 highly qualified specialists dedicated to realizing our ambitious targets.

For further information please contact:

Andrew C. Weiss
Senior Vice President, Head of Investor Relations & Corporate Communications
Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, CH-4123 Allschwil
+41 (0) 58 844 10 10
www.idorsia.com