Media Release
December 15, 2022

Idorsia initiates OPUS a Phase 3 program to investigate cenerimod for the treatment of patients with systemic lupus erythematosus

- Idorsia to host an investor webcast to discuss the Phase 3 program today at 15:00hrs CET

Allschwil, Switzerland – December 15, 2022
Idorsia Ltd (SIX: IDIA) today announced that the first patient has entered screening to participate in OPUS, a Phase 3 program to investigate the efficacy and safety of cenerimod, Idorsia's novel, highly selective $S1P_1$ receptor modulator, as an oral treatment for adult patients with moderate to severe systemic lupus erythematosus.

Systemic lupus erythematosus (SLE), the most common form of lupus, is an autoimmune disease. While the cause of SLE is not fully known, T and B lymphocytes are considered the key immune cells that play a role in the development of SLE. In individuals with SLE, both T and B cells become overactive, infiltrate different tissues and produce autoantibodies, leading to inflammation and organ damage.

Anca Askanase, MD, MPH, Director of the Columbia Lupus Center, and Professor of Medicine, Columbia University and an investigator in both the CARE study and OPUS program commented:
"The extraordinary heterogeneity in the pathogenesis and clinical manifestations of SLE highlight the need for medications with broad coverage of abnormal immune responses. The hope for cenerimod, as an $S1P_1$ receptor modulator, is that, with an oral therapy, it can correct several aspects of these immune dysregulations that cause the symptoms of lupus. There is solid scientific rationale, and consistent clinical and laboratory evidence, to suggest that cenerimod has great potential in the treatment of lupus. Accordingly, I'm eager to enroll my patients in the cenerimod Phase 3 program."

Alberto Gimona, MD and Head of Global Clinical Development of Idorsia, commented:
"In Phase 2 studies, cenerimod 4 mg consistently showed clinically meaningful and sustained improvement from baseline on multiple measures of SLE disease activity compared to placebo. The effect of the 4 mg dose appears to be higher in patients with severe and immunologically active disease. Across all doses including the 4 mg dose, cenerimod was well tolerated with an adverse event profile consistent with the mechanism of action, allowing us to move forward with the dose that has demonstrated optimal efficacy. I am very excited to announce that the Phase 3 program is now enrolling patients."

About the OPUS program
The OPUS program (Oral $S1P_1$ Receptor ModUlation in SLE) consists of two Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy, safety, and tolerability of cenerimod in adult patients with moderate to severe SLE on top of background therapy.

The main objectives of the program are to evaluate the effectiveness of cenerimod 4 mg at reducing disease activity, as well as controlling the disease, compared to placebo. The primary endpoint is change from baseline to Month 12 in the modified Systemic Lupus Erythematosus Disease Activity

Index 2000 (mSLEDAI-2K)* score. Secondary endpoints include the SLE Responder Index (SRI-4) at Month 12 and, for the first time in a lupus registration study, measures of 'sustained disease control': Time to first confirmed 4-month sustained mSLEDAI 2K response; Time to first confirmed 4-month sustained response in mucocutaneous manifestations (i.e., rash, alopecia, mucosal ulcers).

The program is expected to enroll 840 patients with SLE from around 25 countries, including Japan. Following a Phase 2a study with cenerimod showing a dose-dependent reduction in plasma interferon-alpha, feedback from the lupus community, and data from the CARE Phase 2b study that suggests that the treatment effect of cenerimod was greater in patients with higher disease activity and persistent inflammation, the Phase 3 study includes revised eligibility criteria, as well as a screening period of up to 60 days to ensure that only patients with true moderate to severe SLE are enrolled. Those who complete the 12-month double-blind treatment period will have the option to enroll into an open-label extension (OLE) study, where all patients will receive cenerimod for at least one year.

The investigation of cenerimod for the treatment of SLE has been designated as a "fast-track" development program by the FDA. This designation is intended to promote communication and collaboration between the FDA and pharmaceutical companies for drugs that treat serious conditions and fill an unmet medical need. The Phase 3 program has been discussed with health authorities.

Alberto Gimona continued:
"With OPUS investigating an oral treatment option for lupus, we are offering a potential alternative to currently available biologic treatments that are either self-injected or received via infusion in hospital on top of standard care. By adding a new key secondary endpoint of 'sustained disease control', Idorsia has designed a program that not only fulfills regulatory requirements, but also has the potential to provide a more holistic view on how patients respond to treatment. Since the course of the disease can vary widely for patients during the study, taking a measurement at a fixed timepoint gives only a snapshot on how the investigational treatment is performing. Instead, by measuring the ability to sustain control of the disease for at least 4 months, this endpoint becomes the most meaningful measure of disease activity for patients and their physicians."

About the efficacy of cenerimod in the CARE Phase 2b study
The decision to move into Phase 3 was based on the results of the CARE study which were recently shared as an oral presentation by A. Askanase, MD, MPH at the American College of Rheumatology (ACR) Convergence 2022: Abstract number 1656 "Efficacy and Safety of Cenerimod in Patients with Moderate to Severe Systemic Lupus Erythematosus (SLE): A Multicenter, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled, Dose-Finding Phase 2b Trial."

The double-blind study equally randomized 427 adult patients with moderate to severe SLE on stable background therapy, to cenerimod (0.5, 1, 2, 4 mg) or placebo. The study duration was 18 months, two 6-month treatment periods and a 6-month follow-up. After the first 6 months, patients on 0.5, 1, 2 mg cenerimod and on placebo continued the same blinded treatment, whereas patients taking cenerimod 4 mg were re-randomized to blinded cenerimod 2 mg or placebo allowing to assess reversibility of lymphocyte reduction.

The primary endpoint was change from baseline to Month 6 in the mSLEDAI-2K. Secondary endpoints were SRI-4 and BILAG-2004 improvement. Safety endpoints included adverse events (AEs) and AEs of special interest (AESI). Of 427 randomized patients, 339 completed 12 months of treatment. Baseline characteristics were balanced across groups. The study did not meet its primary endpoint after type I error control. However, the reduction in mSLEDAI-2K from baseline to Month 6 with cenerimod 4 mg versus placebo was nominally statistically significant: least squares [LS] mean difference (95% CI) -1.19(-2.25, -0.12), p=0.0291. This effect was greater in patients with greater disease severity (BILAG-

2004 Grade B in ≥2 organ systems and/or Grade A in ≥1 organ system at BL; LS mean difference [95%CI] -1.39 [-2.59, -0.19]) and patients with high Interferon Type 1 (IFN-1) gene expression signature status (LS mean difference [95%CI] -2.79[-4.50, -1.08]). The definition of high versus low IFN-1 gene expression signature status was recently shared as a poster presentation at ACR Convergence 2022: Abstract number 1002 "Investigation of Pharmacodynamic Biomarkers in a Phase 2b Study in Patients with Moderate to Severe SLE Treated with the $S1P_1$ Receptor Modulator Cenerimod."

At Month 6, the proportion of SRI-4 responders was higher in patients randomized to cenerimod 4 mg versus placebo. This difference was also greater in IFN-1 high patients (difference +24%). Sustained mSLEDAI-2K response started earlier in patients on cenerimod 4 mg versus placebo; this difference was greater in the IFN-1 high subgroup. Lymphocyte count decreased in all cenerimod groups; greater decreases were seen with the 2 and 4 mg doses.

At baseline, patients with SLE were identified as either IFN-1 high or IFN-1 low. The distribution was well balanced in the placebo (n=86) and cenerimod 4 mg group (n=85) with approximately 50% IFN-1 high in both treatment arms. At 6 months, cenerimod 4 mg treatment modulated gene expression signatures and proteins linked to several of those molecular pathways associated with SLE pathogenesis.

Martine Clozel, MD and Chief Scientific Officer of Idorsia, concluded:
"Cenerimod acts on both T cells and B cells and at a fundamental stage in the autoimmune response, meaning it has the potential to alter the course of lupus. Cenerimod showed the potential to modify several inflammatory pathways demonstrating its broad immune-modulatory pharmacodynamics. In our Phase 2b study, patients with a high interferon-1 gene expression signature showed greater levels of improvement, this gives us even more confidence in the potential of cenerimod because this pathway is already validated in the treatment of lupus."

About the safety of cenerimod in the CARE Phase 2b study
Cenerimod was well tolerated with similar rates of AEs reported across all treatment groups, 0.5 mg: 49.4%; 1 mg: 64.7%; 2 mg: 59.3%; 4 mg: 58.3%; placebo: 54.7%, during six months of treatment. The most frequent treatment emergent AEs reported over 5% incidence in any group and higher than placebo during six months of treatment were: abdominal pain, headache, and lymphopenia. A reversible decrease in lymphocyte count is linked to the mechanism of action of cenerimod and as expected lymphopenia was more often seen in patients treated with the higher 2 mg and 4 mg doses. Importantly, there was no increased rate of infections compared to placebo: 0.5 mg: 23.5%; 1 mg: 11.8%; 2 mg: 19.8%; 4 mg: 20.2%; placebo: 18.6%.

At Month 12, the incidence of AEs reported were between 60% and 80% across all treatment groups with no dose relationship: 0.5 mg: 63.1%; 1 mg: 81.2%; 2 mg: 77.0%; placebo: 70.9%. For the 4 mg group which was re-randomized to either placebo or 2 mg cenerimod, the AE incidences were 77.1% (switch from 4 mg to 2 mg) and 65.7% (switch from 4 mg to placebo). Compared to placebo, as seen during the first 6 months, treatment with cenerimod was not associated with an increased risk of infections.

* Since cenerimod induces a reduction in lymphocyte count as part of its mechanism of action, the SLEDAI-2K, a recognized index used to assess disease activity in patients with lupus, was modified (mSLEDAI-2K) to exclude leukopenia - a reduction of 1 point from 105 possible total points.

Notes to the editor

About systemic lupus erythematosus

Systemic lupus erythematosus (SLE), the most common form of lupus, is an autoimmune disease, which means that the body's immune system malfunctions and attacks the body's own tissues. While some autoimmune diseases affect just one organ, in the case of lupus, many parts of the body can be affected, such as the skin, joints, kidneys, blood cells, lungs, and other organs. As a result, symptoms vary widely and are often similar to other conditions, which need to be ruled out before a diagnosis can be made. Lupus therefore often goes undetected or misdiagnosed for long periods. Yet early diagnosis is important to manage the symptoms of lupus, initiate treatment to reduce the risk of long-term complications, and enable access to wider support (e.g. local patient groups).

It is estimated that 1.5 million Americans, and at least 5 million people worldwide, have a form of lupus, and that 90% of people living with lupus are women, with most developing the disease between the ages of 15 and 44. There is a higher prevalence of lupus among people of Asian and Afro-Caribbean origin than in Caucasians.

There is no cure for SLE and a significant need exists for safe and effective therapies. Most people with SLE are prescribed a combination of different medications to manage their symptoms, improve their quality of life and reduce the risk of more serious complications. The choice of treatment depends on how the patient with SLE presents, which part of their body is affected and the severity of the condition at the time.

The only FDA-approved treatments for SLE are acetylsalicylic acid (aspirin), hydroxychloroquine (an antimalarial), corticosteroids, belimumab, and anifrolumab. Some other immunosuppressive therapies are used off-label.

About $S1P_1$ receptor modulation

While the cause of SLE is not fully known, T and B lymphocytes are considered the key immune cells that play a role in the development of SLE. In individuals with SLE, both T and B cells become overactive. The main consequence of this increased activity is the infiltration of immune cells into different tissues and the production of autoantibodies (antibodies that recognize and destroy the body's own cells), leading to inflammation and organ damage.

T and B lymphocytes have a cell surface receptor called sphingosine-1-phosphate receptor 1 ($S1P_1$). These receptors enable T and B lymphocytes to detect the signaling molecule S1P – sphingosine 1 phosphate – which is responsible for lymphocyte trafficking from the lymph nodes to the circulation.

By binding to $S1P_1$ receptors, a receptor modulator can trigger the internalization of those receptors. This effectively blinds T and B lymphocytes to the S1P gradient, thereby holding them in the lymph nodes and reducing autoreactive T and B cells in the circulation and consequently, also in the tissues.

Following the reduction of circulating T and B cells, a reduction in autoantibodies and immune cytokines – markers of the underlying disease processes – is seen. Idorsia believes that this will ultimately further reduce inflammation and tissue damage, key contributors to the disease.

Cenerimod in systemic lupus erythematosus

Cenerimod is a highly selective $S1P_1$ receptor modulator, being investigated as an oral once-daily tablet. Cenerimod potentially offers a novel approach for the treatment of SLE, a disease with a significant impact on patients and limited treatment options.

Cenerimod temporarily stops the body from detecting S1P chemical 'signposts' that would otherwise trigger immune cell migration and inflammation. Unlike other potential treatments for lupus that act on one specific 'pathway' involved in the disease, cenerimod is thought to work by targeting multiple different pathways that researchers believe all contribute to the symptoms of lupus. Of note, the patients with high level of IFN-1 phenotypes correlated with other inflammatory pathways, revealing a complex inflammatory pathogenesis in SLE. Cenerimod showed the potential to modify several of these inflammatory pathways demonstrating its broad immune-modulatory pharmacodynamics.

Cenerimod is the result of 20 years of research by Idorsia and has been tested in several clinical studies, including the CARE Phase 2b study ([abstract 1626]. Arthritis Rheumatol. 2022; 74 (suppl 9)) and a Phase 2a proof-of-concept study (Hermann V, et al. Lupus Sci Med. 2019;6:e000354) in patients with SLE and a clinical pharmacology program.

About Anca Askanase MD, MPH

Professor of Medicine, Founder and Director of the Columbia University Lupus Center, Associate Director Division of Rheumatology and Director of Rheumatology Clinical trials at Columbia University, Clinician, diagnostician, and researcher specializing in complex Systemic Lupus Erythematosus (SLE)
Prof. Askanase's research in lupus encompasses multiple areas:

- lupus epidemiology including cohort and registry studies to allow for in depth characterization of disease phenotype and comorbidities;
- outcomes research to identify biomarkers and develop objective and novel instruments to more accurately diagnose lupus, track disease activity, and define treatment response;
- clinical trials to increase treatment options.

Much of her research is conducted in collaboration with national and international lupus researchers. She founded the CUIMC Lupus cohort (n=450), and is an active participant in the SLICC and LuCIN SLE registries. Ongoing projects include the use of optical tomography to evaluate lupus arthritis, development of virtual lupus disease activity measures for use in clinical research, and lupus outreach to disparate populations in NYC. Dr Askanase serves as a consultant to Idorsia.

Key Literature

- Askanase A, et al. Efficacy and Safety of Cenerimod in Patients with Moderate to Severe Systemic Lupus Erythematosus (SLE): A Multicenter, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled, Dose-Finding Phase 2b Trial [abstract 1626]. Arthritis Rheumatol. 2022; 74 (suppl 9).
- Strasser D, et al. Investigation of Pharmacodynamic Biomarkers in a Phase 2b Study in Patients with Moderate to Severe SLE Treated with the $S1P_1$ Receptor Modulator Cenerimod [abstract 1002]. Arthritis Rheumatol. 2022; 74 (suppl 9).
- Hermann V, et al. First use of cenerimod, a selective $S1P_1$ receptor modulator, for the treatment of SLE: a double-blind, randomised, placebo-controlled, proof-of-concept study. Lupus Sci Med. 2019;6:e000354.
- Juif P, et al. Pharmacokinetics and Pharmacodynamics of Cenerimod, A Selective S1P 1 R Modulator, Are Not Affected by Ethnicity in Healthy Asian and White Subjects. Clin Transl Sci. 2021;14:143–7.
- Strasser DS, et al. Preclinical to clinical translation of cenerimod, a novel $S1P_1$ receptor modulator, in systemic lupus erythematosus. RMD Open. 2020;6:e001261.
- Piali L, et al. Cenerimod, a novel selective $S1P_1$ receptor modulator with unique signaling properties. Pharmacol Res Perspect. 2017;5:e00370.
- McGinley MP, et al. Sphingosine 1-phosphate receptor modulators in multiple sclerosis and other conditions. Lancet. 2021;398:1184-1194.
- Lasa JS, et al. Safety of S1P Modulators in Patients with Immune-Mediated Diseases: A Systematic Review and Meta-Analysis. Drug Saf. 2021;44:645-660.
- Stepanovska B, et al. Targeting the S1P receptor signaling pathways as a promising approach for treatment of autoimmune and inflammatory diseases. Pharmacol Res. 2020;154:104170.
- Barber MRW, et al. Global epidemiology of systemic lupus erythematosus. Nat Rev Rheumatol. 2021;17:515-532.
- Kaul A, Gordon, et al. Systemic lupus erythematosus. Nat Rev Dis Primers. 2016;2:16039.
- Davis LS, et al. Research and therapeutics—traditional and emerging therapies in systemic lupus erythematosus. Rheumatol. 2017;56:i100-i113.
- Birt JA, et al. Patient Experiences, Satisfaction, and Expectations with Current Systemic Lupus Erythematosus Treatment: Results of the SLE-UPDATE Survey. Rheumatol Ther. 2021;8:1189-1205.
- Tse K, et al. The ALPHA Project: Establishing consensus and prioritisation of global community recommendations to address major challenges in lupus diagnosis, care, treatment and research. Lupus Sci Med. 2021;8:e000433.

Investor webcast

An investor conference call and webcast will be held to discuss the initiation of the Phase 3 study with cenerimod for patients with systemic lupus erythematosus, followed by a Q&A session.

Date: Thursday, December 15, 2022
Time: 15:00 CET | 14:00 GMT | 09:00 EST

Dial-in procedure:

1. Participants are required to register in advance of the conference (link already open for registration) using the link provided below. Upon registration, each participant will be provided with participant dial in numbers, and a unique personal PIN.
2. In the 10 minutes prior to the call start time, participants will need to use the conference access information provided in the e-mail received at the point of registering. Participants may also use the Call Me feature instead of dialing the nearest dial in number.

Online Registration: **LINK**

Webcast participants should visit Idorsia's website www.idorsia.com 10-15 minutes before the webcast is due to start.

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.

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 58 844 10 10
investor.relations@idorsia.com – media.relations@idorsia.com – www.idorsia.com

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