Media Release
November 1, 2021

Ad hoc announcement pursuant to Art. 53 LR

Idorsia to advance cenerimod into Phase 3 development for treatment of patients with systemic lupus erythematosus

- Cenerimod 4 mg showed clinically meaningful improvement in the mSLEDAI-2K* primary efficacy endpoint and other measures of efficacy, consistent with the effect seen on biological activity
- Effect of cenerimod 4 mg is particularly observable in patients with high disease activity and increases over time
- Good safety profile – consistent with the mechanism of action – across all doses
- Phase 3 program to be discussed with health authorities and advanced as rapidly as possible

Allschwil, Switzerland – November 01, 2021
Idorsia Ltd (SIX: IDIA) today announced that on the basis of the results seen in CARE, the Phase 2b study which investigated the effect of cenerimod, a novel $S1P_1$ receptor modulator, as an oral treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), the company has decided to advance into Phase 3.

The CARE study equally randomized 427 adult patients with SLE on background therapy, to cenerimod (0.5, 1, 2, 4 mg) or placebo. Patients randomized to cenerimod 4 mg showed an improvement in the modified-Systemic Lupus Erythematosus Disease Activity Index-2000 (mSLEDAI-2K) score compared to placebo from baseline to Month 6 (p=0.029). However, this result did not reach statistical significance in the formal testing strategy when adjusting for multiplicity of tests for the four doses against placebo.

The increasing improvement compared to placebo in mSLEDAI-2K with cenerimod 4 mg over time was further supported by a consistent improvement across several patient sub-populations, particularly in patients with more severe disease activity; on Systemic Lupus Erythematosus Responder Index 4 (SRI-4); and was associated with an effect on several biological markers of disease activity.

Cenerimod was well tolerated in all treatment groups such that similar rates of AEs were 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 adverse events 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%.

While $S1P_1$ receptor modulators are known to transiently affect heart rate (HR) at initiation of therapy, to potentially decrease pulmonary function and increase blood pressure, cenerimod showed a transient, asymptomatic, dose-dependent decrease in HR at first dose; over the 6 months of treatment, effects on pulmonary function could not be discerned from placebo, and there was minimal to no effect on blood pressure.

Guy Braunstein, MD and Head of Global Clinical Development of Idorsia, commented:
"I'm very pleased to see that the results with 4 milligrams of cenerimod, particularly the safety profile, have confirmed the data generated in the proof of concept study. We have seen a large effect on biomarkers of disease activity, and this has translated into improvement on multiple clinical measures. The six months of treatment results have provided us with the information we need to design our Phase 3 program in SLE and to discuss with health authorities, including the patient population, the optimal dose and endpoints. I also look forward to seeing the results of the next treatment period of CARE, where patients will continue to receive blinded treatment for a further six months. A lot can be learned from the long-term treatment data, further characterizing the efficacy, safety and tolerability of cenerimod."

Martine Clozel, MD and Chief Scientific Officer of Idorsia, commented:
"Cenerimod is an oral drug that offers a completely novel approach to the treatment of SLE. It is a highly selective $S1P_1$ receptor modulator, with biased $S1P_1$ receptor signaling, which can control lymphocyte trafficking out of the lymph nodes into the circulation. The presence of autoreactive T cells and B cells and the subsequent production of autoantibodies is key to the inflammation and organ damage seen in lupus. By acting on both of these cell types and at a fundamental stage in the autoimmune response, cenerimod has the potential to alter the course of the disease. Furthermore, I believe that the good safety profile we have observed, can be explained in part by the mechanism of action and by observations we made in preclinical studies, where cenerimod did not induce any bronchoconstriction or vasoconstriction."

The company will now fully analyze the data, including patient reported outcomes showing the effect of cenerimod on quality of life measures, and will discuss the Phase 3 program with health authorities as soon as possible. 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.

Detailed results of CARE will be made available to the scientific community through scientific disclosure at upcoming congresses and in peer-reviewed publications.

Jean-Paul Clozel, MD and Chief Executive Officer of Idorsia, concluded:
"I am very pleased to observe an oral drug given once a day with an evolving safety profile coming up to the standards set by biologics. As with many of our projects, Idorsia is benefiting from our rich drug discovery and development experience, especially in the field of $S1P_1$ receptor modulators. Idorsia must advance the clinical development program as fast as possible and, if the Phase 3 confirms the results with cenerimod, get this new therapeutic option to patients with SLE."

About CARE

CARE is a multiple-dose, efficacy, safety, and tolerability study investigating cenerimod for the treatment of adult patients with moderately to severely active, autoantibody-positive SLE. The study assesses the efficacy and safety of cenerimod treatment to determine the appropriate dose and endpoints for further development in SLE. In addition, the study evaluates the effects on quality of life and fatigue, using patient-reported outcome instruments, as well as the effects on SLE biomarkers. 427 patients were randomized in a 1:1:1:1:1 ratio to either cenerimod 0.5, 1, 2, 4 mg, or placebo. After 6 months of treatment, patients receiving cenerimod 4 mg were re-randomized in a 1:1 ratio to either cenerimod 2 mg or placebo, while the other treatment arms continued with the study treatment for a further treatment period of 6 months, which is currently ongoing.

* 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 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. Some autoimmune diseases affect just one organ, but 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 playing 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, it is hypothesized that a reduction in autoantibodies and immune cytokines – markers of the underlying disease processes – would also be seen, ultimately further reducing inflammation and tissue damage, key contributors to the disease.

Cenerimod in systemic lupus erythematosus

Cenerimod, the result of 20 years of research in Idorsia's labs, is a highly selective $S1P_1$ receptor modulator, given 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.

In a mouse model of SLE, mice typically develop an aggressive version of a lupus-like disease, with increased inflammation, autoantibodies and immune cytokines, resulting in damage to the kidney and death. When treated with cenerimod, an increase in survival was observed. This was underpinned by improved kidney structure and function, as well as marked decreases in important key markers of disease.

The effect of cenerimod on lymphocyte trafficking was confirmed in humans when administration of cenerimod induced a dose-dependent, sustained, and reversible reduction in circulating lymphocyte count.

In a Phase 2 proof-of-concept study investigating the effect of cenerimod on circulating lymphocytes, disease activity, safety, and pharmacokinetics in patients with SLE, cenerimod dose dependently reduced total lymphocyte count from baseline to end of treatment ($p<0.001$). In addition, the antibody-producing B cells, which are elevated in patients with SLE and critical to disease progression, were markedly reduced by cenerimod. Cenerimod was well tolerated at all dose levels. The occurrence of adverse events was similar in all five treatment groups.

Key Literature

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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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