Media Release
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Encouraging Phase 2 data on cenerimod – Idorsia's S1P1 receptor modulator currently investigated for SLE – presented at ACR 2019

- A Phase 2 safety study showed that cenerimod reduced circulating lymphocytes in a dose-dependent manner and was safe and well tolerated at doses up to 4 mg in patients with systemic lupus erythematosus (SLE).
- Exploratory analyses indicated an encouraging numerical reduction in the modified SLEDAI-2K, an important measure of disease activity and in anti-dsDNA antibodies.
- The company is currently running a multiple-dose, efficacy and safety study with cenerimod for the treatment of adult patients with moderately to severely active, autoantibody-positive SLE.

Allschwil, Switzerland – November 11, 2019
Idorsia Ltd (SIX: IDIA) today announced that data from a Phase 2 study with cenerimod, a selective sphingosine-1-phosphate 1 ($S1P_1$) receptor modulator, were presented at the 2019 American College of Rheumatology (ACR) / Association for Rheumatology Professionals (ARP) Annual Meeting in Atlanta, Georgia, US.

Systemic lupus erythematosus (SLE), the most common form of lupus, is an autoimmune disease. In SLE, the body's immune system malfunctions and attacks the body's own tissues, which can affect the skin, joints, gut, blood cells, lungs, and other organs. While the cause of SLE is not fully known, T and B lymphocytes are considered the key immune system cells that play a key role in the development of SLE.

Cenerimod is a selective sphingosine-1-phosphate 1 ($S1P_1$) receptor modulator, which potentially offers a novel approach for SLE – a disease with limited treatment options. Idorsia is investigating cenerimod, an oral once-daily tablet in patients with SLE. Cenerimod has the potential to add a distinct mechanism to the treatment armamentarium for this underserved patient population.

Martine Clozel, MD and Chief Scientific Officer, commented:
"I am very encouraged by the excellent data presented with cenerimod, the result of 20 years of research in our labs. As expected, we saw a dose-dependent reduction in lymphocyte counts in patients with lupus. Perhaps more importantly, we saw that the antibody-producing B-cells, which are elevated in patients with lupus and critical to the disease processes, were markedly reduced. In the limited current treatment landscape, I believe that the properties of cenerimod and the mechanism of $S1P_1$ receptor modulation provides significant potential to address the pathophysiology of lupus, reducing circulating autoreactive T and B cells thereby stopping the production of pathogenic autoantibodies."

Phase 2 study results presented at 2019 ACR/ARP Annual Meeting
Viktoria Hermann, MD from Idorsia gave an oral presentation entitled "Cenerimod, a Selective $S1P_1$ Receptor Modulator, in Systemic Lupus Erythematosus".

Abstract: Hermann V, et al. First Use of Cenerimod, a Selective sphingosine-1-phosphate 1 ($S1P_1$) Receptor Modulator, for the Treatment of Systemic Lupus Erythematosus: A Double-Blind, Randomised, Placebo-Controlled, Phase II, Proof-of-Concept Study [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10).

Aberrantly activated T- and B-lymphocytes play a major pathophysiological role in SLE. Cenerimod, a potent, selective sphingosine-1-phosphate 1 receptor modulator, blocks the egress of lymphocytes from lymphoid organs, thereby reducing their availability, thus providing rationale for development. The study investigated the effect of cenerimod on circulating lymphocytes, disease activity, safety and pharmacokinetics in SLE patients.

The study was conducted in two parts, A and B, which were separated by an independent safety review. Patients with SLEDAI-2K score ≥2 points for mucocutaneous or musculoskeletal manifestations and positive serum test for ANA or anti-dsDNA antibodies were randomized evenly in Part A to cenerimod 0.5, 1, 2 mg or placebo once daily and 3:1 in Part B to cenerimod 4 mg or placebo once-daily and treated for 12 weeks. All 67 patients (A: 49; B: 18) met at least 4 ACR criteria in the past, 70% had 4 to 11 ACR criteria ongoing at screening. Mean (SD) mSLEDAI-2K was 7.7 (±3.1) at baseline. Predefined Day 1 safety assessments included heart rate (HR) monitoring and hourly 12-lead ECG monitoring (pre-dose, to 6 hours post-dose). Endpoints included treatment-emergent adverse events (TEAEs), changes in total lymphocyte count, SLEDAI-2K score (modified [mSLEDAI] to exclude leucopoenia), anti-dsDNA antibody, a disease relevant biomarker, and pharmacokinetic assessments.

Part A included 49 patients (12:12:13:12 receiving cenerimod 0.5, 1, 2 mg or placebo, respectively); Part B included 18 patients (13 cenerimod 4 mg; 5 placebo). Cenerimod dose-dependently reduced total lymphocyte count from baseline to end of treatment (EOT; $p< 0.001$). In pairwise comparisons, cenerimod 1, 2, and 4 mg significantly decreased lymphocytes versus placebo (all $p< 0.001$). Exploratory analyses indicated clinical and biological improvement with cenerimod 4 mg with an estimated mean treatment effect on change from baseline to EOT in mSLEDAI-2K score of −2.420 ($p=0.0306$), and a decrease in anti-dsDNA of −28.80 U/mL ($p=0.0146$) compared with placebo. All treatment groups reported similar and non-dose-related rates of TEAEs (cenerimod 0.5: 41.7%; 1: 41.7%; 2: 46.2%; 4 mg: 38.5%; and placebo: 58.8%). After the first dose, cenerimod induced minimal, transient and dose-dependent decreases in HR; no patient had an HR < 40 bpm at any time post baseline. Small decreases in pulmonary function, not dose-related, were observed in cenerimod-treated patients at EOT. Cenerimod did not increase blood pressure or show any effects on laboratory variables. Trough plasma concentrations revealed that steady-state conditions were reached after 4–8 weeks of once-daily dosing and dose-proportionality was observed.

The results of this study have recently been published as a peer-reviewed manuscript in Lupus Science & Medicine:

Hermann V, Batalov A, Smakotina S, 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 Science & Medicine 2019;6:e000354. doi:10.1136/lupus-2019-000354

Guy Braunstein, MD and Head of Idorsia Global Clinical Development, commented:
"This was the first study to investigate cenerimod in patients with SLE and confirmed its lymphocyte lowering effects in this patient population. Considering this was a small, 12-week study in patients with mild-to-moderate SLE, we were encouraged by the early signs of reduced disease activity. We are now investigating whether this translates into clinical efficacy in the ongoing longer-term efficacy and safety study."

In addition to the Phase 2 data, posters already presented have highlighted further results of a qualitative study of fatigue in SLE and preclinical studies with cenerimod:

- Assessment of Fatigue in Adults with Moderate to Severe Systemic Lupus Erythematosus (SLE): A Qualitative Study to Explore the Content Validity of a Fatigue Questionnaire
  Abstract: Mannix S, et al. Arthritis Rheumatol. 2019; 71 (suppl 10).

- Cenerimod, a Potent and Selective Sphingosine-1-Phosphate Receptor 1 Modulator, Controls Systemic Autoimmunity and Organ Pathology in Mouse Models of Systemic Lupus Erythematosus and Sjögren's Syndrome
  Abstract: Gerossier E, et al. Arthritis Rheumatol. 2019; 71 (suppl 10).

- In Vitro Characterization of the Effect of Cenerimod, a Potent and Selective Sphingosine-1-Phosphate Receptor 1 ($S1P_1$) Modulator, on $S1P_1$ Receptor Expression, Receptor Internalization, and Migration of Primary Human T cells in the Presence or Absence of Glucocorticoids
  Abstract: Kulig P, et al. Arthritis Rheumatol. 2019; 71 (suppl 10).

A fourth poster is still to be presented on Tuesday, November 12, 2019:
- Cenerimod, a Potent, Selective and Orally Active Sphingosine-1-phosphate Receptor 1 Modulator, Reduced Blood Antibody-secreting Cells in Patients with SLE
  Abstract: Strasser D, et al. Arthritis Rheumatol. 2019; 71 (suppl 10).

In December 2018, Idorsia initiated a multiple-dose, efficacy and safety study with cenerimod for the treatment of adult patients with moderately to severely active, autoantibody-positive SLE. The multicenter, randomized, double-blind, placebo-controlled, parallel-group study will enroll around 500 patients, who will be randomized into four cenerimod treatment arms: 0.5, 1, 2, and 4 mg once-daily orally or placebo for up to 12 months. Patients will receive study treatment in addition to background SLE therapy, which will be kept as stable as possible to avoid confounding the treatment effect. The study aims to validate the appropriate dose, patient population and endpoints for further development in SLE.

In December 2017, the US FDA designated the investigation of cenerimod for the treatment of SLE as a Fast Track development program. The Fast Track designation is intended to promote communication and collaboration between the FDA and the company for drugs that treat serious conditions and fill an unmet medical need.

Notes to the editor

About systemic lupus erythematosus

SLE – known more simply as "lupus" since it is 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, causing inflammation and organ damage. Some autoimmune diseases affect individual organs, but in the case of lupus, most parts of the body can be affected: most commonly the skin, joints, gut, blood cells, and lungs, as well as the brain, heart, and kidneys.

Lupus can range from mild to life-threatening and can randomly become worse (so-called 'flare ups') and then better again, which can make living with lupus unpredictable and its impact on day-to-day life wide-ranging. Around five million people worldwide have a form of lupus and while it affects people of all races, genders, and ages, as much as ninety percent of diagnosed cases are in women. The condition is also more common in people of Afro-Caribbean and Asian origin compared to Caucasians and is likely to affect these ethnic groups more severely.

There is no cure for lupus. Most people with lupus are prescribed a combination of different medications including anti-inflammatory, anti-malarial drugs, corticosteroids, immunomodulators.

Key scientific literature

1. Hermann V, et al. Lupus Science & Medicine 2019;6:e000354. doi:10.1136/lupus-2019-000354
2. Juif P-E,et al. Int. J. Mol. Sci. 2017, 18, 2636; doi:10.3390/ijms18122636
3. Piali L, et al. Pharmacol Res Perspect. 2017 Dec;5(6).
4. Borchers AT, et al. Autoimmun Rev. 2010; 9(5):A277-87.
5. Pons-Estel GJ, et al. Semin Arthritis Rheum. 2010; 39(4):257-68.
6. Govoni M, et al. Lupus. 2006; 15:110-113.
7. Rahman A, Isenberg DA. N Engl J Med. 2008; 358:929-39.
8. Abu-Shakra M, et al. J Rheumatol 1995; 22(7):1259-64.

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 one of Europe's leading biopharmaceutical companies, 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 750 highly qualified specialists dedicated to realizing our ambitious targets.

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