Media Release
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Idorsia submits a New Drug Application to the US FDA for aprocitentan for the treatment of patients with difficult-to-control hypertension

- The application includes data from the Phase 3 registration study of patients with resistant hypertension, where aprocitentan demonstrated a sustained blood pressure reduction over 48 weeks and was well-tolerated

Allschwil, Switzerland – December 20, 2022
Idorsia Ltd (SIX: IDIA) today announced that it has submitted a New Drug Application (NDA) to the US Food and Drug Administration (FDA) seeking approval for aprocitentan, Idorsia's investigational, novel dual endothelin receptor antagonist, for the treatment of patients with difficult-to-control hypertension.

The NDA includes data from a comprehensive clinical and non-clinical development program. In the Phase 3 registration study, PRECISION, aprocitentan showed statistically significant and clinically meaningful reduction in blood pressure (BP) which was maintained for up to 48 weeks when added to combination background antihypertensive therapy in patients with resistant hypertension. In PRECISION, aprocitentan was generally well tolerated with no major safety concerns. The most frequent adverse event with aprocitentan was mild-to-moderate edema/fluid retention.

Full results from the PRECISION study were recently published in *The Lancet* "A randomized controlled trial of the dual endothelin antagonist aprocitentan for resistant hypertension" and presented as a Late-Breaking Science presentation during the American Heart Association (AHA) Scientific Sessions 2022. More details and commentary can be found in the dedicated press release and an investor webcast featuring Prof. Markus Schlaich, an investigator in PRECISION, which are available on Idorsia's corporate website: www.idorsia.com

Jean-Paul Clozel, MD and Chief Executive Officer, commented:
"I'm very pleased to see this application going to the FDA. Patients with uncontrolled blood pressure are at risk of major cardiovascular events.[1] These risks are even higher for patients whose blood pressure is uncontrolled despite treatment with three or more antihypertensives[2], known as resistant hypertension[3,4]. Controlling blood pressure for these patients, who often have several other aggravating risk factors such as obesity, diabetes, renal impairment, or ischemic heart disease, could prevent organ damage such as end-stage renal disease, heart failure, or even death. The sooner we can bring a new therapeutic option for these patients, the better."

It has been more than 30 years since a new anti-hypertensive therapy working by a new mechanism has been brought to patients. By targeting a currently unopposed pathophysiologic pathway, aprocitentan represents a potential novel, effective, and well-tolerated treatment for difficult-to-control hypertension.

Idorsia is developing aprocitentan together with Janssen Biotech Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson. Janssen Biotech has sole commercialization rights worldwide.

Notes to the editor

The endothelin system in systemic hypertension

Endothelin-1 (ET-1) is a potent vasoconstrictor that also induces neurohormonal activation, vascular hypertrophy and remodeling, cardiac hypertrophy and fibrosis, and endothelial dysfunction. In hypertension, both ET_A and ET_B receptors mediate harmful effects of ET-1.[5] As a vasoconstrictor, co-mitogenic agent, linking pulse pressure and vascular remodeling, and mediator of aldosterone and catecholamine release, endothelin is a key player in hypertension and end-organ damage.[6,7]

About difficult-to-control (resistant) hypertension

Hypertension (high blood pressure) is one of the most common cardiovascular risk factors, and its prevalence continues to rise. According to a recent study, there are more than 1.3 billion people living with hypertension worldwide[8] – a startling number, which has almost doubled in the past 40 years. Left uncontrolled, people have a greater risk of life-threatening conditions such as heart attack, stroke, and chronic kidney disease.[9]

Patients with hypertension can often successfully control their blood pressure by combining a healthier lifestyle with effective medication. However, approximately 10% of patients have difficult-to-control hypertension where the blood pressure remains high despite receiving at least three antihypertensive medications of different pharmacological classes, including a diuretic, at optimal doses,[3,10] (also categorized in hypertension guidelines and the medical community as having resistant hypertension).

The endothelin pathway has been implicated in the pathogenesis of hypertension, especially in volume- and salt-dependent forms, which are a common feature in patients with resistant hypertension, but it is currently not targeted therapeutically, thereby leaving this relevant pathophysiologic pathway unopposed with currently available medications.[3,11,12] This pathway is activated in patients prone to developing resistant hypertension, such as Black or African American patients, patients with obesity or obstructive sleep apnea,[13-15] and in comorbid conditions frequently associated with resistant hypertension such as diabetes and chronic kidney disease.[16-19]

About aprocitentan

Aprocitentan is an investigational, novel, oral, dual endothelin receptor antagonist (ERA), which potently inhibits the binding of ET-1 to ET_A and ET_B receptors. Aprocitentan has a low potential for drug-drug interaction and a mechanism of action that is ideally suited for the pathophysiology of resistant hypertension.

About PRECISION[20,21] (NCT03541174)

PRECISION was a multicenter, blinded, randomized, parallel-group, Phase 3 study, which was performed in hospitals or research centers in Europe, North America, Asia, and Australia. Patients were eligible for randomization if their sitting systolic blood pressure was 140 mm Hg or higher despite taking standardized background therapy consisting of three antihypertensive drugs, including a diuretic. The study consisted of three sequential parts: Part 1 was the 4-week double-blind, randomized, and placebo-controlled part, in which 730 patients were randomized to aprocitentan 12.5 mg (n=243), aprocitentan 25 mg (n=243), or placebo (n=244) in a 1:1:1 ratio; Part 2 was a 32-week single (patient)-blind part, in which all patients received aprocitentan 25 mg (n=704); and Part 3 was a 12-week double-blind, randomized, and placebo-controlled withdrawal part, in which patients were re-randomized to aprocitentan 25 mg (n=307) or placebo (n=307) in a 1:1 ratio. The primary and key secondary endpoints were changes in unattended office systolic blood pressure from baseline to week 4 and from withdrawal baseline to week 40, respectively. Secondary endpoints included 24-h ambulatory blood pressure changes.

At baseline, 69.2% of patients were obese or severely obese, 54.1% had diabetes, 22.2% had stage 3-4 chronic kidney disease and 19.6% had congestive heart failure. At screening, 63% of all patients who were randomly assigned were prescribed four or more antihypertensive drugs.

Key PRECISION findings[21]

The least square mean change in office SBP at 4 weeks was –15.3 mmHg for aprocitentan 12.5 mg, –15.2 mmHg for 25 mg, and –11.5 mmHg for placebo, for a difference versus placebo of **–3.8 mmHg** (p=0.0042) and **–3.7 mmHg** (p=0.0046), respectively. Office diastolic blood pressure (DBP) also decreased with both aprocitentan doses compared to placebo (–3.9 mmHg for the 12.5 mg dose and –4.5 mmHg for the 25 mg dose). Office SBP and DBP were maintained during Part 2 in patients previously receiving aprocitentan and decreased within the first 2 weeks of Part 2 before stabilizing in those previously receiving placebo. In Part 3, office SBP after 4 weeks of withdrawal (the key secondary endpoint) increased significantly with placebo compared to aprocitentan (**5.8 mmHg**; p<0.0001). Office DBP also increased with placebo compared to aprocitentan (5.2 mmHg; p<0.001). The difference between the two groups remained up to week 48.

The results from ambulatory BP monitoring confirmed those derived from office measurements. At the end of Part 1, aprocitentan, after placebo correction, decreased both the 24-hour ambulatory SBP (**–4.2 mmHg for the 12.5 mg** dose and **–5.9 mmHg for the 25 mg** dose) and DBP (–4.3 mmHg for the 12.5 mg dose and –5.8 mmHg for the 25 mg dose). The placebo-corrected SBP lowering effect was –5.1 mmHg and –7.4 mmHg during the nighttime and –3.8 mmHg and –5.3 mmHg during the daytime, for the 12.5 mg and 25 mg doses, respectively. In Part 3, after 4 weeks of withdrawal (week 40), both the 24-hour ambulatory SBP and DBP increased with placebo compared with aprocitentan (6·5 mm Hg and 6·8 mm Hg respectively).

Treatment-emergent adverse events (TEAEs) during the 4-week double-blind study period (Part 1) were reported in 27.6% and 36.7% of the patients treated with 12.5 and 25 mg aprocitentan, respectively, versus 19.4% in the placebo group. The most frequent adverse event was fluid retention which was reported more frequently with aprocitentan than with placebo in a dose-dependent fashion (9.1%, 18.4%, and 2.1% for patients receiving aprocitentan 12.5 mg, 25 mg and placebo, during Part 1, respectively; 18.2% for patients receiving aprocitentan 25 mg during Part 2; and 2.6% and 1.3% for patients on aprocitentan 25 mg and placebo, during Part 3, respectively). Fluid retention was generally mild-to-moderate. Discontinuation due to edema/fluid retention was reported for seven patients.

About the collaboration agreement with Janssen Biotech, Inc.

In 2017, Idorsia entered into a collaboration agreement with Janssen Biotech, Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, to jointly develop aprocitentan and any of its derivative compounds or products. Idorsia received a one-time milestone payment of USD 230 million. Both parties have joint development rights over aprocitentan. Idorsia has conducted the Phase 3 development and is overseeing the regulatory review for the treatment of patients with difficult-to-control hypertension. The costs are shared equally between both partners. Janssen Biotech, Inc. has sole commercialization rights worldwide, whereas Idorsia is entitled to receive tiered royalties on annual net sales in each calendar year (20% up to USD 500 million, 30% from USD 500 million up to USD 2.0 billion, and 35% above USD 2.0 billion) for the licensed products in the collaboration indications. Janssen Biotech, Inc. will oversee the Phase 3 development and submission for any additional indications.

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 1'200 highly qualified specialists dedicated to realizing our ambitious targets.

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