Media Release
September 6, 2023

Ad hoc announcement pursuant to Art. 53 LR

Idorsia reacquires the world-wide rights to aprocitentan

- Aprocitentan, Idorsia's oral, dual endothelin receptor antagonist is currently under review with health authorities for the treatment of patients with resistant hypertension.
- Idorsia will pay Janssen a conditional consideration up to a total cap of CHF 306 million
- Idorsia is initiating activities to determine the best approach to maximize the value of aprocitentan.

Allschwil, Switzerland – September 6, 2023
Idorsia Ltd (SIX: IDIA) today announced that it has entered into an agreement with Janssen Biotech Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, for the return of rights for aprocitentan to Idorsia. In return, Idorsia is committed to pay up to 306 million Swiss francs, subject to marketing application approval by the US FDA and Europe's EMA.

Jean-Paul Clozel, CEO of Idorsia, commented:
"I'm happy that we have come to an agreement for the return of aprocitentan to Idorsia. Aprocitentan has demonstrated significant and clinically meaningful sustained blood pressure lowering benefits with a good safety profile, particularly suited to the high-risk patient population with resistant hypertension. Revolutionizing the use of endothelin receptor antagonism is something the team at Idorsia knows all about. We will now determine the best approach to maximizing the value of our exciting new anti-hypertension therapy."

The founding team at Idorsia brought the first oral, dual endothelin receptor antagonist (ERA) to market, followed by the discovery, development, and launch of a next generation oral, dual ERA. The team will now evaluate options for realizing the value which the company has created by successfully developing aprocitentan, the first anti-hypertensive therapy which works via a new mechanism of action in 30 years.

About the agreement
Idorsia will reacquire the development and commercialization rights for aprocitentan from Janssen. In return, Idorsia will pay Janssen a conditional consideration up to a total cap of CHF 306 million, depending on Idorsia's revenues, as follows:

- 30% of any consideration received by Idorsia from a potential out-licensing or divestment of aprocitentan,
- 10% of any consideration received by Idorsia from a potential out-licensing or the divestment of any other Idorsia product, following the first approval of aprocitentan, and
- low- to mid-single digit royalties on total group product net sales, beginning from the quarter after first aprocitentan approval.

Janssen funding obligations to aprocitentan cease at the effective date of the agreement. Janssen licenses to aprocitentan IP (excluding pulmonary hypertension) will terminate and Janssen will transfer the brand name and relating commercial materials to Idorsia. Janssen will retain licenses in the pulmonary hypertension field.

The agreement also eliminates the revenue-sharing agreement in respect of ponesimod.

The agreement will be effective following receipt of the clearance relating to the United States Hart-Scott Rodino Antitrust Improvements Act of 1976.

André C. Muller, Chief Financial Officer, commented:
"If aprocitentan is approved in the US and Europe as we expect, Idorsia would have an additional product in its portfolio giving the company more strategic flexibility, and potentially allows Janssen to recoup over time their investment in aprocitentan."

About the regulatory status of aprocitentan

A new drug application (NDA) for aprocitentan was filed with the US FDA in December 2022 (Prescription Drug User Fee Act (PDUFA) current date: December 19, 2023), and the market authorisation application (MAA) was submitted to the EMA at the end of January 2023.

Jean-Paul Clozel, concluded:
"The review process with the US FDA is progressing well, though it is likely to require an extension to the review period of up to 3 months as the company will provide additional Risk Evaluation and Mitigation Strategy (REMS) materials to support a streamlined REMS which is designed specifically for patients taking aprocitentan."

About aprocitentan in resistant hypertension

Full results from the PRECISION study were published in November 2022 in The Lancet "A randomized controlled trial of the dual endothelin antagonist aprocitentan for resistant hypertension". More details and commentary can be found in the dedicated press release and an investor webcast featuring Prof. Markus Schlaich, an investigator in PRECISION.

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]. 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 resistant hypertension.

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.[4] 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.[5,6]

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[6] – 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.[7]

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,[3,8] (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. The endothelin pathway has not been targeted by existing anti-hypertensive therapies until now, thereby leaving this relevant pathophysiologic pathway unopposed with

currently available medications.[3,9,10] The endothelin system is also activated in patients prone to developing resistant hypertension, such as Black or African American patients, patients with obesity or obstructive sleep apnea,[11-13] and in comorbid conditions frequently associated with resistant hypertension such as diabetes and chronic kidney disease.[14-17]

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[18,19] (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. 63% of randomized patients were receiving at least 4 anti-hypertensive therapies at screening.

Key PRECISION findings[19]

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, a strong predictor of cardiovascular mortality,[1,2] 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.

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 20-year heritage of drug discovery, a broad portfolio of innovative drugs in the pipeline, an experienced team of professionals covering all disciplines from bench to bedside, and commercial operations in Europe, Japan, and the US – the ideal constellation for bringing innovative medicines to patients.

Idorsia was listed on the SIX Swiss Exchange (ticker symbol: IDIA) in June 2017 and has over 1,300 highly qualified specialists dedicated to realizing our ambitious targets.

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