Media Release
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New Phase 3 data with aprocitentan for patients with resistant hypertension has been presented at the European Society of Hypertension Annual Meeting 2023

Allschwil, Switzerland – June 26, 2023
Idorsia Ltd (SIX: IDIA) today announced that further data for aprocitentan, Idorsia's investigational dual endothelin receptor antagonist evaluating the treatment of patients with resistant hypertension, were presented as an oral presentation entitled "Effects of the dual endothelin antagonist aprocitentan on ambulatory blood pressure indices in patients with resistant hypertension – results from the PRECISION study" by Prof. Markus Schlaich, MD, at the European Society of Hypertension's 32nd European Meeting of Hypertension and Cardiovascular Protection.

The Phase 3 PRECISION study demonstrated both the safety and the efficacy of aprocitentan to lower office blood pressure (BP) in patients with resistant hypertension. The presentation focused on the effects on relevant indices of ambulatory BP measurements (ABPM), including post-hoc analysis of patients at high risk of cardiovascular events based on night-time BP values. Ambulatory BP, and particularly nighttime ambulatory BP, is a better predictor of cardiovascular outcomes than office BP.[1,2]

One aspect of ABPM is the ability to record the variation of BP during a 24-hour period. The placebo-corrected systolic BP-lowering by aprocitentan at week 4 was more pronounced during night-time **(–5.1 and –7.4 mmHg)** compared with daytime **(–3.8 and –5.3mmHg**) for the 12.5 and 25mg doses, respectively. Physiologically BP is on average 10% lower during the night, a phenomenon called "dipping". Patients who don't achieve this 10% decrease are called "non-dippers" and are at increased risk of cardiovascular events[3]. At baseline, non-dipper (defined as participants with average night-time decrease of less than 10%) rates were 66%, 62%, and 60% for the 12.5mg, 25mg of aprocitentan, and placebo groups, respectively. In non-dippers, aprocitentan induced a particularly pronounced reduction in night-time systolic BP compared with dippers for both 12.5mg **(-11.25 vs -2.79mmHg; p<0.01)** and 25mg **(-13.12 vs -6.29mmHg; p<0.01)**. After 4 weeks of treatment, normalization of the dipping pattern was achieved in 44%, 40% and 31% of non-dippers for 12.5mg, 25mg of aprocitentan, and placebo, respectively.

Another aspect of the ambulatory BP is the proportion of times that the BP exceeds normal values of the total number of recorded BP measurements during day, night, and over 24 h, known as BP load. The change in BP load for both daytime and night-time was more pronounced with both doses of aprocitentan (-18.7/-24.5% for 12.5mg; -20.7/-21.1% for 25mg) compared to placebo (-9.2/-6.6 %; p<0.001 for all comparisons).

Prof. Markus Schlaich, MD, FAHA, FESC, ISHF, The University of Western Australia / Royal Perth Hospital and an investigator in the PRECISION study commented:
"The detailed analysis of the PRECISION study with aprocitentan in patients with resistant hypertension continues to excite the expert community. We know that ambulatory blood pressure is a better predictor of cardiovascular outcomes than office blood pressure, particularly the nighttime measure. Aprocitentan was associated with substantial lowering of ambulatory blood pressure, which

was even more pronounced during the night. It restored the normal 'dipping' pattern of blood pressure variation over 24 hours in many patients who had an abnormal pattern and also reduced the percentage of abnormally elevated blood pressure readings known as 'BP load'. These findings support the initial positive results and the potential use of aprocitentan and tackling the endothelin pathway for the first time for these patients who are at high-risk of negative cardiovascular outcomes."

In May 2022, Idorsia announced positive top-line results of the Phase 3 PRECISION study with **aprocitentan** for the treatment of patients with resistant hypertension. Detailed results were published in *The Lancet* and presented as a Late-Breaking Science presentation during the American Heart Association (AHA) Scientific Sessions in November 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. A new drug application (NDA) for aprocitentan was filed with the US FDA in December 2022, and the market authorisation application (MAA) was submitted to the EMA at the end January 2023.

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[7] – 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.[8]

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,[4,9] (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.[4,10,11] 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,[12-14] and in comorbid conditions frequently associated with resistant hypertension such as diabetes and chronic kidney disease.[15-18]

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[19,20] (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[20]

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, was primarily peripheral edema and was manageable by current clinical practice including use of diuretics. Discontinuation due to edema/fluid retention was reported for seven patients.

About Prof. Markus Schlaich, MD

Markus Schlaich is a nephrologist and a European Society of Hypertension (ESH) accredited hypertension specialist. He is a Fellow of the American Heart Association (FAHA), the European Society of Cardiology (FESC), and the International Society of Hypertension (ISHF). He served as an Executive Committee of the ISH from 2018-2020 and is currently on the Management Board of the global ISH *May Measurement Month* campaign. Markus is President of Hypertension Australia and a Trustee of the Foundation for High Blood Pressure Research.

Markus has a strong background in clinical research with a focus on the pathophysiology of hypertension, involvement of the kidneys, and hypertension mediated organ damage. He has a specific interest in treatment modalities targeting the sympathetic nervous system and other relevant pathways such as the endothelin system to improve BP control and thereby outcomes for patients with difficult to control hypertension. For his work he received the Björn Folkow Award from the European Society of Hypertension (ESH) and the Arthur C. Corcoran Award from the AHA Hypertension Council, both in 2021. He has authored more than 450 articles in peer-reviewed journals and serves on the Editorial Board of *Hypertension* and *Journal of Hypertension*. Prof. Schlaich serves as a consultant to Idorsia.

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 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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