Media Release
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The Lancet and AHA late-breaking science session reports significant and sustained effect of aprocitentan on lowering blood pressure for patients with resistant hypertension

- *The Lancet* reports that in patients with resistant hypertension, aprocitentan was well-tolerated and superior to placebo in lowering blood pressure at week 4 with a sustained effect at week 40
- Upon approval, aprocitentan would represent the first new anti-hypertensive mechanism in more than 30 years
- Idorsia to host an investor webcast to discuss the data shared at AHA and in *The Lancet* manuscript tomorrow November 8 at 15:00hrs CET

Allschwil, Switzerland – November 7, 2022
Idorsia Ltd (SIX: IDIA) today announced the publication of "A randomized controlled trial of the dual endothelin antagonist aprocitentan for resistant hypertension" in *The Lancet*. The publication reports the results from the Phase 3 PRECISION study, which found aprocitentan, Idorsia's investigational, novel dual endothelin receptor antagonist, significantly reduced blood pressure (BP) and maintained the effect for up to 48 weeks when added to combination background antihypertensive therapy in patients with difficult-to-control (resistant) hypertension. In parallel, these data were presented by Prof. Markus Schlaich, an investigator in PRECISION, as a Late-Breaking Science presentation during the American Heart Association (AHA) Scientific Sessions 2022.

Hypertension is one of the leading causes of cardiovascular disease worldwide, impacting an estimated 1.3 billion people globally.[1] Approximately 10% of these people have uncontrolled BP, despite receiving at least three antihypertensive medications from different classes, at optimal doses.[2,3] Compared with adults whose hypertension is well controlled, adults with uncontrolled hypertension have greater risk of heart attack, stroke, end-stage renal disease and death.[4]

The endothelin (ET) pathway has been implicated in the pathogenesis of hypertension, but it is currently not targeted therapeutically, thereby leaving this relevant pathophysiologic pathway unopposed with currently available medications.[4-6] 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,[7-9] and in comorbid conditions frequently associated with resistant hypertension such as diabetes and chronic kidney disease.[10-13]

Prof. Markus Schlaich, MD, FAHA, FESC, ISHF, The University of Western Australia / Royal Perth Hospital and an investigator in the PRECISION study commented:
"For decades, healthcare providers have been challenged to help their patients with resistant hypertension achieve better blood pressure control, using treatment options that do not address all of the known mechanisms of the condition. The Phase 3 PRECISION study establishes aprocitentan as a promising new therapeutic approach to achieve sustained blood pressure lowering in addition to guideline recommended triple antihypertensive therapy with both office and ambulatory blood pressure measurements. I'm particularly happy to see a pronounced reduction in nighttime blood pressure, which is superior to other blood pressure measures in predicting cardiovascular mortality.[14,15]"

About PRECISION[16] (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

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 night time 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 with aprocitentan was mild-to-moderate fluid retention leading to discontinuation in seven patients during the study. Fluid retention 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).

Jean-Paul Clozel, MD and Chief Executive Officer, commented:
"Literature tells us that a 5 mmHg reduction in office SBP has been associated with a 10% relative risk reduction in major cardiovascular events.[17] This is of particular relevance in patients at high risk of cardiovascular events.[3,18] As we publish in *The Lancet* today, aprocitentan, by targeting a currently unopposed pathophysiologic pathway, provided clinically meaningful lowering of systolic and diastolic blood pressure in patients with treatment-resistant hypertension over 48 weeks with manageable adverse effects. The authors conclude that aprocitentan represents a 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.[14] 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.[19,20]

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 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 will be responsible for the regulatory submission for the treatment of patients whose hypertension is not adequately controlled. 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.

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 the High Blood Pressure Research Council of 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 400 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.

Key Literature

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17. The Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. Lancet 2021; 397: 1625-36.
18. The Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet 2014; 384: 591–8.
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Investor webcast

An investor conference call and webcast will be held to discuss the data shared at AHA and in *The Lancet* manuscript. The call will start with presentations by Martine Clozel, MD, Chief Scientific Officer at Idorsia and Prof. Markus Schlaich, MD, FAHA, FESC, ISHF, The University of Western Australia / Royal Perth Hospital and an investigator in the PRECISION study followed by a Q&A session.

Date: Tuesday, November 8, 2022
Time: 15:00 CET | 14:00 GMT | 09:00 EST

Dial-in procedure:

1. Participants are required to register in advance of the conference (link already open for registration) using the link provided below. Upon registration, each participant will be provided with participant dial in numbers, and a unique personal PIN.
2. In the 10 minutes prior to the call start time, participants will need to use the conference access information provided in the e-mail received at the point of registering. Participants may also use the Call Me feature instead of dialing the nearest dial in number.

   Online Registration: **LINK**

Webcast participants should visit Idorsia's website www.idorsia.com 10-15 minutes before the webcast is due to start.

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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