Media Release
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New Phase 3 data with aprocitentan for patients with resistant hypertension has been presented at the American Society of Nephrology Kidney Week 2023

Allschwil, Switzerland – November 3, 2023
Idorsia Ltd (SIX: IDIA) announced today that further data for aprocitentan, Idorsia's investigational dual endothelin receptor antagonist for the treatment of patients with resistant hypertension, were presented as an oral presentation entitled "Effects of aprocitentan on blood pressure lowering and proteinuria in patients with chronic kidney disease and resistant hypertension" by George Bakris, MD, at the American Society of Nephrology (ASN) Kidney Week 2023.

Patients with hypertension can often successfully control their blood pressure by combining a healthier lifestyle with effective medication. However, approximately 10% of patients have resistant hypertension where the blood pressure remains high despite receiving at least three antihypertensive medications of different pharmacological classes, including a diuretic, at optimal doses.

The Phase 3 PRECISION study demonstrated both the safety and the efficacy of aprocitentan to significantly lower blood pressure (BP) in patients with resistant hypertension on top of at least three antihypertensive medications of different classes, including a diuretic. 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.

The presentation at ASN Kidney Week 2023 focused on the effect of aprocitentan on BP in a subgroup of 162 patients with stage 3 or 4 chronic kidney disease (CKD), defined by an estimated glomerular filtration rate (eGFR) of 15 to <60mL/min/1.73m2. The presentation included pre-specified exploratory analysis (not adjusted for multiplicity) of aprocitentan on BP measured by an automated Office BP measurement (AOBPM), and post-hoc analysis of ambulatory BP monitoring (ABPM) and urinary albumin-to-creatinine ratio (UACR) – a marker of kidney damage – in this patient population.

Both the 12.5 mg and 25 mg doses of aprocitentan resulted in a pronounced BP reduction from baseline to week 4 compared to placebo in patients with CKD stage 3 or 4. The mean change in office systolic BP at 4 weeks (for patients with both baseline and week 4 values) was –13.7 mmHg for aprocitentan 12.5 mg, –18.4 mmHg for 25 mg, and –6.5 mmHg for placebo, for a difference versus placebo of **–7.2 mmHg** and **–11.9 mmHg**, respectively. The results from ambulatory BP monitoring confirmed those derived from office measurements. The UACR at week 4, was reduced by 28% for aprocitentan 12.5 mg, 44% for aprocitentan 25 mg, and remained stable (reduction of 4%) in the placebo group.

Aprocitentan was generally well tolerated; with the most common adverse events being edema/fluid retention (18% and 24% of patients receiving aprocitentan 12.5mg and 25mg, respectively, versus 2% with placebo, at week 4). Adverse events of fluid retention and edema were primarily peripheral edema of mild intensity, mostly occurring during the first 4 to 8 weeks of treatment and were

effectively managed with additional diuretic therapy. Discontinuation due to edema/fluid retention was reported for 3 out of 162 patients.

George Bakris, MD, Professor of Medicine and Director, Comprehensive Hypertension Center, University of Chicago School of Medicine and an investigator in the PRECISION study commented:
"It is great that the PRECISION study with aprocitentan included such a large cohort of patients with resistant hypertension and CKD stage 3 or 4, as CKD is a frequent cause – and consequence of – resistant hypertension. Very often these high-risk patients are under-represented in clinical studies of hypertension, but it is very important to include these patients in order to translate the clinical data into a real-world situation. We found that aprocitentan, when added to at least three other antihypertensive medications, resulted in a substantial and clinically meaningful reduction of both office and ambulatory blood pressure, as well as a reduction in albuminuria. It is also important that the mechanism is not associated to an increased risk of hyperkalemia, which often limits the use of anti-hypertensive medications in patients with CKD."

Alberto Gimona, Head of Global Clinical Development of Idorsia, concluded:
"While this prespecified subgroup analysis is exploratory in nature, I was very glad to see the marked efficacy of aprocitentan in reducing blood pressure and proteinuria in patients with CKD who are already heavily medicated. I was also glad to see the safety results, while we did see an increased incidence of edema and fluid retention in the first 4 to 8 weeks, this was mostly peripheral edema, the incidence decreased rapidly, and was effectively managed with additional diuretic therapy. In this frail population with a lot of comorbidities, on top of other vasodilators, cases of edema were not unexpected."

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 accepted for review by the US FDA. Following the provision of additional Risk Evaluation and Mitigation Strategy (REMS) materials to support a streamlined REMS designed specifically for aprocitentan, the company is working towards a PDUFA date of March 19, 2024. A 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.[2] 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.[3,4]

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[4] – 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.[5]

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,[1,6] (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.[1,7,8] 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,[9-11] and in comorbid conditions frequently associated with resistant hypertension such as diabetes and chronic kidney disease.[12-15]

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[16,17] (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[17]

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,[18,19] 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 Dr George Bakris, MD

Dr Bakris is a Nephrologist/Certified Hypertension Specialist trained at the Mayo Clinic and the University of Chicago Medicine. He is a Professor of Medicine and Director of the Am. Heart Assoc. Comprehensive Hypertension Center at the University of Chicago Medicine. He has published over 1000 peer-reviewed articles and book chapters in the areas of diabetic kidney disease, hypertension, and nephropathy progression. He is the Editor or Co-Editor of 24 books in the areas of Diabetic Kidney Disease Progression and Hypertension. Additionally, he is the Co-Editor of the 3rd and new 4 edition of Hypertension: A Companion to Braunwald's: The Heart.

Dr Bakris has served on the Cardiorenal Advisory Board of the FDA and consultant to CMS. He has also served on many national guideline committees, including The Joint National Committee JNC 7 executive committee and writing group, the American Diabetes Association (ADA) Clinical Practice Guideline Committee (2002-2004 and 2020-2022), and the National Kidney Foundation (K-DOQI), Blood Pressure and Diabetes Guideline committees. He Chaired the ADA Blood Pressure Consensus Report (2017) and served on the ACC/AHA writing committee on the Resistant Hypertension Consensus report (2018). He is also the senior author on the recent ADA/KDIGO Consensus Report for approaches to diabetic kidney disease (2022).

Dr Bakris is the past president of the American College of Clinical Pharmacology and the American Society of Hypertension (ASH). He is the recipient of the Irvine Page-Alva Bradley Lifetime Achievement Award-Am Heart Assoc. BP Council (2019). He serves on numerous editorial boards and is the current Editor-in-Chief of Am J Nephrology, and Editor, UpToDate, Nephrology section, Hypertension Section, and Assoc. Ed of Diabetes Care and Am. Heart J. Plus. Dr. Bakris serves as a consultant to Idorsia.

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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