Media Release
May 23, 2022

Ad hoc announcement pursuant to Art. 53 LR

Positive Phase 3 study with aprocitentan demonstrates significant antihypertensive efficacy in patients with resistant hypertension

- Aprocitentan reduces blood pressure compared to placebo by week 4 of treatment, the effect is maintained and confirmed over a period of 48 weeks, and is generally well tolerated with no major safety concerns
- Primary and key secondary endpoints were met with statistical significance and clinically meaningful results – the effect was consistent across multiple endpoints and methodologies of blood pressure monitoring
- Idorsia to host an investor webcast to discuss PRECISION top-line results tomorrow May 24 at 14:00hrs CEST

Allschwil, Switzerland – May 23, 2022
Idorsia Ltd (SIX: IDIA) today announced positive top-line results of PRECISION, the Phase 3 study investigating aprocitentan, Idorsia's dual endothelin receptor antagonist, for the treatment of patients whose blood pressure is not adequately controlled despite receiving at least triple antihypertensive therapy – known as resistant hypertension. Aprocitentan **significantly reduced blood pressure** when added to standardized combination background antihypertensive therapy in patients with resistant hypertension over 48 weeks of treatment.

Hypertension is one of the most common cardiovascular risk factors, and its prevalence continues to rise. According to a recent study, there are more than one billion people living with hypertension worldwide – a number which has almost doubled in the past 40 years.[1]

While many patients with hypertension are successfully treated with various existing anti-hypertensive therapies, 10–20% of the hypertensive population have blood pressure that remains high despite receiving at least three antihypertensive medications of different pharmacological classes, including a diuretic, at optimal doses, and they are categorized in hypertension guidelines[2,3,4] and in the medical community as having resistant hypertension. Certain populations are at a particular high risk of developing resistant hypertension later in life; these include patients with a high body mass index (BMI), African Americans, post-menopausal women and patients with obstructive sleep apnea.[5,6,7]

It is estimated that by 2025, there could be approximately 10 million patients in the US who could be classified as having resistant hypertension and a similar number of patients in Europe.[3,4,8] Uncontrolled hypertension can lead to multiple cardiovascular and renal adverse outcomes, including stroke, heart disease, and kidney failure. These co-morbidities increase a patient's vulnerability and the complexity of their treatment.[9,10,11]

Martine Clozel, MD and Chief Scientific Officer of Idorsia, commented:
"I have long been convinced that resistant hypertension is only resistant to treatment because the endothelin system had not been tackled. The observation of high endothelin levels in populations most at risk of developing resistant hypertension, as well as the close association between endothelin and the comorbidities often seen in patients with resistant hypertension, suggested that endothelin is a key contributor to the problem. I believe the top-line results from PRECISION support our initial hypothesis that endothelin is the missing link when hypertension is not adequately controlled with existing therapies."

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 long half-life, a low potential for drug-drug interaction and a mechanism of action that is ideally suited for the pathophysiology of difficult-to-treat forms of hypertension.

About the PRECISION study[12] Danaietash P et al. J Clin Hypertension 2022 (in press) (NCT03541174)

Idorsia, in consultation with regulatory agencies, designed a single, international, multi-center, blinded randomized study with three sequential treatment parts. The study design addressed both the 4-week placebo-controlled efficacy of 12.5 and 25 mg aprocitentan (Part 1) and the durability of its effects in long-term active treatment with 25 mg aprocitentan for a further 32 weeks (Part 2) followed by a 12-week placebo-controlled withdrawal period with patients re-randomized to 25 mg or placebo (Part 3).

Patient population with established resistant hypertension

To confirm a diagnosis of resistant hypertension and exclude pseudo resistant hypertension, 1'965 patients entered a thorough 12-week screening period. During the screening period, qualifying patients were transitioned to guideline-recommended standardized background antihypertensive therapy of a fixed-dose combination of a calcium channel blocker (amlodipine), an angiotensin receptor blocker (valsartan) and a diuretic (hydrochlorothiazide) for at least 4 weeks before entering a 4-week single-blind run-in period. In this period, placebo was added to the background antihypertensive therapy. Patients with systolic blood pressure consistently above 140 mmHg were then randomized to the first treatment part.

Sustained reduction in systolic blood pressure after chronic treatment with aprocitentan

In Part 1, the first double-blind treatment period of 4 weeks, a total of 730 patients were randomized to receive a tablet of aprocitentan 12.5 mg (N=243), 25 mg (N=243), or placebo (N=244) once daily. After 4 weeks of treatment, a statistically significant and clinically meaningful reduction in the primary endpoint measure of systolic blood pressure – assessed by measurement at trough of unattended automated office blood pressure (AOBP) – was observed in both the 12.5 mg ($p<0.005$) and 25 mg ($p<0.005$) aprocitentan groups compared to placebo.

Following the 4-week double-blind, placebo-controlled treatment period, patients entered Part 2, a single-blind treatment period, where all patients were treated with 25 mg aprocitentan for a further 32 weeks. The mean reduction from baseline in systolic blood pressure was maintained during this treatment period, for those patients who were on aprocitentan during Part 1. Patients switching from placebo to aprocitentan rapidly achieved the same blood pressure reduction as seen in Part 1.

This was followed by Part 3, a double-blind, placebo-controlled, randomized withdrawal treatment period where 614 patients were re-randomized to aprocitentan 25 mg or placebo for 12 weeks. After 4 weeks in the withdrawal period, systolic blood pressure increased significantly on placebo compared to aprocitentan 25 mg ($p<0.0001$), the key secondary endpoint. This provided replication of the treatment effect of aprocitentan and confirmed its durable antihypertensive effect.

The reduction in systolic and diastolic blood pressure assessed by measurement of unattended automated office blood pressure during the study, was confirmed by the 24-hour ambulatory blood pressure monitoring (ABPM), demonstrating BP reduction across the entire 24 h period (notably during the night).

Prof. Markus Schlaich, MD, FAHA, FESC, ISHF, The University of Western Australia, Perth, and lead investigator in the PRECISION study commented:
"Despite the availability of many drug classes to target the serious and growing problem of arterial hypertension around the world, we frequently struggle to achieve BP control in many patients, particularly in those with resistant hypertension. As a strong believer in the principles of targeting underlying pathophysiologic mechanisms, the findings from this study demonstrate the crucial contributions of the endothelin pathway and highlight the enormous potential of aprocitentan to help improve blood pressure control and thereby cardiovascular outcomes in this high-risk patient cohort. The consistency of the observations made during the study and in particular the use of the withdrawal study design after chronic use will set a new standard in the evaluation of the treatment of resistant hypertension."

About the safety of aprocitentan in PRECISION

The topline results show that aprocitentan was generally well tolerated with no major safety concerns in this patient population at both doses and with a low discontinuation from study treatment due to an adverse event in the first 4 weeks double-blind study period: 2.5% and 2.0% for aprocitentan 12.5 mg and 25 mg groups respectively versus 0.8% in the placebo group. Treatment-emergent adverse events (TEAEs) during the 4-week double-blind study period 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 TEAEs reported over 3% incidence and higher than placebo was edema / fluid retention.

There were no additional emerging safety findings in the subsequent treatment period taking the total to 48 weeks. Importantly, the overall incidence of Major Adverse Cardiac Events (MACE) reflected the expected occurrence in this patient population. Approximately 30% of patients developed edema / fluid retention, at one time point during the entire study duration, with >95% being mild to moderate in intensity. Two (<1%) of these adverse events were serious (both on aprocitentan 25mg). Only seven (<1%) of patients discontinued treatment due to edema / fluid retention. Edema / fluid retention was mostly reported by patients within the first 4-week double-blind study period (9.1% and 18.4% for aprocitentan 12.5 mg and 25 mg groups respectively, versus 2.1% in the placebo group).

Conclusion of the Phase 3 PRECISION study

Aprocitentan is an investigational treatment with a new mode of action for patients whose hypertension is not adequately controlled despite the use of at least three other classes of antihypertensives, including a diuretic. Aprocitentan reduces blood pressure compared to placebo by week 4 of treatment and the effect is maintained over a period of 48 weeks. The safety profile, together with the long half-life, and low potential for drug-drug interactions observed in the clinical pharmacology program, is conducive for a chronic treatment to be used for patients who often have several comorbidities and are treated with multiple pharmacological therapies. The effect demonstrated in the Phase 3 study was consistent across multiple methodologies of blood pressure monitoring and in key sub-populations.

Jean-Paul Clozel, MD and Chief Executive Officer of Idorsia, commented:
"I am delighted that in this patient population, where hypertension is so difficult to control, the treatment effect of aprocitentan was clear and consistent – despite aprocitentan being given on top of at least three therapies. During the course of the 48 weeks of treatment we have collected information on safety and efficacy which will allow us to fully characterize the benefit of aprocitentan, especially for the sub-populations in greatest need of new antihypertensives. I am very proud that Idorsia is once again at the forefront of medical research."

Alberto Gimona, Head of Global Clinical Development of Idorsia, concluded:
"A big 'thank you' goes to the investigators and their patients who took part in this study. Their dedication has contributed to the outstanding conclusion of PRECISION, and potentially to the availability of a new antihypertensive, the first working via a new pathway for decades. Idorsia will now discuss the results with health authorities with the aim to file the new drug application with the US FDA by the end of the year, closely followed by other health authorities. We will also make the detailed results of the Phase 3 study available through scientific presentation and peer-reviewed publications."

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.

Notes to the editor

The endothelin system in systemic hypertension[13]

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.[15]

Additional aprocitentan data[16] Verweij P., et al. Hypertension. 2020

In May 2017, the results of a double-blind, randomized, placebo-controlled with an active-reference arm, dose-finding study with aprocitentan in patients with essential hypertension, were reported. The study evaluated the efficacy, safety and tolerability of a once-a-day oral regimen of 4 dose levels of aprocitentan (5, 10, 25, and 50mg) to identify the optimal doses for further studies.

In this study, 490 patients were randomized to receive either aprocitentan 5, 10, 25, 50 mg, placebo, or lisinopril 20 mg once daily. After 8 weeks of treatment the mean reduction from baseline in diastolic blood pressure - as measured at trough with a novel automated office blood pressure device - ranged between 6.3 and 12.0 mmHg in a statistically significant dose-dependent manner for the aprocitentan groups versus a decrease of 4.9 mmHg in the placebo group and a decrease of 8.4 mmHg in the lisinopril group (in the per-protocol population comprised of 410 patients). Systolic blood pressure reductions ranged from 10.3 to 18.5 mmHg in a statistically significant dose-dependent manner in the aprocitentan groups and were 7.7 and 12.8 mmHg in the placebo and lisinopril groups, respectively. These findings were confirmed in all randomized patients (Intent-to-Treat principle) and by 24 hours Ambulatory Blood Pressure Monitoring.

The safety population included 327 patients in the aprocitentan groups, 82 patients in the placebo group and 81 in the lisinopril group. Aprocitentan was well tolerated across all four doses in this patient population. Discontinuation from study treatment due to an adverse event ranged between 1.2% and 3.7% for the aprocitentan groups versus 6.1% in the placebo group and 3.7% in the lisinopril group. The overall frequency of adverse events was similar to those observed in the placebo group. There were two cases of increased liver enzymes above three times the upper limit of the normal range, one in the placebo and one in the aprocitentan 5 mg group. Four cases of peripheral edema were observed, two in the aprocitentan 25 mg group and two in the aprocitentan 50 mg group. Mean body weight remained unchanged from baseline in the aprocitentan 5, and 10 mg groups, increased by 0.4 kg in the aprocitentan 25 and 50 mg groups, and by 0.3 kg in the placebo group and decreased by 0.3 kg on lisinopril. There was an expected dose related decrease from baseline in the hemoglobin concentration in the aprocitentan groups (ranging from 1.3 to 6.7 g/L) versus increases of 2.2 and 0.1 g/L in the placebo and lisinopril groups, respectively.

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.

Reference

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Investor webcast

An investor conference call and webcast will be held to discuss the Phase 3 results with aprocitentan. The call will start with presentations by senior management, followed by a Q&A session (live access to the speakers).

Date: Tuesday May 24, 2022
Time: 14:00 CEST | 13:00 BST | 08:00 EDT

Webcast participants should visit Idorsia's website www.idorsia.com 10-15 minutes before the webcast is due to start.
Conference call participants should start calling the number below 10-15 minutes before the conference is due to start.

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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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