Media Release
June 20, 2018

Idorsia initiates PRECISION – Phase 3 study with aprocitentan for resistant hypertension management

- Idorsia to host an investor webcast to discuss the Phase 3 program today at 14:00hrs CEST

Allschwil, Switzerland – June 20, 2018
Idorsia Ltd (SIX: IDIA) today announced that the first patient has been enrolled into PRECISION, a Phase 3 study to investigate the efficacy and safety of aprocitentan for resistant hypertension management in adults.

Hypertension, or high blood pressure, remains the most frequent addressable risk factor of cardiovascular morbidity/mortality outcomes, ahead of smoking and obesity, as reported by the 2015 Global Burden of Disease, Injuries, and Risk Factor Project collaborating with WHO.

Patients whose blood pressure remains high despite receiving at least three antihypertensive medications from different classes, including a diuretic, at maximal tolerated dose are categorized as having resistant hypertension. Patients with resistant hypertension are typically older and often suffer from obesity, sleep apnea, and/or diabetes mellitus. 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.

Prof. John Chalmers, MD, Senior Director of The George Institute for Global Health and Professor of Medicine at the University of NSW Sydney, commented:
"Despite hypertension being a serious and growing problem around the world, there is surprisingly little research going on in the field. It has been over 30 years since an anti-hypertensive drug working via a new pathway has been brought to the market. Moreover, depending on the source of information, it is estimated that anywhere from 5 to 30 per cent of the hypertension patient population can be classified as treatment 'resistant' due to their uncontrolled blood pressure levels despite receiving multiple antihypertensive medications, though 'true resistant hypertension' may be much less frequent, of the order of 5 to 10%. There is an urgent public health need for additional therapies acting on pathways different from those currently used, in line with the underlying disease mechanism."

Clinical and preclinical evidence suggest that resistant hypertension may be endothelin-dependent. Indeed, the endothelin system plays an important role in forms of volume and salt-dependent hypertension, a common feature in patients with resistant hypertension. Endothelin-1 is a potent vasoconstrictor and also induces neurohormonal activation, vascular hypertrophy and remodeling, cardiac hypertrophy and fibrosis, and endothelial dysfunction.

Aprocitentan is an orally active dual endothelin receptor antagonist. Aprocitentan counteracts these deleterious effects in animal models of hypertension, including in salt-sensitive models. In such models, aprocitentan also provide significant blood pressure lowering effects on top of existing therapies (e.g. renin angiotensin system blockers).

In a dose-finding study to explore the efficacy, safety and tolerability of aprocitentan in 490 patients with essential hypertension, aprocitentan significantly lowered blood pressure in a dose-dependent manner.

Martine Clozel, MD and Chief Scientific Officer, commented:
"The dose response of aprocitentan was consistent across blood pressure measurements, resulting in a minimum effective dose of 10 mg and an anticipated therapeutic dose of 25 mg. Aprocitentan was well tolerated across all doses. The clinical pharmacology profile suggests that it has a low propensity for drug-drug interaction, and could therefore be combined with other background hypertension therapies as well as other medications. This means that a compound targeting the endothelin pathway, one of the pathways in hypertension, could become a new treatment option for difficult to treat patients."

About the PRECISION study

PRECISION is a multi-center, double-blinded, placebo-controlled, randomized, parallel-group, Phase 3 study to demonstrate the blood pressure lowering effect of aprocitentan when added to standard-of-care in resistant hypertension patients. Idorsia, following consultation with regulatory agencies, has designed an efficient, single Phase 3 study. The study will address both the short-term efficacy of aprocitentan and the durability of its effect on long-term treatment in a placebo-controlled manner.

Patients with history of resistant hypertension will undergo a thorough screening and run-in period. This will confirm the diagnosis of resistant hypertension by excluding pseudo or apparent resistant hypertension. During the screening period, patient's background anti-hypertensive therapies will be transitioned to a standardized fixed combination of a calcium channel blocker (amlodipine), an angiotensin receptor blocker (valsartan) and a diuretic (hydrochlorothiazide).

Patients with true resistant hypertension will then be randomized to receive aprocitentan 12.5 mg, 25 mg, or placebo once-daily. The study consists of 3 sequential treatment periods. The first is a double-bind treatment period designed to demonstrate the effect of aprocitentan on blood pressure at Week 4, compared to placebo. Patients then enter a treatment period where they are treated with 25 mg aprocitentan for 32 weeks. This is followed by a double-blind, randomized withdrawal treatment period where patients will remain either on aprocitentan 25 mg or switch to placebo for 12 weeks. The latter treatment period is designed to demonstrate the durability of the blood pressure lowering effect of aprocitentan. Patients will then enter a 30-day safety follow-up period.

From the initial screened patient population, at least 600 patients will be randomized and at least 300 patients are expected to complete the study. The study will be conducted in approximately 100 sites in around 20 countries.

Guy Braunstein, MD and Head of Global Clinical Development, commented:
"The efficient study design of PRECISION has been established following consultation with regulatory agencies, including the FDA. The design will ensure that we are focused only on patients with true resistant hypertension. It intends also to minimize the placebo response in the treatment period. This maximizes the chance to demonstrate both the short-term blood pressure lowering effect of aprocitentan, when added to standard-of-care, and the durability of its effect on long-term resistant hypertension management. If successful, the study should provide all the information required for filing and bring a therapy to patients who have exhausted many other options."

In December 2017, Idorsia entered into a collaboration with Janssen Biotech, Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, to jointly develop and commercialize aprocitentan and any of its derivative compounds or products.

Notes to the editor

About resistant hypertension

According to international guidelines, RHT is defined as uncontrolled blood pressure – i.e. failure to lower blood pressure to a pre-defined threshold and is associated with a higher risk of cardiovascular disease.

The diagnosis of true RHT (vs. apparent RHT) requires appropriate methodology to measure blood pressure in order to eliminate white-coat effects, as well as clinical expertise to exclude secondary causes of hypertension, avoid poor medication dosage and/or selection and insufficient therapeutic adherence.

The estimated prevalence of RHT varies from 5% to 30% of the hypertensive population. This unusually broad range is mainly due to the different sources of information, e.g., insurance healthcare system, registries, specialized centers, or controlled clinical trials. 'True resistant hypertension' is more likely to be in the order of 5% to 10% of the hypertensive population.

RHT is associated with a higher risk of cardiovascular events. This has been demonstrated in different settings (i.e., clinical trials, observational studies, and international registries) comparing RHT versus non-RHT patients with adjustment for patient and clinical characteristics, i.e., level of control of blood pressure, gender, presence of chronic kidney disease, and/or diabetes mellitus.

Patients with resistant hypertension often have a medical history of diabetes mellitus and may develop chronic kidney disease as a complication of the hypertension, increasing their vulnerability and the complexity of treatment.

The RHT population is, by definition, on a background therapy of three drugs (usually A + C + D) at maximal or optimal dose, where, according to most clinical guidelines, "A" is always an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and "D" is always a long-acting thiazidic diuretic. "C" stands for a calcium channel blocker (CCB), which is the most commonly used type of third background agent in RHT. However, individualization therapy is needed for some patients, such as those with ischemic heart disease, who may then use a beta-blocker (A + B + D) instead of a CCB as a third agent.

As for RHT patients, blood pressure remains uncontrolled despite the third-therapy step mentioned above, the generally recommended therapeutic approach for the fourth antihypertensive medication is to add a drug with a different mechanism of action, compared to the three medications already prescribed. These includes well-known therapeutic antihypertensive classes such as mineral corticoid receptor antagonists or beta blockers, if not previously used. These therapies have their own limitations though and are associated with adverse effects that often lead to discontinuation of therapy, which reinforces the medical need for new treatment options in resistant hypertension.

Data supporting aprocitentan for the treatment of resistant hypertension

In May 2017, the results of a multi-center, double-blind, double-dummy, randomized, placebo-controlled with an active-reference arm, parallel group, dose-finding study with aprocitentan, an orally active dual endothelin receptor antagonist, 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. John Chalmers, MD, PhD, FRACP

John Chalmers is Senior Director of The George Institute for Global Health and Professor of Medicine at the University of NSW Sydney. He is Emeritus Professor of Medicine at the University of Sydney and at Flinders University of South Australia, and a Fellow of the Australian Academy of Science. His research has focused on the prevention of cardiovascular diseases in high risk groups including those with diabetes, with elevated blood pressures and with previous stroke. He was the Principal Investigator for the PROGRESS and ADVANCE trials and one of the founders of the Blood Pressure Lowering Treatment Trialists' Collaboration. He was awarded the Volhard Medal of the International Society of Hypertension (1998), the Zanchetti award of the European Society of Hypertension (2008) and the Research Medal of the National Heart Foundation of Australia (2009). He is a past President of the Royal Australasian College of Physicians and the International Society of Hypertension and Past Chairman of the National Health and Medical Research Council of Australia and of the Scientific Advisory Board of the World Heart Federation. He has published over 700 papers in the scientific literature. He was appointed a Companion in the Order of Australia (1991) and more recently appointed as an Officer in the French National Order of Merit (2010).

References

- Iglarz M, et al. Clin Sci 2010; 119:453-63
- 2015 Global Burden of Disease, Injuries, and Risk Factor Project collaborating with WHO
- Gaddam, et al. Arch Intern Med. 2008 Jun 9;168(11):1159-64.
- Achelrod D, et al. Am J Hypertens. 2015 Mar;28(3):355-61

Investor webcast

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

Date: **Wednesday June 20, 2018**
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 one of Europe's leading biopharmaceutical companies, with a strong scientific core.

Headquartered in Switzerland - a biotech-hub of Europe - Idorsia is specialized in the discovery and development of small molecules, to transform the horizon of therapeutic options. Idorsia has a broad portfolio of innovative drugs in the pipeline, an experienced team, a fully-functional research center, and a strong balance sheet – the ideal constellation to bringing R&D efforts to business success.

Idorsia was listed on the SIX Swiss Exchange (ticker symbol: IDIA) in June 2017 and has over 650 highly qualified specialists dedicated to realizing our ambitious targets.

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