Media Release
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Idorsia's aprocitentan improved key prognostic indicators in patients with difficult-to-control hypertension

- New analysis from landmark Phase 3 PRECISION trial published in the *Journal of Hypertension* highlights aprocitentan led to improvements in dipping pattern and BP load
- Findings reinforce the role of aprocitentan's novel endothelin pathway mechanism in addressing significant medical need in difficult-to-control hypertension

Allschwil, Switzerland – November 10, 2025
Idorsia Ltd (SIX: IDIA) announced the publication of a new analysis from the landmark Phase 3 PRECISION study in the *Journal of Hypertension* titled "Effects of aprocitentan on prognostically relevant ambulatory blood pressure-derived variables in resistant hypertension"[1]. The analysis examined the changes in variables derived from ambulatory BP monitoring that are shown to drive better outcomes for patients at high risk of cardiovascular events.

Aprocitentan (TRYVIO™/JERAYGO™), the first approved antihypertensive targeting the endothelin pathway, substantially lowered 24-hour blood pressure (BP) in patients with confirmed resistant hypertension, with particularly pronounced effects at night. Night-time BP is a strong indicator of poor long-term outcome. The new analysis shows that aprocitentan on top of at least triple anti-hypertensive therapy improved multiple characteristics of resistant hypertension that are linked to poor clinical outcomes, including reducing blood pressure load and normalizing night-time "dipping" patterns, and is efficacious in patients with increased arterial stiffness and salt sensitivity.

Markus Schlaich, MD, FAHA, FESC, ISHF, The University of Western Australia / Royal Perth Hospital and an investigator in the PRECISION study commented:
"Aprocitentan resulted in substantial and sustained improvements in ambulatory BP parameters which are predictive of cardiovascular risk. As a result, aprocitentan is positioned as a promising option that could reduce cardiovascular events and improve long-term outcomes in patients with resistant hypertension."

Michael A. Weber, MD, preventative cardiologist and hypertension specialist at Downstate College of Medicine of the State University of New York, commented:
"The availability of aprocitentan in routine clinical practice is a welcome and much needed addition to our armamentarium to effectively treat a broad range of patients with difficult-to-control hypertension. It has the added benefit of targeting the otherwise unopposed yet highly relevant endothelin mechanism in the pathogenesis of hypertension, potentially yielding therapeutic effects beyond BP lowering *per se*."

John M. Flack, MD, MPH, Director, Hypertension Center, Southern Illinois University School of Medicine, commented:
"This is an important analysis as it provides insight into the benefit of targeting the endothelin system with aprocitentan to address the needs of the many patients with difficult-to-control hypertension, without risks of hyperkalemia, known drug interactions or worsening renal function. This makes aprocitentan a unique and important treatment option for physicians who are struggling to maintain 24-hour blood pressure control in their patients, particularly at night."

There are 1.4 billion people worldwide living with hypertension.[2] Hypertension remains a leading global health challenge and the number one modifiable risk factor for early morbidity and mortality. Despite advances in treatment, many patients still struggle with uncontrolled blood pressure, leaving them at significantly higher risk of heart attack, stroke, kidney failure, and premature death.[3] In the US, approximately 50% of patients living with hypertension on multiple treatments do not have their blood pressure under control.[4] Consistent 24-hour blood pressure control is an important clinical outcome in patients with difficult-to-control hypertension.[5-7] Multiple studies have demonstrated that 24-hour blood pressure is a more powerful predictor of cardiovascular events than a clinic-based measurement.[8-10]

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.[11] 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.[12,13]

About the analysis[1]

The Phase 3 PRECISION study demonstrated both the safety and the efficacy of aprocitentan to lower office BP in patients with resistant hypertension. The post-hoc analysis evaluated the BP-lowering effects of aprocitentan on derivatives of ambulatory BP measurements (ABPM) – dipping pattern, BP load, heart rate, arterial stiffness, and salt sensitivity.

The analysis revealed that in addition to significant and sustained daytime and nighttime ambulatory BP reduction, aprocitentan was associated with:

- In patients classified as non-dippers – those who do not have the normal nighttime BP drop – aprocitentan treatment resulted in a higher proportion achieving normalization of their dipping pattern compared to placebo. This normalization of the nocturnal BP fall is a positive prognostic indicator with a lower risk of cardiovascular disease.
- Aprocitentan significantly reduced the BP load – the proportion of time BP exceeds threshold values – by about 20% during both daytime and nighttime, potentially lowering the risk of hypertension-mediated organ damage.
- Despite the BP lowering effect of aprocitentan, heart rate remained unchanged at Week 36.
- The blood pressure lowering effect of aprocitentan was consistently observed regardless of the patients' baseline arterial stiffness or salt sensitivity, indicating aprocitentan's effectiveness even in patients with clinical features traditionally associated with poor BP control.

About aprocitentan

Aprocitentan is Idorsia's once-daily, orally active, dual endothelin receptor antagonist, which inhibits the binding of ET-1 to ETA and ETB receptors. Aprocitentan is approved as TRYVIO® in the US for the treatment of systemic hypertension in combination with other antihypertensives and has been commercially available since October 2024. For more information see the Full Prescribing Information including BOXED Warning (**PI** and **Medication Guide**). TRYVIO is now included in the American College of Cardiology's (ACC) and the American Heart Association's (AHA) new comprehensive clinical practice guidelines for the management of high blood pressure. Aprocitentan is approved as JERAYGO® for the treatment of resistant hypertension in combination with other antihypertensives in the European Union, the UK, and Switzerland, and a marketing authorization application is under review in Canada.

About PRECISION[14,15] (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[15]

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.

Notes to the editor

About Dr. 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 530 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 Dr Michael A. Weber, MD
Dr. Weber is Professor of Medicine at the SUNY Downstate College of Medicine in Brooklyn, New York. He received his medical degree from Sydney University in Australia.

His career has been focused primarily on hypertension and preventive cardiology. He has published numerous research articles in the medical literature and has authored or edited several books.

Dr. Weber was the Editor-in-Chief of The Journal of Clinical Hypertension for over 10 years. Dr. Weber was one of the founders of The American Society of Hypertension and has served as its President. He also served as Chair of the ASH Hypertension Specialists Program. He is a Fellow of The American College of Physicians, The American College of Cardiology and The American Heart Association. He has served on the Cardiovascular and Renal Drugs Advisory Board of the Food and Drug Administration. He has also served for ten years as Chairman of the Formulary Committee of a major pharmacy benefits provider serving many of the leading health plans in the United States.

His main current research interests are in clinical trials of patients at high risk of cardiovascular events or strokes. He is also participating actively in trials in patients with metabolic disorders such as diabetes and kidney disease. Dr. Weber currently serves on the Steering Committees of several national and international clinical trials. Dr. Weber serves as a consultant to Idorsia.

About Dr John M. Flack, MD
Dr. Flack, an Alpha Omega Alpha (AOA) graduate of the University of Oklahoma School of Medicine, is the Sergio Rabinovich Endowed Chair of Internal Medicine and the Professor and Chair of the Departments of Medicine and Population Science at Southern Illinois University School of Medicine. He is also Director of the Hypertension Clinic.

He is a board-certified Internal Medicine specialist and an internationally renowned hypertension specialist/cardiovascular epidemiologist with widely recognized clinical/research expertise in hypertension in African Americans, resistant/refractory hypertension, device-based therapies for hypertension and racial cardiovascular health disparities. Dr. Flack is the current President of the American Hypertension Specialist Certification Program. He has published over 250 peer-reviewed manuscripts and book chapters and is an Associate Editor for the journal Hypertension. He maintains an active clinical practice in complex hypertension at SIU where he teaches and mentors medical students and residents and undertakes innovative, cutting-edge research.

Dr. Flack has received numerous awards including the Distinguished Research Award (1993) from the International Society on Hypertension in Blacks (ISHIB), the Daniel D. Savage Memorial Scientific Award (1998) from the Association of Black Cardiologist (ABC), the F. Dewey Dodrill Award for Excellence (2007) from the American Heart Association (AHA), the Detroit News Michiganian of the Year (2009), and the University of Oklahoma Academic Physician of the Year (2012). Also, he has been repeatedly named to Top Doctor, Best Doctor, and Super Doctor lists. Previously, he served as a voting member of the FDA Cardio-Renal Advisory Board. Dr. Flack was recently conferred the status of Master by the American College of Physicians (ACP); he also previously served as a member of the ACP Board of Regents. Dr. Flack serves as a consultant to Idorsia.

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About Idorsia

The purpose of Idorsia is to challenge accepted medical paradigms, answering the questions that matter most. To achieve this, we will discover, develop, and commercialize transformative medicines – either with in-house capabilities or together with partners – and evolve Idorsia into a leading biopharmaceutical company, with a strong scientific core.

Headquartered near Basel, Switzerland – a European biotech hub – Idorsia has a highly experienced team of dedicated professionals, covering all disciplines from bench to bedside; QUVIVIQ™ (daridorexant), a different kind of insomnia treatment with the potential to revolutionize this mounting public health concern; strong partners to maximize the value of our portfolio; a promising in-house development pipeline; and a specialized drug discovery engine focused on small-molecule drugs that can change the treatment paradigm for many patients.

Idorsia is listed on the SIX Swiss Exchange (ticker symbol: IDIA).

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