



Media Release March 20, 2024

Ad hoc announcement pursuant to Art. 53 LR

US FDA approves Idorsia's once-daily TRYVIO (aprocitentan) – the first and only endothelin receptor antagonist for the treatment of high blood pressure not adequately controlled in combination with other antihypertensives

- TRYVIO™ (aprocitentan) is indicated for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adult patients who are not adequately controlled on other drugs.
- TRYVIO is the first oral anti-hypertensive therapy which works via a new therapeutic pathway to be approved in almost 40 years.
- Idorsia plans to make TRYVIO available to the millions of patients in the US who are not controlled on other drugs in the second half of 2024.
- Idorsia to host an investor webcast to discuss the approval today, March 20, at 15:00hrs CET.

Radnor, PA – March 20, 2024

Idorsia Pharmaceuticals U.S. Inc. announced today that the US Food and Drug Administration (FDA) has approved TRYVIO™ (aprocitentan) for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adult patients who are not adequately controlled on other drugs.¹ Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions.¹ The recommended dosage of TRYVIO is 12.5 mg orally once daily, with or without food.¹

Jean-Paul Clozel, MD and Chief Executive Officer of Idorsia commented:

“Today, there are millions of Americans whose blood pressure is not well-controlled despite existing therapies. This is a major public health issue leading to a high incidence of cardio- and cerebrovascular events. In order to help address this issue, Idorsia developed aprocitentan, an endothelin receptor antagonist suited to the treatment of these patients. Idorsia conducted an ambitious clinical program in patients remaining hypertensive despite a minimum of three drugs at their optimal dose and sometimes up to four, five, or even six antihypertensives. I'm very proud of the Idorsia team and very happy that physicians will have a new treatment option to treat patients whose blood pressure is not controlled.”

TRYVIO (aprocitentan) is an endothelin receptor antagonist that inhibits the binding of endothelin (ET)-1 to ET_A and ET_B receptors.^{1,2} The effects of ET-1 bear many similarities with the pathophysiology of hypertension,³ and ET-1 is a major driver of aldosterone production.⁴ Until the approval of TRYVIO, no systemic antihypertensive medications targeted the ET pathway,⁵ as approved antihypertensive therapies focus on the regulation of salt and water (diuretics), antagonism of the renin-angiotensin-aldosterone (RAAS) system, reduction of influx of extracellular calcium into the cell (calcium channel blockers), sympatholytic activity (beta blockers, central alpha-agonist agents), or non-selective vasodilatory effects.^{6,7}

TRYVIO was evaluated as a monotherapy in a Phase 2 study in patients with hypertension,⁸ and as an add-on therapy in a Phase 3 study called PRECISION in patients with confirmed resistant hypertension.⁹ In PRECISION, aprocitentan was well tolerated and superior to placebo in lowering blood pressure at week 4, with a sustained effect at week 40.¹⁰

Martine Clozel, MD and Chief Scientific Officer of Idorsia, commented:

“Early on, we realized that endothelin was involved in patients with hypertension, especially in those remaining uncontrolled despite other anti-hypertensive drugs. Since the endothelin pathway was not yet tackled in these patients, we selected aprocitentan, an endothelin receptor antagonist with the ideal properties for use in this condition. We were delighted when we saw the safety and efficacy data with TRYVIO, even on top of multiple antihypertensives, in patients whose hypertension is not adequately controlled. The recognition of its potential with today’s FDA approval is great news for prescribers and patients.”

Michael A. Weber, MD, Professor of Medicine, Division of Cardiovascular Medicine State University of New York, and an investigator in the PRECISION study commented:

“Today, we are not able to reduce blood pressure below recommended levels in at least 10% of the hypertensive patients we treat. As well, it is often patients at high risk of adverse cardiovascular outcomes and typically with comorbidities who pose this challenge. We have had to wait for over 30 years to see the approval of an oral anti-hypertensive agent that works on a new therapeutic pathway, so TRYVIO provides transformational progress in the field of systemic hypertension. It is taken as a single daily oral dose that works in combination with whatever other drugs are being prescribed and without drug-drug interactions in patients with the burden of uncontrolled hypertension. TRYVIO is easy for physicians to prescribe and easy for patients to use.”

Phase 3 clinical study^{1,9,10}

The efficacy of TRYVIO (aprocitentan) was evaluated in a multipart, Phase 3 multicenter study (PRECISION, NCT03541174) in adults with systolic blood pressure (SBP) ≥ 140 mmHg who were prescribed at least three antihypertensive medications. The trial included a placebo run-in period, which was followed by three parts as described below. Prior to the placebo run-in period, all patients were switched to standard background antihypertensive therapy consisting of an angiotensin receptor blocker, a calcium channel blocker, and a diuretic, which was continued throughout the study. Patients with concomitant use of beta-blockers continued this treatment throughout the study.

Following the 4-week placebo run-in period, 730 patients were randomized equally to aprocitentan at either 12.5 mg, 25 mg, or placebo once daily during the initial 4-week double-blind (DB) treatment period (part 1). At the end of 4 weeks, all patients entered the single-blind treatment period (part 2) where they received 25 mg aprocitentan once daily for 32 weeks. At the end of the 32 weeks, patients were re-randomized to receive either 25 mg aprocitentan or placebo, once daily, during a 12-week DB-withdrawal period (part 3).

The primary efficacy endpoint was the change in sitting SBP (SiSBP) from baseline to Week 4 during part 1, measured at trough by unattended automated office blood pressure (uAOBP).

The key secondary endpoint was the change in SiSBP measured at trough by uAOBP from Week 36 (i.e., prior to randomized withdrawal to 25 mg aprocitentan or placebo in part 3) to Week 40.

Patients had a mean age of 62 years (range 24 to 84 years) and 60% were male. Patients were White (83%), African American (11%) or Asian (5%). Approximately 10% were Hispanic. The mean body mass index (BMI) was 34 kg/m² (range 18 to 64 kg/m²). At baseline, 19% of patients had an eGFR 30–59 mL/min/1.73 m² and 3% had an eGFR 15–29 mL/min/1.73 m². At baseline, 24% of patients had a



urine albumin-to-creatinine ratio (UACR) of 30–300 mg/g and 13% had a UACR >300 mg/g. Approximately 54% of patients had a medical history of diabetes mellitus, 31% ischemic heart disease, and 20% congestive heart failure. At baseline, 63% of patients reported taking four or more antihypertensive medications.

TRYVIO 12.5 mg was statistically superior to placebo in reducing SiSBP at Week 4 (part 1). The treatment effect was consistent for sitting diastolic BP (SiDBP).

The persistence of the BP-lowering effect of TRYVIO was demonstrated in part 3 of the trial, in which patients on aprocitentan were re-randomized to placebo or 25 mg aprocitentan following a period during which all patients were treated with 25 mg. In patients re-randomized to placebo, the mean SiSBP increased, whereas in patients re-randomized to 25 mg aprocitentan the mean effect on SiSBP was maintained and was statistically superior to placebo at Week 40. The treatment effect was consistent for SiDBP.

Most of the BP-lowering effect occurred within the first two weeks of treatment with TRYVIO. TRYVIO is not approved for use at a 25 mg dose. The efficacy for the 25 mg aprocitentan dose as measured in the primary end point of change in sitting SBP (SiSBP) from baseline to Week 4 in part 1, was similar to the 12.5 mg dose and thus aprocitentan 12.5 mg is the approved dose.

TRYVIO's BP-lowering effect appeared consistent among subgroups defined by age, sex, race, BMI, baseline eGFR, baseline UACR, medical history of diabetes, and between BP measurement methodologies (uAOBP and ambulatory BP measurements).

The most frequently reported adverse reactions to TRYVIO during the 4-week double-blind placebo-controlled treatment period (part 1) of the PRECISION study were edema/fluid retention and anemia. During the initial 4-week double-blind placebo-controlled treatment period (part 1), 0.8% of patients experienced an adverse reaction of hypersensitivity (i.e., rash, erythema, allergic edema) on TRYVIO compared to no reports in patients treated with placebo. One patient experienced allergic dermatitis requiring hospitalization while receiving aprocitentan 25 mg. TRYVIO is contraindicated in patients who are hypersensitive to aprocitentan or any of its excipients. Use of TRYVIO is contraindicated in pregnancy.

Lowering BP reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes. There are no controlled trials demonstrating reduction of risk of these events with TRYVIO.

Alberto Gimona, MD and Head of Global Clinical Development of Idorsia, commented:

“When designing PRECISION, we did not shy away from including patients who are most at risk of the serious negative consequences of hypertension. In addition, while all patients needed to be on three antihypertensives to join the study, 63 percent of patients were on four or more anti-hypertensives. The study was therefore truly reflective of the real-world patient population whose blood pressure is not adequately controlled on other drugs. TRYVIO demonstrated a clear and consistent effect across all endpoints of blood pressure measurement and in key sub-populations. As a result, TRYVIO brings hope as a novel, effective and well-tolerated treatment option for patients with hypertension not adequately controlled.”



Tosh Butt, President and General Manager of Idorsia US commented:

“The approval of TRYVIO in the US marks another major milestone for Idorsia. With TRYVIO, we've got an innovative medicine with a unique mode of action in systemic hypertension. The team at Idorsia has a deep understanding and rich history in the field of endothelin receptor antagonism. We are eager to provide physicians and patients with a novel medicine working in a new pathway in uncontrolled hypertension that can provide additional blood pressure control. We recognize that the resources required to reach the entire prescribing community could be substantial, so we will carefully craft the TRYVIO launch strategy in the coming months, while preparing to make TRYVIO available during the second half of 2024.”

The team at Idorsia has been working on the research and development of endothelin receptor antagonists for more than 30 years, successfully bringing three other molecules from this class to patients in different indications. ET-1, via its receptors (ET_A and ET_B), mediates a variety of deleterious effects such as vasoconstriction, fibrosis, cell proliferation, and inflammation. In hypertension, ET-1 can cause endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation, and increased aldosterone synthesis.¹

Martine Clozel, MD and Chief Scientific Officer of Idorsia, concluded:

“After more than 30 years working in the field of endothelin science, our research has brought about changes in the treatment paradigm of several cardiovascular diseases. Now we are bringing significant medical progress for patients with systemic hypertension. I am convinced that with the data we have seen, the approval of TRYVIO heralds a new era of endothelin research beyond hypertension, where we intend to investigate the utility of apocitentan for first-in-class applications in new indications.”

TRYVIO REMS

TRYVIO is available only through a restricted program under a REMS called the TRYVIO REMS because of the risk of embryo-fetal toxicity. Prescribers must be certified with the TRYVIO REMS by enrolling and completing training. Pharmacies that dispense TRYVIO must be certified with the TRYVIO REMS.

Important Safety Information

TRYVIO may cause serious side effects, including:

TRYVIO can cause major birth defects if used by pregnant patients and has a BOXED Warning for embryo-fetal toxicity.

- **People who can become pregnant must not be pregnant when they start taking TRYVIO or become pregnant during treatment with TRYVIO or for 1 month after stopping treatment with TRYVIO.**
- **People who can become pregnant should have a negative pregnancy test** before starting treatment with TRYVIO, each month during treatment with TRYVIO, and 1 month after stopping TRYVIO.
- **People who can become pregnant should use acceptable birth control before starting treatment with TRYVIO, during treatment with TRYVIO, and for 1 month after stopping TRYVIO** because the medicine may still be in your body.

People can only receive TRYVIO through a restricted program called the TRYVIO REMS. If you are a person who can become pregnant, your healthcare provider will talk to you about pregnancy testing recommendations and the need to use acceptable birth control, the benefits and risks of TRYVIO, and the need to report suspected pregnancy right away to your healthcare provider.



What is TRYVIO?

TRYVIO is a prescription medicine used to treat high blood pressure (hypertension) in adults who are taking other high blood pressure medicines and whose blood pressure is not well controlled.

Do not take TRYVIO if you are

- pregnant or currently trying to become pregnant.
- allergic to aprocitentan or any of the ingredients in TRYVIO.

Before taking TRYVIO, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have heart failure
- have anemia
- have kidney problems or get dialysis
- are pregnant or plan to become pregnant during treatment with TRYVIO. TRYVIO can cause serious birth defects.
- are breastfeeding or plan to breastfeed. It is not known if TRYVIO passes into your breastmilk. **Do not breastfeed** if you take TRYVIO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

TRYVIO may cause other serious side effects, including:

- **Liver problems.** TRYVIO may cause liver problems. Your healthcare provider should do blood tests to check your liver before starting treatment and as needed during treatment with TRYVIO. Tell your healthcare provider if you have any of the following symptoms of liver problems during treatment with TRYVIO:
 - nausea or vomiting
 - pain in the upper right stomach
 - tiredness
 - loss of appetite
 - yellowing of your skin or whites of your eyes
 - dark urine
 - fever
 - itching
- **Fluid retention.** Fluid retention and swelling are common during treatment with TRYVIO and can be serious. Tell your healthcare provider right away if you have any unusual weight gain, trouble breathing, or swelling of your ankles or legs. Your healthcare provider may treat you with other medicines (diuretics) if you develop fluid retention or swelling.
- **Low red blood cell levels (anemia).** Anemia is common during treatment with TRYVIO and can be serious. Your healthcare provider will do blood tests to check your red blood cells before starting and as needed during treatment with TRYVIO.
- **Decreased sperm count.** TRYVIO may cause decreased sperm counts in males and may affect the ability to father a child. Tell your healthcare provider if being able to have children is important to you.

Your healthcare provider may stop treatment with TRYVIO if you develop certain side effects. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of TRYVIO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

For more information see the Full Prescribing Information including BOXED Warning ([PI](#)) and Medication [Guide](#)).

Notes to the editor

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 16 books. Together with Dr. Suzanne Oparil, he is responsible for the widely used reference volume, Hypertension.

Dr. Weber is the Editor-in-Chief of The Journal of Clinical Hypertension. 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, and continues as a consultant to that Agency. 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 outcomes trials. Dr. Weber serves as a consultant to Idorsia.

References

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Investor webcast

An investor conference call and webcast will be held to discuss the TRYVIO FDA approval. The call will start with presentations by senior management, followed by a Q&A session.

Date: Wednesday, March 20, 2024

Time: 15:00 CET | 14:00 GMT | 10:00 ET

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 US

Idorsia US, an affiliate of Idorsia, is reaching out for more – we have more ideas, we see more opportunities, and we want to help more patients. To achieve this, we will help develop Idorsia into a leading biopharmaceutical company, with a strong scientific core. With commercial operations based outside of Philadelphia, PA, one of densest communities of life sciences talent in the world, we are helping to realize the company's ambition of bringing innovative medicines from bench to bedside. Our goal is to build a commercial footprint that will deliver Idorsia's deep pipeline of products from its R&D engine to the US market – with the potential to change the lives of many patients.

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 and North America – 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 800 highly qualified specialists dedicated to realizing our ambitious targets.

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The above information contains certain "forward-looking statements", relating to the company's business, which can be identified by the use of forward-looking terminology such as "estimates", "believes", "expects", "may", "are expected to", "will", "will continue", "should", "would be", "seeks", "pending" or "anticipates" or similar expressions, or by discussions of strategy, plans or intentions. Such statements include descriptions of the company's investment and research and development programs and anticipated expenditures in connection therewith, descriptions of new products expected to be introduced by the company and anticipated customer demand for such products and products in the company's existing portfolio. Such statements reflect the current views of the company with respect to future events and are subject to certain risks, uncertainties and assumptions. Many factors could cause the actual results, performance or achievements of the company to be materially different from any future results, performances or achievements that may be expressed or implied by such forward-looking statements. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected.