Media Release
April 26, 2024

Ad hoc announcement pursuant to Art. 53 LR

JERAYGO (aprocitentan) recommended for approval in Europe for the treatment of resistant hypertension

- Idorsia receives a positive opinion from the Committee for Medicinal Products for Human Use for JERAYGO™ (aprocitentan) as the first and only endothelin receptor antagonist for the treatment of resistant hypertension in adult patients in combination with at least three antihypertensive medicinal products.
- A CHMP positive opinion is one of the final steps before marketing authorization can be granted by the European Commission – a final decision is expected in approximately two months.

Allschwil, Switzerland – April 26, 2024
Idorsia Ltd (SIX: IDIA) announced today that the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA), adopted a positive opinion for the use of JERAYGO™ (aprocitentan) for the treatment of resistant hypertension in adult patients in combination with at least three antihypertensive medicinal products. The CHMP has adopted a positive opinion for the use of 12.5 mg JERAYGO orally once daily. The dose can be increased to 25 mg once daily for patients tolerating the 12.5 mg dose and in need of tighter blood pressure (BP) control.

Detailed recommendations for the use of JERAYGO will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorization has been granted by the European Commission, expected in approximately two months.

Hypertension is one of the leading causes of cardiovascular disease worldwide, impacting an estimated 1.3 billion people globally.[1] Approximately 10% of these people have uncontrolled BP, despite receiving at least three antihypertensive medications from different classes, at optimal doses and they are categorized in hypertension guidelines[2,3] as having resistant hypertension. Compared with adults whose hypertension is well controlled, adults with uncontrolled hypertension have greater risk of heart attack, heart failure, stroke, end-stage renal disease and death.[4]

Jean-Paul Clozel, MD and Chief Executive Officer of Idorsia commented:
"Uncontrolled hypertension, particularly resistant hypertension, where blood pressure remains uncontrolled despite the use of multiple antihypertensive therapies, affects millions of Europeans and is a major public health issue leading to a high risk of heart attack, heart failure, stroke and renal disease, not to mention the increased risk of death. Idorsia has tackled this need by developing aprocitentan, or JERAYGO, the brand name in Europe, an endothelin receptor antagonist discovered by our team and optimized for the treatment of resistant hypertension. As a result of our efforts, physicians and patients in Europe are one step closer to having a new oral antihypertensive therapy – the first in almost 40 years – that is working via a new therapeutic pathway."

The positive CHMP opinion is supported by a comprehensive clinical and non-clinical development program. Aprocitentan was evaluated as a monotherapy in a Phase 2 study in patients with

hypertension,[11] and as an add-on therapy in a Phase 3 study called PRECISION in patients with confirmed resistant hypertension.[12] In the Phase 3 registration study, PRECISION, aprocitentan showed statistically significant and clinically meaningful reduction in blood pressure (BP) which was maintained for up to 48 weeks when added to a combination of background antihypertensive therapies in patients with resistant hypertension. In PRECISION, aprocitentan was generally well tolerated with no major safety concerns. The most frequent adverse event with aprocitentan was mild-to-moderate edema/fluid retention.

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. Endothelin (ET)-1, via its receptors (ET_A and ET_B), mediates a variety of effects such as vasoconstriction, fibrosis, cell proliferation, inflammation, aldosterone production[7] and is upregulated in hypertension. Aprocitentan is a dual ERA that inhibits the binding of ET-1 to ET_A and ET_B receptors and hence the effects mediated by these receptors.[5] The effects of ET-1 bear many similarities with the pathophysiology of hypertension,[6,8] and the resistance to other antihypertensive drugs in some patients (often with risk factors such as obesity, sleep apnea, older age, kidney failure, type 2 diabetes, and African Americans), can be explained by an endothelin-dependent hypertension[8]. This is now confirmed by the efficacy of aprocitentan in the PRECISION study.

About the Phase 3 PRECISION study (NCT03541174)[12]
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 (SBP) 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 SBP 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. At screening, 63% of all patients who were randomly assigned were prescribed four or more antihypertensive drugs.

Key PRECISION findings[13]
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 (the primary endpoint). 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 (week 40) (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 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 night time 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).

The effect of aprocitentan was consistent across subgroups of age (including patients ≥ 75 years), sex, race (including patients with Black or African American origin), BMI, baseline urine albumin-to-creatinine ratio (UACR), baseline estimated Glomerular Filtration Rate (eGFR) and medical history of diabetes, and was consistent with the effect in the overall population.

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 with aprocitentan was mild-to-moderate edema/fluid retention leading to discontinuation in seven patients during the study. Edema/fluid retention 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).

Regulatory status of aprocitentan

The positive opinion recommending JERAYGO, is a scientific recommendation issued by the EMA's CHMP, which is sent to the European Commission (EC) for the adoption of a decision on an EU-wide marketing authorization. An EC marketing authorization through the centralized procedure is valid in all European Union Member States, as well as the European Economic Area countries Iceland, Liechtenstein and Norway, and Northern Ireland under the Northern Ireland Protocol.

In March, TRYVIO™ (aprocitentan) was approved by the US Food and Drug Administration (FDA).

Notes to the editor

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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 25-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 750 highly qualified specialists dedicated to realizing our ambitious targets.

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