Media Release
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Ad hoc announcement pursuant to Art. 53 LR

Idorsia announces the results of REACT a Phase 3 study of clazosentan in patients following aneurysmal subarachnoid hemorrhage

Allschwil, Switzerland – February 6, 2023
Idorsia Ltd (SIX: IDIA) today announces the initial findings of REACT, a Phase 3 study which investigated the efficacy and safety of clazosentan in preventing clinical deterioration due to delayed cerebral ischemia, in patients following aneurysmal subarachnoid hemorrhage (aSAH). The study did not meet the primary endpoint. The company will fully analyze the efficacy and safety data to understand this unexpected result.

Jean-Paul Clozel, MD and Chief Executive Officer of Idorsia, commented:
"I am very disappointed with the negative result of REACT. The study was based on strong scientific and medical rationale and executed diligently by a committed team of experts at Idorsia and by the investigators. On behalf of everyone at Idorsia, I'd like to thank the investigator teams and expert advisors for their tireless support to conduct this study in such a challenging medical condition."

The company will publish the data and interpretation in scientific literature in due course.

About the REACT study[1] NCT03585270
REACT, a multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study with clazosentan in patients with aneurysmal subarachnoid hemorrhage (aSAH), assessed the efficacy and safety of clazosentan in preventing clinical deterioration due to delayed cerebral ischemia, in adult patients following aSAH. REACT included patients aged 18 to 70 years with World Federation of Neurological Societies grades 1-4 after recovery from the aneurysm-securing procedure and "thick and diffuse clots" on the admission CT scan. REACT randomized 409 patients – treated either with microsurgical clipping or endovascular coiling aneurysm securing procedures – in a 1:1 ratio to receive placebo or clazosentan 15 mg/h. Patients were enrolled in the REACT study at 74 sites in 15 countries across North America and Europe. In general, the standard of care for managing aSAH was allowed, and the administration of nimodipine (oral or intravenous) was permitted if it was routine standard of care at the site.

Notes to the editor

Clazosentan in aSAH[2-4]
An aSAH involves sudden life-threatening bleeding occurring in the subarachnoid space. It is caused by the rupture of an aneurysm – a weak, bulging spot on the wall of a cerebral artery. An emergency procedure (endovascular coiling or microsurgical clipping) is required to secure the aneurysm to prevent rebleeding.

The subarachnoid bleeding and subsequent release of endothelin-1 – a potent vasoconstrictor produced mainly by the neighboring vascular endothelium – can lead to cerebral vasospasm (constriction of arteries in the brain), which usually starts 3 days after aSAH onset and peaks in intensity between 8 and 11 days. This diminishes blood flow to the brain, and about one-third of all aSAH patients consequently experience worsening of their neurological condition. Cerebral vasospasm is one of the leading secondary causes of disability in patients with aSAH.

Clazosentan is a fast-acting, endothelin A (ET_A) receptor antagonist, that Idorsia has developed as a continuous intravenous infusion for the prevention of clinical deterioration due to delayed cerebral ischemia (DCI) in patients following aSAH. Clazosentan is approved for the prevention of cerebral vasospasm, vasospasm-related cerebral infarction, and cerebral ischemic symptoms after aSAH in Japan.

Previous global clinical studies with clazosentan[5-8]

Several studies have built our understanding of the role of clazosentan in preventing cerebral vasospasm. In 2006, results were reported for clazosentan in the prevention of angiographic vasospasm in patients with aSAH. The Phase 2 dose-finding study, CONSCIOUS 1, demonstrated dose-dependent prevention of vasospasm.

This was followed by two Phase 3 studies, CONSCIOUS-2 and CONSCIOUS-3, to assess the effect of clazosentan on the incidence of cerebral vasospasm-related morbidity and all-cause mortality. In 2010, CONSCIOUS-2 showed that the 5 mg/h dose of clazosentan was too low and did not allow a statistically significant treatment effect to be observed, resulting in the premature termination of CONSCIOUS-3. However, an exploratory analysis of the data collected in CONSCIOUS-3 showed that a higher dose of clazosentan (15 mg/h) significantly reduced cerebral vasospasm-related morbidity and all-cause mortality, with a 44% relative risk reduction (p=0.0074). The 15 mg/h dose also significantly reduced the incidence of delayed ischemic neurological deficit (DIND), with a 54% relative risk reduction (p=0.0038). In addition, clazosentan reduced the need for rescue therapy for vasospasm. Clazosentan did not improve long-term clinical outcome in that study.

The studies confirmed the well-documented safety profile of clazosentan, which has now been administered to more than 2000 patients around the world in a controlled clinical setting. The side effects of clazosentan can be managed according to clear protocol guidelines: hypotension can be mitigated using blood pressure control with vasopressors in the ICU, while lung complications (such as pulmonary edema) can be managed by avoiding excessive fluid administration so as to maintain euvolemia.

Key literature

1. Bruder et al, BMC Neurology, 2022
2. Thompson et al, Neurology and Therapy, 2022
3. Chalet et al, Neurology and Therapy, 2023
4. Juif et al, Frontiers in Pharmacology, 2021
5. Vajkoczy et al, J Neurosurg, 2005
6. Macdonald et al, Stroke, 2008
7. Macdonald et al, Lancet Neurology 2011
8. Macdonald et al, Stroke, 2012

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 1200 highly qualified specialists dedicated to realizing our ambitious targets.

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