Media Release
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Idorsia submits NDA for clazosentan to Japanese PMDA

Allschwil, Switzerland – March 1, 2021
Idorsia Ltd (SIX: IDIA) today announced the submission of a New Drug Application (NDA) to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for clazosentan, a fast-acting, selective endothelin A (ET_A) receptor antagonist, for the prevention of cerebral vasospasm, vasospasm-related cerebral infarction and cerebral ischemic symptoms after aneurysmal subarachnoid hemorrhage (aSAH).

The application is supported by replicated results from the Japanese registration program which consisted of two double-blind, randomized, placebo-controlled studies assessing the efficacy and safety of clazosentan in reducing vasospasm-related morbidity and all-cause mortality events in adult Japanese patients following aSAH. Patients were randomized to receive continuous infusion of either 10 mg/hr clazosentan or placebo for up to 15 days following the onset of aSAH. The two studies followed the same design, with one enrolling 221 patients whose aneurysm was secured by surgical clipping and the other enrolling 221 patients whose aneurysm was secured by endovascular coiling.

Satoshi Tanaka, Dr Med Sci. and President of Idorsia Pharmaceuticals Japan, commented:
"The development of clazosentan has taken many years to bring us to the filing of an NDA and we were very fortunate to not be held back by the COVID-19 pandemic in Japan. The team has worked rapidly to analyze the data and prepare the dossier for the PMDA so that we can bring clazosentan to the patients as soon as possible. We will now work together with the authorities through the regulatory process, and in parallel, prepare the scientific publication and the commercial launch which we hope to see in the first half of 2022."

Both studies showed that clazosentan reduced the occurrence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aSAH with statistical significance ($p<0.01$ for both studies). The composite endpoint was defined by at least one of the following: All death / New cerebral infarction due to cerebral vasospasm / Delayed ischemic neurologic deficit due to cerebral vasospasm and adjudicated blindly by an independent committee. The effect of clazosentan on all-cause morbidity and mortality was also significant ($p<0.05$) in a pre-planned analysis of the pooled studies whereas a numerical trend was observed in each study on this endpoint.

The studies confirmed the well-documented safety profile of clazosentan which has now been administered to approximately 2000 patients around the world. In these registration studies in Japanese patients post-aSAH there were no unexpected safety findings. Treatment-emergent adverse events occurring in >5% of the clazosentan group (with a difference of >2% compared to placebo) were vomiting and signs of hemodilution or fluid retention (i.e., hyponatremia, hypoalbuminemia, anemia, pleural effusion, brain and pulmonary edema).

Notes to the editor

Available data in Japanese patients

A Phase 2 study in Japanese and Korean patients showed that 10 mg/hr of clazosentan administered by continuous intravenous infusion significantly reduced vasospasm and vasospasm-related morbidity and mortality events. The results are published in Cerebrovascular Diseases (Fujimura M, et al. Cerebrovasc Dis 2017;44:59–67). On that basis, a registration program was initiated with clazosentan in Japan in May 2016.

About the global registration program "REACT"

In February 2019, Idorsia initiated REACT, a prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study to investigate the efficacy and safety of clazosentan for the prevention of clinical deterioration due to vasospasm-related delayed cerebral ischemia in adult patients following aSAH. The Phase 3 study builds upon the learnings from the previous clazosentan studies to identify patients at high risk of vasospasm and delayed cerebral ischemia, the optimal dose, the best measure to demonstrate efficacy and an optimized patient management guideline to ensure patient safety.

Approximately 400 patients – treated either with microsurgical clipping or endovascular coiling – are being enrolled at approximately 95 sites across 15 countries. Patients are randomized to receive continuous infusion of either clazosentan (15 mg/hr) or placebo prophylactically, on top of local standard of care, for a period of up to 14 days. REACT is enrolling aSAH patients identified as being at high risk of developing vasospasm and subsequent delayed cerebral ischemia because of high-volume hemorrhage, as assessed by CT scan on hospital admission. Patients experiencing asymptomatic cerebral vasospasm, as measured by angiography, within 14 days of aSAH may also be included. Results of the study are targeted for the second half of 2022.

About aneurysmal subarachnoid hemorrhage and cerebral vasospasm

Aneurysmal subarachnoid hemorrhage is a rare condition involving 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. Emergency surgical repair (endovascular coiling or microsurgical clipping) is required to stop the hemorrhage.

The bleeding and the release of a vasoconstrictor (endothelin) by the neighboring vascular endothelium can lead to cerebral vasospasm (constriction of arteries in the brain), usually occurring between 4 and 14 days after aneurysm securing. This diminishes blood flow to the brain, and about one third of patients consequently experience worsening of their neurological condition. Cerebral vasospasm is one of the leading secondary causes of disability and death in patients with aSAH.

The incidence of aSAH is estimated to be between 6 and 9 per 100,000 per year worldwide. Notably, aSAH is a significant problem in Japan, with an incidence at least twice as high as in many other countries of the world.

Approximately 50% of the overall aSAH population present with thick, diffuse blood clots characterized by a large amount of subarachnoid blood on the admission CT scan. These patients have a significantly higher risk of experiencing cerebral vasospasm.

Available clinical data with clazosentan

Several studies have built our understanding of the role of clazosentan in preventing or reversing 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, administered by continuous intravenous infusion, 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), administered by continuous intravenous infusion, 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, 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.

A Phase 2 study in Japanese and Korean patients showed that 10 mg/hr of clazosentan significantly reduced vasospasm and vasospasm-related morbidity and mortality events.

A pilot study evaluating the early effect of clazosentan on reversing established cerebral vasospasm in large proximal cerebral artery segments at 3 hours post initiation suggests that, with early administration, clazosentan has the potential to improve

large-vessel vasospasm. In a post-hoc analysis of the effect of clazosentan on reversing established cerebral vasospasm in the entire cerebral vasculature (including smaller distal vessel segments and the cerebellar arteries), a clearly visible improvement was observed in vessel diameter at 3 and 24 hours.

The studies confirmed the well-documented safety profile of clazosentan, which has now been administered to approximately 2000 patients around the world. The side effects of clazosentan are managed based on 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 aiming to maintain euvolemia by avoiding excessive fluid administration.

Key literature

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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 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 900 highly qualified specialists dedicated to realizing our ambitious targets.

About Idorsia Pharmaceuticals Japan

Idorsia Pharmaceuticals Japan was established, under the leadership of Dr Satoshi Tanaka, in 2018 to conduct clinical development and prepare the commercialization of Idorsia's innovative and promising compounds for patients in Japan.

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