Media Release
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The Journal of Neurosurgery reports impact of clazosentan on cerebral vasospasm-related morbidity and all-cause mortality after aneurysmal subarachnoid hemorrhage

- Results published in the Journal of Neurosurgery show that clazosentan significantly reduced the combined incidence of vasospasm-related morbidity and all-cause mortality post-aSAH with no unexpected safety findings.
- The pivotal studies in Japanese patients supported the approval of Pivlaz™ (clazosentan) in Japan in January 2022, Pivlaz is expected to be available in April 2022.

Allschwil, Switzerland – April 4, 2022
Idorsia Ltd (SIX: IDIA) and Idorsia Pharmaceuticals Japan today announce the publication of "Effects of clazosentan on cerebral vasospasm-related morbidity and all-cause mortality after aneurysmal subarachnoid hemorrhage: two randomized phase 3 trials in Japanese patients" in the Journal of Neurosurgery[1]. Clazosentan, a selective endothelin A (ET_A) receptor antagonist, significantly reduced the combined incidence of vasospasm-related morbidity and all-cause mortality post-aSAH with no unexpected safety findings[1].

Aneurysmal subarachnoid hemorrhage (aSAH) is a sudden, life-threatening bleeding occurring in the subarachnoid space, caused by the rupture of an aneurysm.[2,3] An urgent intervention involving endovascular coil embolization or microscopic clipping is required to prevent rerupture.[2] Clot hemolysis and the release of vasoconstricting agents can contribute to cerebral vasospasm, which typically begins approximately 3 days after aSAH onset, peaks in severity at days 8–11, and resolves by day 21.[4] If untreated, cerebral vasospasm can be a key factor of morbidity and mortality in patients with aSAH.[2] Cerebral vasospasm may lead to delayed ischemic neurological deficit (DIND) in up to 40% of aSAH cases, and half of the patients with vasospasm develop cerebral infarction.[3] With an occurrence of 22.5 per 100,000 person-years, aSAH is 2–3 times more frequent in Japan than in the rest of the world[5] and is therefore a significant problem in this country.

Two prospective, multicenter, double-blind, randomized, placebo-controlled, pivotal Phase 3 studies assessing the efficacy and safety of clazosentan in reducing vasospasm-related morbidity and all-cause mortality events in adult Japanese patients post-aSAH, were conducted in parallel in 57 neuro surgical centers in Japan. Patients were randomized 1:1 to receive continuous infusion of either 10 mg/hr of clazosentan or placebo within 48 hours of the onset of aSAH for up to a cumulative maximum of 15 days after aSAH. Protocols were identical, each study enrolling 221 patients, except for the securing intervention, which was either endovascular coiling (JapicCTI-163369; the "coiling study") or surgical clipping (JapicCTI-163368; the "clipping study").

Both studies showed that clazosentan, compared to placebo, reduced the occurrence of cerebral vasospasm-related morbidity and all-cause mortality events by >50% within 6 weeks post-aSAH with statistical significance ($p<0.01$ for both studies). The composite endpoint, adjudicated blindly by an independent committee, was defined by at least one of the following: Delayed ischemic neurologic deficit (DIND) due to cerebral vasospasm / New cerebral infarction due to cerebral vasospasm / All-cause death. The effect of clazosentan on all-cause morbidity and mortality events within 6 weeks of

aSAH was also significant (p<0.05) in a pre-planned pooled analysis of both studies whereas a numerical trend was observed in each study on this endpoint. The pooled analysis of secondary endpoints indicated that clazosentan decreased the event rates for individual components of the primary composite endpoints. In this analysis, vasospasm-related DIND was reduced by 60% (p = 0.0004) and vasospasm-related new cerebral infarcts were reduced by 55% (p<0.0001).

The studies confirmed the well-documented safety profile of clazosentan which has now been studied in more than 2000 patients around the world. In these two registration studies 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 edema and pulmonary edema).

Teiji Tominaga, M.D., Ph.D., Professor & Chairman, Department of Neurosurgery, Tohoku University Graduate School of Medicine commented:
"The studies we publish in the Journal of Neurosurgery confirm that treatment with clazosentan significantly reduces the consequences that, as neurosurgeons, we all dread after successfully repairing a ruptured brain aneurysm. The results with clazosentan versus placebo were very impressive with a reduction in the risk of vasospasm-related DIND by almost two thirds, a clear reduction in the risk of vasospasm-related new cerebral infarcts by more than half, and – consistent with this effect – the need for rescue therapy, such as balloon angioplasty to open spastic vessels, was reduced by 57%."

Professor Tominaga, concluded:
"Clazosentan is the only innovation in more than 20 years for the prevention of cerebral vasospasm after SAH treatment and the associated new cerebral infarctions and ischemic symptoms. I believe we can change the lives of many patients suffering from this unpredictable and devastating condition."

About PIVLAZ™ (clazosentan) 150 mg

PIVLAZ (clazosentan) is a potent, selective endothelin A (ET_A) receptor antagonist which targets the root cause of cerebral vasospasm. PIVLAZ was designed to inhibit ET-1–mediated cerebral vasospasm by blocking the interaction between ET-1 and the ETA receptor.[7,8]

In January 2022, the Japanese health authorities approved PIVLAZ™ (clazosentan) 150 mg, for the prevention of cerebral vasospasm, vasospasm-related cerebral infarction and cerebral ischemic symptoms after aneurysmal subarachnoid hemorrhage (aSAH) securing. Idorsia Japan is on track to make PIVLAZ available to physicians to start treating patients in April 2022.

Notes to the editor

About REACT – the global registration program for clazosentan

REACT is a Phase 3 study to investigate the efficacy and safety of clazosentan for the prevention of clinical deterioration due to vasospasm-related delayed cerebral ischemia (DCI) in adult patients following aSAH. The Phase 3 study incorporates the learnings from the clazosentan program[9,10,11] to identify patients at high risk of vasospasm and delayed cerebral ischemia, the optimal dose, the best measure to demonstrate efficacy, and an optimized set of patient management guidelines to ensure patient safety. The study aims to randomize approximately 400 patients – treated either with microsurgical clipping or endovascular coiling – at around 95 sites across 15 countries and is expected to conclude around the end of 2022. 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. Clazosentan has been granted orphan drug designation in Europe (2003) and the US (2006), providing an exclusivity period of 10 and 7 years, respectively, after approval.

References

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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.

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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