# Media Release
# November 23, 2020

## Idorsia announces positive results of the two Japanese registration studies with clazosentan

- Clazosentan demonstrates significant reduction of vasospasm-related morbidity and all-cause mortality in patients following aneurysmal subarachnoid hemorrhage (aSAH)
- Clazosentan demonstrates significant reduction of all-cause morbidity and mortality in patients following aSAH in a pre-planned pooled analysis of data from both studies.
- Idorsia Japan to file New Drug Application (NDA) with the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) in the first half of 2021
- Global Phase 3 study "REACT" investigating the efficacy and safety of clazosentan for the prevention of clinical deterioration due to vasospasm-related delayed cerebral ischemia in adult patients following aSAH continues to actively recruit

**Allschwil, Switzerland – November 23, 2020**
Idorsia Ltd (SIX: IDIA) today announced **positive top-line results** of the Japanese registration program investigating clazosentan in adult Japanese patients post-aSAH.

The program 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 study 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.

Both studies demonstrated 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). Cerebral vasospasm-related morbidity and all-cause mortality was blindly adjudicated by an independent committee and defined by at least one of the following: All Death / New cerebral infarction due to cerebral vasospasm / Delayed Ischemic Neurologic Deficit (DIND) due to cerebral vasospasm. Clazosentan showed a numerical reduction of all-cause morbidity and mortality in both studies. The effect of clazosentan on this endpoint was significant ($p<0.05$) in a pre-planned pooled analysis. Further analysis is ongoing including additional pooled analysis of data from both studies.

The studies confirmed the well documented safety profile of clazosentan which has now been administered to over 2000 patients around the globe. In these registration studies in Japanese patients post-aSAH there were no unexpected safety findings. Treatment emergent adverse events occurring >5% in 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).

**Satoshi Tanaka, Dr Med Sci. and President of Idorsia Pharmaceuticals Japan, commented:**
"I want to start by thanking the investigators and their highly skilled staff for the excellent conduct of the study. I also thank the Idorsia Japan team, many of whom have worked on clazosentan for many years and never doubted the benefit that it could bring to the patients, I'm very proud of the whole team. Most of all I want to thank the patients who have taken part in this study and their families, they can all be very proud of being part of this very important advancement for Japanese patients whose lives are so impacted by this devastating consequence of aSAH. My team will now rapidly analyze the study in full detail with the objective to file the NDA with the PMDA in the first half of 2021 and make the full results available through scientific publication."

**Teiji Tominaga, M.D., Ph.D., Professor & Chairman, Department of Neurosurgery, Tohoku University Graduate School of Medicine commented:**
"The clinical consequences of the vasospasm that can follow aSAH can be far reaching, ranging from neurological to other physical problems that can be very severe in nature. aSAH is a significant problem in Japan with an incidence around twice as high as in other countries around the world. This makes the medical need particularly high in Japan and the discovery of a new therapeutic option that can help Japanese patients to overcome the consequences of this devastating condition is important. I have worked with the team to develop clazosentan since the first studies, it is very rewarding to see the years of research come to fruition with these great results."

**Jean-Paul Clozel MD and Chief Executive Officer of Idorsia commented:**
"I would like to congratulate the Japanese team, which under the leadership of Dr. Satoshi Tanaka, has driven the development of clazosentan with such enthusiasm, determination, and scientific excellence. The results are highly clinically relevant and bring significant advancement for patients while confirming a safety profile that should not limit the use of the drug. The data are very impressive and give us further reason to intensify our efforts to finish the recruitment into the global REACT study as soon as possible."

**Jean-Paul concluded on a personal note:**
"Martine and I have worked on the role of endothelin and the potential of endothelin receptor antagonism in aSAH for more than 25 years, with the first publication back in 1993. We had a very clear goal; to help patients following aSAH, who are often young adults and whose lives can be devastated by the terrible consequences of cerebral vasospasm. Thanks to the creation of Idorsia, to the confidence of its investors, and determination of the team, we are now on a good track to bring a major breakthrough therapy to these patients. This is immensely rewarding for all of us."

**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. Completion of the study is targeted for the second half of 2022.

## 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 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 four and fourteen days after aSAH. 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 those that experience aSAH.

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

### Available clinical data with clazosentan

Previously, clazosentan was investigated for the prevention of angiographic vasospasm in patients with aSAH in a Phase 2 study, CONSCIOUS-1, which demonstrated dose-dependent prevention of vasospasm.

This study 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. The dose of clazosentan (5 mg/h) used in CONSCIOUS-2 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, i.e. 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 with a 54% relative risk reduction (p=0.0038). In addition, clazosentan reduced the need for rescue therapy for vasospasm. Clazosentan did not show any effect of clazosentan on long-term clinical outcome.

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A pilot study evaluating the early effect of clazosentan on reversing established cerebral vasospasm in large proximal cerebral artery segments at three hours post-initiation suggests that clazosentan has the potential to improve large vessel vasospasm upon early administration. 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 in vessel diameter at three and 24 hours could be observed.

The above studies have also established an extensive safety profile with over 2,000 patients treated. 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 one of Europe's leading biopharmaceutical companies, with a strong scientific core.

Headquartered in Switzerland - a biotech-hub of Europe - Idorsia is specialized in the discovery and development of small molecules, to transform the horizon of therapeutic options. Idorsia has a broad portfolio of innovative drugs in the pipeline, an experienced team, a fully-functional research center, and a strong balance sheet – the ideal constellation to bringing R&D efforts to business success.

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.

## 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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