Bayer initiates landmark Phase III study program to investigate oral FXIa inhibitor asundexian

- The OCEANIC program will start with two Phase III studies investigating the efficacy and safety of asundexian in prevention of stroke events in patients with atrial fibrillation as well as patients with a non-cardioembolic ischemic stroke or high-risk transient ischemic attack involving up to 30,000 patients
- Bayer drives the development of its FXIa inhibitor, with the goal of offering a potential new class of antithrombotics for improved outcomes for patients using selective coagulation modulation

Berlin, August 28, 2022 – Bayer announced today the start of a Phase III clinical development program “OCEANIC” to investigate the efficacy and safety of asundexian, an oral Factor XIa (FXIa) inhibitor, as a potential new treatment in patients with atrial fibrillation and in patients with a non-cardioembolic ischemic stroke or high-risk transient ischemic attack.

Factor XI is a protein in the blood which is converted into its active enzyme form (Factor Xla) as part of the blood coagulation cascade. Factor XI is a promising and differentiated target for the development of safer anticoagulants because of its critical role in pathological versus normal thrombus formation uncoupling hemostasis from thrombosis. Patients with congenital Factor XI genetic deficiency demonstrate a lower risk for venous thromboembolism and ischemic stroke but rarely have spontaneous bleeding.¹ The OCEANIC program is designed to assess the potential of asundexian to protect patients from pathological thrombus formation without a corresponding increase in bleeding risk aiming to improve the benefit-risk profile compared to current treatment options. FXIa inhibitors that selectively modulate coagulation through FXIa inhibition could represent a
fundamentally new approach to antithrombotic treatment, as they prevent thrombosis yet still allow haemostatic clots that are crucial to repair injury.

The initiation of the OCEANIC program is based on the data from the Phase II PACIFIC program. The PACIFIC-STROKE\textsuperscript{2} and PACIFIC-AMI\textsuperscript{3} Phase IIb trials compared the safety and efficacy of asundexian with placebo in patients following acute non-cardioembolic ischemic stroke or acute myocardial infarction (AMI), respectively. Both trials showed consistent safety results for asundexian comparable to placebo arm, regardless of background therapy. The data from the completed PACIFIC Phase IIb clinical trial program, including previously published data from the PACIFIC-AF\textsuperscript{4} (atrial fibrillation) study, further support the hypothesis that asundexian may reduce the risk of thrombotic events without significantly impacting the risk of bleeding.

“Concerns regarding bleeding risk result in the fact that, currently, many patients are treated sub-optimally or not at all”, said Dr. Ashkan Shoamanesh, Associate Professor of Medicine (Neurology) at McMaster University. “In the PACIFIC trials, we saw encouraging bleeding data, suggesting that asundexian may prevent thromboembolic events without a corresponding increase in bleeding risk. If confirmed, asundexian could offer a potential new therapy and help improve patient care.”

“We have had significant advances for our patients requiring anticoagulation with the introduction of the direct oral anticoagulants. But we still have patients who do not get the therapy, or for whom there is a need for alternative treatment options in thrombosis prevention,” said Manesh Patel, Richard S. Stack Distinguished Professor, Chief of the Division of Cardiology and Co-Director of the Heart Center at Duke University. “The Phase III OCEANIC program is the essential next step to generate more data for asundexian as a potential new treatment option for this large disease area.”

“With deep experience and disease understanding, Bayer is particularly strong in the field of anticoagulation and has made significant contributions to the lives of over 100 million patients. Focusing on Factor Xla inhibition, we are striving for another paradigm shift to investigate a new class of antithrombotics with the potential of an improved benefit-risk profile compared to current treatment options,” said Christian Rommel, Member of the Executive Committee of Bayer AG’s Pharmaceutical Division and Head of Research and Development. “The underlying science of FXIa and the phase II data especially supporting the safety of asundexian make us confident to move the investigational
compound forward into Phase III addressing significant therapeutic areas. OCEANIC is one of the largest Phase III endeavours Bayer has undertaken so far. Our clear goal is to develop a new treatment option to prevent thrombotic events.”

The OCEANIC Phase III clinical development program will start with two large multinational studies, OCEANIC-AF and OCEANIC-STROKE, expected to enroll up to 30,000 patients in over 40 countries.

OCEANIC-AF will test asundexian against apixaban in patients with atrial fibrillation. The primary objective of OCEANIC-AF is to determine the effects on prevention of stroke and systemic embolism and, in addition, to show a lower risk for bleeding in patients receiving asundexian when compared to patients receiving apixaban. The first patients are expected to be enrolled later this year.

OCEANIC-STROKE will be a placebo-controlled study on top of standard of care antiplatelet therapy in patients after a non-cardioembolic ischemic stroke or high-risk ischemic attack. The primary objective of the Phase III study OCEANIC-STROKE is to show a lower risk for ischemic stroke in comparison to placebo, without a significant increase in bleeding risk. By selectively modulating coagulation, the once-daily oral FXIa inhibitor asundexian is being investigated as a potential new treatment option in thrombosis prevention.

**About the PACIFIC-STROKE trial**

PACIFIC-STROKE was a randomized, placebo-controlled, double-blind parallel-group, Phase IIb dose-finding trial to evaluate the safety and efficacy of asundexian in patients following an acute non-cardioembolic ischemic stroke. The trial objectives were to evaluate the dose response for efficacy and the bleeding profile of asundexian in comparison to placebo on top of single (SAPT) or dual (DAPT) antiplatelet therapy in patients following acute non-cardioembolic ischemic stroke. The primary efficacy endpoint was the composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI and the primary safety endpoint was ISTH major bleeding and clinically relevant non-major bleeding. 1808 patients participated in the trial at 196 sites and 23 different countries. All patients had to start trial treatment within 48 hours after the onset of the symptoms and continued treatment for 26 to 52 weeks. Patients were given asundexian 10 mg, 20 mg, or 50 mg oral tablets or placebo once daily on top of SAPT or DAPT. Asundexian demonstrated comparable safety versus placebo arm when given on top of
standard of care antiplatelet therapy. Though not powered to show efficacy, the trial generated data on prevention of recurrent ischemic stroke events. The PACIFIC-STROKE trial results have been accepted in a peer-reviewed journal.

**About the PACIFIC-AMI trial**

PACIFIC-AMI was a multi-center, randomized, placebo-controlled, double-blind parallel-group, Phase IIb dose-finding trial to evaluate the safety and efficacy of asundexian in patients following an AMI. The trial compared asundexian 10 mg, 20 mg or 50 mg oral tablets taken once a day versus placebo on top of standard of care dual antiplatelet therapy (DAPT). The primary efficacy endpoint was the composite of CV death, myocardial infarction (MI), stroke and stent thrombosis and the primary safety endpoint was Bleeding Academic Research Consortium (BARC) bleeding definition type 2, 3 and 5. 1601 patients were randomized into the trial across 157 sites and 23 countries. All patients were initiated on treatment within 5 days of hospitalization for the index AMI event and continued treatment for 26 to 52 weeks. Asundexian was well-tolerated with comparable safety data, including bleeding, versus the placebo arm when combined with dual antiplatelet therapy (DAPT). The trial was not powered to test for differences in thrombotic events. The PACIFIC-AMI trial results were simultaneously published online today in the journal *Circulation* (August 28, 2022).

**About the PACIFIC-AF Trial**

PACIFIC-AF was a randomized, double-blind Phase II dose-finding study, comparing asundexian 20 mg or 50 mg once-daily with apixaban twice daily in patients with AF and a CHA\textsubscript{2}DS\textsubscript{2}-VASc score ≥2 if male or ≥3 if female, with increased bleeding risk. The primary endpoint was the composite of major or clinically relevant non-major bleeding. At both 20 mg and 50 mg doses, asundexian resulted in significantly lower rates of bleeding compared with apixaban (incidence proportion of 0.33 for pooled doses), with near complete in-vivo FXIa inhibition. This trial was not powered to discern or test differences in the rates of thrombotic events.

**About the FXIa Clinical Trial Program**

The PACIFIC Phase IIb clinical trial program consisted of three Phase IIb studies, each one focusing on one of the following medical conditions: atrial fibrillation (irregular heartbeat), a recent non-cardioembolic ischemic stroke or a recent acute myocardial infarction (heart attack). The PACIFIC clinical trials comprised part of the broadest Phase IIb FXIa program in the world, involving more than 4,000 patients to date. The program
continued the legacy of Bayer’s rivaroxaban program, the largest and most extensive research program ever conducted in the thrombosis space and delivers on Bayer’s commitment to address unmet needs in a growing range of underserved cardiovascular patient communities.

More information about these trials is available at http://www.clinicaltrials.gov/. The National Clinical Trial numbers for these studies are PACIFIC-STROKE (non-cardioembolic ischemic stroke) NCT04304508, PACIFIC-AMI (myocardial infarction) NCT04304534 and PACIFIC-AF (atrial fibrillation) NCT04218266.

About Asundexian and FXIa Inhibitors
FXIa inhibition specifically targets a protein involved in pathological thrombus formation but leaves the pathway involved in physiological healing of vessel wall injuries intact. By selectively modulating the coagulation system, asundexian may offer the potential to prevent events like stroke and acute myocardial infarction (AMI) without a corresponding increase in bleeding risk. Asundexian is currently being evaluated as a potentially improved treatment option in thrombosis prevention. Asundexian is a once-daily, oral investigational agent and has not been approved by any health authority for use in any country, for any indication.

About Atrial Fibrillation
AF is the most common sustained cardiac rhythm disorder. In AF, the upper chambers (atria) of the heart contract irregularly.5 As a result, the atria do not empty completely, and blood does not flow properly, potentially allowing blood clots to form. These blood clots can break loose and travel to the brain, resulting in a stroke.6

About Stroke
Stroke is the second most common cause of death worldwide. Strokes can be classified into two major categories: haemorrhagic stroke and ischemic stroke. 85% of all strokes are ischemic strokes, caused by an interruption of blood supply to the brain due to a blockage e.g., a blood clot. When the blood cannot reach the brain, brain cells die due to lack of oxygen. Stroke may result in severely restricted movement, paralysis, loss of speech or vision, which may be permanent, or even death.
**About Bayer**

Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. Its products and services are designed to help people and the planet thrive by supporting efforts to master the major challenges presented by a growing and aging global population. Bayer is committed to driving sustainable development and generating a positive impact with its businesses. At the same time, the Group aims to increase its earning power and create value through innovation and growth. The Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2021, the Group employed around 100,000 people and had sales of 44.1 billion euros. R&D expenses before special items amounted to 5.3 billion euros. For more information, go to www.bayer.com.

**Contact for media inquiries:**

**Anne Jorgal, phone +49 30 2215-41592**

Email: anne.jorgal@bayer.com

**Pamela Cohen, phone +49 30 2215-41587**

Email: pamela.cohen@bayer.com

**Contact for investor inquiries:**

**Bayer Investor Relations Team, phone +49 214 30-72704**

Email: ir@bayer.com

www.bayer.com/en/investors/ir-team

Find more information at https://pharma.bayer.com/

Follow us on Facebook: http://www.facebook.com/bayer

Follow us on Twitter: @BayerPharma

**Forward-Looking Statements**

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer’s public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.
References
2. Study to Gather Information About Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following a Recent Non Cardioembolic Ischemic Stroke Which Occurs When a Blood Clot Has Formed Somewhere in the Human Body (But Not in the Heart) Travelled to the Brain. (PACIFIC-STROKE), https://www.clinicaltrials.gov/ct2/show/NCT04304508
3. Study to Gather Information About the Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following an Acute Heart Attack (PACIFIC-AMI), https://www.clinicaltrials.gov/ct2/show/NCT04304534