

Bayer AG – Investor Relations

Asundexian Investor Webinar

29 August 2022

Welcome

Oliver Maier

Head of Investor Relations, Bayer AG

Good afternoon and good morning. It's a pleasure to be with you today and I welcome you to our next webinar. This time it is for our Pharma division, again, as the focus will be on our pipeline candidate asundexian. As we hope to convey you in this webinar, clinical and pre-clinical data of asundexian strongly confirm that it may provide a new promising therapeutic option to further advance innovative medicines in the treatment of cardiovascular diseases, building on Bayer's strong heritage and decades of market expertise in this field.

Following the data presentation of the PACIFIC-AF study at the American Congress of Cardiology in April this year, the study results of PACIFIC-STROKE and PACIFIC-AMI, two Phase 2b trials that were run to examine the safety of asundexian and to deliver dosing-relevant information to pursue its further clinical development, have been released at the 70th Congress of the European Society of Cardiology yesterday. We are more than happy that two of the investigators who participated in these studies, Ashkan Shoamanesh, who was an investigator in PACIFIC-STROKE, and John Eikelboom, who was part of PACIFIC-AMI programme, were able to make themselves available for today's webinar. A very warm welcome again, gentlemen, to the webinar today. Ashkan and John will be sharing the results of these studies with you today. In addition, Manesh Patel, one of the investigators of PACIFIC-AF, will give a recap of the results from this study in a pre-recorded presentation.

But before going into the results of PACIFIC study programme in detail, Christian Rommel, our Head of R&D at Pharma, will start with a brief introduction of today's treatment options in cardiovascular diseases, the leading role that Bayer plays in that field and asundexian's potential. Following the three presentations of the study data, Christoph Koenen, our Head of Clinical Development and Operations, will summarise the key findings of the PACIFIC study programme and provide an update on the further clinical development of asundexian.

Today's webinar is scheduled for about one hour. It's also my great pleasure to have Stefan Oelrich, the President of Bayer's Pharmaceuticals Division, joining our Q&A session today. Instructions how to raise your questions are available in the Zoom chat and I'll also remind you later on again.

Before we begin, I would bring your attention to the forward-looking statements included in the materials today and currently on the screen.

[See disclaimer](#)

With that, I'll hand the call over to Christian.

RESTRICTED

Factor XIa Inhibition – Striving to Go Beyond Limits

Christian Rommel, Ph.D.

Head of R&D, Bayer Pharmaceuticals

Thank you, Oliver, for the introduction and welcome everybody also from my side. We are excited to give you an update on our oral Factor XIa candidate asundexian today, a molecule that has the potential to overcome the limits of today's options in the treatment of major cardiovascular diseases.

Cardiovascular diseases still are among the two biggest killers in terms of number of deaths worldwide, and cardiovascular events can change the lives of patients and their families overnight. With our more than 150-year heritage in developing health solutions, our therapies have improved the lives of people impacted by cardiovascular diseases across a broad range, including atrial fibrillation, myocardial infarction, coronary artery diseases, pulmonary hypertension and, most recently, with Kerendia chronic kidney disease.

In the space of anticoagulation therapies, significant progress has been achieved since the beginning in the first half of the past century. After decades of use of heparin and vitamin K antagonists, direct thrombin inhibitors and direct Factor Xa inhibitors – the so called DOACs – define the treatment standard today, and Bayer is a world-leading expert and innovator in that field. Following its approvals in 2008 to prevent venous thromboembolism and in 2011 to prevent stroke in atrial fibrillation, Xarelto has been approved to treat a wide range of further thrombotic disorders over time, with more than 100 million patients being treated to date world-wide.

When talking about strokes, nearly 90% of these events are ischemic and occur when a vessel supplying blood to the brain is obstructed. Around 20% of ischemic strokes are of cardioembolic nature, caused by the occlusion of cerebral vessels with debris from a cardiac source, while around 75% are of non-cardioembolic source. About 9 million patients are diagnosed with non-cardioembolic stroke in the seven key markets and typically treated with single or dual-antiplatelet therapy. For cardioembolic stroke, it is expected that it affects around 3% of the entire population and 13 million patients in seven key markets by 2030. Today, patients with cardioembolic stroke typically receive DOACs or vitamin K antagonists as standard therapy.

Despite major advances in clinical science, many people continue to be at risk of preventable stroke due to suboptimal treatment. As a consequence, there still remains a considerable unmet medical need in stroke management among all stakeholders. First and foremost of course, from the patients' perspective, there is an unmet need for stroke protection that, and this is what they fear most, comes without bleeding increase. In fact, they would additionally be interested in anti-thrombotics that further reduce patient-relevant bleeding.

From the healthcare providers' point of view, there is a desire for improved efficacy and safety versus DOACs. Also, HCPs still struggle, among others, with frail, elderly or multi-morbid patients because of bleeding risk. And finally, payers very much care about safety in patients that are currently not receiving OACs or reduced dose DOACs due to a history of bleeding or renal impairment. In addition, they are looking for improved outcomes in patients who are treated with DOACs, but are at high risk of bleeding events.

Our ambition at Bayer is to overcome these limits of today's treatments. We are striving to establish a superior standard of care with a new, first-in-class therapy that aims to mark a significant advance in patient care. Key is the reduction of the incidence of preventable cardiovascular events while delivering a minimised bleeding risk.

To understand what this means from a mode of action perspective let's have a quick look into the general aspects of anticoagulation pathway and regular haemostasis and physiology. Without an anticoagulant we have normal biological processes that lead to a coagulation cascade, activation and haemostasis, and a beneficial clot formation. However, unfortunately, sometimes this process gets over-activated and leads to a pathologic thrombus that can further lead to downstream heart attacks, strokes or limb events.

Commonly used anti-coagulants produce therapeutic anti-thrombotic effects either by inhibiting thrombin or Factor Xa, or by lowering the plasma levels of the precursors of these key enzymes in this cascade. However, these drugs do not distinguish between thrombin generation contributing to thrombosis and thrombin generation required for haemostasis. Thus, anti-coagulants increase bleeding risk, and many patients who would benefit from therapy go untreated because comorbidities may expose them to an unacceptable risk for haemorrhage.

Blood coagulation Factor XI has emerged as a promising target for new anti-thrombotics. As the Factor XI pathway contributes to thrombus formation to a greater extent than to normal haemostasis, pharmacological inhibition of this coagulation factor may offer the possibility of anti-coagulation therapies with lower bleeding risk. The idea behind Factor XI inhibition is that Factor XI activation happens from contact activation after that initial thrombus starts to form and then leads to that amplification. So, by inhibiting Factor XI, the hope is that we will prevent thrombin amplification and pathologic thrombus formation while still preserving the tissue factor pathway that produces thrombin and still leads – ensures that beneficial clots or haemostasis in hopes of uncoupling haemostasis from thrombosis.

Looking into what we know today, there is strong human genetic, pre-clinical and clinical evidence that supports Factor XIa inhibition as a target. Hereditary deficiency of Factor XI is known as haemophilia C. It is generally associated with a relatively mild-to-moderate bleeding phenotype compared with haemophilia A or B. In fact, Factor XI-deficient individuals – I referred already to human genetics. Factor XI-deficient individuals rarely suffer from spontaneous bleeding, and epidemiological studies suggest that Factor XI deficiency confers reduced risk of thrombotic disorders.

These epidemiological findings are supported by the fact that Factor XI-knockout mice are protected from thrombosis while no profound bleeding phenotype is observed. In addition, as was confirmed by in vivo animal models, inhibiting Factor XI resulted in strong anti-thrombotic effects while bleeding time even at a very high dose or on top of dual-antiplatelet therapy did not increase.

And even more important, also clinical studies showed that various Factor XIa inhibition candidates were well tolerated, efficacious and came with lower bleeding.

Supported by such lines of evidence, targeting Factor XI may serve as a powerful route to new anti-thrombotics that may be associated with less bleeding risk than currently available options. However, it has long been a challenge to identify potent Factor XIa inhibitors with a pharmacokinetic profile suitable for oral administration.

This is where asundexian comes into play. It is a small molecule with a half-life between 14 and 17 hours in the human body and a renal elimination rate of about 15%. Asundexian has shown to be well-tolerated in Phase 1 trials and to achieve dose-dependent Factor XIa inhibition with no interaction with clopidogrel regarding bleeding time. It does not inhibit or induce cytochrom P450

3A4 nor is it impacted by food or pH modulating drugs. All its characteristics are independent from age or sex. In a nutshell: asundexian is a really fine, well-behaving small molecule.

In parallel to the development of asundexian we also advanced the analytical methods to determine Factor XI activity in patients. Today's standard assay aPTT builds on the measurement of activated partial thromboplastin time, a process that starts with contact activation in the human plasma as shown on the left hand side of the slide. Following a multi-step biochemical pathway, the time between activation and clot formation can be correlated to Factor XIa activity. Our so-called AXIA assay also starts with contact activation in human plasma but instead of assessing the time of a multi-step biochemical pathway it determines Factor XIa activity via fluorometric detection of a substrate that is sensitive to Factor XIa concentrations.

Based on these results from pre-clinical and Phase 1 studies, we've started the PACIFIC programme to evaluate asundexian across three separate potential clinical indications around two and a half years ago. PACIFIC-AF evaluated asundexian compared to apixaban in around 750 patients. PACIFIC-STROKE evaluated three doses of asundexian in patients with stroke compared to a single or dual-antiplatelet therapy and placebo. And in PACIFIC-AMI, again three doses of asundexian have been studied in patients with acute myocardial infarction.

We will now be sharing the results of these three studies with you. Professor Patel will start with a pre-recorded presentation on the PACIFIC-AF data before Professor Shoamanesh presents PACIFIC-STROKE and Professor Eikelboom the results from PACIFIC-AMI.

Thank you very much. Oliver, I will hand over back to you.

Oliver Maier

Thank you, Christian. I think the video is going to get started now.

Main Results of the PACIFIC-AF Trial

Manesh R. Patel, M.D.,

Duke Clinical Research Institute, Duke University; Coordinating Principal Investigator of PACIFIC-AF

On behalf of the PACIFIC-AF investigators it's my honour to present to you the PACIFIC-AF results. These results were presented at the American College of Cardiology earlier this year and published in *The Lancet*.

The PACIFIC-AF study was a randomised, active comparator, double blind, double dummy, parallel group dose-finding study, a Phase 2 study evaluating asundexian compared to apixaban in patients with atrial fibrillation.

Around 750 patients with atrial fibrillation were randomised to one of three doses: asundexian 50mg, asundexian 20mg and the third arm was apixaban dosed as per usual approved dosing. These atrial fibrillation patients received one of those three therapies in a blinded fashion for 12 weeks, and at the end of the study they had a two-week post-study drug observation period. The primary safety endpoint of this study was bleeding as assessed by ISTH major and non-major clinically relevant bleeding.

We also quantified Factor XI using a proprietary Factor XI inhibition assay, and we looked at exploratory efficacy, endpoint stroke, systemic embolism, cardiovascular death and MI. However, given the size and the duration of this study, the primary objective of PACIFIC-AF was to evaluate the oral Factor XI inhibitor asundexian when compared to apixaban and see if that led to a lower incident of bleeding in patients with atrial fibrillation.

Now the assay was performed in around 220 patients per arm and was studied at four weeks when patients were on the study drug. The Factor XI activity inhibition data were really important also. We were able to see with trough and peak dosing that the 50mg dose of asundexian had near-complete inhibition of Factor XI, with less than 10% of any activity in the lower level of quantification at 3.7, and that the 20mg dose of asundexian again had over 80% inhibition of Factor XI, near 90% at peak.

The primary outcome of the study, the safety and bleeding outcomes, were important in that they showed that there was no major ISTH major bleeding seen in any treatment arm. However, when apixaban was compared to both doses and pooled doses of asundexian for ISTH major bleeding or clinically relevant non-major bleeding, minor bleeding or all bleeding consistent findings were seen, and those showed that the incidence ratio was significantly reduced when the pooled dosing of asundexian was looked at or the 50mg dosing of asundexian was looked at, with over 50% less bleeding in both of those analyses. The drugs were well tolerated with similar rates of adverse events. The exploratory efficacy findings showed a small number of events, less than 10, with no significant findings across any since they were so small. This was expected so no conclusion could be drawn regarding efficacy.

In summary, asundexian is a small oral Factor XI inhibitor that was well-tolerated in a Phase 2 trial of 750 patients with atrial fibrillation. There were significantly lower bleeding rates that were seen in patients randomised to either dose of asundexian when compared to apixaban. It does seem that Factor XI inhibition is a promising strategy to prevent pathologic thrombi, while minimising the bleeding in patients with atrial fibrillation. Thank you for listening to the PACIFIC-AF trial.

Oliver Maier

Thanks to Manesh for his crisp recap. Professor Shoamanesh, are you ready to continue with PACIFIC-STROKE, please? That would be very nice.

Main Results of the PACIFIC-STROKE Trial

Ashkan Shoamanesh, M.D.

McMaster University in Hamilton, Canada; Investigator of PACIFIC-STROKE

Sure, thank you, Mr Maier, and hello to everyone. I'm Ashkan Shoamanesh. I'm an associate professor of neurology at McMaster University as well as a stroke neurologist, and I'm very pleased to be presenting the primary results of the PACIFIC-STROKE trial on behalf of the PACIFIC-STROKE steering committee and its investigators.

The objectives of PACIFIC-STROKE were two, one, assess the dose-response of three different dosages of asundexian compared to placebo on the primary efficacy outcome, and separately to evaluate the incidence of the primary safety outcomes to determine the dosage that is most efficacious and safe for testing in a Phase 3 trial.

Our primary efficacy outcome was the incidence of symptomatic ischemic stroke or covert brain infarction detected on MRI at six months following a non-cardioembolic ischemic stroke for each of the different doses of asundexian tested and placebo. Our primary safety outcome was the composite of the International Society of Thrombosis and Haemostasis-defined major bleeding and clinically relevant non-major bleeding pooled across all asundexian doses and compared to placebo. Lastly, a primary analysis was a dose response of the effect of asundexian on the primary efficacy outcome at six months.

PACIFIC-STROKE was a prospective, randomised, double blind, placebo-controlled Phase 2 dose-ranging study where patients with non-cardioembolic ischemic stroke presenting within 48 hours of symptom onset, who were intended to be treated with antiplatelet treatment, were randomly assigned to three different doses of asundexian, 10, 20 and 50mg daily or matching placebo. All participants were required to undergo an MRI at baseline either prior to or up to 72 hours following randomisation and then again at six months or end of study treatment. Total duration of treatment was six to 12 months, and in total we enrolled 1,808 patients between June 2020 and July 2021 at close to 200 sites in 23 countries.

Of the 1,808 patients randomised, 22 individuals, or 1%, never received study drug, leaving 1,786 patients who started the treatment phase, and these 1,786 patients contributes to our on treatment or treatment emergent safety analyses. However, all 1,808 patients contributed to our intention to treat primary efficacy analysis. There was also 11% of the residual patients, who were 205 individuals, who discontinued study drug and did not complete the treatment phase, and that was either because of a new diagnosis of AF which mandated transition to an oral anticoagulant agent, withdrawal or consent, loss of follow up or death. At end study there were 369 individuals who did not have an adequate MRI to report the outcome of covert brain infarction. In these individuals, unless they actually had a symptomatic ischemic stroke to fulfil the primacy efficacy outcome, the outcome of covert brain infarction was essentially derived from standard algorithm or imputed due to standard algorithm.

All baseline characteristics and stroke characteristics were well-balanced between the treatment arms. Overall in the population the mean age was 67, and 34% were female. 83% of participants self-identified as being of white race and 15% of Asian race. Hypertension was prevalent in 77% and diabetes in 28%, and 16% of the population had a prior stroke or TIA. The mean hours from qualifying stroke to randomisation was 36, and the local site investigator characterised or categorised the qualifying stroke sub-type as being either due to large artery atherosclerotic disease in 18%, small vessel occlusion in 45% or cryptogenic in 35%. Our participants who underwent vascular imagining, a third of the population had some degree extra-cranial or intra-cranial atherosclerotic disease identified. The mean NIH stroke scale was three, so this was a mild severity of stroke population. 12% underwent thrombolysis for their index stroke and 43% of the population had initial treatment with dual-antiplatelet therapy following randomising for a mean duration of 70 days.

In our primary efficacy analysis, we did not observe a dose response with asundexian for the composite outcome of recurrent symptomatic ischemic stroke or covert brain infarcts on MRI at six months. This outcome occurred in 19% of those assigned to placebo, 19% of those assigned to asundexian 10mg daily, 22% of those assigned to asundexian 20mg daily and 20% of those assigned to asundexian 50mg daily.

However, this seemed to have – this lack of effect seemed to have been driven by complete lack of effect on covert brain infarcts on MRI at six months. This sub-clinical type of brain infarction accounted for three quarters of all our primary outcomes, and in 70% of cases these were small sub-cortical infarcts that were deemed to be due to cerebral small vessel disease. There's good

biological rationale why patients with this type of ischemic stroke or brain infarction would not respond to Factor XI inhibition.

On the other hand, when looking at the more clinically relevant component of our primary efficacy outcome, that being symptomatic ischemic stroke recurrence, there was a noticeable trend, with a 20% risk reduction in this outcome at total study follow-up of 10.6 months with asundexian 50mg daily versus placebo. We did not notice any substantial reduction in any of our other pre-specified secondary outcomes, such as any recurrent stroke, the composite of ischemic stroke, vascular death, or MI or all-cause mortality.

Interestingly, in post-hoc secondary analysis we did see a very large effect size with asundexian 20mg daily and asundexian 50mg daily on the outcome of transient ischemic attack, with both of these dosing regimens resulting in an 82% relative risk reduction in this outcome. When looking at the composite outcome of recurrent ischemic stroke and TIA, we did notice a dose-dependent reduction in this composite outcome, with it occurring in 8.3% of those assigned to placebo and being reduced to 7.7% in those receiving asundexian 10mg daily, 6.2% in those receiving asundexian 20mg daily and 5.4% in those receiving asundexian 50mg daily leading to a 36% relative risk reduction in this composite outcome, with the highest dose of asundexian 50mg. This was statistically significant.

In addition, based on our previously published trial, the COMPASS trial, where patients advanced systemic atherosclerotic disease derived net benefit and robust ischemic stroke prevention with dual pathway inhibition by combining anticoagulants, and in that case it was vascular dosing of Factor Xa inhibitor, rivaroxaban 2.5mg twice daily combined with aspirin, we were very interested in looking at pre-specified sub-groups that had atherosclerosis and assessing whether there was any heterogeneity in the treatment effect in these particular sub-groups of interest.

Indeed, when looking at patients that were characterised as having had their qualifying stroke due to large artery atherosclerotic disease, we did notice a more robust reduction in the composite outcome of ischemic stroke and TIA, with this outcome being reduced from 16% in individuals assigned to placebo to 9% in those assigned to asundexian 50mg daily, leading to a robust 44% reduction in this outcome in the sub-group, and even more so in patients that had any degree of extra-cranial or intra-cranial atherosclerotic disease identified in vascular imaging, this outcome was reduced from 8% in the placebo arm to 3% in the asundexian 50mg daily arm, leading to a 61% relative risk reduction in this combined outcome, and this was statistically significant.

Importantly, we did not see any associated increase, or statistically significant increase, in major bleeding or intra-cranial bleeding with asundexian treatment when used on top of antiplatelet therapy in this population. Our primary safety analysis, when combining all major or clinically relevant non-major bleeding events in patients assigned to any asundexian dose, this outcome occurred in 3.9% of those treated with asundexian versus 2.4% of those treated with placebo, and this was not statistically significant. Also, when we looked at the outcome of all bleeding there was really even no numerical suggestion of any increase and treatment resulted in similar events of all bleeding across the board.

The bleeding outcome that is of greatest interest to stroke neurologists, particularly when initiating an anticoagulant early following an ischemic stroke and on top of antiplatelet therapy is that of haemorrhagic transformation, where bleeding into the vulnerable brain tissue that's been infarcted, and there was absolutely no suggestion of either mild or more severe haemorrhagic transformation with asundexian treatment versus placebo in this population.

To conclude, in this Phase 2 trial, inhibition of Factor XIa with asundexian did not reduce the composite covert brain infarction or ischemic stroke, and no dose response could be shown in patients with acute non-cardioembolic ischemic stroke. This seemed to be driven by lack of effect

in covert brain infarction sub-clinical events that are largely due to small vessel disease, and again there are good reasons and previous literature to suggest that this stroke sub-type would not have benefited or would be less likely to benefit from Factor XI inhibition.

However, we did notice a dose-dependent effect on the composite outcome of symptomatic ischemic stroke and TIA, both clinical outcomes, and this was particularly robust in patients receiving asundexian 50mg daily and in sub-groups with underlying atherosclerotic disease. These benefits were seen without an associated increase in the risk of major intra-cranial bleeding with asundexian treatment.

Overall, we were very excited by these promising results from this Phase 2 trial and hope to validate them in an adequately powered Phase 3 trial to be able to develop a new treatment paradigm for secondary stroke prevention, where we can reduce the risk of stroke recurrence without compromising safety.

That concludes my portion of this talk, and I will hand it over to John Eikelboom who will present the results of the PACIFIC-AMI trial.

Main Results of the PACIFIC-AMI Trial

John Eikelboom, M.D.

McMaster University in Hamilton, Canada; Investigator of PACIFIC-AMI

Thank you so much, Ashkan. I'm really delighted to be able to share with you the main results of the PACIFIC-AMI trial on behalf of the steering committee and investigators.

This is the third Phase 2 trial of asundexian, and the objective was to evaluate the safety and explore the efficacy of the same three doses of asundexian tested in the stroke trial, but now in patients with acute myocardial infarction. Importantly, in this trial all patients were treated with dual-antiplatelet therapy. This was a prospective trial. It was blinded, very rigorously performed. 1,600 patients were enrolled. The four arms were asundexian 10, 20 and 50mg once daily and the fourth arm was placebo.

There are three important analyses that emerge from this trial. The first is the effect of asundexian on Factor XIa inhibition, using the important assay that Bayer has developed. Factor XIa inhibition was measured at trough and at peak approximately four weeks after enrolment.

The second set of analyses, the main clinical analyses, were on safety. This was an on-treatment analysis that included all events up to two days after the last dose of study drug. This was a pre-specification to combine the asundexian doses and compare them with placebo, as well as to separately look at the 50mg dose versus placebo.

The third set of analyses are related to efficacy. This was an intention-to-treat analysis, including all events and pre-specified was an analysis combining the 20 and 50mg doses that were tested in atrial fibrillation as well as comparing the 50mg dose alone against placebo. For both safety and efficacy, cause-specific hazard ratios were calculated.

The main results. We enrolled 1,601 patients after screening 1,664. 1,593 patients received at least one dose of study drug, and therefore in the final analysis 1,593 were part of the safety analysis and all patients were part of the efficacy analysis.

As one might expect in a carefully conducted randomised trial, baseline characteristics were well balanced among the groups. The median age was 68. Approximately 23% were women. The other characteristics at baseline were typical of those of patients with acute myocardial infarction. Notably, one half, by design, had STEMI, the other half non-STEMI. 99% of patients underwent PCI, and all patients received dual-antiplatelet therapy, 80% with ticagrelor or prasugrel and 20% with clopidogrel.

Factor XIa inhibition at four weeks is presented here, and the pattern of results is identical to that described by Dr Patel in the AF trial. Importantly, at the higher dose there was greater than 90% inhibition of Factor XIa.

With respect to bleeding there was no significant difference in the primary bleeding outcome of BARC 2, 3 or 5 bleeding between asundexian and placebo. Again, this is on top of dual-antiplatelet therapy.

In the pre-specified analysis, as demonstrated, all versions of asundexian the hazard ratio of 0.98. For asundexian 50 the hazard ratio 1.2 compared to placebo, not statistically significantly different.

On the next slide, any bleeding paralleled the pattern for BARC bleeding. No significant excess of bleeding with any of the doses of asundexian compared with placebo.

With respect to efficacy on the next slide, we did not see a significant reduction in the primary efficacy outcome of CV death, MI, stroke or stent thrombosis. The pre-specified analyses are presented. The hazard ratio is 1.05 for the combined 20 and 50mg dose versus placebo, and 1.01 versus the – with the 50mg versus placebo. It is important to remember that in this trial there were only 25 efficacy events per arm. Contrast that with approximately 75 bleeding events in each arm, and in a definitive Phase 3 trial we would expect about 300 events per arm such as in ATLAS. We have less than 10% the number of events per arm in this Phase 2 study than we saw in the ATLAS trial. Next slide.

Adverse events, there is nothing notable on this slide. It takes some time to work our way through the individual adverse events. I won't do that, but very reassuring similar event rates across the arms.

Let me conclude. This is first randomised placebo-controlled trial of a small molecule Factor XI inhibitor on top of dual-antiplatelet therapy in patients following acute myocardial infarction. With asundexian 50mg we achieved near-complete inhibition of Factor XIa on top of dual-antiplatelet therapy. No increase in significant BARC 2, 3 or 5 bleeding. No significant excess of any bleeding. We did not see a reduction in ischemic events nor did we expect to. There were no other safety signals.

These data taken together with the totality of the evidence, including genetic and pre-clinical evidence, supports the further investigation of asundexian on top of dual-antiplatelet therapy in a powered Phase 3 trial.

Thank you very much. That brings me to the end of my presentation, and I would like to hand over to Dr Koenen.

Modulating Coagulation: The Future of Asundexian

Christoph Koenen, M.D.

Head of Clinical Development & Operations, Bayer Pharmaceuticals

Thank you very much, Professor Eikelboom, and hello everyone from my side. Based on the results of the PACIFIC programme that you have seen today I'm delighted to share today with you our strategy on the future of modulating coagulation with asundexian.

However, before I go into details of the upcoming Phase 3 clinical development programme let me summarise briefly the key findings and conclusions of the PACIFIC study programme.

All three studies were primarily set up and conducted to further evaluate the safety of asundexian as well as dose-finding studies. In PACIFIC-AF, we saw asundexian reducing ISTH major bleeding or clinically relevant non-major bleeding by 67%. This was also consistent regarding all bleeds. Let me again point out that all of these studies were not powered to show an efficacy benefit versus any of the control arms.

In PACIFIC-Stroke, no significant increase in the risk of major or intra-cranial bleeding were observed in the asundexian treatment versus placebo. However, a 60% reduction of stroke and TIA was observed in a non-pre-specified sub-group analysis of patients with pre-existing atherosclerosis.

In PACIFIC-AMI no increase in any of the observed bleeding rates was observed, and that was for all tested asundexian doses. A surprising result of PACIFIC-AMI was the low overall event rate, which is a reflection of the progress we have made in the treatment of acute myocardial infarction overall.

In summary, all three studies showed a consistent and dose-dependent reduction of Factor XI level, with the 50mg once-daily dose resulting in near maximum inhibition of more than 90%. Also, asundexian demonstrated that it's well-tolerated across all studies and it showed a compelling safety dataset. On top of this, first signals of improved efficacy were seen in the PACIFIC-STROKE study.

These clinical results confirm the preclinical findings that we had observed at the onset of the programme. As you can see here on the left hand side of the slide, asundexian shows a very strong dose-dependent reduction in thrombus formation. And you can also see that this matches very well the level of inhibition of Factor XIa, so Factor XIa inhibition very closely predicts the anti-thrombotic effect. And in these pre-clinical models it has shown that this is achieved without any impact on bleeding time or blood loss.

The right-hand side of the slide shows the correlation of individuals which have a low level of Factor XI and their risk of developing a stroke. Very impressively, low Factor XI activity is correlated to lower stroke risk, while no link is observed to bleeding risk. In sum, genetic observations together with pre-clinical findings, as well as the results from the clinical studies that we have shown you today make us very excited about Factor XI as a concept and particularly about asundexian.

As Christian mentioned in his presentation, atrial fibrillation is still a major risk factor for stroke and a burden for patients, physicians and healthcare systems. In particular, the risk of developing a stroke is around five times higher for patients suffering from A-fib, compared to those who do not. Also, atrial fibrillation-related strokes are, on average, more disabling and more likely to recur than

non-AF-related strokes, and they result in longer hospital stays and greater healthcare burdens than other non-AF-related strokes. Even worse, actual or perceived bleeding risk is a key driver for under prescription, resulting in around 40% of eligible patients with A-fib not receiving appropriate oral anticoagulation. Therefore, there is still a very high unmet need for new therapeutic options in this space.

Similarly, patients with prior stroke have a high risk of a recurrent stroke. The importance of effective treatments to prevent that becomes obvious when considering that three out of four patients that present with an ischemic stroke that is non-cardioembolic in nature. While antiplatelet agents are recommended for the secondary prevention of non-cardioembolic stroke there is a need for antithrombotic strategies that are more effective, also with regard to major vascular events in patients with prior stroke.

To address these risk factors and unmet needs that I've just pointed out with novel therapeutic options, we will pursue with the further clinical development of asundexian as a first step in these two indications.

OCEANIC-AF will evaluate asundexian against apixaban in patients with atrial fibrillation. The plan is to evaluate the effect of asundexian on stroke reduction and reduction in systemic embolism. From a safety perspective, we hope to demonstrate that asundexian results in fewer bleeding events compared to apixaban.

OCEANIC-STROKE will evaluate asundexian against placebo in patients with a non-cardiometabolic stroke or higher risk for transient ischemic attacks on top of standard of care. From the efficacy perspective we hope to show that asundexian on top of standard of care will result in fewer stroke events. From a safety perspective, we hope to demonstrate that asundexian does not cause any increase in bleeding compared to placebo.

Our purpose in Bayer, 'Science for a better life', inspires us to innovate, invest and deliver clinical advancements in the management of thrombosis. In driving forward our Factor XIa inhibitor programme, Bayer is building on deep clinical insights gained from the most extensive research programme in thrombosis to date. In doing so, we continue to deliver on our commitment to patients, families and healthcare professionals impacted by cardiovascular disease.

In thrombosis prevention, we are building on the market leading position of Xarelto and we are striving to go beyond still existing treatment limits with our OCEANIC programme for asundexian.

With our recent launch of Kerendia, we have made a new and innovative medicine available for patients suffering from chronic kidney disease. We are currently running a Phase 3 trial of Kerendia with the goal of expanding it to use in heart failure, potentially contemplating the use of Verquvo in this indication. All these activities follow a common theme. We remain fully committed to develop clinically meaningful innovations in cardiovascular diseases.

This concludes my summary of the PACIFIC study programme and the way forward with asundexian. I will now hand over to Oliver to open the Q&A session.

Questions and Answers

Oliver Maier

Great, thank you very much Christoph and thanks to all the speakers, very much appreciate the presentations, your comments, and remarks. And with that, let's move to the Q&A. I see about five

hands up. I'm time sensitive, so I'll spare you all the housekeeping items on raise your hand and lower your hand. I think we've done that a couple of times and you guys are on top of this.

Only finally, as we have a quite large group of five people in the Q&A session today, please indicate at the beginning whom you like to address your questions to. That helps a little bit to coordinate the Q&A. While Ashkan and John are happy I think to comment on all study-related inquiries, Christian is looking forward for your questions on the overall R&D strategy and Christoph on the clinical programme. And obviously, Stefan will cover all financial and commercial inquiries, and all of the above I would think.

The first question I see should come from Richard Vosser from JP Morgan. Richard, you're first.

Richard Vosser, JP Morgan

Thanks very much. Two questions please. First question just on – and it's to Dr Ashkan and – Ashkan and John. Basically, was there any benefit in the covert infarcts in the stroke trial in non-small vessel disease, so in the large vessel and the undetermined strokes? If there wasn't, or if there was, why would there be no benefit on the covert infarcts but a clinical benefit on some of their manifestations, like the hard endpoints of stroke and TIA, and does that difference lead to any concerns about the magnitude of efficacy of the Factor XI inhibitors, I think both of them? Then a question for Christian. Just, which non-cardioembolic strokes would you actually enrolled in OCEANIC-STROKE based on the results of the PACIFIC-STROKE? Doesn't seem to be much benefit in small vessel disease, so would you exclude those and what are the implications on the market sizing there? I'll stop there. Thanks very much.

Ashkan Shoamanesh

Great. I'll take the first question. We actually did look at this and we haven't presented it yet, but our colleague Professor Valeria Caso from University of Perugia in Italy is going to be presenting the results at the World Stroke Congress in Singapore in a couple of months. Indeed, when we dissected out covert brain infarcts into those that were small sub-cortical infarcts due to small vessel disease versus those that had cortical involvement or were larger than 15mm, so indicating that they arose from larger or medium-sized arteries, we did see a robust effect size that was over 30% risk reduction on these cortical infarcts and larger infarcts. We were actually reassured by this in that there is significant consistency in the results indicating that it's really patients with small vessel disease that weren't responding, whereas those with larger infarcts were.

Christian Rommel

Richard, nice to meet you again here in our meeting. I'll hand over the question to Christoph sitting next to me. He will lead our large Phase 3 development strategy and program. Christoph.

Christoph Koenen

Thanks for the question. First of all, we're still in the process of – in a dialogue with regulatory authorities around the world around the exact design of the Phase 3 programmes. We have however seen in PACIFIC-STROKE a clear indication that patients with pre-existing atherosclerosis and large artery strokes seem to benefit more from a treatment with asundexian and that's the reason why we will most likely focus on a patient population that is equivalent to that.

Christian Rommel

In the near term. We will of course continue getting the data and we look at other opportunities, and we will inform you along the way.

Richard Vosser

Cool. Thank you very much.

Oliver Maier

Thank you, Richard. Next one comes from – I see from Michael Leuchten at UBS. Michael, you're next.

Michael Leuchten, UBS

Thank you, Oliver. Two questions to Dr Shoamanesh, please. Just going back to the covert infarcts, you said it yesterday and you repeated it today that there is genetic reason why one should maybe expect there not to be an impact on small vessel disease patients, but you did design the study in a way that those patients were included, so just wondering why you went down that path. What did taking that risk allow you to now do going forward, just the pros and cons of doing that?

Then going back to the bleeding profile, obviously very hard to read anything into those confidence interval, however, numerically you see a higher number of major and clinically relevant bleeds. Would you be able to tell us what the major bleed rates were, asundexian versus placebo, and how do you look at a cascade of those bleeds because it's all well and good looking at a confidence interval and saying there is no statistical difference, but how do you know they couldn't go the other way? Where do you get the confidence? Thank you.

Ashkan Shoamanesh

Thanks. For your first question, as you saw, patients with non-cardioembolic ischemic stroke come close to different stroke sub-types, one of them being small vessel disease. We actually don't know definitively the degree of thrombosis that is involved in the pathogenesis of stroke in patients with lacunar stroke or small vessel disease. The problem with that is that patients with lacunar stroke tend to have largely non-disabling strokes, so they don't pass or die shortly after their events so by the time that their brains reach pathology several years have passed, so you can't actually see or visualise whether there was an active thrombus that was associated with that infarct.

What we do have is some indirect evidence from actually clinical trials that there is thrombosis involved because, one, we know antiplatelet therapy, at least antiplatelet monotherapy does reduce the risk of lacunar stroke in patients with small vessel disease, and we also know that patients who present with lacunar strokes respond to thrombolysis. Those two indirect observations would suggest that there is thrombosis at play.

However, the degree of thrombosis is uncertain and whether or not any anticoagulant would benefit these patients has never been shown. So anticoagulation has never been shown to benefit these patients, and remember we're using a Factor XIa inhibitor here on top of background antiplatelet treatment. Another thing to consider is when you look at the mechanism of Factor XI inhibition, we're trying to prevent small clots that are forming as part of the tissue factor pathway from propagating and becoming pathogenic clots. When you're dealing with very small arteries that are well less than 1mm in diameter, that initial thrombosis can actually occlude the vessel, so you don't

– so you wouldn't need the entire propagation of that clot to occlude it, and that may be another distinct reason why these patients aren't responding.

To get to your question as to what were the risk and benefits involved of going broader, well I think any time when we design a Phase 2 study, we're doing it to inform and isolate the most – the greatest likelihood of success for a Phase 3 trial. By going broad initially, because there was some indirect suggestion that thrombosis is involved in patients with lacunar stroke, we wanted to go broad, look at the effect in all these different stroke sub-types, and then have as much information and insight as possible to then narrow down the target population that gives us the greatest chance for success in the Phase 3. Even in retrospect or in hindsight we would not have changed going broad initially, because we think we have the best information now to succeed in a pivotal trial.

Oliver Maier

Great. Thank you, Ashkan. I think that answers your question, Michael. I think the next one I see is from James Quigley, Morgan Stanley. James, you're next.

James Quigley, Morgan Stanley

Hey there, thanks for taking my questions. I've got two, one for Ashkan and one for either Christian or Stefan. In PACIFIC-STROKE did you see any sort of pattern as to when the bleeding events occurred? Were they early on in the trial or later on, and was there any trend towards greater bleeding with patients who were on the dual-antiplatelet therapies versus single-antiplatelet therapies? Then, for the Phase 3 programme generally, you're not taking forward, or it doesn't look like you're taking forward in AMI, or your competitor is taking forward in ACS yesterday, mentioned yesterday, so are you doing more analysis here to decide how broad the programme could be, or is this a budget phasing impact or what are the key reasons for selecting the two trials that you have done so far? Thank you.

Ashkan Shoamanesh

I guess I'll take the first question. There was a bit of suggestion of early bleeding events. However, this did not seem to be – we've yet to dissect whether it was more pronounced in people who received dual-antiplatelet therapy or not. Overall, pre-clinical data would suggest that there is no interaction of excess bleeding with antiplatelet treatment. Similar to what was in discussion with my colleague Mike Sharma they saw in the AXIOMATIC trial, it seems that the bleeding events were really confined to the timeframe where patients were receiving dual-antiplatelet treatment, so it really seems that it's the dual-antiplatelet treatment that's driving the bleeding and that it's independent of Factor XI inhibition.

I'll also mention, because I actually just realised I didn't answer one of the earlier – the second part to the earlier question about was there any difference between clinically relevant non-major bleeding or ISTH major bleeding, and indeed we actually found that ISTH major bleeding was similar across all treatment arms, and this numerical increase was due – was driven by clinically relevant non-major bleeding. When we combine this – usually when we see an increase in clinically relevant non-major bleeding there is an increase in all bleeding, and we did not see that. When we combine this one numerical signal of increase in clinically relevant non-major bleeding, but then we add it to the totality of the evidence across PACIFIC-AF, PACIFIC-STROKE, PACIFIC-AMI where we don't see any other bleeding signal we think this is probably a numerical chance finding rather than a real effect. Again, the greatest bleeding outcome of concern to us was, one, ISTH major bleeding, two, intra-cranial bleeding and we didn't see any suggestion of an increase in either of those outcomes.

Christian Rommel

As to your other questions, we've got a lot of new data, and as a data-driven R&D team here we go forward as we shall pursue the near-term plan, yet we recognise and believe in the broader potential of asundexian, and we're looking at this right now and we're not excluding any of the other indications you mentioned, but give us some time to dig in the data and come up with a smart plan. As I said, and I hope you agree with us, the near-term data are obvious and we'll go forward now and look at our options. Stefan, anything you want to add?

Stefan Oelrich, President, Pharmaceuticals Division, Bayer

No, I think that hits it. James, I think just maybe as you, when we looked at the data we were surprised how well the standard of care actually prevented people from re-infarctions which is, I think, a really positive find for patients out there that dual-antiplatelet therapy proves to be very effective plus probably also, since the ATLAS trials, an improved way of treating these patients as they come out of an AMI. We'll look into it as Christian says. This is just the beginning of our OCEANIC journey and stay tuned.

Oliver Maier

Thank you, Stefan. I see two more hands. Next one I see is from Sachin, Sachin Jain from Bank of America. Sachin, you're next.

Sachin Jain, Bank of America

Hi there. Thanks for taking my questions. Three topics, please. Firstly on the Phase 2 data and Phase 3 progression decision. I guess the share price reaction today is, from the conversation I had, largely around whether you have enough of an efficacy signal across your three Phase 2 studies to progress, and in particular the lack of dose response on clinical efficacy seen in Phase 2, acknowledging the small number of events which is different to your pre-clinical model. That's a big picture question, I guess to Christoph, as do you believe from the clinical data, as different from pre-clinical, you have enough confidence in dose selection around efficacy to progress.

Second question is on the OCEANIC-AF. Could you just clarify whether it's a non-inferiority study on efficacy versus Eliquis and whether you have any pre-specified sub-groups looking at patients with higher bleed risk to increase the differentiation versus Xa which will be generic not soon after you launch.

Then the final question is a commercial one on non-embolic stroke, just to distil down how you see the addressable market. If we work on the assumption that you focus on a subset X small vessel disease, which is the majority of – or a large chunk of non-embolic stroke, is it still fair to think the addressable market in non-embolic stroke is bigger than the existing SPAF market? Thank you.

Christoph Koenen

Let me start by again pointing out the reason why we conducted Phase 2, of course, was to look at the safety data, primarily bleeding, and we obviously were successful in showing that we can achieve a bleeding reduction versus apixaban versus showing no increase in bleeding versus placebo, which are very encouraging results. When it comes to efficacy, again none of the studies were powered to show an efficacy benefit, but when you look at the studies in detail the PACIFIC-AF study was a study against an active comparator, apixaban, which is obviously a very effective way to prevent stroke in patients with atrial fibrillation, and we did not observe a difference as the

study was not powered, but that is of course not indicative necessarily of what we're going to see in a larger study.

For the PACIFIC-STROKE study, we were able to show a 60% reduction of stroke as well as TA in a non-pre-specified sub-group in patients that had pre-existing atherosclerosis, and we do interpret this as an encouraging efficacy signal that encourages us to move forward in this patient population in Phase 3.

Stefan Oelrich

Christian, you also take the question on non-inferiority.

Christoph Koenen

Sorry, I'm happy to take that as well. Sorry, I forgot that. Again, we're still in the process of negotiating with different health authorities around the study design. The usual way of conducting studies in this field is that you do test for non-inferiority in a clinical study, but you then adequately power the study to show superiority as well.

Stefan Oelrich

Maybe just to complement that question, of course it is – it would be interesting to also look at sub-populations which are at higher risk for bleeding.

Christian Rommel

Stefan, there was the commercial question as well.

Stefan Oelrich

The last question on the market attractiveness, let me put it that way, when I look at the overall market attractiveness that follows after yesterday, first of all let me tell you that I'm very confident with how things came out yesterday. We saw very intriguing signals for efficacy, and if you do a like for like comparison with the other programme that was presented yesterday, I think we really look strong. That gives us a lot of confidence for Phase 3.

Equally, on SPAF I think you made the point there is a great unmet need in patients that today are not eligible because physicians deem them to be at high risk for bleeding, not eligible for any of the existing therapies. The commercial value of these two we see as extremely strong. How much that is, we will give you some more colour on this in due time. Let us first get going after consulting with the respective agencies on how the final design for the Phase 3 looks like of these two first programmes, and I think then we can also give you a little bit more colour on commercial value of those two, as we normally do when we go into Phase 3.

Sachin Jain

Can I just take one more for Christoph? It was back on the efficacy, if you could just touch on the lack of dose response on clinical efficacy in Phase 2 and how you're choosing your Phase 3 dose, which I don't think has been communicated yet.

Christoph Koenen

There's obviously two ways of looking at the dose response. One is looking at the clinical efficacy that we have seen in our Phase 2 trials, but then there's of course the XIa inhibition, where we have seen a clear dose response. The way you can approach this is that you can of course make sure that you achieve near-complete XIa inhibition over a 24-hour period, and that is something that we can clearly show with a 50mg once daily dose, and you then look at whether you see an increase in bleeding with increasing dose, and you could clearly show that an increase in dose does not lead to an increase in bleeding, and therefore we actually think we have established a dose response as well as we have established that a higher dose does not lead to an increase in bleeding.

Sachin Jain

Thank you.

Oliver Maier

Thank you, Sachin. I'm conscious of time. Nevertheless I think we have time for – I see one more hand and I think we should take it. Pete Verdult from Citi, you're next.

Stefan Oelrich

We can't hear you, Pete.

Oliver Maier

Yeah, you have to unmute, Pete.

Peter Verdult, Citi

You think I'd learn after two years. Sorry about that. I'll start again. I've only got one question left. Most have been already asked. The simple question for Christoph. OCEANIC-STROKE, how aggressive is the enrichment going to be for patients with atherosclerosis given the post-hoc exploratory signal that you're alluding to from the Phase 2 programme? Is that going to be something you're going to be pursuing quite aggressively in the Phase 3? Thank you.

Christoph Koenen

I cannot tell you exactly how aggressively we're going to enrich the patient population, but like I pointed out before we are looking into pre-specifying the population more than we have done in Phase 2, and this is something that we have to negotiate and work on, both with regulators as well as our investigators.

Peter Verdult

Thank you.

Oliver Maier

Thank you, Pete. We have a follow-up from Richard, if that's okay. I hope that's really the last one. Richard, go ahead.

Richard Vosser

Yeah, thank you very much. There was just one question which was to ask both doctors on their thoughts on the science which potentially suggests that myocardial infarctions have – are not that affected – or Factor XI doesn't have much impact on myocardial infarctions compared to Factor Xa but seems to retain the benefit on strokes compared to the Factor Xas. Just their thoughts there. It seemed to be coming out in the AMI trial, and there's some genetic evidence as well that the discussion yesterday had a look at. Just both doctors' thoughts on that would be great. Thanks very much.

John Eikelboom

I'll make a quick comment. Yes, you're absolutely correct. The genetic data indicate that there may be a differential effect of genetically low Factor XI levels on stroke versus MI. The trial was obviously too small, but I think we should remind ourselves that people with coronary disease are at risk of atherosclerotic events. For every three MIs during the long-term phase, in coronary disease there are two strokes. For every four MIs in the acute phase there's one stroke. It's not just about modulating the coronary vessel. It's about modulating cardiovascular risk, and therefore in my opinion it remains just as important to evaluate the Factor XI in coronary disease as it is in atrial fibrillation and cerebrovascular disease.

Ashkan Shoamanesh

Yes, I definitely agree with John that the numbers are too small to really start making any true hypotheses in terms of efficacy between AMI versus stroke, but when you do add the genetic data there is a potential biological reason there. I'll also mention that this isn't the first time we've seen a bit of this dichotomy. In the COMPASS trial that I mentioned in my presentation there was a large effect size when combining Factor Xa inhibition with rivaroxaban, with antiplatelet therapy with aspirin versus aspirin alone on ischemic stroke, and there was no robust effect on myocardial infarction. Particularly when you look at the populations of AMI versus the population of the STROKE trial, the AMI population also has a high proportion who undergo PCI. They have much more robust antiplatelet therapy on board, so it may be that their optimisation of risk is at a higher level than what we're seeing in the stroke population at present with current best medical practice, and that may be one of the differentiating factors.

Christoph Koenen

If I may add just a couple of sentences, based on what we've shown you today we have made a strategic decision to focus on stroke in the OCEANIC programme initially. We have to further understand the data of the AMI study to then really make a data-informed decision which specific patient population we would want to go into in this respect and where we think we could make the greatest difference with Factor XIa inhibition and asundexian.

Richard Vosser

Thank you very much. Very kind, Oliver, for squeezing me in.

Oliver Maier

Absolutely, Richard. Thank you so much.

Closing Remarks

Oliver Maier

Head of Investor Relations, Bayer AG

With that, I think that concludes our programme for today. I really would like to thank all of you for your participation. Big shout out to everyone joining us today from the UK. I know it's a bank holiday. Even more so. Thanks for joining. We hope you enjoyed this event and found it useful. I'd like to thank everybody for their continued interest and wish everybody to stay safe and looking forward to stay in touch. Thank you, everybody. Bye bye.

Cautionary Statements Regarding Forward-Looking Information

This presentation 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 <http://www.bayer.com/>.

The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Guidance at constant currencies, not including portfolio divestitures if not mentioned differently.