Asundexian — Further advancing innovative therapeutic options in the treatment of cardiovascular diseases

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Christoph Koenen
M.D., Head of Clinical Development & Operations, Bayer Pharmaceuticals
Agenda

1. Welcome
   - Oliver Maier
   - Head of Investor Relations Bayer AG

2. Prepared Remarks
   - Christian Rommel
     - Ph.D., Head of R&D, Bayer Pharmaceuticals
   - Manesh R. Patel
     - M.D., Duke Clinical Research Institute, Duke University, USA, Coordinating Principal Investigator of PACIFIC-AF
   - Ashkan Shoamanesh
     - M.D., McMaster University in Hamilton, Canada, Investigator of PACIFIC-Stroke
   - John Eikelboom
     - M.D., McMaster University in Hamilton, Canada, Investigator of PACIFIC-AMI
   - Christoph Koenen
     - M.D., Head of Clinical Development & Operations, Bayer Pharmaceuticals

3. Q&A
Cautionary statements regarding forward-looking information

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

Striving to go beyond limits

Dr. Christian Rommel
Ph.D., Head of R&D, Bayer Pharmaceuticals
The Treatment of Cardiovascular Disease has Advanced Over the Past Decades, and Bayer has Played a Key Role

- **Adalat**
- **Aspirin**
- **Glucobay**
- **Antithrombotics in ACS PCI and stents**
  - Approved for VTEp in 2008
  - Approved for SPAF in 2011
  - Approved for DVT in 2011
  - Approved for PE in 2012
  - Approved for ACSsp in 2013
  - Approved for CAD/PAD in 2018
- **Pritor Kinzal**
- **Adempas**
- **Kerendia**
- **Start of the statin era**
- **Angiotensin II receptor blockers in hypertension**
- **DOACs recommended over warfarin in stroke guidelines**
- **Entresto for CHF**
- **SGLT2 inhibitors move from type 1 and 2 diabetes to kidney and CV endpoints**

Timeline:

- 1899
- 1975
- 1990
- 1990s
- 2000s
- 2002
- 2008
- 2010s
- 2013
- 2021

- Verquvo
The Evolution of Anticoagulants\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Year</th>
<th>Anticoagulant</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1939</td>
<td>Heparin (i.v., s.c.)</td>
<td>Indirect inhibitor of clotting factors</td>
</tr>
<tr>
<td>1941</td>
<td>Dicoumarol (oral) VKA</td>
<td></td>
</tr>
<tr>
<td>1954</td>
<td>Warfarin (oral) VKA</td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td>Low-molecular weight heparin (i.v., s.c.) Indirect inhibitor of clotting factors</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Fondaparinux (i.v., s.c.) Indirect FXa inhibitor</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Bivalirudin (i.v.) Direct thrombin inhibitor</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>DOACs (oral) Direct FXa/thrombin inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

Despite Availability of (D)OACs There Remains Considerable Unmet Medical Need in Stroke Management

**Ischemic Stroke Facts**

- ~9m prevalent diagnosed cases in key 7 markets
- Standard of care: SAPT/DAPT

**Unmet Medical Need for Patients**

- Patients want stroke protection (what they fear most) without bleeding increase\(^1\)
- Patients would additionally be interested in anti-thrombotics that further reduces patient relevant bleeding

**Unmet Medical Need for HCPs**

- **Efficacy** (improved efficacy & safety vs. DOACs) – meets an aspirational treatment goal that HCPs do not spontaneously imagine
- HCPs still struggle, among others, with frail / elderly / multi-morbid patients because of bleeding risk

**Unmet Medical Need for Payers**

- **Safety** in patients currently not receiving OACs or reduced dose DOACs due to a history of bleeding or renal impairment
- **Improved outcomes** in patients who are treated with DOACs, but are at high risk of (bleeding) events

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Market research conducted in 2019 – 450 HCPs interviewed per indication in total in US + DE + JP + FR; peak share assumptions by HCPs were calibrated by Clancy method, to avoid over-estimating the peak potential

\(^1\) Patient Early Positioning Research March 2021

\(^2\) Vitamin K antagonists
Normal Physiology: Without an Anticoagulant

When no anticoagulant is used, a clot is formed to stop the bleeding—

But a pathological thrombus could also be created.
With a DOAC
(e.g., apixaban or rivaroxaban)

BUT can also prevent the beneficial blood clots that stop bleeding in damaged vessels.

When a DOAC is used, FXa is inhibited, which prevents pathological thrombi—
With a Factor XI Inhibitor
(Hypothesis: Uncoupling Hemostasis from Thrombosis)

When a Factor XI inhibitor is used, thrombin amplification is inhibited, which prevents pathological thrombi—AND the tissue factor pathway still produces thrombin, which allows beneficial blood clots to form.
# Current Evidence Supporting FXI(a) Inhibition as a Target

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited FXI deficiency¹</td>
<td>// Individuals with FXI deficiency are reported to have a reduced incidence of VTE and stroke</td>
</tr>
<tr>
<td></td>
<td>// Hemorrhage occasionally reported after trauma or surgery (dental extractions, tonsillectomies, surgery in the urinary and</td>
</tr>
<tr>
<td></td>
<td>genitail tracts, and nasal surgery)</td>
</tr>
<tr>
<td>FXI-knockout mice²</td>
<td>// Homozygous FXI-knockout mice are protected from thrombosis</td>
</tr>
<tr>
<td></td>
<td>// At the same time, they do not show a bleeding phenotype differing from wild-type mice</td>
</tr>
<tr>
<td>In vivo animal models³</td>
<td>// Reducing/inhibiting FXI showed strong antithrombotic effects in vivo</td>
</tr>
<tr>
<td></td>
<td>// No increase in bleeding time even at very high doses or on top of dual antiplatelet therapy</td>
</tr>
<tr>
<td>FXI clinical experience</td>
<td>// Antisense technology of IONIS⁴: Phase 2 study in TKA: Improved VTE risk reduction together with numerically less bleeding</td>
</tr>
<tr>
<td></td>
<td>vs enoxaparin (of note, surgery was performed at suppressed FXI levels)</td>
</tr>
<tr>
<td></td>
<td>// Anti-FXI-AB (MAA868⁵ and xisomab); Anti-FXa-AB (osocimab²): Published data from Phase 1 studies confirmed good safety and</td>
</tr>
<tr>
<td></td>
<td>tolerability even when high levels of FXI or FXa inhibition were maintained for more than 1 month. TKA study for osocimab</td>
</tr>
<tr>
<td></td>
<td>completed confirming FXa-inhibition being efficacious and well tolerated.</td>
</tr>
<tr>
<td></td>
<td>// Oral selective FXa inhibitor (milvexian): Phase 2 work showing FXa inhibition efficacious in prevention of VTE and associated</td>
</tr>
<tr>
<td></td>
<td>with low risk of bleeding.</td>
</tr>
</tbody>
</table>

Asundexian: Oral Factor XI Inhibitor

- Small molecule FXIa inhibitor
- $t_{1/2}$ 14.2-17.4 hours
- 15% Renal Elimination
- Well-tolerated in Phase 1 trials
- Dose-dependent FXIa inhibition
- Does not interact with clopidogrel to affect bleeding time
- No difference across age or sex
- Does not inhibit or induce CYP3A4
- Not impacted by food or pH modulating drugs
Building on Today’s Standard Assay, We Have Developed AXIA to Determine Factor XIa Inhibition

**aPTT**

Contact activation in human plasma

- FXIa
- Ca²⁺
- FXa
- Thrombin
- Clot

**AXIA**

Target assay in plasma

- FXIa
- concentration-dependent reduction of FXIa activity by asundexian

* 5 min endpoint measurement in clinical trial samples

**Method description:** Heitmeier S et al., J. Thromb. Haemost. 20(2022)1400

Use in Pacific-AF: Picini JF et al., Lancet399(2022)1383

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aPTT = clotting time in human plasma after contact activation (standard assay)

AXIA = FXIa activity in human plasma after contact activation (validated by external partners)
PACIFIC Program
Concerted evaluation across large several Phase 2 programs

Atrial fibrillation
- 20mg asundexian
- 50mg asundexian
- apixaban

~750 patients randomized
Results at ACC 2022

// One coordinated IDMC
// One blinded CEC with uniform process

Non-cardioembolic ischemic stroke
- 10mg asundexian
- 20mg asundexian
- 50mg asundexian
- placebo
+ single or
dual antiplatelet therapy

~1,800 patients randomized
Results at ESC 2022

Acute myocardial infarction
- 10mg asundexian
- 20mg asundexian
- 50mg asundexian
- placebo
+ dual antiplatelet therapy

~1,600 patients randomized
Results at ESC 2022
Main Results of the PACIFIC-AF Trial

Dr. Manesh R. Patel, MD
Duke Clinical Research Institute, Duke University
on behalf of the PACIFIC-AF Investigators

Disclaimer: Asundexian is currently investigational and has not been approved for use in any country
**Primary Objective:**

to evaluate that the oral FXIa inhibitor asundexian when compared to apixaban leads to a **lower incidence of bleeding** in participants with AF

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Disclaimer: Asundexian is currently investigational and has not been approved for use in any country
Measuring pharmacodynamic effect of asundexian

// Assay used: activated Factor Xia inhibition assay (AXIA)¹

// ~220 patients/ arm
// 4 weeks on once daily drug
// ~ trough (24-28 hours from last dose) and then again 2-4 hours afterwards
// Quantify degree of Factor Xla inhibition


Disclaimer: Asundexian is currently investigational and has not been approved for use in any country
FXIa Activity - Inhibition Data from PACIFIC-AF

Vertical bars indicate the percent reduction in FXIa activity when compared with baseline.

FXIa=activated coagulation factor XI.

LLOQ=lower level of quantification.

Primary Safety Outcome (ISTH bleeding classification)\textsuperscript{1}

On-treatment analysis, % of patients

- No ISTH major bleeding in any treatment arm
- Significantly lower observed rates of ISTH major and clinically relevant non-major bleeding for either dose of asundexian compared with apixaban in patients with atrial fibrillation at risk of stroke
- Consistent for BARC and TIMI bleeding definitions


Disclaimer: Asundexian is currently investigational and has not been approved for use in any country.
## Exploratory Efficacy Analysis

<table>
<thead>
<tr>
<th></th>
<th>Asundexian 20 mg</th>
<th>Asundexian 50 mg</th>
<th>Apixaban</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 251</td>
<td>N = 254</td>
<td>N = 250</td>
<td>N = 755</td>
</tr>
<tr>
<td></td>
<td>IR (90% CI)</td>
<td>IR (90% CI)</td>
<td>IR (90% CI)</td>
<td></td>
</tr>
<tr>
<td>CV death, MI, ischemic stroke, or systemic embolism</td>
<td>2 (0.80 %)</td>
<td>4 (1.57 %)</td>
<td>3 (1.20 %)</td>
<td>9 (1.19 %)</td>
</tr>
<tr>
<td>CV death</td>
<td>1 (0.40 %)</td>
<td>3 (1.18 %)</td>
<td>3 (1.20 %)</td>
<td>7 (0.93 %)</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>1 (0.39 %)</td>
<td>0</td>
<td>1 (0.13 %)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2 (0.80 %)</td>
<td>1 (0.39 %)</td>
<td>0</td>
<td>3 (0.40 %)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All cause mortality (ITT)</td>
<td>2 (0.80 %)</td>
<td>4 (1.57 %)</td>
<td>4 (1.60 %)</td>
<td>10 (1.32 %)</td>
</tr>
</tbody>
</table>

As expected only single efficacy endpoints were reported in the study.

→ No conclusion on efficacy can be drawn

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Asundexian, a small oral FXIa inhibitor was well tolerated in a Phase 2 trial of 750 patients with atrial fibrillation

Significantly lower observed rates of ISTH major and clinically relevant non-major bleeding for either dose of asundexian compared with apixaban in patients with atrial fibrillation at risk of stroke

Factor XI inhibition is a promising strategy to prevent pathologic thrombi while minimizing bleeding risk in AF patients

These data support the further investigation of asundexian in patients following atrial fibrillation

Main Results of the PACIFIC-STROKE Trial

Dr. Ashkan Shoamanesh,
M.D., FRCPC on behalf of the PACIFIC-Stroke Steering Committee and Investigators

Disclaimer: Asundexian is currently investigational and has not been approved for use in any country
PACIFIC-Stroke study

Objectives:
• To assess the dose-response of 3 different dosages of asundexian compared with 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.

Primary Efficacy Outcome:
• The incidence of symptomatic ischemic stroke or covert brain infarcts detected by MRI at 6 months following a non-cardioembolic ischemic stroke for each of the different doses of asundexian and placebo.

Primary Safety Outcome:
• The composite of ISTH\(^1\) major bleeding and clinically relevant non-major bleeding pooled across all asundexian doses and compared to placebo.

Primary analysis:
• Dose response effect of asundexian on the primary efficacy outcome at 6 months.

PACIFIC-Stroke: Schema

Prospective, randomized, double-blind, placebo-controlled, phase 2, dose-ranging study

Patients with Non-Cardioembolic Ischemic stroke ≤48 hrs from symptom onset

- Asundexian 50 mg QD n = 447
- Asundexian 20 mg QD n = 450
- Asundexian 10 mg QD n = 455
- Placebo QD n = 456

Background APT

Day 1
- Randomization
- MRI prior to or up to 72 hours post randomization

6-12 Months
- EOT
- MRI

EOS

Enrollment: 1808 patients between June 15, 2020 and July 22, 2021 at 196 sites in 23 countries
Results of PACIFIC-Stroke
Study flow

- Randomized: 1808
  - Treatment Phase Started: 1786
    - Treatment Phase Completed: 1581
      - Included in Analysis: Efficacy 1808, Safety 1786
        - Never received study drug 22 (1%)
          - Did not complete treatment phase 205 (11%)
            - Discontinued study drug due to AF 85 (5%)
            - Withdrawal of consent 57 (3%)
            - Lost-to-follow up 19 (1%)
            - Death 44 (2%)
        - Did not have follow-up MRI 369 (20%)
### Baseline and Qualifying Stroke Characteristics

**Well Balanced Across Treatment Arms**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=1808)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), mean ± SD</td>
<td>67 ±10</td>
</tr>
<tr>
<td>Female</td>
<td>34%</td>
</tr>
<tr>
<td>Race - White</td>
<td>83%</td>
</tr>
<tr>
<td>- Asian</td>
<td>15%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>77%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28%</td>
</tr>
<tr>
<td>Previous Stroke or TIA</td>
<td>16%</td>
</tr>
<tr>
<td>Hours from qualifying stroke to randomization, mean ± SD</td>
<td>36 ±10</td>
</tr>
<tr>
<td>Qualifying stroke subtype</td>
<td></td>
</tr>
<tr>
<td>- Large artery atherosclerosis</td>
<td>18%</td>
</tr>
<tr>
<td>- Small vessel occlusion</td>
<td>45%</td>
</tr>
<tr>
<td>- Cryptogenic</td>
<td>35%</td>
</tr>
<tr>
<td>Extra- or intracranial atherosclerosis</td>
<td>34%</td>
</tr>
<tr>
<td>NIHSS score at randomization, mean ± SD</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>Thrombolysis for index stroke</td>
<td>12%</td>
</tr>
<tr>
<td>Initial dual antiplatelet therapy</td>
<td>43%</td>
</tr>
</tbody>
</table>
Primary Efficacy Outcome
Ischemic Stroke or Covert Infarcts at 6 months

Asundexian 10 18.9%
Asundexian 20 22.0%
Asundexian 50 20.1%
Placebo 19.1%

No observed dose-response (Emax2 model t statistic: -0.68, p=0.80)
### Secondary Efficacy Outcome

Incident covert brain infarct(s) on MRI at 6 months (75% of events; 69% small subcortical infarcts)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Asundexian, 10 mg (N=455)</th>
<th>Asundexian, 10 mg vs. placebo</th>
<th>Asundexian, 20 mg (N=450)</th>
<th>Asundexian, 20 mg vs. placebo</th>
<th>Asundexian, 50 mg (N=447)</th>
<th>Asundexian, 50 mg vs. placebo</th>
<th>Placebo (N=456)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>63 (13.8%)</td>
<td><strong>0.99 (0.75 - 1.30)</strong></td>
<td>74 (16.4%)</td>
<td><strong>1.17 (0.90 - 1.51)</strong></td>
<td>74 (16.6%)</td>
<td><strong>1.17 (0.91 - 1.52)</strong></td>
<td>64 (14.0%)</td>
</tr>
</tbody>
</table>

**No effect on covert brain infarct**
Secondary Efficacy Outcomes
Total follow-up (median 10.6 months)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Asundexian, 10 (N=455)</th>
<th>Asundexian, 10 vs. placebo</th>
<th>Asundexian, 20 (N=450)</th>
<th>Asundexian, 20 vs. placebo</th>
<th>Asundexian, 50 (N=447)</th>
<th>Asundexian, 50 vs. placebo</th>
<th>Placebo (N=456)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>No. of patients (%)</td>
<td>HR (90% CI)</td>
<td>No. of patients (%)</td>
<td>HR (90% CI)</td>
<td>No. of patients (%)</td>
<td>HR (90% CI)</td>
<td>No. of patients (%)</td>
</tr>
<tr>
<td>26 (5.7%)</td>
<td>0.93 (0.59-1.45)</td>
<td>26 (5.8%)</td>
<td>0.94 (0.60-1.47)</td>
<td>22 (4.9%)</td>
<td>0.80 (0.50-1.27)</td>
<td>28 (6.1%)</td>
<td></td>
</tr>
<tr>
<td>Any recurrent stroke</td>
<td>26 (5.7%)</td>
<td>0.86 (0.56-1.34)</td>
<td>26 (5.8%)</td>
<td>0.88 (0.56-1.36)</td>
<td>25 (5.6%)</td>
<td>0.85 (0.54-1.32)</td>
<td>30 (6.6%)</td>
</tr>
<tr>
<td>Ischemic stroke, vascular death or myocardial infarction</td>
<td>33 (7.3%)</td>
<td>0.94 (0.63-1.40)</td>
<td>30 (6.7%)</td>
<td>0.87 (0.58-1.30)</td>
<td>33 (7.4%)</td>
<td>0.96 (0.64-1.43)</td>
<td>35 (7.7%)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>10 (2.2%)</td>
<td>1.00 (0.48-2.09)</td>
<td>6 (1.3%)</td>
<td>0.60 (0.26-1.41)</td>
<td>17 (3.8%)</td>
<td>1.72 (0.89-3.32)</td>
<td>10 (2.2%)</td>
</tr>
</tbody>
</table>

Positive trend shown for reduction in ischemic stroke with asundexian 50 mg
## Secondary Exploratory Outcomes

Total follow-up (median 10.6 months)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Asundexian, 10 (N=455)</th>
<th>Asundexian, 10 vs. placebo</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients (%)</td>
<td>HR (90% CI)</td>
<td>No. of patients (%)</td>
<td>HR (90% CI)</td>
<td>No. of patients (%)</td>
<td>HR (90% CI)</td>
<td>No. of patients (%)</td>
</tr>
<tr>
<td>TIA</td>
<td>10 (2.2%)</td>
<td><strong>0.91 (0.44-1.87)</strong></td>
<td>2 (0.4%)</td>
<td><strong>0.18 (0.05-0.64)</strong></td>
<td>2 (0.4%)</td>
<td><strong>0.18 (0.05-0.65)</strong></td>
<td>11 (2.4%)</td>
</tr>
<tr>
<td>Recurrent ischemic stroke or TIA</td>
<td>35 (7.7%)</td>
<td><strong>0.92 (0.63-1.35)</strong></td>
<td>28 (6.2%)</td>
<td><strong>0.74 (0.49-1.12)</strong></td>
<td>24 (5.4%)</td>
<td><strong>0.64 (0.41-0.98)</strong></td>
<td>38 (8.3%)</td>
</tr>
</tbody>
</table>

Dose dependent reduction of composite of ischemic stroke or TIA with asundexian
Outcome: Recurrent stroke and TIA
Exploratory post-hoc subgroup analysis

A. Patients with large artery stroke (TOAST, N=320)

- Asundexian 50: 9.0%
- Placebo: 15.8%

HR 0.56, 90% CI 0.26 – 1.19

B. Patients with any extra-/intracranial atherosclerosis (vascular imaging, N=791)

- Asundexian 50: 3.1%
- Placebo: 8.1%

HR 0.39, 90% CI 0.18 – 0.85

Patients with atherosclerosis had fewer recurrent stroke and TIA with asundexian 50
Bleeding Outcomes

A. Major or Clinically-Relevant Non-Major Bleeding (ISTH)\(^1\)

HR 1.57, 90% CI 0.91 – 2.71

<table>
<thead>
<tr>
<th>Group</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASU 10</td>
<td>4.3%</td>
</tr>
<tr>
<td>ASU 20</td>
<td>3.1%</td>
</tr>
<tr>
<td>ASU 50</td>
<td>4.3%</td>
</tr>
<tr>
<td>ASU pooled</td>
<td>3.9%</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

B. All Bleeding

<table>
<thead>
<tr>
<th>Group</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASU 10</td>
<td>8.3%</td>
</tr>
<tr>
<td>ASU 20</td>
<td>10.8%</td>
</tr>
<tr>
<td>ASU 50</td>
<td>10.8%</td>
</tr>
<tr>
<td>ASU pooled</td>
<td>10.0%</td>
</tr>
<tr>
<td>Placebo</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

C. Hemorrhagic transformation in patients with baseline MRI after randomization

<table>
<thead>
<tr>
<th></th>
<th>Asundexian 10 (N=277)</th>
<th>Asundexian 20 (N=265)</th>
<th>Asundexian, 50 (N=277)</th>
<th>Placebo (N=296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI1 and 2</td>
<td>29.6%</td>
<td>29.4%</td>
<td>30.3%</td>
<td>32.8%</td>
</tr>
<tr>
<td>PH1 and 2</td>
<td>1.1%</td>
<td>0.4%</td>
<td>0%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

No significant increase in bleeding and hemorrhagic transformation of index stroke

Conclusions

• In this phase 2 trial, inhibition of factor Xla with asundexian did not reduce the composite of covert brain infarction or ischemic stroke and no dose response could be shown in patients with acute, non-cardioembolic ischemic stroke.
  • Driven by lack of effect on covert brain infarction (largely due to small vessel disease)

• Treatment with asundexian 50mg reduced recurrent symptomatic ischemic strokes and TIAs, particularly among those with atherosclerosis

• No significant increase in the risk of major or intracranial bleeding with asundexian

• The promising results from this phase 2 trial require validation in an adequately-powered phase 3 randomised trial
Main Results of the PACIFIC-AMI Trial

Prof. John Eikelboom,
M.D., on behalf of the PACIFIC-AMI Steering Committee and Investigators

Disclaimer: Asundexian is currently investigational and has not been approved for use in any country.
**Objective:**
To evaluate safety and explore the efficacy of 3 doses of asundexian vs placebo in patients with acute MI treated with dual antiplatelet therapy.

**Study Design**

Prospective, randomized, double-blind, placebo-controlled, phase 2, dose-ranging study

- **1600 patients with acute myocardial infarction**
- Aspirin + P2Y12i
- Day 1 Randomization
- 6-12 Months EOT
- EOS
- Asundexian 50 mg QD n = 400
- Asundexian 20 mg QD n = 400
- Asundexian 10 mg QD n = 400
- Placebo QD n = 400
- 2 weeks post study drug observation period

**Quantification of Factor Xla inhibition**

**Safety outcomes:**
- Significant (BARC type 2, 3, or 5) bleeding and any bleeding

**Efficacy outcome:**
- CV-death, MI, stroke, or stent thrombosis
Analyses

**Factor XIa inhibition (AXIA Assay)**
- Percent factor XIa activity at trough (~24-28 hrs from last dose) and peak (~2-4 hrs after dose) at 4 weeks compared to baseline
- Measures enzymatic factor XIa activity in citrated plasma by assessing cleavage of a specific fluorogenic peptide FXIa substrate after contact activation with cephalin/kaolin over time

**Safety Analyses**
- On-treatment analysis include events up to 2 days after the last dose of study drug
- Analyses comparing all asundexian doses and the 50 mg dose versus placebo
- Cause-specific HR (90% CI) from stratified cause-specific Cox proportional hazards model adjusted for the competing risks of death and study drug discontinuation

**Efficacy Analyses**
- Intention-to-treat analysis including all events
- Analyses comparing the asundexian 20+50 mg doses and the 50 mg dose versus placebo
- Cause-specific HR (90% CI) from stratified cause-specific Cox proportional hazards model adjusted for the competing risk of non-CV death
Results
Disposition Study Flow
157 sites, 14 countries
June 2020 to July 2021

Screened 1664

Randomized 1601

Treatment Phase Started 1593

Treatment Phase Completed 1238

Included in Analysis
Efficacy: 1601
Safety: 1593

Screening failures 63
Inclusion/exclusion criteria 51
Withdrawal by subject 7
Other reasons 5

Never took any study drug 8

Did not complete treatment phase 363
Adverse event 155
Patient decision 110
Other reasons 34
Physician decision 27
Withdrawal by participant 20
Death 17
## BaseLine Characteristics

Well Balanced Across Treatment Arms

<table>
<thead>
<tr>
<th></th>
<th>Asundexian 10 mg</th>
<th>Asundexian 20 mg</th>
<th>Asundexian 50 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 397</td>
<td>N = 401</td>
<td>N = 402</td>
<td>N = 401</td>
</tr>
<tr>
<td>Age (yrs), median</td>
<td>67 (62, 73)</td>
<td>68 (61, 73)</td>
<td>68 (63, 73)</td>
<td>68 (60, 73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, %</td>
<td>23</td>
<td>22</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>84</td>
<td>86</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>Asian</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Weight (kg), median</td>
<td>80 (70, 91)</td>
<td>80 (70, 92)</td>
<td>80 (72, 94)</td>
<td>81 (70, 92)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>42</td>
<td>38</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>27</td>
<td>33</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Prior stroke, %</td>
<td>5.8</td>
<td>4.5</td>
<td>6.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Days from MI, median</td>
<td>4 (3, 5)</td>
<td>4 (3, 5)</td>
<td>4 (3, 5)</td>
<td>4 (3, 5)</td>
</tr>
<tr>
<td>Type of MI, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>54</td>
<td>54</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>46</td>
<td>46</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>PCI for Index MI, %</td>
<td>100</td>
<td>99</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>P2Y12i, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor/Prasugrel</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

ESC Congress 2022 Barcelona
Onsite & Online
Factor XIa Inhibition at 4 Weeks
Vertical bars indicate the % residual FXIa activity compared to baseline

FXIa=activated coagulation factor XI; LLOQ=lower level of quantification

Pre-dose = 100%

LLOQ = 3.7%

Asundexian 20 mg
- Trough: 16.59 (15.55-17.64)
- Peak: 10.78 (5.96-15.61)

Asundexian 10 mg
- Trough: 21 (0.18-0.25)
- Peak: 14 (0.08-0.19)

Asundexian 50 mg
- Trough: 9 (0.08-0.09)
- Peak: 7 (0.05-0.08)

Analysis value (95% CI)

Mean ratio to baseline (95% CI)
Bleeding Outcomes
Significant (BARC 2, 3, or 5) Bleeding

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asundexian 10 mg</td>
<td>7.6%</td>
</tr>
<tr>
<td>Asundexian 20 mg</td>
<td>8.1%</td>
</tr>
<tr>
<td>Asundexian 50 mg</td>
<td>10.5%</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

Asundexian All vs Placebo
HR (90% CI): 0.98 (0.71 to 1.35)

Asundexian 50 vs Placebo
HR (90% CI): 1.20 (0.83 to 1.75)

Two patients with ICH, 1 with asundexian 50 mg and one with placebo. No fatal bleeding.
Bleeding Outcomes

Any Bleeding

Asundexian 10 mg: 17.7%
Asundexian 20 mg: 18.9%
Asundexian 50 mg: 20.4%
Placebo: 21.3%
Efficacy Outcome
CV Death, MI, Stroke or Stent Thrombosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asundexian 10 mg</td>
<td>6.8%</td>
</tr>
<tr>
<td>Asundexian 20 mg</td>
<td>6.0%</td>
</tr>
<tr>
<td>Asundexian 50 mg</td>
<td>5.5%</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

Asundexian 20+50 vs Placebo
HR (90% CI): 1.05 (0.69 to 1.61)

Asundexian 50 vs Placebo
HR (90% CI): 1.01 (0.61 to 1.66)
## Adverse Events

### Similar Across Arms

<table>
<thead>
<tr>
<th></th>
<th>Asundexian 10 mg (N=395)</th>
<th>Asundexian 20 mg (N=397)</th>
<th>Asundexian 50 mg (N=402)</th>
<th>Placebo (N=399)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event (AE)</td>
<td>285 (72.2%)</td>
<td>307 (77.3%)</td>
<td>316 (78.6%)</td>
<td>303 (75.9%)</td>
</tr>
<tr>
<td>Study drug-related AE</td>
<td>64 (16.2%)</td>
<td>67 (16.9%)</td>
<td>86 (21.4%)</td>
<td>66 (16.5%)</td>
</tr>
<tr>
<td>AE leading to study drug discontinuation</td>
<td>35 (8.9%)</td>
<td>40 (10.1%)</td>
<td>39 (9.7%)</td>
<td>44 (11.0%)</td>
</tr>
<tr>
<td>Hepato-biliary related AE</td>
<td>8 (2.0%)</td>
<td>11 (2.8%)</td>
<td>12 (3.0%)</td>
<td>6 (1.5%)</td>
</tr>
<tr>
<td>Serious adverse event (SAE)</td>
<td>79 (20.0%)</td>
<td>84 (21.2%)</td>
<td>71 (17.7%)</td>
<td>85 (21.3%)</td>
</tr>
<tr>
<td>Study drug-related SAE</td>
<td>4 (1.0%)</td>
<td>4 (1.0%)</td>
<td>2 (0.5%)</td>
<td>5 (1.3%)</td>
</tr>
<tr>
<td>SAE leading to study drug discontinuation</td>
<td>10 (2.5%)</td>
<td>12 (3.0%)</td>
<td>15 (3.7%)</td>
<td>16 (4.0%)</td>
</tr>
<tr>
<td>AE with an outcome of death</td>
<td>8 (2.0%)</td>
<td>4 (1.0%)</td>
<td>8 (2.0%)</td>
<td>5 (1.3%)</td>
</tr>
<tr>
<td>Common (&gt;5%) AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22 (5.6%)</td>
<td>28 (7.1%)</td>
<td>22 (5.6%)</td>
<td>25 (6.3%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>16 (4.1%)</td>
<td>21 (8.1%)</td>
<td>18 (4.5%)</td>
<td>21 (5.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22 (5.6%)</td>
<td>21 (5.3%)</td>
<td>23 (5.7%)</td>
<td>18 (4.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (5.8%)</td>
<td>28 (7.1%)</td>
<td>15 (3.7%)</td>
<td>31 (7.8%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (4.6%)</td>
<td>19 (4.8%)</td>
<td>21 (5.2%)</td>
<td>20 (5.0%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>18 (4.6%)</td>
<td>19 (4.8%)</td>
<td>21 (5.2%)</td>
<td>20 (5.0%)</td>
</tr>
<tr>
<td>COVID-19</td>
<td>14 (3.5%)</td>
<td>18 (4.5%)</td>
<td>23 (5.7%)</td>
<td>19 (4.8%)</td>
</tr>
</tbody>
</table>
Summary and Conclusion

• First randomized placebo controlled trial with a small molecule factor Xla inhibitor (asundexian), on top of dual antiplatelet therapy, in patients following an acute myocardial infarction.

• Asundexian 50 mg daily resulted in near complete (>90%) inhibition of factor Xla activity.

• On top of dual antiplatelet therapy, no increase in significant (BARC 2, 3 or 5) or any bleeding with any dose of asundexian compared with placebo.

• No reduction in ischemic events with any dose of asundexian compared with placebo, however only 95 events across 4 arms and thus wide confidence intervals.

• No other safety signals.

• These data, together with existing genetic and preclinical evidence, support the further investigation of asundexian on top of dual antiplatelet therapy in an adequately powered phase 3 clinical trial of patients following an acute myocardial infarction.
Modulating coagulation: The future of asundexian

Dr. Christoph Koenen
M.D., Head of Clinical Development & Operations, Bayer Pharmaceuticals
## PACIFIC Results Show Compelling Safety Data and Tolerability of asundexian at near max. FXIa Inhibition and also First Efficacy Signals

### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>PACIFIC-AF</th>
<th>PACIFIC-Stroke</th>
<th>PACIFIC-AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Prevention of stroke in patients with atrial fibrillation</td>
<td>Prevention of secondary non-cardioembolic stroke in patients following a recent non-cardioembolic stroke</td>
<td>Prevention of a major cardiovascular event in patients following an acute myocardial infarction</td>
</tr>
<tr>
<td>Safety</td>
<td>// 67% reduction in ISTH major or clinically relevant non-major bleeding // also consistent regarding all bleeds</td>
<td>// no significant increase in the risk of major or intracranial bleeding</td>
<td>// no increase in any or in BARC 2, 3 or 5 bleeding with any dose of asundexian compared with placebo // only few bleeding outcome events</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Phase 2 studies were not powered to show efficacy benefit</td>
<td>// 60% reduction of stroke and TIA observed in a non-prespecified subgroup analysis of patients with pre-existing atherosclerosis</td>
<td>// no reduction in ischemic events with any dose of asundexian</td>
</tr>
<tr>
<td>FXI inhibition</td>
<td>@10 mg qd: not part of the study</td>
<td>@10 mg qd: &gt;70% @20 mg qd: &gt;80% @50 mg qd: &gt;90%</td>
<td></td>
</tr>
<tr>
<td>Key findings/ Conclusions</td>
<td>// dose dependent and, at 50 mg, near complete FXIa inhibition // safe and well tolerated</td>
<td>// efficacy benefits demonstrated in subgroup</td>
<td>// did not show expected trend in efficacy // further investigations necessary</td>
</tr>
</tbody>
</table>

**Unique pharmacological profile**
Results from PACIFIC Program also Fully Confirm Preclinical Findings

Separating thrombosis protection from haemostasis via selective modulation of the coagulation system

Research models:
- Evaluated the pharmacology of asundexian (BAY 2433334), in vitro and in various animal models
- Asundexian inhibited human FXIa with high potency and selectivity
- FXIa activity correlates linearly with anti-thrombotic effect
- No impact on bleeding time

Human Genetic studies:
- Evidence for reduction in stroke risk
- No impact on bleeding


AF is a Major Risk Factor for Stroke and a Burden for Patients and Healthcare Systems\(^1\)–\(^3\)

There remains an unmet need for patients with AF

// Actual or perceived bleeding risk is a key driver for under prescription; \(\sim40\%\) of eligible patients with AF do not receive appropriate oral anticoagulation\(^4\)

Patients with AF have a \(\sim5\times\) higher risk of stroke than individuals without AF\(^1\)

AF-related strokes are, on average, more disabling and more likely to recur than non-AF-related strokes\(^2\)

AF-related strokes result in longer hospital stays and greater healthcare burdens than non-AF-related strokes\(^3\)

AF, atrial fibrillation.
Patients with Prior Stroke Have a High Risk of Recurrent Stroke

There remains an unmet need for patients with prior stroke

- **Antiplatelet agents** are recommended for the secondary prevention of non-cardioembolic stroke

- **Antithrombotic strategies** that are more effective than antiplatelet therapy alone for the prevention of stroke and other major vascular events in patients with prior stroke are required

Distribution of ischemic stroke subtypes across North American and European studies

- **75%** of strokes are non-cardioembolic

- 25% Large artery atherosclerotic stenosis
- 25% Lacunes, small artery disease
- 25% Cryptogenic/ESUS
- 5% Major-risk source cardiogenic embolism, e.g. AF
- 5% Unusual, e.g. arteritis

AF, atrial fibrillation; ESUS, embolic stroke of undetermined source.

The OCEANIC program consists of two Phase III studies:

**OCEANIC-AF**
will test **asundexian** against **apixaban** in patients with **atrial fibrillation**.

**OCEANIC-STROKE**
will test **asundexian** against placebo in patients with a **non-cardioembolic ischemic stroke** or **high-risk TIA** treated with standard of care **antiplatelet therapy**.

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*The OCEANIC program design is currently under development. More information about the previous PACIFIC trials is available at [http://www.clinicaltrials.gov/](http://www.clinicaltrials.gov/). The National Clinical Trial numbers for these studies are PACIFIC-STROKE (non-cardioembolic ischemic stroke) NCT04304568, PACIFIC-AMI (myocardial infarction) NCT04304534 and PACIFIC-AF (atrial fibrillation) NCT04215266.*
Bayer Remains Committed to Develop Clinically Meaningful Innovations in Cardiovascular Diseases

Our understanding of the relationship between CVD, renal disease and diabetes is growing
Questions & Answers

Stefan Oelrich
Member of the Board of Management of Bayer AG, President Pharmaceuticals

Christian Rommel
Ph.D., Head of R&D, Bayer Pharmaceuticals

Ashkan Shoamanesh
M.D., McMaster University in Hamilton, Canada, Investigator of PACIFIC-Stroke

John Eikelboom
M.D., McMaster University in Hamilton, Canada, Investigator of PACIFIC-AMI

Christoph Koenen
M.D., Head of Clinical Development & Operations, Bayer Pharmaceuticals