# Asundexian

## Further advancing innovative therapeutic options in the treatment of cardiovascular diseases

**Investor Webinar**

August 29, 2022


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# Agenda

1 **Welcome**

**Oliver Maier**
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2 **Prepared Remarks**

**Christian Rommel**
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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.

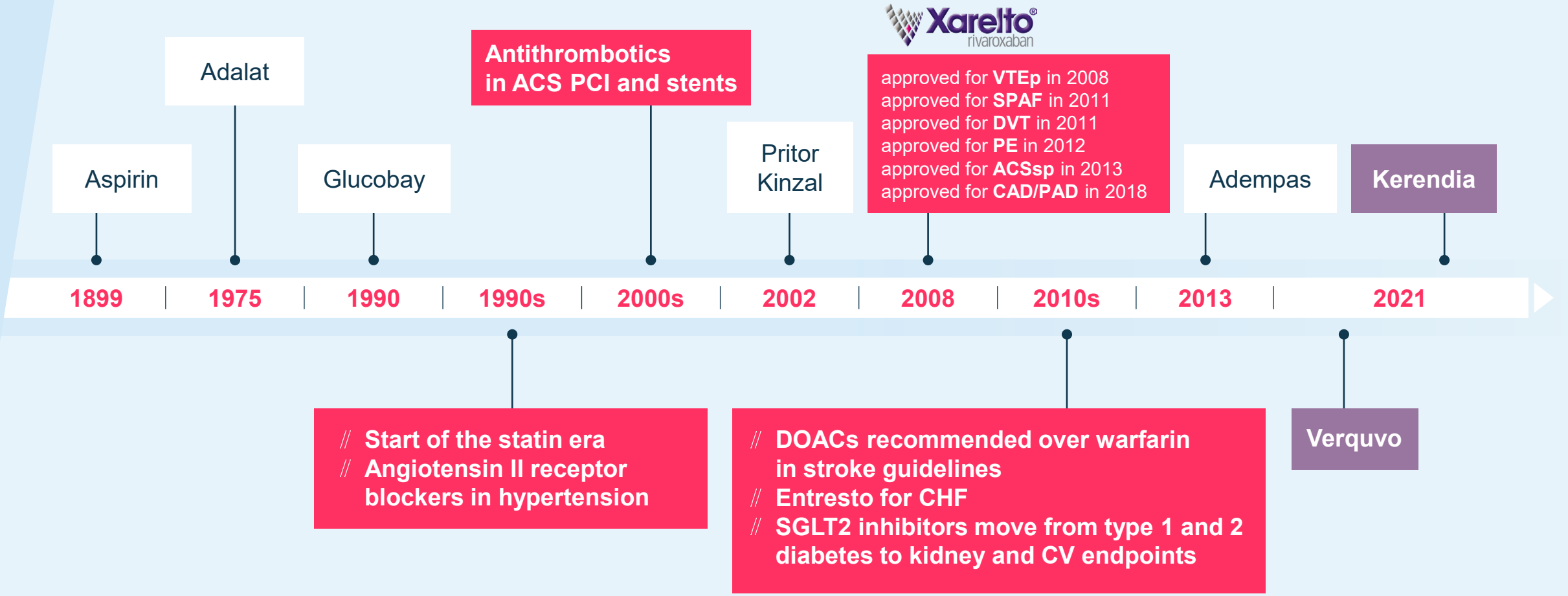
# Factor XIa inhibition –

# Striving to go beyond limits

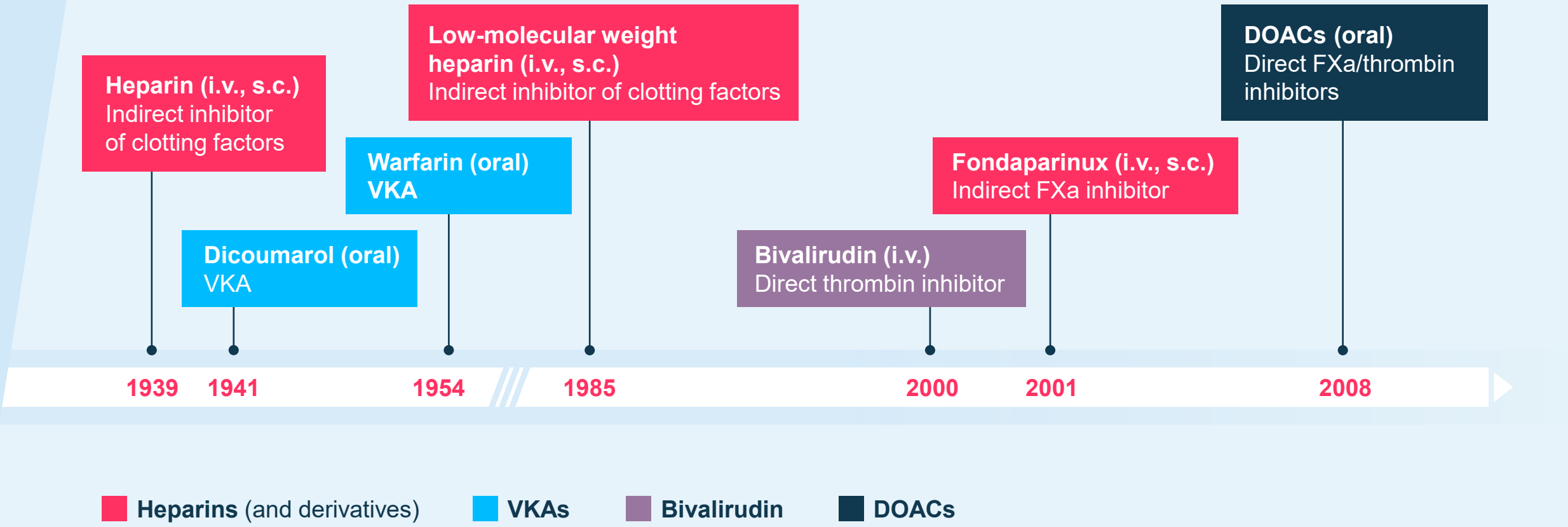
**Dr. Christian Rommel**

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



# The Evolution of Anticoagulants[1,2]

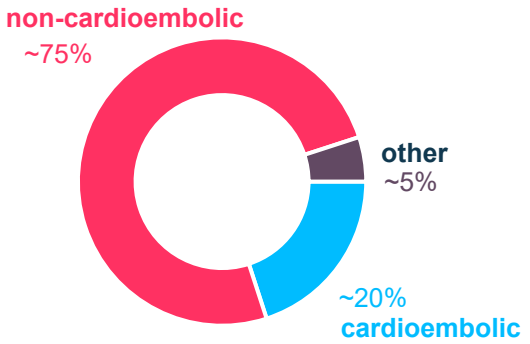



FXa, activated factor X; i.v., intravenous; NOAC, non-vitamin K antagonist oral anticoagulant; s.c., subcutaneous; VKA, vitamin K antagonist. [1] Weitz JI, Fredenburgh FC. Arterioscler Thromb Vasc Biol 2018;38:304–310; [2] Franchini M et al. Blood Transfus 2016;14:175–184.

# 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




- Prevalence: ~3% in entire population by 2030, ~13m patients in key 7 markets
- Standard of care: DOACs (VKA[2])

## 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

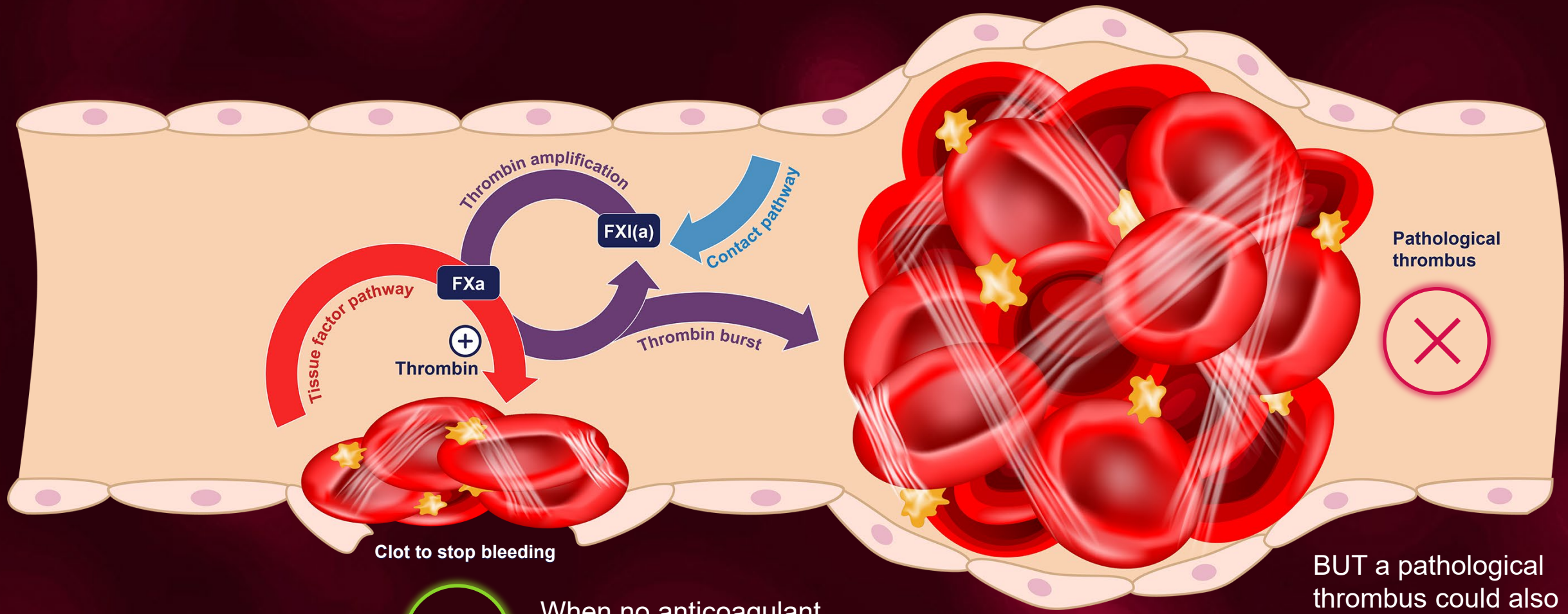
## Unmet Medical Need **for Payers**

- **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

Market research conducted in 2019 400 – 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

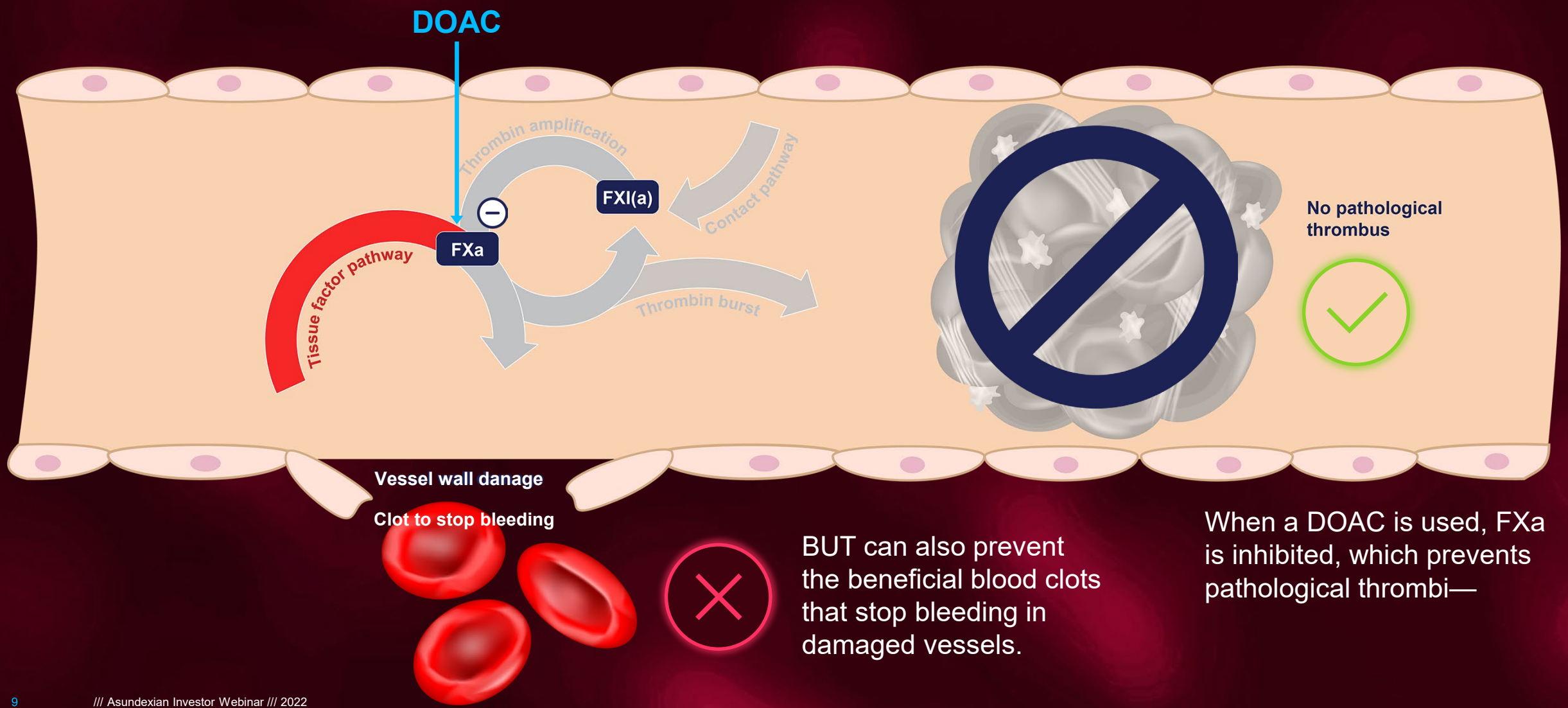
# Normal Physiology:
## Without an Anticoagulant




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)

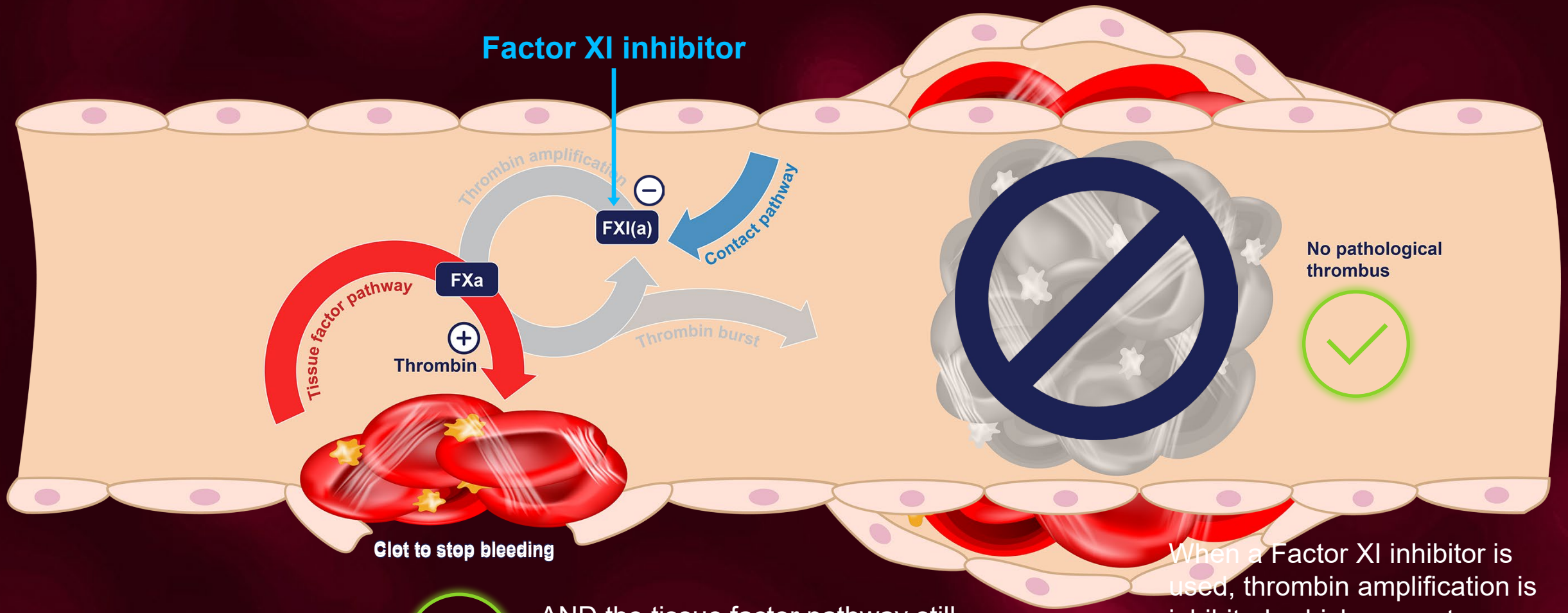



BUT can also prevent the beneficial blood clots that stop bleeding in damaged vessels.

When a DOAC is used, FXa is inhibited, which prevents pathological thrombi—

# With a Factor XI Inhibitor

## (Hypothesis: Uncoupling Hemostasis from Thrombosis)




AND the tissue factor pathway still produces thrombin, which allows beneficial blood clots to form.

When a Factor XI inhibitor is used, thrombin amplification is inhibited, which prevents pathological thrombi—

# Current Evidence Supporting FXI(a) Inhibition as a Target

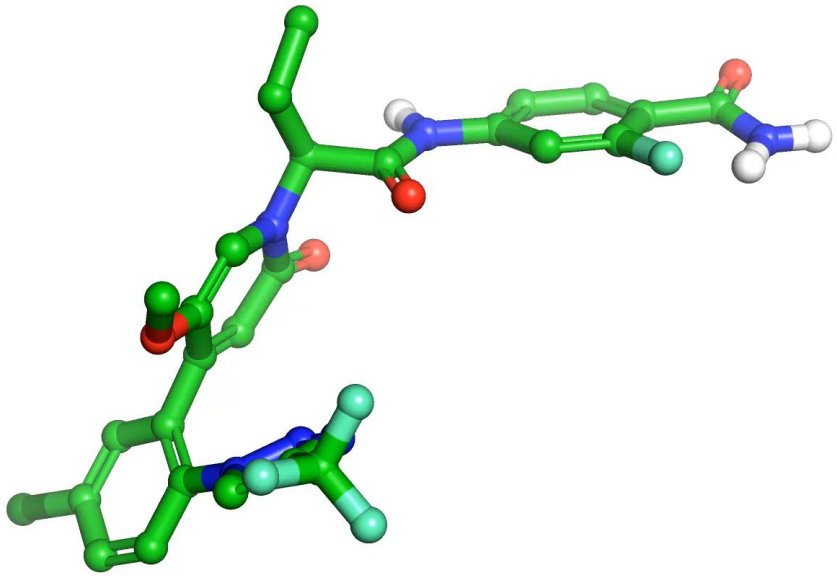
| CONDITION | OBSERVATION |
|---|---|
| **Inherited FXI deficiency[1]** | // Individuals with FXI deficiency are reported to have a **reduced incidence of VTE and stroke**<br>// **Hemorrhage occasionally** reported after trauma or surgery (dental extractions, tonsillectomies, surgery in the urinary and genital tracts, and nasal surgery) |
| **FXI-knockout mice[2]** | // Homozygous FXI-knockout mice **are protected from thrombosis**<br>// At the same time, they **do not show a bleeding phenotype** differing from wild-type mice |
| ***In vivo* animal models[3]** | // Reducing/inhibiting FXI showed **strong antithrombotic** effects *in vivo*<br>// **No increase in bleeding time** even at very high doses or on top of dual antiplatelet therapy |
| **FXI clinical experience** | // **Antisense technology of IONIS[4]**: **Phase 2 study in TKA**: Improved VTE risk reduction together with numerically less bleeding vs enoxaparin (**of note, surgery was performed at suppressed FXI levels**)<br>// **Anti-FXI-AB** (MAA868[5] and xisomab); **Anti-FXIa-AB** (osocimab[2]): Published data from Phase 1 studies confirmed **good safety and tolerability** even when high levels of **FXI or FXIa inhibition** were maintained for more than **1 month**. TKA study for osocimab completed confirming FXIa-inhibition being efficacious and well tolerated. **Oral selective FXIa inhibitor** (milvexian): Phase 2 work showing FXIa inhibition efficacious in **prevention of VTE** and associated with **low risk of bleeding**.[6] |

[1] Puy C et al. Thromb Res. 2016;141(Suppl 2):S8–S11 [2] Schumacher WA et al. Arterioscler Thromb Vasc Biol. 2010;30(3):388-92 [3] Data on file [4] Büller HR et al. N Engl J Med. 2015;372(3):232-40
[5] Koch AW et al. Blood. 2019;133(13):1507-1516 [6] Weitz et al. N Engl J Med. 2021;385(23):2161-2172

# Asundexian: Oral Factor XI Inhibitor

- Small molecule FXIa inhibitor
  - t1/2 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

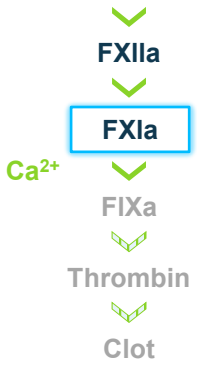
$C_{26}H_{21}ClF_4N_6O_4$

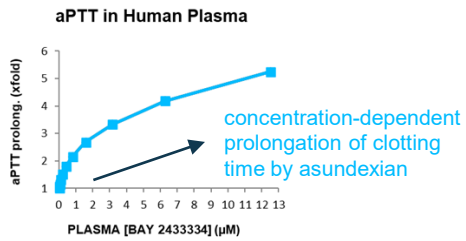


# Building on Today's Standard Assay, We Have Developed AXIA to Determine Factor XIa Inhibition

## aPTT

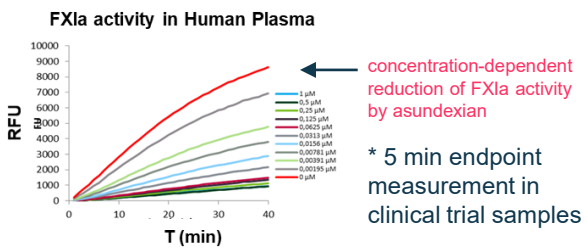
Contact activation in human plasma



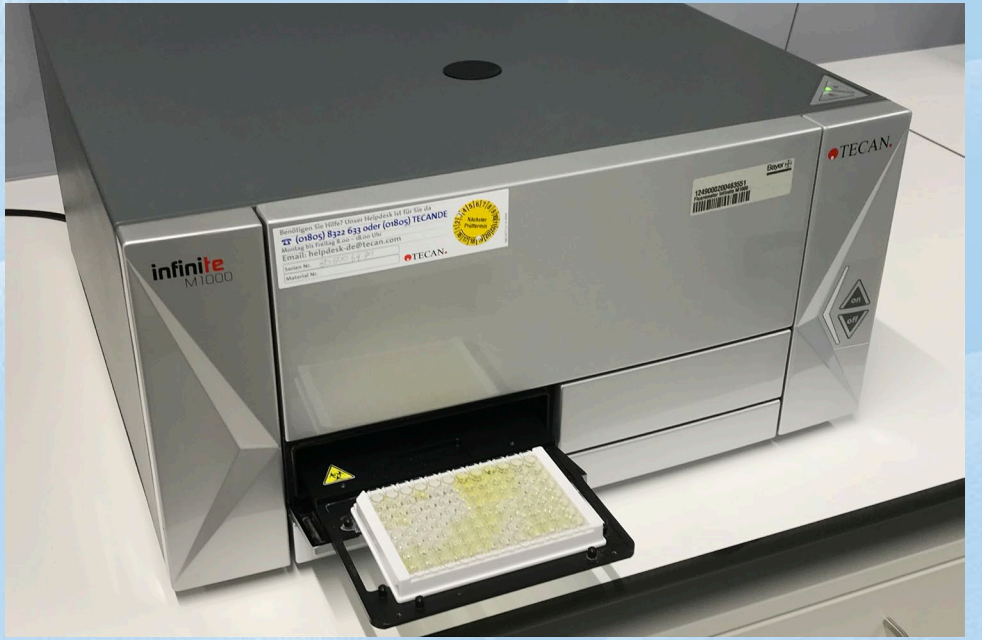

› Pathway-related assay in plasma

## AXIA


* 5 min endpoint measurement in clinical trial samples

› Target assay in plasma




aPTT = clotting time in human plasma after contact activation (standard assay)
AXIA = FXIa activity in human plasma after contact activation (validated by external partners)

Method description: Heitmeier S et al., J. Thromb.Haemost. 20(2022)1400
Use in Pacific-AF: Picini JF et al., Lancet399(2022)1383

# PACIFIC Program

## Concerted evaluation across large several Phase 2 programs


**Atrial fibrillation**

// 20mg asundexian
// 50mg asundexian
// apixaban

**~750 patients randomized**
**Results at ACC 2022**


**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*

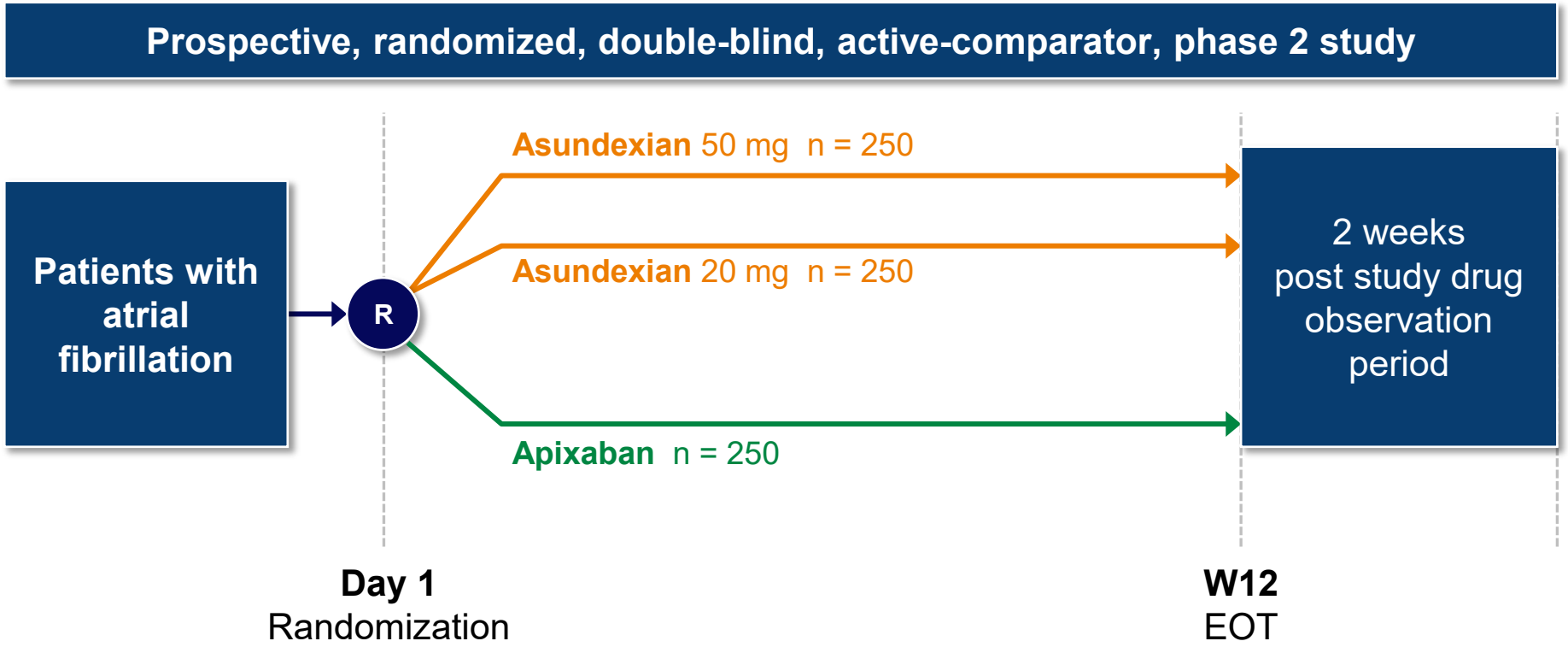
**~1,600 patients randomized**
**Results at ESC 2022**

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

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

# *Main Results of the PACIFIC-AF Trial*

# PACIFIC-AF[1]




**Primary safety endpoint:** bleeding (ISTH major and non-major clinically relevant bleeding)

**Quantification of Factor XI inhibition**

**Exploratory efficacy endpoint:** stroke, systemic embolism, CV death, MI

**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

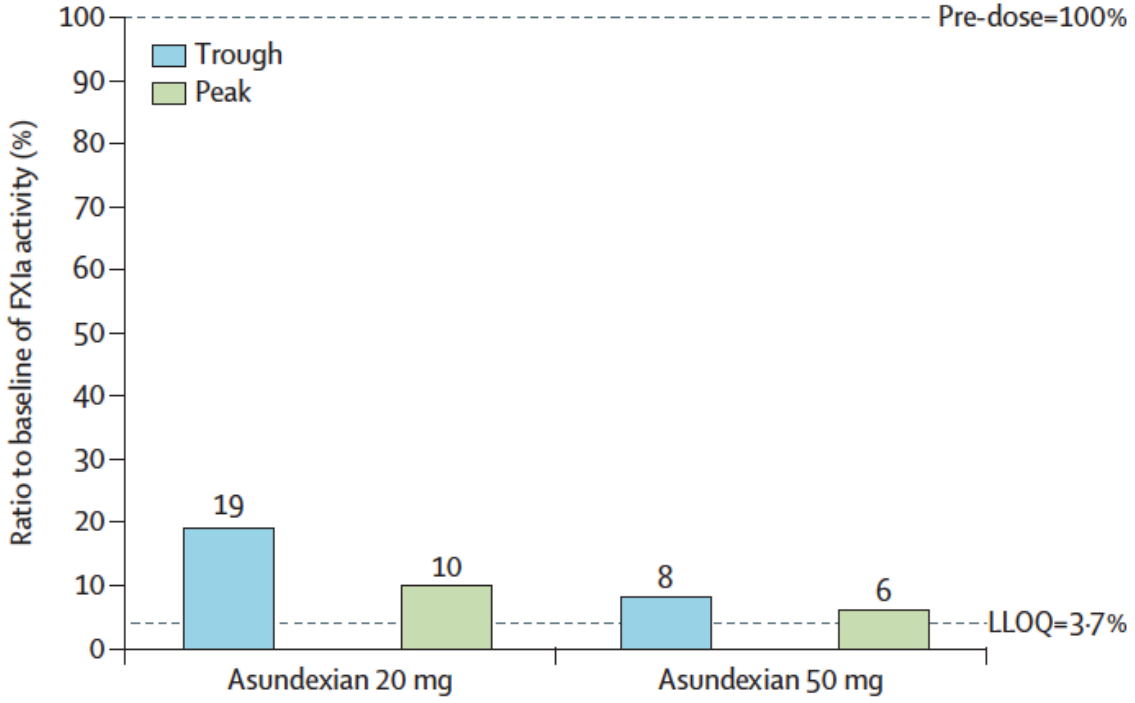
1. Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR; PACIFIC-AF Investigators. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022 Apr 9;399(10333):1383-1390. doi: 10.1016/S0140-6736(22)00456-1. Epub 2022 Apr 3. PMID: 35385695.

# 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 XIa inhibition

1. Heitmeier S, Visser M, Tersteegen A, et al. Pharmacological profile of asundexian, a novel, orally bioavailable inhibitor of factor XIa. J Thromb Haemost 2022; published online March 15. https://doi.org/10.1111/jth.15700." and which explains a bit more how the AXIA works. Meanwhile this is also available as "Heitmeier, S., et al. (2022). Pharmacological profile of asundexian, a novel, orally bioavailable inhibitor of factor XIa. J Thromb Haemost 20(6): 1400-1411

# FXIa Activity - Inhibition Data from PACIFIC-AF[1]




| | Asundexian 20 mg | | Asundexian 50 mg | |
|---|---|---|---|---|
| n | 224 | 222 | 228 | 228 |
| Analysis value (95% CI) | 14·82 (12·65–16·99) | 7·42 (6·33–8·51) | 6·59 (5·15–8·02) | 4·32 (3·60–5·05) |
| Mean ratio to baseline (95% CI) | 0·19 (0·16–0·22) | 0·10 (0·08–0·12) | 0·08 (0·07–0·10) | 0·06 (0·05–0·07) |

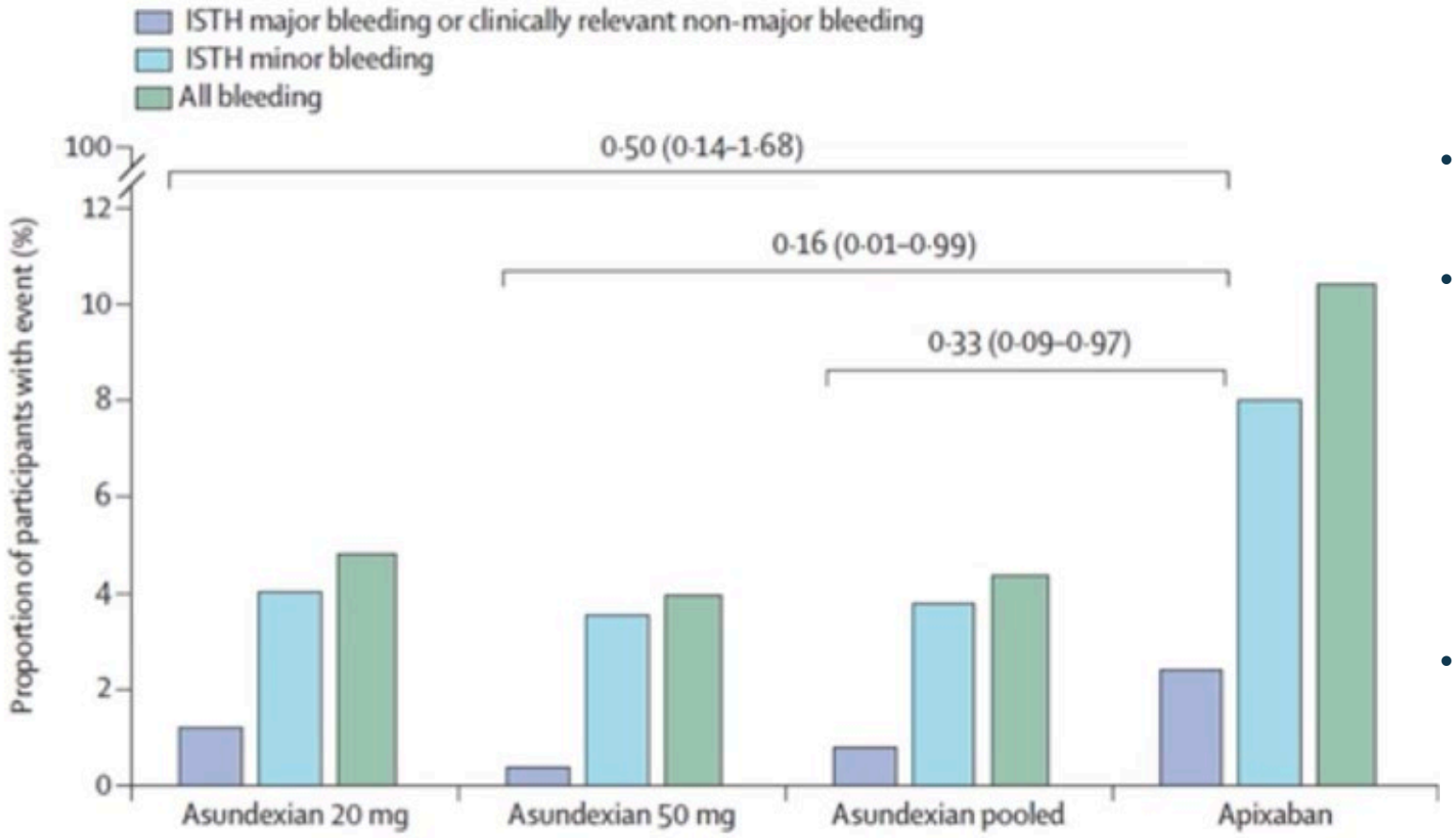
Vertical bars indicate the percent reduction in FXIa activity when compared with baseline.
FXIa=activated coagulation factor XI.

LLOQ=lower level of quantification.

1. Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR; PACIFIC-AF Investigators. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022 Apr 9;399(10333):1383-1390. doi: 10.1016/S0140-6736(22)00456-1. Epub 2022 Apr 3. PMID: 35385695.

# Primary Safety Outcome (ISTH bleeding classification)[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

1. Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR; PACIFIC-AF Investigators. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022 Apr 9;399(10333):1383-1390. doi: 10.1016/S0140-6736(22)00456-1. Epub 2022 Apr 3. PMID: 35385695.

# Exploratory Efficacy Analysis[1]

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

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

→ No conclusion on efficacy can be drawn

1. Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR; PACIFIC-AF Investigators. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022 Apr 9;399(10333):1383-1390. doi: 10.1016/S0140-6736(22)00456-1. Epub 2022 Apr 3. PMID: 35385695.

# Summary of PACIFIC-AF Trial Outcomes[1]

- 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

1. Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR; PACIFIC-AF Investigators. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022 Apr 9;399(10333):1383-1390. doi: 10.1016/S0140-6736(22)00456-1. Epub 2022 Apr 3. PMID: 35385695.

# Main Results of the PACIFIC-STROKE Trial

**Dr. Ashkan Shoamanesh,**

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

# 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:**

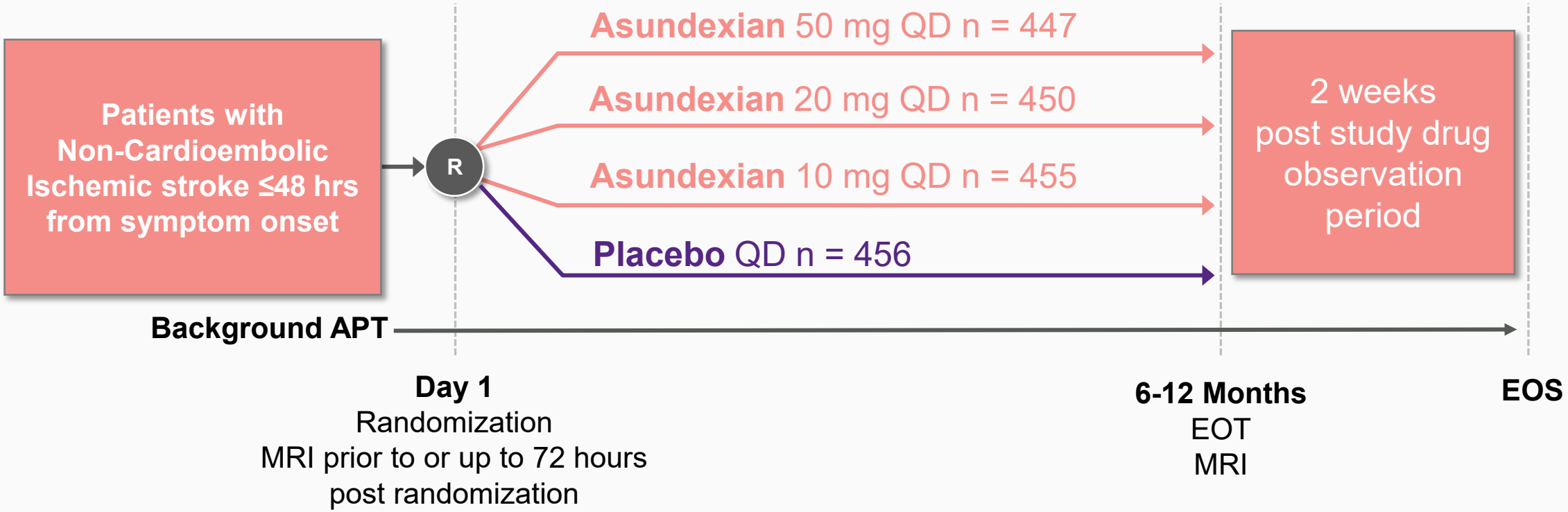
- Dose response effect of asundexian on the primary efficacy outcome at 6 months



[1]Schulman, S et al. J Thromb Haemost 2005; 3:692-4

# PACIFIC-Stroke: Schema

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




**Enrollment:** 1808 patients between June 15, 2020 and July 22, 2021 at 196 sites in 23 countries

# Results of PACIFIC-Stroke

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

BAYER

PACIFIC STROKE

# Study flow

**Randomized**
1808

**Never received study drug 22 (1%)**

**Treatment Phase Started**
1786

**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%)*

**Treatment Phase Completed**
1581

**Included in Analysis**
Efficacy 1808
Safety 1786

**Did not have follow-up MRI 369 (20%)**

# Baseline and Qualifying Stroke Characteristics

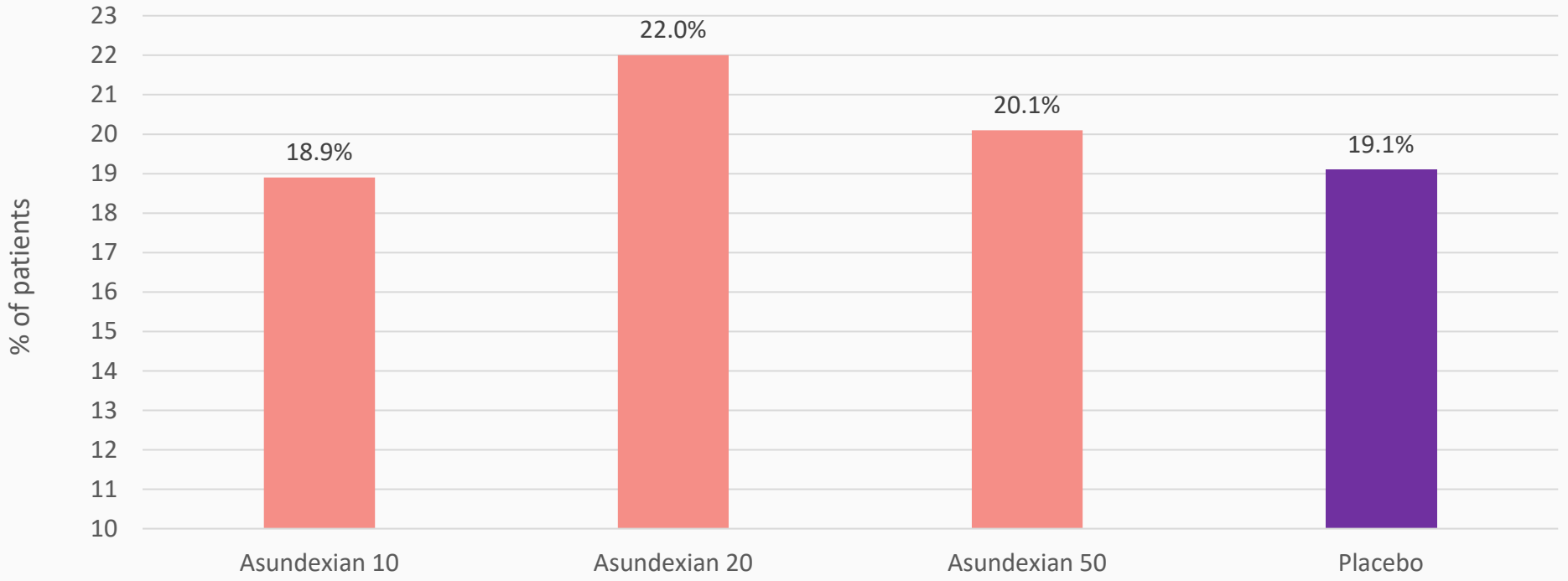
## Well Balanced Across Treatment Arms

| | All patients (n=1808) |
|---|---|
| Age (yrs), mean ± SD | 67 ±10 |
| Female | 34% |
| Race - White<br>- Asian | 83%<br>15% |
| Hypertension | 77% |
| Diabetes mellitus | 28% |
| Previous Stroke or TIA | 16% |
| Hours from qualifying stroke to randomization, mean ± SD | 36 ±10 |
| Qualifying stroke subtype<br>- Large artery atherosclerosis<br>- Small vessel occlusion<br>- Cryptogenic | <br>18%<br>45%<br>35% |
| Extra- or intracranial atherosclerosis | 34% |
| NIHSS score at randomization, mean ± SD | 3 ± 2 |
| Thrombolysis for index stroke | 12% |
| Initial dual antiplatelet therapy | 43% |

PACIFIC STROKE

# Primary Efficacy Outcome

## Ischemic Stroke or Covert Infarcts at 6 months




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)

| Outcome | Asundexian, 10 mg (N=455) | Asundexian, 10 mg vs. placebo | Asundexian, 20 mg (N=450) | Asundexian, 20 mg vs. placebo | Asundexian, 50 mg (N=447) | Asundexian. 50 mg vs. placebo | Placebo (N=456) |
|---|---|---|---|---|---|---|---|
| | No. of patients (%) | CIR (90% CI) | No. of patients (%) | CIR (90% CI) | No. of patients (%) | CIR (90% CI) | No. of patients (%) |
| **Incident covert brain infarct(s) on MRI** | 63 (13.8%) | **0.99 (0.75 - 1.30)** | 74 (16.4%) | **1.17 (0.90 - 1.51)** | 74 (16.6%) | **1.17 (0.91 - 1.52)** | 64 (14.0%) |

No effect on covert brain infarct

# Secondary Efficacy Outcomes

## Total follow-up (median 10.6 months)

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

Positive trend shown for reduction in ischemic stroke with asundexian 50 mg

# Secondary Exploratory Outcomes

## Total follow-up (median 10.6 months)

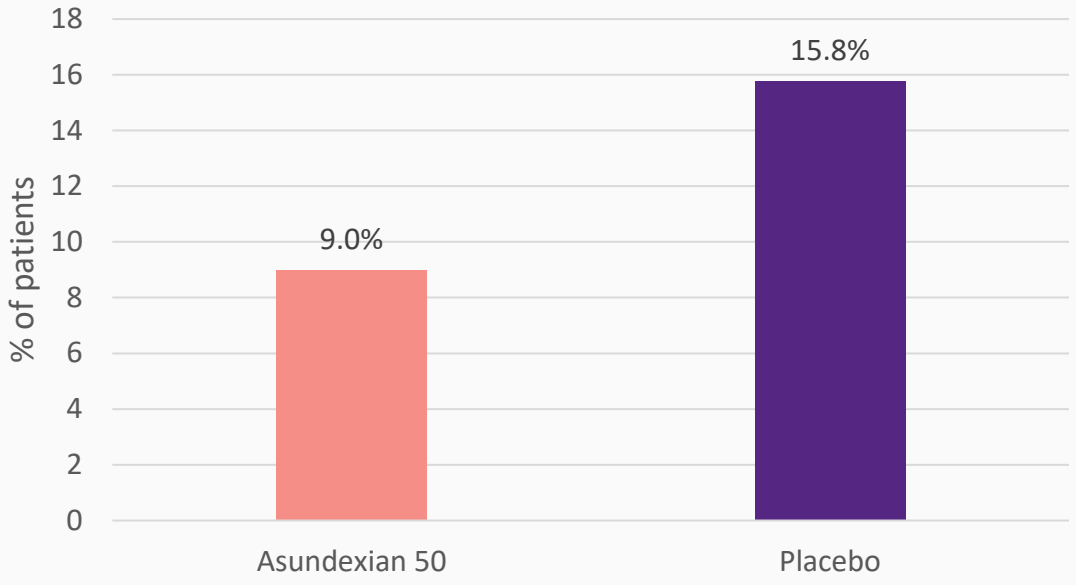
| Outcome | Asundexian, 10 (N=455) | Asundexian, 10 vs. placebo | Asundexian, 20 (N=450) | Asundexian, 20 vs. placebo | Asundexian, 50 (N=447) | Asundexian 50 vs. placebo | Placebo (N=456) |
|---|---|---|---|---|---|---|---|
| | No. of patients (%) | HR (90% CI) | No. of patients (%) | HR (90% CI) | No. of patients (%) | HR (90% CI) | No. of patients (%) |
| **TIA** | 10 (2.2%) | **0.91 (0.44-1.87)** | 2 (0.4%) | **0.18 (0.05-0.64)** | 2 (0.4%) | **0.18 (0.05-0.65)** | 11 (2.4%) |
| **Recurrent ischemic stroke or TIA** | 35 (7.7%) | **0.92 (0.63-1.35)** | 28 (6.2%) | **0.74 (0.49-1.12)** | 24 (5.4%) | **0.64 (0.41-0.98)** | 38 (8.3%) |

Dose dependent reduction of composite of ischemic stroke or TIA with asundexian

# Outcome: Recurrent stroke and TIA

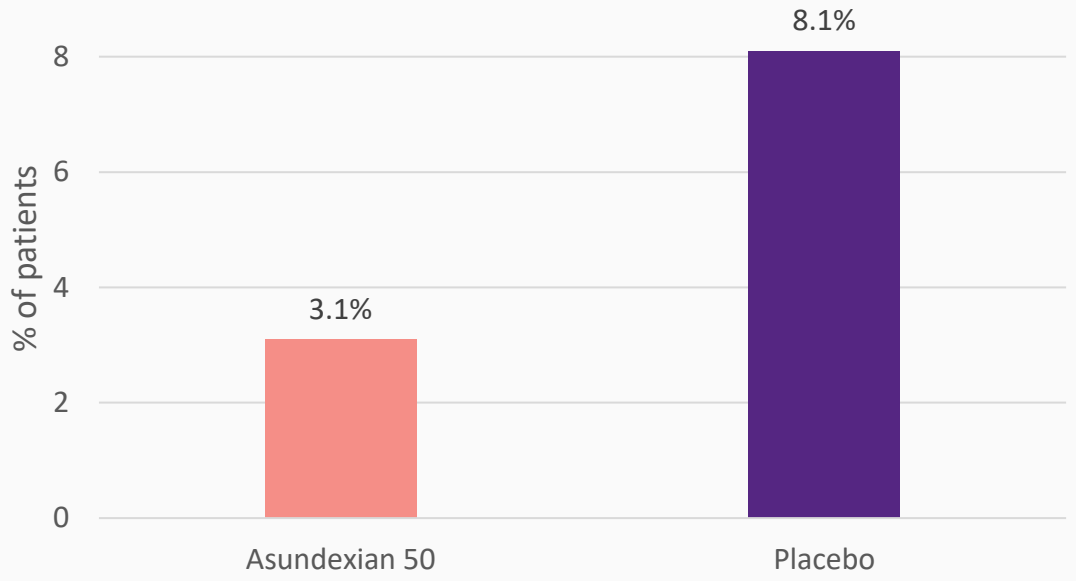
## Exploratory post-hoc subgroup analysis

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




HR 0.56, 90% CI 0.26 – 1.19

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

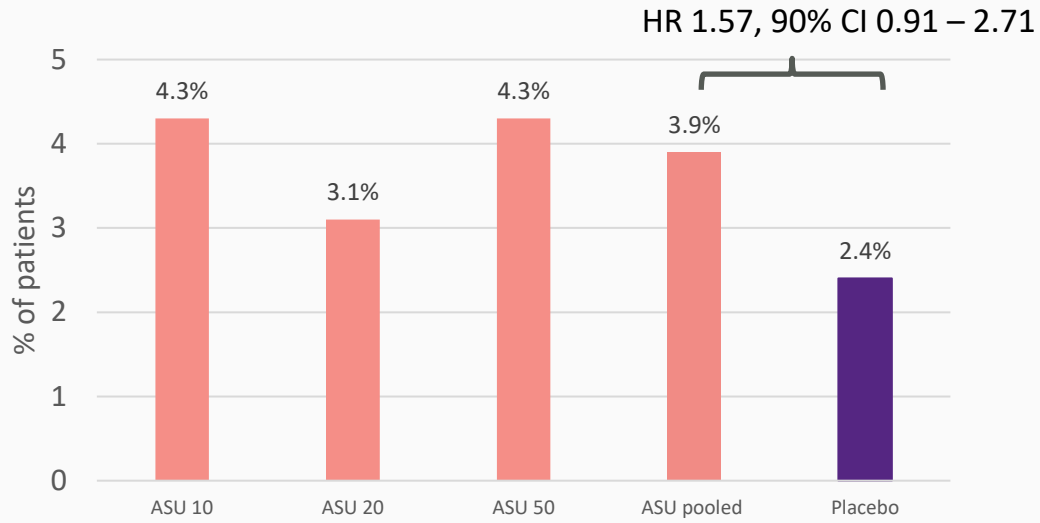



**HR 0.39, 90% CI 0.18 – 0.85**

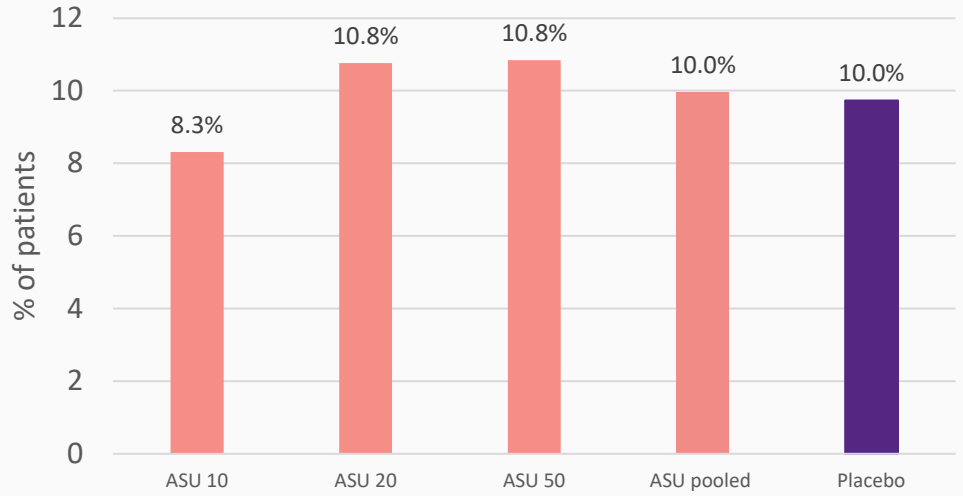
Patients with atherosclerosis had fewer recurrent stroke and TIA with asundexian 50

# Bleeding Outcomes

## A. Major or Clinically-Relevant Non-Major Bleeding (ISTH)[1]




## B. All Bleeding




## C. Hemorrhagic transformation in patients with baseline MRI after randomization

| | Asundexian 10 (N=277) | Asundexian 20 (N=265) | Asundexian, 50 (N=277) | Placebo (N=296) |
|---|---|---|---|---|
| **HI1 and 2** | 29.6% | 29.4% | 30.3% | 32.8% |
| **PH1 and 2** | 1.1% | 0.4% | 0% | 1.4% |

No significant increase in bleeding and hemorrhagic transformation of index stroke



ASU = Asundexian, HI = hemorrhagic infarct, PH = parenchymal hematoma

[1]Schulman, S et al. J Thromb Haemost 2005; 3:692-4

# Conclusions

- In this phase 2 trial, inhibition of factor XIa 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,**

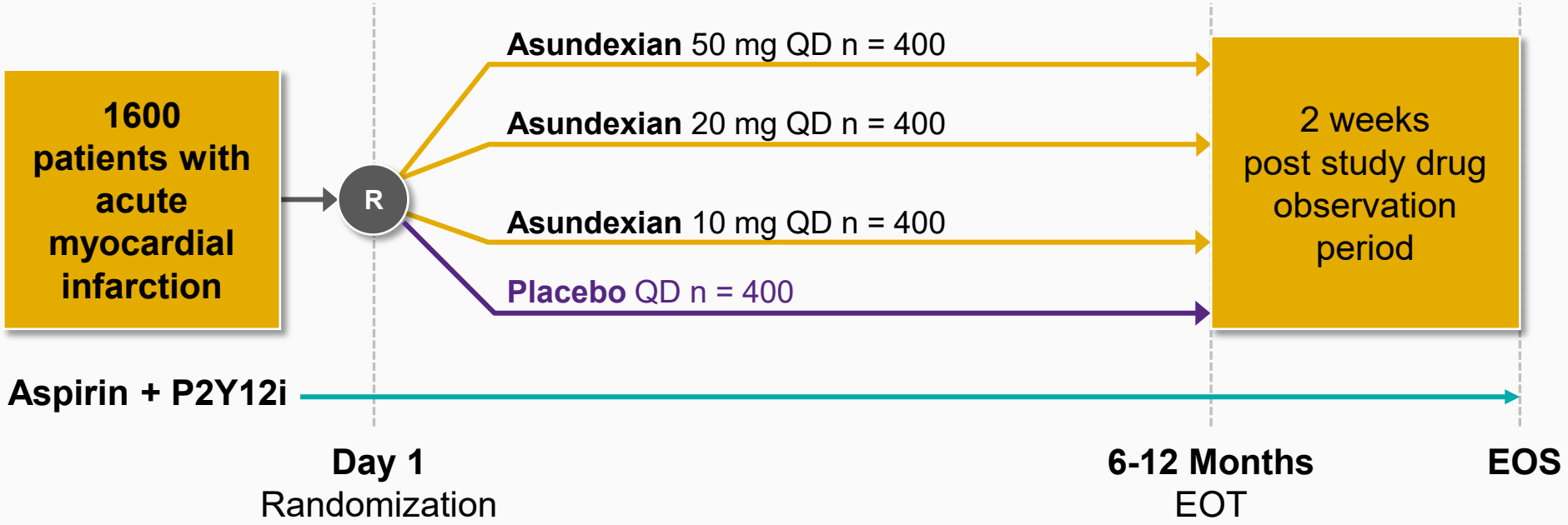
M.D., on behalf of the PACIFIC-AMI Steering Committee and Investigators

# Study Design

**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

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




**Quantification of Factor XIa 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

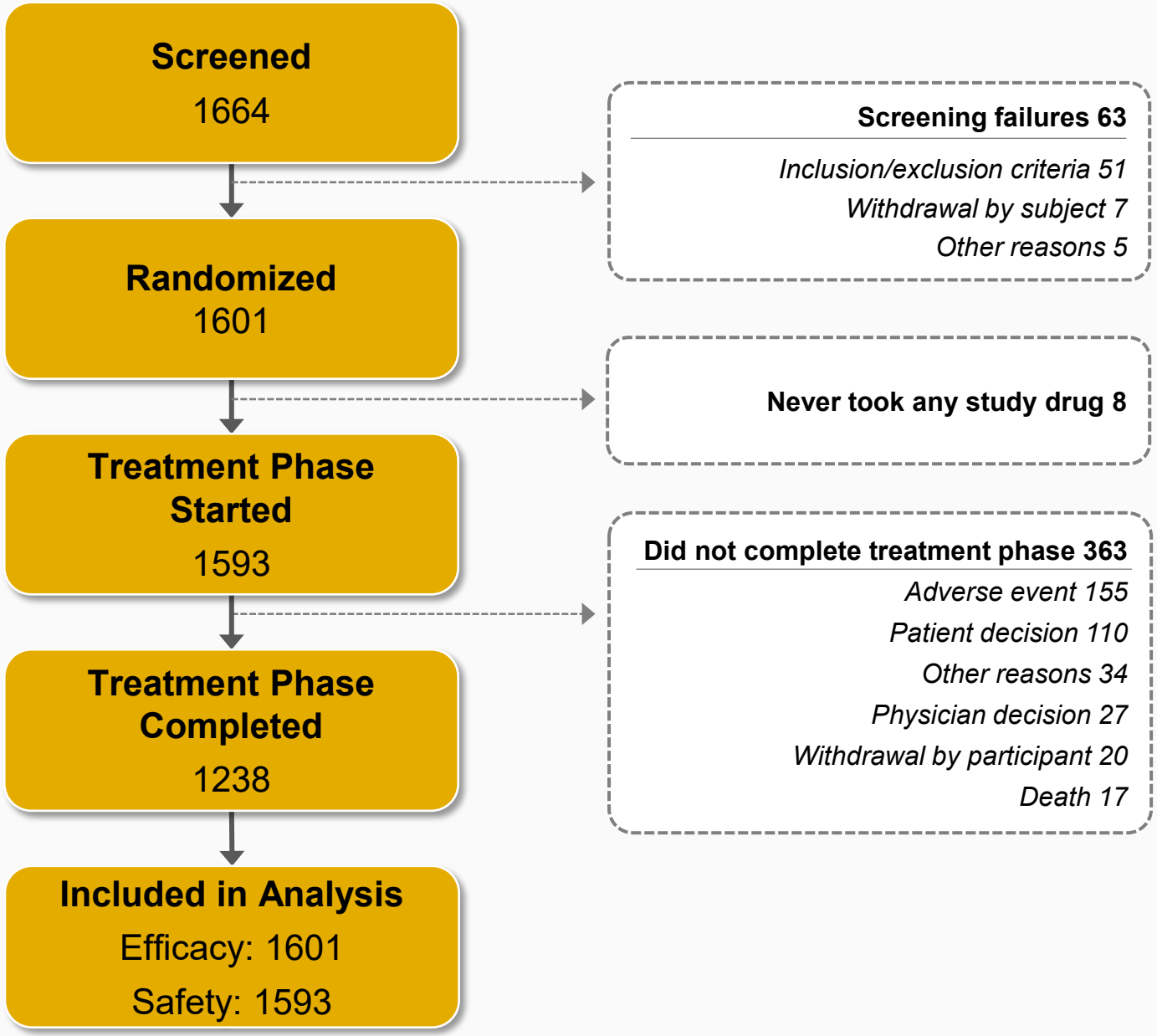
## Efficacy Analyses

- 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



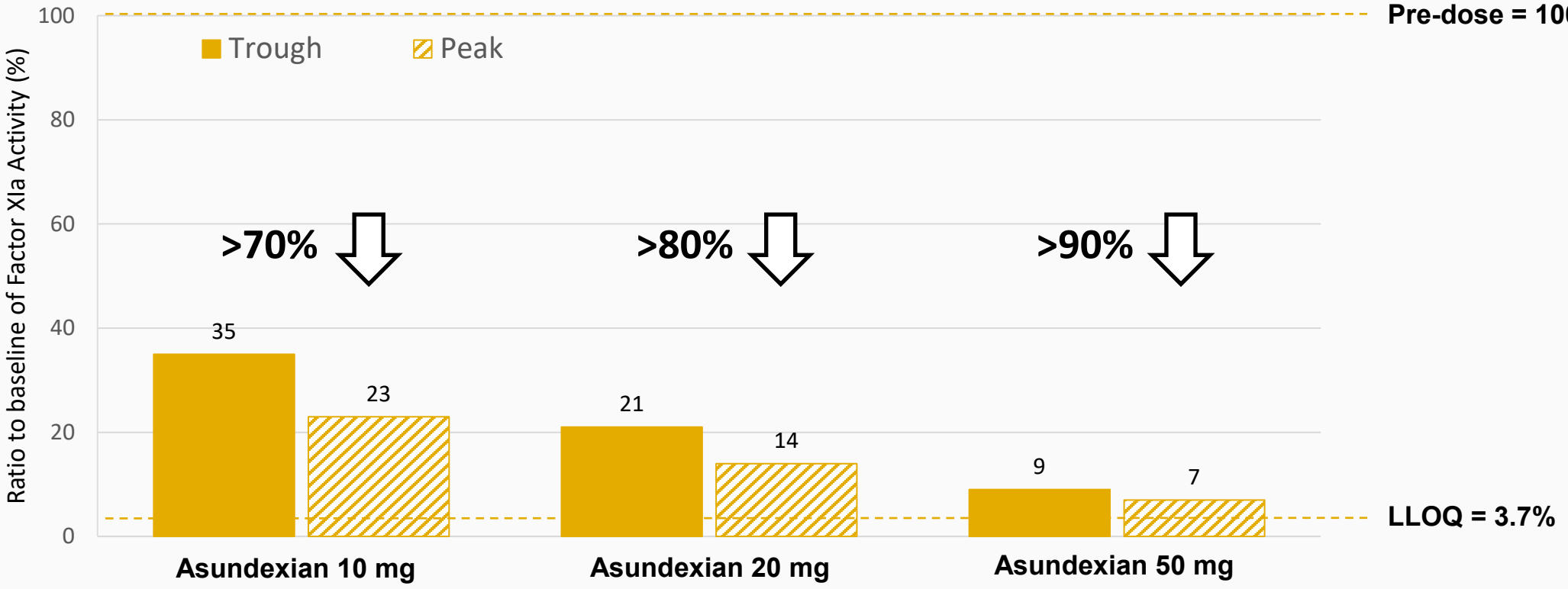
# Baseline Characteristics

## Well Balanced Across Treatment Arms

| | Asundexian 10 mg N = 397 | Asundexian 20 mg N = 401 | Asundexian 50 mg N = 402 | Placebo N = 401 |
|---|---|---|---|---|
| Age (yrs), median (25th, 75th) | 67 (62, 73) | 68 (61, 73) | 68 (63, 73) | 68 (60, 73) |
| Female, % | 23 | 22 | 25 | 22 |
| Race, % White<br>Asian | 84<br>13 | 86<br>13 | 86<br>12 | 85<br>13 |
| Weight (kg), median (25th, 75th) | 80 (70, 91) | 80 (70, 92) | 80 (72, 94) | 81 (70, 92) |
| Diabetes mellitus, % | 42 | 38 | 39 | 42 |
| Prior MI, % | 27 | 33 | 25 | 27 |
| Prior stroke, % | 5.8 | 4.5 | 6.5 | 5.0 |
| Days from MI, median (25th, 75th) | 4 (3, 5) | 4 (3, 5) | 4 (3, 5) | 4 (3, 5) |
| Type of MI, % STEMI<br>NSTEMI | 54<br>46 | 54<br>46 | 50<br>50 | 46<br>54 |
| PCI for Index MI, % | 100 | 99 | 100 | 99 |
| P2Y12i, % Ticagrelor/Prasugrel<br>Clopidogrel | 80<br>20 | 80<br>20 | 80<br>20 | 80<br>20 |

# Factor XIa Inhibition at 4 Weeks

## Vertical bars indicate the % residual FXIa activity compared to baseline




| | Asundexian 10 mg | | Asundexian 20 mg | | Asundexian 50 mg | |
|---|---|---|---|---|---|---|
| | n=327 | n=320 | n=347 | n=344 | n=347 | n=338 |
| **Analysis value (95% CI)** | 35.58 (28.68-32.48) | 18.34 (13.34-23.34) | 16.59 (15.55-17.64) | 10.78 (5.96-15.61) | 7.19 (6.39-7.99) | 5.09 (4.11-6.07) |
| **Mean ratio to baseline (95% CI)** | 0.35 (0.33-0.37) | 0.23 (0.15-0.30) | 0.21 (0.18-0.25) | 0.14 (0.08-0.19) | 0.09 (0.08-0.09) | 0.07 (0.05-0.08) |

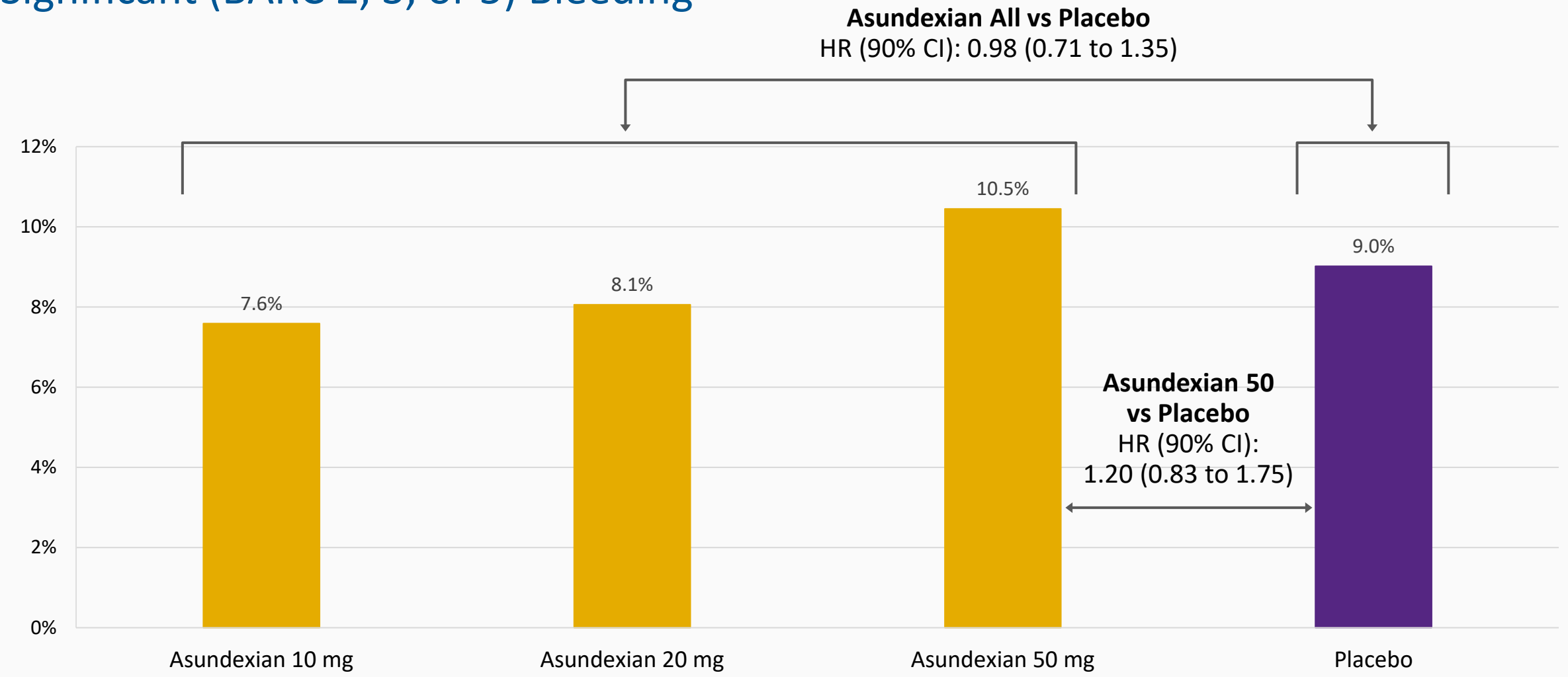


FXIa=activated coagulation factor XI; LLOQ=lower level of quantification

# Bleeding Outcomes

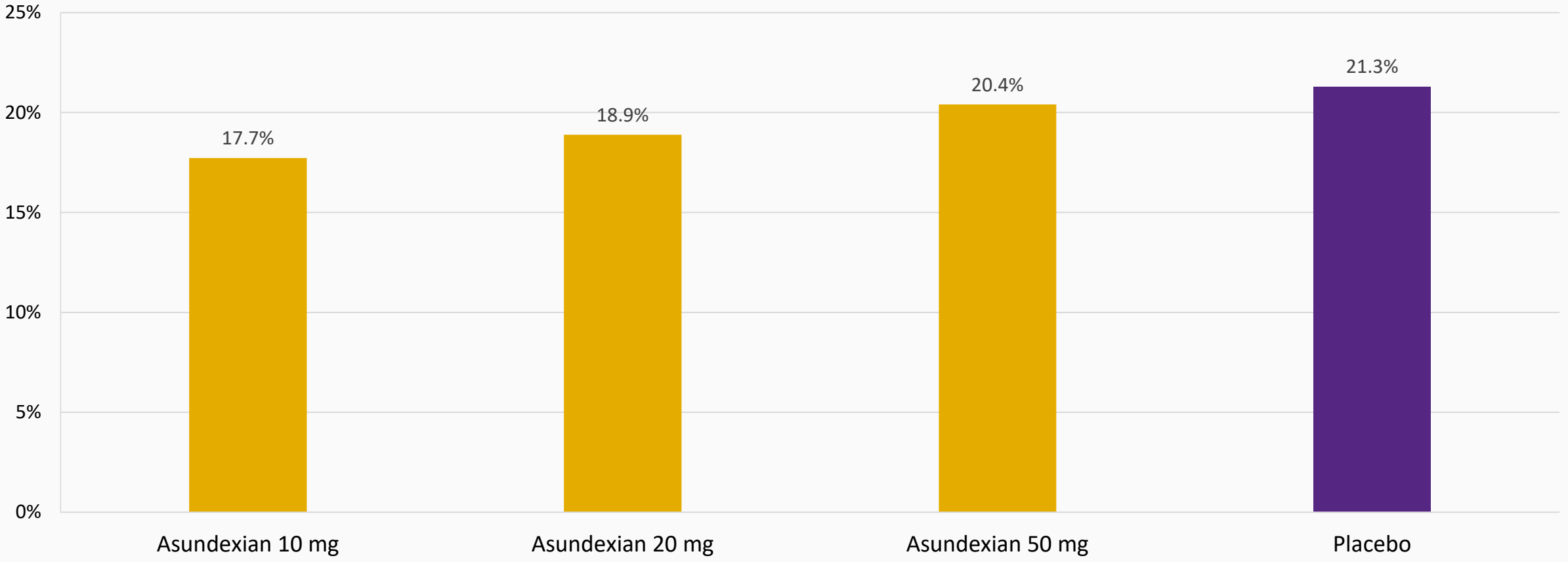
## Significant (BARC 2, 3, or 5) Bleeding

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



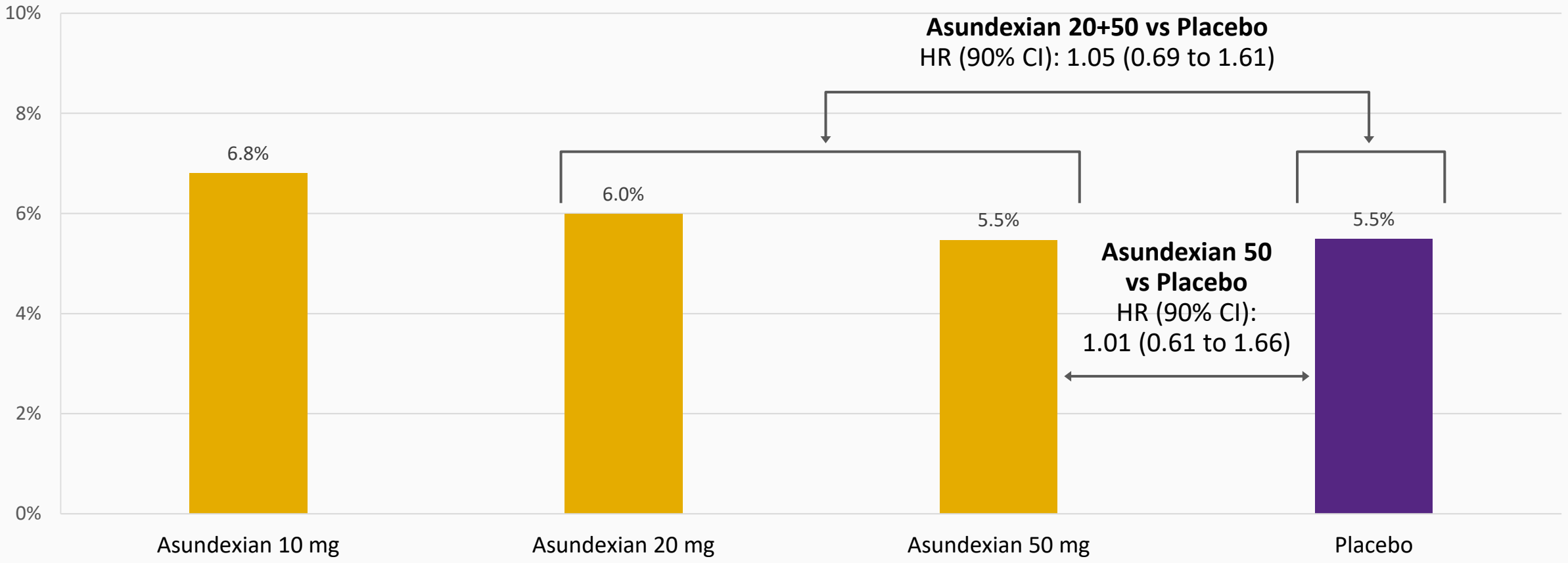
# Bleeding Outcomes

## Any Bleeding



# Efficacy Outcome

## CV Death, MI, Stroke or Stent Thrombosis



# Adverse Events

## Similar Accross Arms

PACIFIC AMI

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

# Summary and Conclusion

PACIFIC AMI

- First randomized placebo controlled trial with a small molecule factor XIa 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 XIa 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* | *PACIFIC-AF* | *PACIFIC-Stroke* | *PACIFIC-AMI* |
|---|---|---|---|
| **Indication** | **Prevention** of **stroke** in patients with **atrial fibrilation** | **Prevention** of **secondary non-cardioembolic stroke** in patients following a **recent non-cardioembolic stroke** | **Prevention** of a major cardiovascular event in patients following an **acute myocardial infarction** |
| **Safety** | // **67% eduction** in **ISTH major** or clinically relevant **non-major bleeding**<br>// **also consistent regarding all bleeds** | // **no significant increase** in the risk of **major** or **intracranial bleeding** | // **no increase** in any or **in BARC 2, 3** or **5 bleeding** with any dose of **asundexian** compared with **placebo**<br>// only **few bleeding** outcome events |
| **Efficacy** | **Phase 2 studies were not powered to show efficacy benefit** | | |
| | // study was not powered to show an **efficacy benefit** vs. **control arm** | // **60% reduction of stroke and TIA** observed in a non-prespecified subgroup analysis of patients **with pre-existing atherosclerosis** | // **no reduction** in **ischemic events** with any dose of **asundexian** |
| **FXI inhibition** | **@10 mg qd**: not part of the study | **@10 mg qd: >70%** | |
| | **@20 mg qd: >80%**<br>**@50 mg qd: >90%** | | |
| **Key findings/ Conclusions** | // dose dependent and, at 50 mg, near complete FXIa inhibition<br>// **safe** and **well** tolerated | | |
| | | // **efficacy benefits** demonstrated in subgroup | // did not show expected trend in **efficacy**<br>// further **investigations** necessary |
| | **unique pharmacological profile** | | |

# Results from PACIFIC Program also Fully Confirm Preclinical Findings

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

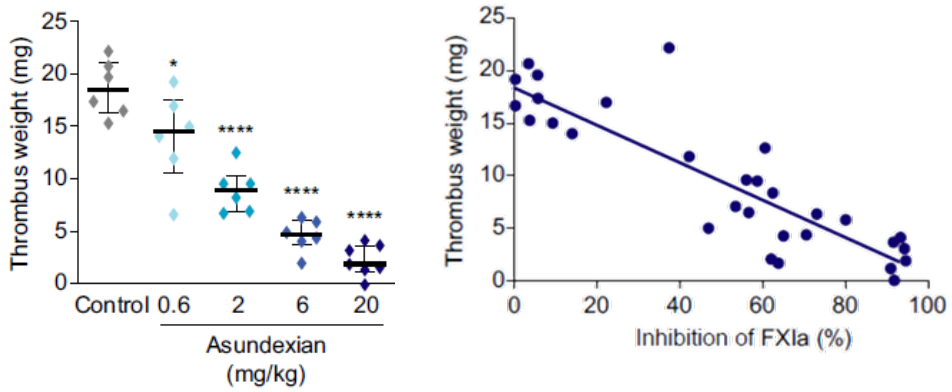
### Research models:

// 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

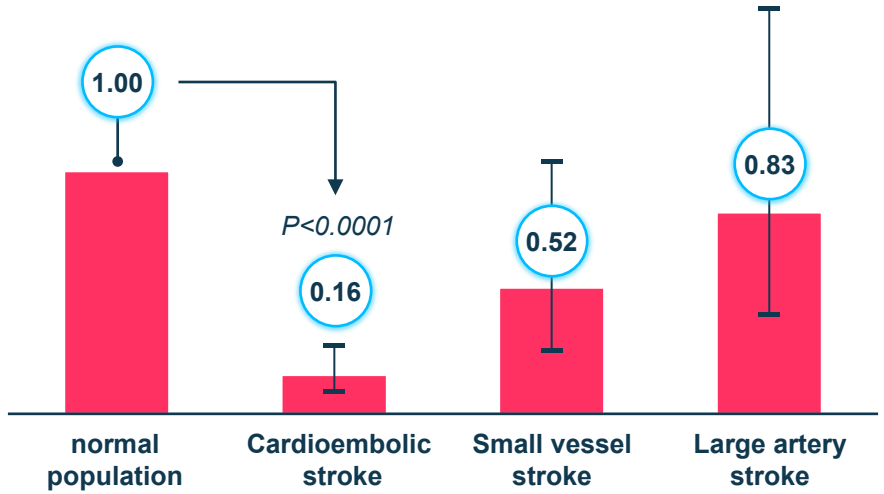



*Heitmeier S, et al. J Thromb Haemost.* 2022;20:1400–1411

### Human Genetic studies:

// Evidence for **reduction in stroke risk**

// **No impact** on bleeding




*Georgi, et al. Stroke. 2019;50:3004-3012.*

# 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**; **~40%** of eligible patients with AF **do not receive appropriate oral anticoagulation**[4]

5× Patients with AF have a **~5× 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.
[1] Wolf PA et al. Stroke 1991;22:983–988; [2] Alkhouli M et al. J Am Coll Cardiol 2018;71:2790–2801; [3] Thygesen SK et al. Clin Epidemiol 2009;1:55–65;
[4] Petty D, Fay M. Prescriber 19 May 2014. Available from: https://www.prescriber.co.uk/wp-content/uploads/sites/23/2015/12/Improving-anticoagulant-prescribing-for-AF.pdf. Accessed August 2021.

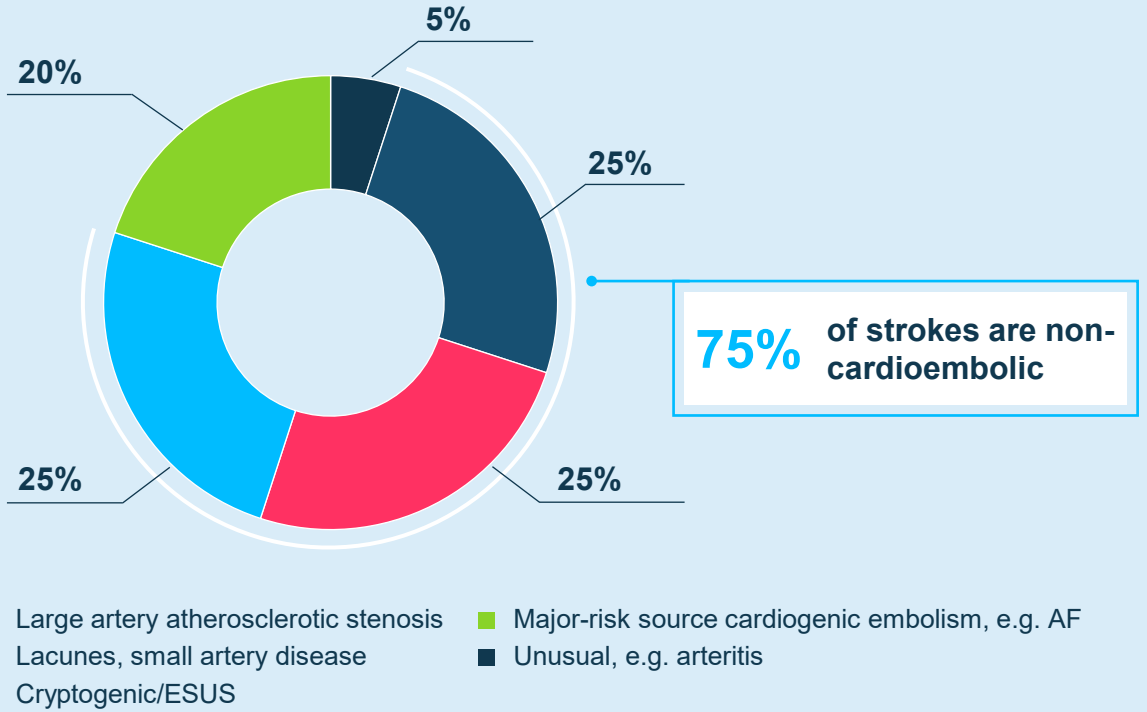
# Patients with Prior Stroke Have a High Risk of Recurrent Stroke[1]

## There remains an unmet need for patients with prior stroke

// **Antiplatelet agents** are recommended for the **secondary prevention** of **non-cardioembolic stroke**[3]

// **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[1,4]

## Distribution of ischemic stroke subtypes across North American and European studies[2]




AF, atrial fibrillation; ESUS, embolic stroke of undetermined source.
[1] Kleindorfer DO *et al. Stroke* 2021;52:e364–e467; [2] Hart R *et al. Lancet Neurol* 2014:13;429–438; [3] Dawson J *et al. Eur Stroke J* 2022; doi: 10.1177/23969873221100032; [4] Sharma M *et al. Circulation* 2019;139:1134–45.

# OCEANIC Phase III Program*

// **The OCEANIC program consists of two Phase III studies:**

## OCEANIC-AF

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

OCEANIC AF

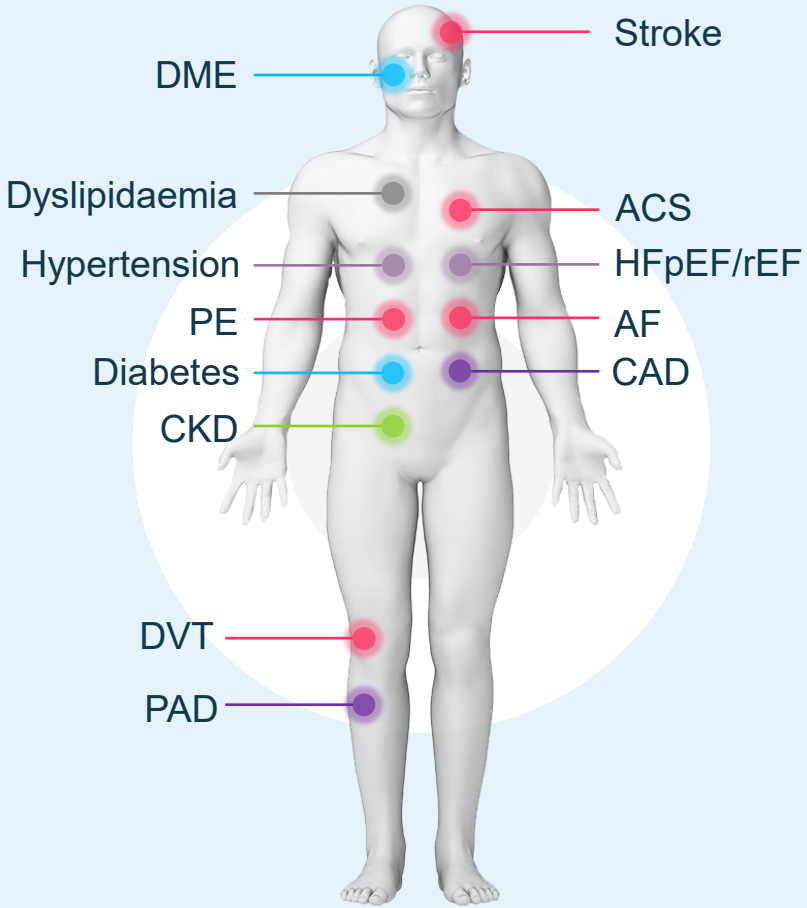
## OCEANIC-STROKE

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

OCEANIC STROKE

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

# Bayer Remains Committed to Develop Clinically Meaningful Innovations in Cardiovascular Diseases




**Our understanding of the relationship between CVD, renal disease and diabetes is growing**

- Thrombosis
- Heart disease
- Kidney disease
- Vascular disease
- Diabetes
- Other/Metabolic

# Questions & Answers

**Stefan Oelrich**

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

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