Multicenter, Randomized, Active Comparator-Controlled, Double-Blind, Double-Dummy, Parallel Group, Dose-Finding Phase 2 Study Comparing the Safety of the Oral FXIa Inhibitor Asundexian with Apixaban in Patients with Atrial Fibrillation: PACIFIC-AF

Manesh R. Patel, MD on behalf of the PACIFIC-AF Investigators
Disclosures

Research Grants:
  PACIFIC-AF: Bayer
  Other Research Support: Janssen, Heartflow, Idorsia, NHLBI, Novartis

Advisory Board/Consulting: Bayer, Janssen, Heartflow, Medscape
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)

DOAC

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

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>
</table>
| FXI-knockout mice<sup>1</sup> | • Homozygous FXI-knockout mice are protected from thrombosis  
• At the same time, they do not show a bleeding phenotype differing from wild-type mice |
| In vivo animal models<sup>2</sup> | • Reducing/inhibiting FXI showed strong antithrombotic effects *in vivo*  
• No increase in bleeding time even at very high doses or on top of dual antiplatelet therapy |
| Inherited FXI deficiency<sup>3</sup> | • Individuals with FXI deficiency are reported to have a reduced incidence of VTE and stroke  
• Hemorrhage occasionally reported after trauma or surgery (dental extractions, tonsillectomies, surgery in the urinary and genital tracts, and nasal surgery) |
| FXI clinical experience | • Antisense technology of IONIS<sup>4</sup>: 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)  
• Anti-FXI-AB (MAA868<sup>5</sup> and xisomab); Anti-FXla-AB (osocimab<sup>2</sup>): 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.<sup>6</sup> |

---


<sup>2</sup> Data on file


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
The PACIFIC Trials: Coordinated Phase 2 Programs

Together, will allow to assess the bleeding and efficacy profile of asundexian

Primary objective of PACIFIC-AF: evaluate comparative bleeding rate of asundexian vs apixaban in patients with AF

No assessment of efficacy possible given low event #

PACIFIC-AMI and PACIFIC-STROKE as placebo-controlled studies on top of antiplatelet therapy

PACIFIC-AF is the first Phase 2 study that will read out
PACIFIC Program

Concerted evaluation across large several Phase 2 programs

PACIFIC AF
Atrial fibrillation
20mg asundexian
50mg asundexian
apixaban

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

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

750 patients randomized
Results at ACC 2022

1800 patients randomized
Results later this year

1600 patients randomized
Results later this year

// One coordinated IDMC
// One blinded CEC with uniform process
Randomized, Active Comparator-Controlled, Double-Blind, Double-Dummy, Parallel Group, Dose-Finding Phase 2 Study to Compare the Safety of the Oral FXIa Inhibitor Asundexian to Apixaban in Patients with Atrial Fibrillation (PACIFIC-AF)

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
AXIA: Factor XIa Inhibition Assay

// Proprietary assay
// ~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
Results of PACIFIC-AF
Disposition / Study Flow

- **Enrolled**: 862
- **Randomized (FAS)**: 755
- **Treatment Phase started (SAF)**: 753
- **Treatment Phase completed**: 671

**Screening failures 107**
- Inclusion/exclusion criteria 69
- Withdrawal by subject 28
- Other reasons 10

**Never took any study drug 2**

**Did not complete treatment phase 82**
- Adverse event 38
- Other reasons 25
  - Death 6
  - Physician decision 6
  - Withdrawal by subject 6
  - Non-compliance with study drug 1
Demographics and Medical History — Well Balanced Across Treatment Arms

<table>
<thead>
<tr>
<th></th>
<th>Asundexian 20 mg N = 251</th>
<th>Asundexian 50 mg N = 254</th>
<th>Apixaban N = 250</th>
<th>Total N = 755</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (SD)</td>
<td>73.6 (8.0)</td>
<td>73.1 (8.5)</td>
<td>74.3 (8.3)</td>
<td>73.7 (8.3)</td>
</tr>
<tr>
<td>Female</td>
<td>103 (41.0%)</td>
<td>97 (38.2%)</td>
<td>109 (43.6%)</td>
<td>309 (40.9%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>211 (84.1%)</td>
<td>212 (83.5%)</td>
<td>209 (83.6%)</td>
<td>632 (83.7%)</td>
</tr>
<tr>
<td>Asian</td>
<td>39 (15.5%)</td>
<td>40 (15.7%)</td>
<td>40 (16.0%)</td>
<td>119 (15.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>226 (90.0%)</td>
<td>227 (89.4%)</td>
<td>220 (88.0%)</td>
<td>673 (89.1%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>142 (56.6%)</td>
<td>153 (60.2%)</td>
<td>152 (60.8%)</td>
<td>447 (59.2%)</td>
</tr>
<tr>
<td>Cardiac failure chronic</td>
<td>108 (43.0%)</td>
<td>107 (42.1%)</td>
<td>117 (46.8%)</td>
<td>332 (44.0%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>76 (30.3%)</td>
<td>71 (28.0%)</td>
<td>85 (34.0%)</td>
<td>232 (30.7%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>83 (33.1%)</td>
<td>74 (29.1%)</td>
<td>87 (34.8%)</td>
<td>244 (32.3%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>55 (21.9%)</td>
<td>84 (33.1%)</td>
<td>77 (30.8%)</td>
<td>216 (28.6%)</td>
</tr>
<tr>
<td>CHA2DS2-VASc score (SD)</td>
<td>3.99 (1.39)</td>
<td>3.83 (1.29)</td>
<td>4.10 (1.46)</td>
<td>3.97 (1.38)</td>
</tr>
</tbody>
</table>

Duke Clinical Research Institute

PACIFIC AF
### Medical History of Special Interest

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Asundexian 20 mg N = 251</th>
<th>Asundexian 50 mg N = 254</th>
<th>Apixaban N = 250</th>
<th>Total N = 755</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular accident</td>
<td>22 (8.8%)</td>
<td>18 (7.1%)</td>
<td>25 (10.0%)</td>
<td>65 (8.6%)</td>
</tr>
<tr>
<td>Coronary artery bypass</td>
<td>22 (8.8%)</td>
<td>16 (6.3%)</td>
<td>17 (6.8%)</td>
<td>55 (7.3%)</td>
</tr>
<tr>
<td>Peripheral arterial occlusive disease</td>
<td>16 (6.4%)</td>
<td>10 (3.9%)</td>
<td>20 (8.0%)</td>
<td>46 (6.1%)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>13 (5.2%)</td>
<td>10 (3.9%)</td>
<td>13 (5.2%)</td>
<td>36 (4.8%)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>7 (2.8%)</td>
<td>14 (5.5%)</td>
<td>3 (1.2%)</td>
<td>24 (3.2%)</td>
</tr>
<tr>
<td>Carotid revascularization</td>
<td>3 (1.2%)</td>
<td>2 (0.8%)</td>
<td>4 (1.6%)</td>
<td>9 (1.2%)</td>
</tr>
<tr>
<td>Embolism arterial</td>
<td>3 (1.2%)</td>
<td>2 (0.8%)</td>
<td>2 (0.8%)</td>
<td>7 (0.9%)</td>
</tr>
</tbody>
</table>
FXIa Activity - Inhibition Data

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)

On-treatment analysis, % of patients

- No ISTH major bleeding in any treatment arm
- Less bleeding in the 2 asundexian arms reported, when compared to apixaban for different severities of bleeding
- Consistent also for BARC and TIMI bleeding definitions
Primary Safety
(Pooled) ratio of the incidence proportions for the safety outcome in the treatment emergent data scope

<table>
<thead>
<tr>
<th></th>
<th>Asundexian 20 mg vs. Apixaban</th>
<th>Asundexian 50 mg vs. Apixaban</th>
<th>Asundexian (pooled) vs. Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIR (90% CI)</td>
<td>CIR (90% CI)</td>
<td>CIR (90% CI)</td>
</tr>
<tr>
<td>ISTH major bleeding or CRNM bleeding</td>
<td>0.50 (0.14 - 1.68)</td>
<td>0.16 (0.01 - 0.99)</td>
<td>0.33 (0.09 - 0.97)</td>
</tr>
<tr>
<td>ISTH major bleeding</td>
<td>n.c.</td>
<td>n.c.</td>
<td>n.c.</td>
</tr>
<tr>
<td>CRNM bleeding</td>
<td>0.50 (0.14 - 1.68)</td>
<td>0.16 (0.01 - 0.99)</td>
<td>0.33 (0.09 - 0.97)</td>
</tr>
<tr>
<td>ISTH minor bleeding</td>
<td>0.50 (0.23 - 0.99)</td>
<td>0.44 (0.18 - 0.86)</td>
<td>0.47 (0.28 - 0.83)</td>
</tr>
<tr>
<td>All bleeding</td>
<td>0.46 (0.23 - 0.83)</td>
<td>0.38 (0.16 - 0.68)</td>
<td>0.42 (0.26 - 0.67)</td>
</tr>
</tbody>
</table>
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Asundexian 20 mg N = 249 (100%)</th>
<th>Asundexian 50 mg N = 254 (100%)</th>
<th>Apixaban N = 250 (100%)</th>
<th>Asundexian Total N = 503 (100%)</th>
<th>Total N = 753 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>118 (47.4%)</td>
<td>120 (47.2%)</td>
<td>122 (48.8%)</td>
<td>238 (47.3%)</td>
<td>360 (47.8%)</td>
</tr>
<tr>
<td>Any study drug-related AE</td>
<td>29 (11.6%)</td>
<td>26 (10.2%)</td>
<td>37 (14.8%)</td>
<td>55 (10.9%)</td>
<td>92 (12.2%)</td>
</tr>
<tr>
<td>Any AE leading to discontinuation of study drug</td>
<td>15 (6.0%)</td>
<td>16 (6.3%)</td>
<td>13 (5.2%)</td>
<td>31 (6.2%)</td>
<td>44 (5.8%)</td>
</tr>
<tr>
<td>Any study drug-related SAE</td>
<td>4 (1.6%)</td>
<td>0</td>
<td>0</td>
<td>4 (0.8%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>AE with outcome death</td>
<td>1 (0.4%)</td>
<td>3 (1.2%)</td>
<td>2 (0.8%)</td>
<td>4 (0.8%)</td>
<td>6 (0.8%)</td>
</tr>
</tbody>
</table>

Asundexian was well tolerated in patients with AF.
## Exploratory Efficacy Analysis

<table>
<thead>
<tr>
<th></th>
<th>Asundexian 20 mg N = 251</th>
<th>Asundexian 50 mg N = 254</th>
<th>Apixaban N = 250</th>
<th>Total N = 755</th>
</tr>
</thead>
<tbody>
<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
Summary
Summary of Findings

// First randomized active comparator (apixaban) data with small molecule Factor XIa inhibitor (asundexian)

// Near complete inhibition of Factor XI activity with 20 and 50 mg dose asundexian

// Only few bleeding outcome events were observed
  // 48 participants with a bleeding event in total

// Point estimators of risk ratios in favor of asundexian
  // For the pooled 20 and 50 mg doses as well as for 50 mg alone the confidence intervals could exclude 1 for CRNM bleeding as well as for minor bleeding and all bleeding
  // Overall bleeding rates lower than expected
    (for Apixaban: 4% assumed vs. 2.4% observed)

// As expected — no information on efficacy events: limited events with fewer than 10 events total
Conclusions

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

Significantly lower bleeding rates were seen for patients randomized to either dose of asundexian compared to apixaban.

Factor XI inhibition is a promising strategy to prevent pathologic thrombi while minimizing bleeding risk in AF patients — Phase 3 trial required.

Safety of the oral factor Xla inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

Jonathan P Piccini, Valeria Caso, Stuart J Connolly, Keith A A Fox, Jonas Oldgren, W Schuyler Jones, Diana A Gorog, Vaclav Durdil, Thomas Viethen, Christoph Neumann, Hariri Mundl, Manesh R Patel, on behalf of the PACIFIC-AF Investigators*
Next Steps:
Engaging Patients and International Communities to Perform Clinical CV Outcomes Trial

// Net clinical benefit endpoints in upcoming OCEANIC AF trial will be informed by patient preference survey

// AFIBOPPORTUNITIES.COM

// Live Spring, 2022

// Engaging investigators who want to be part of innovative patient-centered trials
(Manesh.Patel@Duke.EDU)
SC Members
Manesh Patel
Valeria Caso
Stuart Connolly
Keith Fox
Jonas Oldgren
Jonathan Piccini

IDMC Members
Jonathan Halperin
Steven Greenberg
Thomas Cook
Saskia Middeldorp
Christoph Bode

Investigators & Teams
Johann Auer
Andreas Schober
Christopher Adlbrecht
Matthias Frick
Michael Lichtenauser
Robert Schönbauer
Daniel Scherr
Markus Stühlinger
Helmut Pürerfellner
Johan Vijgen
Karl Dujardin
Rene Tavernier
Tom Rossenbacker
Hein Heidbuchel
Gert Vervoort
Thomas Vanassche
Christian Constance
Jafna Cox
Laurent Macle
Isabelle Nault
Zdenek Coufal
Ondrej Cermak
Hana Linkova
Jiri Kettner
Ivo Podpera
Vlastimil Vancura
Vratislav Dedek
Vaclav Durdl
Nicolas Lellouche
GuillaumeTaldir
Emmanuel Boiffard
Hervé Gorka
Fabrice Extramiana
Haten Boughanmi
Meyer Elbaz
Robert Kiss
Bela Benczur
Laszlo Nagy
Andras Matoltsy
Bela Merkely
Kalman Toth
Zsolt Zilahi
Daniel Aradi
Leonardo Bolognese
Simona D’Orazio
Cecilia Becattini
Vito Maurizio Parato
Pietro Ameri
Maria Lorenza Muiesan
Pasquale Pignatelli
Eiji Tamiya
Shinichi Higashiue
Katsusmi Saito
Yuichiro Nakamura
Akira Shimane
Tetsuo Betsuyaku
Hideki Ueno
Koshi Matsuo
Yoshiki Hata
Iveta Sime
Ilze Reinholde
Janina Romanova
Natalja Pontaga
Artis Kalnins
Arcils Gersamija
Nadezda Rozkova
Ignasi Anguera Camós
Rafael Salguero Bodes
Juan José Gómez-Doblas
Ignacio Ferreira González
Xavier Viñolas Prat
Carl-Johan Lindholm
Håkan Wallén
Ken Eliasson
Jens Olsson
Markus Lind
Niclas Svedberg
Thomas Mooe
Christian Müller
Tobias Reichlin
Hans Rickli
Laurent M. Haegeli
Angelo Auricchio
François Mach
Joris de Groot
Dominik Linz
Marco Alings
Louis Bartels
Ron Pisters
Aaf Kuijper
Ewout van den Bos
Jeroen Stevenhagen
Gregory Lip
Anthony Gunstone
Diana Gorog
Roxy Senior
Yuk-Ki Wong

Duke Clinical Research Institute
PACIfic AF
Thank you!