Key Findings in XANTUS: The First Global Prospective Real World Evidence of Rivaroxaban in AF

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<tbody>
<tr>
<td>Research Support</td>
<td>None</td>
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<tr>
<td>Employee</td>
<td>None</td>
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<tr>
<td>Consultant and/or Honoraria</td>
<td>Bayer HealthCare, Boehringer-Ingelheim, Bristol-Myers Squibb, Johnson and Johnson, Sanofi-Aventis, Takeda, Portola</td>
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<td>Stockholder</td>
<td>None</td>
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<td>Speakers Bureau</td>
<td>Pfizer, GSK</td>
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<tr>
<td>Scientific Advisory Board</td>
<td>Bayer HealthCare, Johnson and Johnson,</td>
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</tbody>
</table>
New anticoagulants

**ORAL**
- TTP889
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban
- Dabigatran

**PARENTERAL**
- TFPI (tifacogin)
- APC (drotrecogin alfa)
- sTM (ART-123)
- Fondaparinux
- DX-9065a
- Otamixaban

Adapted from Weitz & Bates, *J Thromb Haemost* 2005
Stroke Prevention in AF
“At its best a trial shows what can be accomplished with a medicine under careful observation and certain restricted conditions. The same results will not invariably or necessarily be observed when the medicine passes into general use.”

Austin Bradford Hill – Father of the modern RCT

“Between measurements based on randomized controlled trials and benefit in the community there is a gulf which has been much underestimated”

A. L. Cochrane – Cataloguer of RCTs
Post-authorization Studies

- Post-marketing surveillance surveillance studies (PMSS) : Data base analyses
- Registries
- Non-interventional studies
Prospective
Phase IV Studies
Europe, Israel and Canada

XANTUS\textsuperscript{1} (N=6784)

Middle East, Eastern Europe, Africa and Latin America

XANTUS-EL\textsuperscript{2} (N=2064)

Asia-Pacific

XANAP\textsuperscript{3} (N=2273)

XANTUS Programme Study Design

- XANTUS, XANTUS-EL and XANAP study protocols were aligned
- Prospective, single-arm, non-interventional studies
  - Major outcomes adjudicated by an independent Central Adjudication Committee

**Population:**
Adult patients with a diagnosis of non-valvular AF newly starting rivaroxaban treatment for prevention of stroke or non-CNS SE

**N=11,121**

**Rivaroxaban:**
- treatment duration and dose at physician’s discretion

**Data collection at initial visit, hospital discharge (if applicable) and quarterly**

**Final visit:**
1 year

**Primary outcomes:**
- major bleeding (ISTH definition), all-cause mortality, any other adverse events

*Exact referral dates for follow-up visits were not defined (every 3 months recommended); #for rivaroxaban discontinuation after ≤1 year, the observation period ended 30 days after the last dose.
Kirchhof P, Turpie AG et al, presented at the European Society of Cardiology 2017, abstract 86691"
XANTUS programme: Primary and Secondary Outcomes

- **Primary outcomes**
  - Major bleeding (ISTH definition)
  - All-cause mortality
  - Any other AEs
  - Any other serious AEs

- **Secondary outcomes**
  - Symptomatic thromboembolic events
  - Non-major bleeding events
    - Any bleeding event that does not meet the criteria for a major haemorrhage
  - AEs and serious AEs across risk scores

- AEs and serious AEs in important subgroups
- Other outcomes collected included:
  - Patient treatment satisfaction using standardized questionnaires
  - Persistence with therapy
  - Healthcare resource use
  - Details of interventions and how they were managed
  - Concomitant medication use
  - Reasons for switching/interrupting rivaroxaban therapy

Kirchhof P, Turpie AG *et al*, presented at the European Society of Cardiology 2017, abstract 86691
XANTUS Global Pooled Analysis

Enrolled N=11,122

Safety population N=11,121

Patients excluded N=5065

- 1 patient did not receive any rivaroxaban
- Primary analysis population: defined as all patients who took at least one dose of rivaroxaban

Western Europe, Canada, Israel N=5287 (47.5%)
- Eastern Europe N=2577 (23.2%)
- East Asia N=2233 (20.1%)
- Middle East, Africa N=690 (6.2%)
- Latin America N=334 (3.0%)

Reasons patient not included in study:
- Patient decision (n=1599, 9.9%)
- Administrative reason (n=468, 2.9%)
- Availability of drug (n=140, 0.9%)
- Medical guidelines (n=426, 2.6%)
- Price of drug (n=612, 3.8%)
- Medical reasons (n=502, 3.1%)
- Internal hospital guidelines (n=37, 0.2%)
- Type of health insurance (n=205, 1.3%)
- Other (n=1716, 10.6%)

*Some patients could have > 1 reason for exclusion
Kirchhof P et al, presented at the European Society of Cardiology 2017, abstract 86691
Baseline Characteristics ROCKET AF and XANTUS Pooled

<table>
<thead>
<tr>
<th>Baseline</th>
<th>ROCKET AF*¹</th>
<th>XANTUS Pooled#²</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS₂, mean</td>
<td>3.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Age, years, median</td>
<td>73</td>
<td>70.5</td>
</tr>
<tr>
<td>Heart failure</td>
<td>63%</td>
<td>21%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90%</td>
<td>76%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40%</td>
<td>22%</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>55%</td>
<td>21%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>17%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Results are not intended for direct comparison

*Characteristics based on ITT population (n=7131), trial included only NVAF patients with moderate-to-high risk of stroke, i.e. CHADS₂ score ≥2; #results based on safety population (n=11,121); 1. Patel MR et al, N Engl J Med 2011;365:883–891; 2. Kirchhof P, Turpie AG et al, presented at the European Society of Cardiology 2017, abstract 86691
XANTUS Programme: Rivaroxaban Treatment Profile

- XANTUS pooled¹: treatment duration (mean ± SD) was 324.5±117.80 days, with a median of 366 days*
- XANTUS pooled¹: treatment persistence at 1 year was 77.4%

*Interquartile range 330–379 days

XANTUS Pooled: Key Overall Outcomes of Safety Population

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence Rate (events/100 patient-years)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>1.7</td>
<td>(1.5–2.0*)</td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>1.0</td>
<td>(0.8–1.2*)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.9</td>
<td>(1.6–2.2*)</td>
</tr>
</tbody>
</table>

*Represents 95% confidence interval
Kirchhof P et al, presented at the European Society of Cardiology 2017, abstract 86691
<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence proportion, n (%)</th>
<th>Incidence rate, events/100 patient-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>172 (1.5)</td>
<td>1.7 (1.5–2.0)</td>
</tr>
<tr>
<td>Fatal*</td>
<td>17 (0.2)</td>
<td>0.2 (0.1–0.3)</td>
</tr>
<tr>
<td>Critical organ bleeding</td>
<td>62 (0.6)</td>
<td>0.6 (0.5–0.8)</td>
</tr>
<tr>
<td>ICH</td>
<td>42 (0.4)</td>
<td>0.4 (0.3–0.6)</td>
</tr>
<tr>
<td>Mucosal bleeding</td>
<td>80 (0.7)</td>
<td>0.8 (0.6–1.0)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>71 (0.6)</td>
<td>0.7 (0.6–0.9)</td>
</tr>
<tr>
<td>Haemoglobin decrease in ≥2 g/dl</td>
<td>58 (0.5)</td>
<td>0.6 (0.4–0.8)</td>
</tr>
<tr>
<td>Transfusion in ≥2 units of packed RBCs or whole blood</td>
<td>73 (0.7)</td>
<td>0.7 (0.6–0.9)</td>
</tr>
<tr>
<td>Non-major bleeding events</td>
<td>1195 (10.7)</td>
<td>12.8 (12.1–13.5)</td>
</tr>
</tbody>
</table>

Rates of fatal bleeding and ICH were low in patients treated with rivaroxaban

*Fatal bleeding using narrow definitions (the patient experienced a treatment-emergent major bleeding event and died within 30 days of the major bleeding event and the adjudicated primary cause of death was either ICH or extracranial bleeding; *Analyses based on 11,121 patients in the safety population
Kirchhof P *et al.*, presented at the *European Society of Cardiology 2017*, abstract 86691
# Adjudicated Treatment-Emergent Thromboembolic Events in Safety Population

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<thead>
<tr>
<th>Incidence proportion, n (%)</th>
<th>Incidence rate, events/100 patient-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thromboembolic events (stroke, TIA, non-CNS SE and MI)</strong></td>
<td>179 (1.6)</td>
</tr>
<tr>
<td><strong>Stroke/non-CNS SE</strong></td>
<td>98 (0.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>87 (0.8)</td>
</tr>
<tr>
<td>Primary ischaemic</td>
<td>64 (0.6)</td>
</tr>
<tr>
<td>Primary haemorrhagic*</td>
<td>20 (0.2)</td>
</tr>
<tr>
<td>Non-CNS SE</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>TIA</td>
<td>41 (0.4)</td>
</tr>
<tr>
<td>MI</td>
<td>42 (0.4)</td>
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Rates of stroke/non-CNS SE were low in patients treated with rivaroxaban#

*Haemorrhagic strokes and haemorrhagic transformations of ischaemic stroke were reported as both stroke and major bleeding (multiple reasons for major bleedings were possible); Analyses based on 11,121 patients in the safety population Kirchhof P et al, presented at the European Society of Cardiology 2017, abstract 86691
Key Outcomes in Safety Population Stratified by CHA$_2$DS$_2$-VASc Score

In general, rates of major outcomes increased with higher CHA$_2$DS$_2$-VASc scores*

*Analyses based on 11,121 patients in the safety population
Kirchhof P et al, presented at the European Society of Cardiology 2017, abstract 86691
Cumulative Rates for Treatment-Emergent Major Bleeding, Stroke/non-CNS SE and Death in Safety Population

Over 96% of the XANTUS pooled safety population* did not experience any of the events of treatment-emergent major bleeding, stroke/non-CNS SE or all-cause death

*Non-CNS SE; #Safety population n=11,121
Kirchhof P et al, presented at the European Society of Cardiology 2017, abstract 86691
**XANTUS Pooled: Key Differences in Outcomes by Region**

**Proportion of patients free from major bleeding or stroke/non-CNS SE consistent between regions (95.7–97.4%)**

**Major bleeding**
Highest in Western Europe/Canada/Israel vs other regions
(2.3 vs 0.7–1.6 events/100 patient-years)

**Stroke/non-CNS SE**
Highest in East Asia vs other regions
(1.8 vs 0–1.0 events/100 patient-years)

**Mortality**
Highest in the Middle East/Africa and Latin America vs other regions
(2.7 vs 1.5–2.0 events/100 patient-years)

*Kirchhof P et al, presented at the European Society of Cardiology 2017, abstract 86691*
Rivaroxaban Is Effective and Provides a Beneficial Safety Profile in the Phase III Clinical Trial

**Efficacy**

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**Baseline**

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<td>Diabetes</td>
<td>40%</td>
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<tr>
<td>Prior stroke§</td>
<td>55%</td>
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<td>Prior MI</td>
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**Safety**

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<td>3.6</td>
</tr>
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<td>ICH</td>
<td>0.5</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>2</td>
</tr>
</tbody>
</table>

*Results based on the as-treated safety population (n=7061); \(^{#}\)Characteristics based on ITT population (n=7131); trial included only NVAF patients with moderate-to-high risk of stroke, i.e. CHADS₂ score ≥2; \(^{‡}\)Results based on the first event in safety population during treatment (n=7111); \(^{§}\)includes prior stroke, SE or TIA

Rivaroxaban Effectiveness and Safety in the Real World

**XANTUS Pooled**

**Effectiveness**

<table>
<thead>
<tr>
<th>Condition</th>
<th>On-treatment event rate (events/100 patient-years)</th>
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<tbody>
<tr>
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<td>1.0</td>
</tr>
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<td>1.9</td>
</tr>
</tbody>
</table>

**Baseline**

- **CHADS<sub>2</sub>, mean**: 2.0
- **Age, years, mean**: 70.5
- **Heart failure**: 21%
- **Hypertension**: 76%
- **Diabetes**: 22%
- **Prior stroke#**: 21%
- **Prior MI**: 9%

**Safety**

- **Major bleeding**: 1.7
- **ICH**: 0.4
- **GI bleeding**: 0.7

*Results based on safety population n=11,121; includes prior stroke, SE or TIA
Kirchhof P Turpie AG et al, presented at the European Society of Cardiology 2017, abstract 86691
Conclusion

- XANTUS is a global programme involving three large prospective studies using identical protocols that describe the use of rivaroxaban in a broad population of patients with non-valvular AF.

- Patients in XANTUS were at lower overall risk than those in the rivaroxaban phase III ROCKET AF clinical trial.

- The rates of major bleeding, intracranial haemorrhage, GI bleeding and stroke with rivaroxaban were low in routine clinical practice.