Ximelagatran Efficacy

Jay Horrow, MD, MS
Senior Director, Clinical Development

AstraZeneca
Proposed Indications for Ximelagatran

- Long-term secondary prevention of VTE after standard treatment for an episode of acute VTE
- Prevention of VTE in patients undergoing knee replacement surgery
- Prevention of stroke and other thromboembolic complications of atrial fibrillation
CE-3

Trial Design—Secondary Prevention of VTE
THRIVE III

**Initial VTE event**

- Ximelagatran 24 mg bid

- Placebo

- **ITT**
  - n = 612

- **AC Therapy**
  - 6 ± 1 mo

- **18 mo**

- **2-wk follow-up**

Baseline:
ultrasonography + perfusion lung scan
Dose Selection for THRIVE III
Doses Achieving Target Melagatran Levels

Source: METHRO II Orthopedic Surgery Trial.
Dose Selection for THRIVE III
Data From Knee and Hip Replacement

METHRO II
n = 1477 patients

- 5000 IU Dalteparin sc once daily: 28%
- 1 mg Dalteparin sc: 38%
- 1.5 mg Melagatran/Ximelagatran: 24%
- 2.25 mg Melagatran/Ximelagatran: 24%
- 3 mg sc Melagatran/Ximelagatran twice daily: 15%
Primary Endpoint
THRIVE III

Rate of recurrence of symptomatic objectively confirmed VTE (DVT or PE)

- Time-to-event analysis
- VTE sign or symptom → objective confirmation
- Blinded independent adjudication committee
  - All clinical endpoints
## Baseline Characteristics

**THRIVE III (ITT Population)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ximelagatran n = 612</th>
<th>Placebo n = 611</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr mean (range)</td>
<td>56 (18 - 87)</td>
<td>58 (19 - 90)</td>
</tr>
<tr>
<td>Female, %</td>
<td>46</td>
<td>49</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Weight, kg mean (range)</td>
<td>82 (45 - 145)</td>
<td>82 (47 - 150)</td>
</tr>
<tr>
<td>BMI, kg/m(^2) mean (range)</td>
<td>28 (18 - 53)</td>
<td>28 (18 - 53)</td>
</tr>
<tr>
<td>CrCL 30 to &lt; 80 mL/min, %</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>≥ 1 prior VTE event, %</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Primary event PE ± DVT, %</td>
<td>34</td>
<td>36</td>
</tr>
</tbody>
</table>
Primary Outcome—Recurrence of VTE Events
THRI VE III (ITT Population)

HR = 0.16 (95% CI 0.09, 0.30)

ARR = 9.8%
p < 0.0001
NNT = 10

ARR = 9.8%
p < 0.0001
NNT = 10

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>Ximelagatran</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>612</td>
<td>611</td>
</tr>
<tr>
<td>3</td>
<td>590</td>
<td>557</td>
</tr>
<tr>
<td>6</td>
<td>546</td>
<td>532</td>
</tr>
<tr>
<td>9</td>
<td>522</td>
<td>502</td>
</tr>
<tr>
<td>12</td>
<td>506</td>
<td>474</td>
</tr>
<tr>
<td>15</td>
<td>474</td>
<td>438</td>
</tr>
<tr>
<td>18</td>
<td>107</td>
<td>86</td>
</tr>
</tbody>
</table>

## Breakdown of Composite Primary Endpoint
### THRIVE III (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Ximelagatran, n = 612</th>
<th>Placebo, n = 611</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Incidence</td>
</tr>
<tr>
<td>DVT only</td>
<td>10</td>
<td>1.6%</td>
</tr>
<tr>
<td>PE only</td>
<td>2</td>
<td>0.3%</td>
</tr>
<tr>
<td>DVT and PE</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
Results Are Robust
THRIEV III

Prespecified sensitivity analyses:

- Primary outcome, per-protocol analysis
- Primary outcome, local reports
- All-cause mortality + total VTE
- Proximal DVT alone

$p < 0.0001$ for all sensitivity analyses
Recurrence of VTE—Subgroup Analysis
THRIVE III (ITT Population)

<table>
<thead>
<tr>
<th>Ximelagatran better</th>
<th>Placebo better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td></td>
</tr>
<tr>
<td>65 - 75</td>
<td></td>
</tr>
<tr>
<td>&gt; 75</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td></td>
</tr>
<tr>
<td>25 - 30</td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td></td>
</tr>
<tr>
<td>CrCL, mL/min</td>
<td></td>
</tr>
<tr>
<td>≥ 80</td>
<td></td>
</tr>
<tr>
<td>50 - &lt; 80</td>
<td></td>
</tr>
<tr>
<td>30 - &lt; 50</td>
<td></td>
</tr>
</tbody>
</table>

Odds ratio (95% CI)
THRIIVE III Conclusions

- Significant reduction in number of recurrent VTE events during 18 mo of continued risk
- Results consistent across multiple endpoints and subgroups
- Number Needed to Treat (NNT) = 10
Proposed Indications for Ximelagatran

- Long-term secondary prevention of VTE after standard treatment for an episode of acute VTE
- Prevention of VTE in patients undergoing knee replacement surgery
- Prevention of stroke and other thromboembolic complications of atrial fibrillation
Choice of Comparator—Warfarin
VTE Prevention in Knee Replacement—EXULT

- Available therapy
  - LMWHs, fondaparinux, warfarin
- Warfarin chosen as comparator
  - Most commonly used pharmacologic prophylaxis with TKR in North America†
  - Warfarin is recommended in treatment guidelines‡
  - Less associated bleeding‡

‡ Geerts. ACCP. Chest. 2001.
Trial Design—Prevention of VTE in TKR
EXULT A and EXULT B

EXULT A
- Ximelagatran 36 mg bid
- Ximelagatran 24 mg bid
- Warfarin

EXULT B
- Warfarin

Day 0
- Begin warfarin evening of surgery
- Begin ximelagatran AM after surgery

Day 1
- Study treatment 7 - 12 days

Days 7 - 12
- Bilateral venography

Follow-up 4 - 6 wks
- Follow-up visit
Primary Endpoint
EXULT A and EXULT B

Composite of the following:

- **Total VTE**
  - Venography† (proximal and distal DVT)
  - Objectively confirmed symptomatic PE
- **All-cause mortality**
- **Blinded independent adjudication committee**
  - All clinical endpoints
  - Both major and minor bleeding

† Commonly accepted endpoint for VTE prophylaxis trials.
## Baseline Characteristics
**EXULT A and EXULT B (36 mg bid Pooled)**

<table>
<thead>
<tr>
<th></th>
<th>Ximelagatran n = 1611</th>
<th>Warfarin n = 1575</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr mean (range)</td>
<td>67 (26 - 91)</td>
<td>67 (32 - 89)</td>
</tr>
<tr>
<td>Female, %</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Weight, kg mean (range)</td>
<td>84 (44 - 159)</td>
<td>84 (41 - 144)</td>
</tr>
<tr>
<td>BMI, kg/m² mean (range)</td>
<td>31 (17 - 56)</td>
<td>31 (14 - 62)</td>
</tr>
<tr>
<td>CrCl 30 to &lt; 80 mL/min, %</td>
<td>34</td>
<td>35</td>
</tr>
</tbody>
</table>
Primary Outcome—Total VTE† and Mortality
EXULT A and EXULT B (ITT Population)

<table>
<thead>
<tr>
<th>Risk of event, %</th>
<th>Ximelagatran 36 mg bid</th>
<th>Warfarin</th>
<th>Ximelagatran 24 mg bid</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20.3</td>
<td>24.9</td>
<td>27.6</td>
<td>22.5</td>
</tr>
<tr>
<td></td>
<td>n = 629</td>
<td>614</td>
<td>608</td>
<td>982</td>
</tr>
</tbody>
</table>

- **EXULT A‡**:
  - **p = 0.003**
  - 26.5% RRR
  - NNT 14

- **EXULT B**
  - **p = 0.0000039**
  - 29.3% RRR
  - NNT 11

† Venous thromboembolism = distal + proximal DVT, + PE; RRR = Relative risk reduction.
## Breakdown of Composite Primary Endpoint
### EXULT A and EXULT B (ITT Population)

<table>
<thead>
<tr>
<th>Event</th>
<th>EXULT A</th>
<th>EXULT B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ximelagatran 36 mg, n = 629</td>
<td>Warfarin n = 608</td>
</tr>
<tr>
<td>Distal DVT</td>
<td>120 (19.1)</td>
<td>161 (26.5)</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>14 (2.2)</td>
<td>24 (3.9)</td>
</tr>
<tr>
<td>PE</td>
<td>2 (0.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>≥1 event</td>
<td>128 (20.3)</td>
<td>168 (27.6)</td>
</tr>
</tbody>
</table>

† Some patients experienced more than 1 event.
Total VTE, All-Cause Mortality—Subgroup Analysis
EXULT A and EXULT B (36 mg bid Pooled, ITT Population)

Difference in incidences (ximelagatran – warfarin)

-30 -20 -10 0 10 20 30
EXULT Conclusions

- Effectiveness superior to well-controlled, adjusted-dose warfarin in preventing VTE
- Efficacy was consistent across subgroups
Proposed Indications for Ximelagatran

- Long-term secondary prevention of VTE after standard treatment for an episode of acute VTE
- Prevention of VTE in patients undergoing knee replacement surgery
- Prevention of stroke and other thromboembolic complications of atrial fibrillation
Study Design
SPORTIF III and SPORTIF V

- Randomized, parallel-group, multicenter trials
  - SPORTIF III: open label, 3407 patients
  - SPORTIF V: double blind, 3922 patients

- Patients eligible for chronic oral anticoagulant therapy†
  - Nonvalvular atrial fibrillation
  - ≥ 1 risk factor for stroke
    • Previous stroke, TIA, or systemic embolism
    • Age ≥ 75 yr
    • History of hypertension
    • Poor left ventricular function
    • Age ≥ 65 yr AND diabetes mellitus
    • Age ≥ 65 yr AND coronary artery disease

† Albers et al. Chest. 2001;119:194S.
Study Design
SPORTIF III and SPORTIF V

- **Treatments**
  - Ximelagatran, 36 mg bid po
  - Warfarin, once-daily, po, dose-adjusted, INR 2.0 to 3.0

- **Primary endpoint**
  - All strokes (ischemic and hemorrhagic)
  - Systemic embolic events

- **Intention-to-treat analysis**
Dose Selection for Phase III in AF

- Increased minor bleeding with 60 mg in SPORTIF II
- 24 mg effective in European Orthopedic Surgery
- Impact of excess strokes with 24 mg far greater than that from bleeding with 36 mg
- 36 mg chosen for phase III AF
Blinding in SPORTIF Pivotal Trials

SPORTIF III: open-label dosing, 3407 patients
- Centralized randomization
- Local assessment: neurologist blinded to treatment
- Central adjudication committee blinded to treatment

SPORTIF V: double blind, 3922 patients
- Centralized randomization
- Local assessment: neurologist blinded to treatment
- Central adjudication committee blinded to treatment
- Double-dummy medication and sham INR values
Choice of Noninferiority Design

- Placebo comparator no longer possible
- Superiority comparison against warfarin not feasible
- Prespecified: 2% per yr absolute margin
  - Clinically tolerable difference in rates
  - Considers warfarin’s clinical profile
  - SPAF III used 3% per yr upper confidence limit†
- Strengths
  - Clinically relevant
  - Prespecified
  - Conservative

Study Design
SPORTIF III and SPORTIF V

Baseline

Ximelagatran 36 mg bid
n = 1704 (SP III); 1960 (SP V)

Warfarin od (INR 2-3)
n = 1703 (SP III); 1962 (SP V)

SPORTIF III open label: 12 to 26 mo

SPORTIF V double blind: 12 to 36 mo

2-wk follow-up

INR in range
66% of time - SP III
68% of time - SP V

Out of range > ½ time†
20.5% - SP III
15.0% - SP V

# Baseline Characteristics

**SPORTIF III and SPORTIF V (Pooled)**

<table>
<thead>
<tr>
<th></th>
<th>Ximelagatran n = 3664</th>
<th>Warfarin n = 3665</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr, mean (range)</strong></td>
<td>71 (29 - 97)</td>
<td>71 (35 - 92)</td>
</tr>
<tr>
<td><strong>Female, %</strong></td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td><strong>Caucasian, %</strong></td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td><strong>Weight, kg, mean (range)</strong></td>
<td>86 (35 - 202)</td>
<td>86 (40 - 204)</td>
</tr>
<tr>
<td><strong>BMI, kg/m², mean (range)</strong></td>
<td>29 (16 - 71)</td>
<td>29 (15 - 74)</td>
</tr>
<tr>
<td><strong>CrCL 30 to &lt; 80 mL/min, %</strong></td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td><strong>Prior stroke or TIA, %</strong></td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td><strong>Persistent AF, %</strong></td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td><strong>AF present &gt; 1 yr, %</strong></td>
<td>81</td>
<td>82</td>
</tr>
</tbody>
</table>
Primary Results
SPORTIF Pivotal Trials (ITT)
Primary Endpoint—Event Rate Differences
SPORTIF III and SPORTIF V (ITT)

**Primary Endpoint—Event Rate Differences**

- **SPORTIF III - ITT**  
  n = 3407

- **SPORTIF V - ITT**  
  n = 3922

**Difference in absolute event rates, %**
(ximelagatran – warfarin)

- Ximelagatran better
  -0.66

- Warfarin better
  +0.45

0.13

1.03
## Breakdown of Composite Primary Endpoint
### SPORTIF III and SPORTIF V (ITT)

<table>
<thead>
<tr>
<th></th>
<th>SPORTIF III</th>
<th></th>
<th>SPORTIF V</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ximelagatran</td>
<td>Warfarin</td>
<td>Ximelagatran</td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td>n = 1704</td>
<td>n = 1703</td>
<td>n = 1960</td>
<td>n = 1962</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>32</td>
<td>46</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>≥ 1 event</td>
<td>40</td>
<td>56</td>
<td>51</td>
<td>37</td>
</tr>
</tbody>
</table>

† Some patients experienced more than one event.
Sensitivity Analysis of Primary Endpoint Including All-Cause Mortality (ITT)

SPORTIF III - primary and all-cause mortality, n = 3407

SPORTIF V - primary and all-cause mortality, n = 3922

Difference in absolute event rates, % (ximelagatran – warfarin)

Ximelagatran better

Warfarin better

-0.87

0.34

+0.10

1.18
Sensitivity Analysis of Primary Endpoint
On Treatment Analysis

Ximelagatran better  Warfarin better

SPORTIF III - OT  n = 3407

SPORTIF V - OT  n = 3922

Difference in absolute event rates, %
(ximelagatran – warfarin)

-0.94  +0.55

-4 -3 -2 -1  0  1  2  3  4
**Ximelagatran vs Placebo (Putative)**

**SPORTIF III and SPORTIF V**

<table>
<thead>
<tr>
<th></th>
<th>Ximelagatran better</th>
<th>Placebo better</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPORTIF III</td>
<td>26%</td>
<td>42%</td>
</tr>
<tr>
<td>SPORTIF V</td>
<td>50%</td>
<td>83%</td>
</tr>
<tr>
<td>SPORTIF pooled</td>
<td>36%</td>
<td>54%</td>
</tr>
</tbody>
</table>

Relative Risk (ximelagatran: placebo), %
Efficacy in Atrial Fibrillation Subgroups
SPORTIF III and SPORTIF V (Pooled, ITT)

- Age, yr
  - 18 - 64
  - 65 - 75
  - > 75

- Gender
  - Male
  - Female

- Race
  - Caucasian
  - Black
  - Asian

- BMI, kg/m²
  - < 25
  - 25 - 30
  - > 30

- CrCL, mL/min
  - ≥ 80
  - 50 - < 80
  - 30 - < 50

Difference in primary event rate, % per yr

Ximelagatran better
Warfarin better
Conclusions—Efficacy of Ximelagatran

Fixed-dose ximelagatran, without coagulation monitoring:

- **36 mg bid noninferior to well-controlled warfarin:** Preventing stroke and other thromboembolic complications associated with AF (SPORTIF III, SPORTIF V)

- **24 mg bid superior to placebo:** Long-term secondary prevention of VTE after standard treatment for an episode of acute VTE (THRIVE III)

- **36 mg bid superior to well-controlled warfarin:** Preventing VTE in patients undergoing knee replacement surgery (EXULT A, EXULT B)