RE-ALIGN: Dabigatran in Patients With a Mechanical Heart Valve

Randomized, phase II study to Evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement
DECLARATION OF INTEREST

- Research contracts
- Consulting/Royalties/Owner/ Stockholder of a healthcare company
Background

• Vitamin K antagonists provide effective protection against thrombosis in patients with a mechanical valve but require food, alcohol and drug restrictions and coagulation monitoring

• Dabigatran 150 mg bid is superior to warfarin in non-valvular atrial fibrillation (RELY)

• Encouraging preclinical data with dabigatran in porcine mechanical valve models
Study design of RE-ALIGN

**Study treatment**

1. **Start warfarin up to day 7**
2. **Warfarin (INR according to guidelines)**
3. **1 week follow-up or transition to RE-ALIGN extension trial**

- **CrCl < 70 mL/min:**
  - DE 150 mg bid

- **CrCl 70 - < 110 mL/min:**
  - DE 220 mg bid

- **CrCl • 110 mL/min:**
  - DE 300 mg bid

**Population A**

- Start DE day 3–7

**Population B**

- B: Surgery (> 3 months)
- A: Surgery

- **Increase dose if dabigatran trough plasma level < 50 ng/mL (by Hemoclot®)**
- **Discontinue dabigatran (switch to nonstudy VKA ) if < 50 ng/mL with 300 mg bid after 2 measurements**
## Adjudicated efficacy outcomes

<table>
<thead>
<tr>
<th></th>
<th>Population A</th>
<th></th>
<th>Population B</th>
<th></th>
<th>All patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran</td>
<td>Warfarin</td>
<td>Dabigatran</td>
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<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td>(n = 133)</td>
<td>(n = 66)</td>
<td>(n = 35)</td>
<td>(n = 18)</td>
<td>(n = 168)</td>
<td>(n = 84)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>9 (7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9 (5)</td>
<td>0</td>
</tr>
<tr>
<td>SE, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TIA, n (%)</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>1 (3)</td>
<td>0</td>
<td>3 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>1 (1)</td>
<td>0</td>
<td>2 (6)</td>
<td>0</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Valve thrombosis without symptoms</td>
<td>2 (2)</td>
<td>0</td>
<td>3 (9)</td>
<td>0</td>
<td>5 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Death/stroke/SE/MI, n (%)</td>
<td>11 (8)</td>
<td>2 (3)</td>
<td>2 (6)</td>
<td>0</td>
<td>13 (8)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Death/stroke/TIA/SE/MI, n (%)</td>
<td>12 (9)</td>
<td>4 (6)</td>
<td>3 (9)</td>
<td>0</td>
<td>15 (9)</td>
<td>4 (5)</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; SE, systemic embolism; TIA, transient ischaemic attack
## Adjudicated safety outcomes

<table>
<thead>
<tr>
<th></th>
<th>Population A</th>
<th>Population B</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran (n = 133)</td>
<td>Warfarin (n = 66)</td>
<td>Dabigatran (n = 35)</td>
</tr>
<tr>
<td>Major bleeding, n (%)</td>
<td>7 (5)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding with pericardial location, n (%)</td>
<td>7 (5)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Any bleeding, n (%)</td>
<td>35 (26)</td>
<td>8 (12)</td>
<td>10 (29)</td>
</tr>
</tbody>
</table>
Possible explanations for negative study results

• Inadequate blood levels of dabigatran

• Play of chance with relatively few events seen in the warfarin arm

• Differences in the mechanism of action of dabigatran compared with warfarin
  • e.g., the inability of dabigatran to suppress activation of coagulation that occurs when blood is exposed to the artificial surface of prosthetic valves
Prosthetic valves and contact activation

Dabigatran vs. Warfarin

Intrinsic Tenase → IXa/VIIIa → Xa → X → Thrombin → Clot formation

Extrinsic Tenase → TF/VIIa → Prothrombinase → Xa

Contact

Injury

Warfarin

Dabigatran
Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

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