Evaluation of the Benefit of Rivaroxaban on the VOYAGER PAD Primary Composite of Irreversible Harm Events of the Limb, Heart and Brain Using the Global Rank and Win Ratio Methods

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VOYAGER PAD Primary Results

6,564 Patients with Symptomatic Lower Extremity PAD* (CLI or Claudication) Undergoing Peripheral Revascularization

*PAD defined as:
- *Ischemic symptoms* (functional limitation, rest pain or ischemic ulceration) AND
- *Imaging evidence of occlusion* AND
- *Abnormal ABI/TBI*

All to receive standard of care including:
- Low dose aspirin
- Clopidogrel per investigator

Primary Endpoint*

<table>
<thead>
<tr>
<th>ITT</th>
<th>HR</th>
<th>CI</th>
<th>P</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR 0.85</td>
<td>(0.76 – 0.96)</td>
<td>P=0.0085</td>
<td></td>
<td>2.6%</td>
<td>39</td>
</tr>
</tbody>
</table>

TIMI Major Bleeding

<table>
<thead>
<tr>
<th>On Treatment</th>
<th>HR</th>
<th>CI</th>
<th>P</th>
<th>ARI</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR 1.43</td>
<td>(0.97 – 2.10)</td>
<td>P=0.0695</td>
<td>0.8%</td>
<td>125</td>
<td></td>
</tr>
</tbody>
</table>

Unplanned Index Limb Revascularization

<table>
<thead>
<tr>
<th>Unplanned Index Limb Revascularization for Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population &amp; data scope</td>
</tr>
</tbody>
</table>

Unplanned Index Limb Revascularization

<table>
<thead>
<tr>
<th>KM(%) at 3 years</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9%</td>
<td>19.9%</td>
<td>17.3%</td>
</tr>
<tr>
<td>2.7%</td>
<td>20.0%</td>
<td>22.5%</td>
</tr>
</tbody>
</table>

*Composite of acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke, cardiovascular death
**Background**

**First Events Prevented / Caused for 10,000 Patients Treated* for 1 Year**

<table>
<thead>
<tr>
<th>Primary Efficacy Outcome</th>
<th>Principal Safety Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events Prevented</td>
<td>Events Caused</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>(acute limb ischemia, major amputation for vascular cause, MI, ischemic stroke, or CV death)</td>
<td>(TIMI major bleeding)</td>
</tr>
</tbody>
</table>

-181

(-269 to -94)

+ 29

(-2 to +60)

**• VOYAGER PAD demonstrated that rivaroxaban reduced the composite endpoint of acute limb ischemia (ALI), major amputation of a vascular etiology, myocardial infarction, ischemic stroke, or CV death**

**• The introduction of major adverse limb events (MALE) into primary endpoints with MACE is novel and the relative severity of components may be unfamiliar**

**• The primary analysis was performed as time to first event with equal weighting of components including fatal and non-fatal events**

**• Analyses evaluating outcomes using ranking of events may provide clinicians a mechanism to interpret the robustness of results when considering the clinical importance of specific components**

**• For therapies with safety considerations analyses of net outcome may provide clinicians another manner to understand benefit-risk**

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*Efficacy and safety on treatment*
Aims and Methods

• To evaluate the robustness of the VOYAGER PAD primary composite endpoints using methods incorporating ranking of components and to evaluate net benefit including composites of efficacy and safety endpoints

• Global rank method
  • Rank all components of the composite by order of clinical importance with a primary and alternative ranking prespecified
  • Each patient assigned a rank with the worse rank for worse outcome and for patients with the same outcome, those occurring earlier assigned the worse rank. Van Elteren test for differences between groups was applied stratified by type of procedure and clopidogrel use consistent with the primary trial analysis.

• Win ratio method
  • Unmatched win ratio method according to Pocock’s rule which ranked CV death higher than non-fatal events and then compared pairs of subjects, one from each treatment group for wins and losses.
  • Finkelstein and Schoenfeld statistics were utilized for the p-value with confidence intervals provided from bootstrapping

• Net benefit – prespecified composites of efficacy and safety events
## Global Rank Method

<table>
<thead>
<tr>
<th>Primary Hierarchy</th>
<th>Alternative Hierarchy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CV death</td>
<td>CV death</td>
</tr>
<tr>
<td>2 Ischemic Stroke</td>
<td>Ischemic Stroke</td>
</tr>
<tr>
<td>3 Acute limb ischemia</td>
<td>Acute limb ischemia</td>
</tr>
<tr>
<td>4 Major amputation of a vascular etiology</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>5 Myocardial Infarction</td>
<td>Major amputation of a vascular etiology</td>
</tr>
</tbody>
</table>

Subjects experience a worse event according to the hierarchy are assigned a worse rank. Among subjects with the same type of event, those having the event earlier are assigned a worse rank.

### Primary Hierarchy Result
- Rivaroxaban superior to placebo
- P-value 0.0158

### Alternative Hierarchy Result
- Rivaroxaban superior to placebo
- P-value 0.0155
## Results – Win Ratio Method

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Outcome Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient in Rivaroxaban arm had CV Death first</td>
<td>A Placebo win</td>
</tr>
<tr>
<td>Patient in Placebo arm had CV death first</td>
<td>B Rivaroxaban win</td>
</tr>
<tr>
<td>Patient in Rivaroxaban arm had non-fatal primary efficacy event first</td>
<td>C Placebo win</td>
</tr>
<tr>
<td>Patient in Placebo arm had non-fatal primary efficacy event first</td>
<td>D Rivaroxaban win</td>
</tr>
<tr>
<td>No CV death or non-fatal primary efficacy events</td>
<td>None of the 4 Categories</td>
</tr>
</tbody>
</table>

Win Ratio: \([\frac{(b+d)}{(a+c)}]\)

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CV Death – fatal event so counted first (worst)

Non-fatal components of the primary endpoint
Results – Win Ratio Method

Win-Ratio 1.16
*Rivaroxaban superior to Placebo*
(95% CI 1.03 – 1.30)
P=0.0167

ITT population & data scope
Results – Net Clinical Benefit

Includes all randomized subjects who received at least one dose of study treatment and includes events through 2 days following treatment discontinuation.
Summary & Conclusions

- Rivaroxaban significantly reduces acute limb ischemia, amputation, MI, ischemic stroke or CV death in PAD after lower extremity revascularization and increases bleeding but with a favorable benefit-risk profile.

- Novel analytic approaches utilizing ranking, weighting, and net outcomes enable clinicians to understand the robustness of results and relative impacts of fatal and non-fatal events to evaluate benefit-risk.

- Exploratory analyses of the VOYAGER PAD results show consistent superiority and net benefit when considered as:
  - Ranked hierarchy of outcomes with CV death as the worst event
  - Win-ratio approach ranking CV death as the worst event
  - Net outcomes including ischemic events, bleeding and mortality

- These findings support the utilization of rivaroxaban in appropriate patients after peripheral revascularization for symptomatic PAD.