PAR receptor as a target for antiplatelet therapy: Focus on Vorapaxar

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JCR- Busan, Korea, December 11, 2015
Disclosures:

- **Ownership:** HeartDrug™ Research, LLC

- **Grants:** Pfizer, Sanofi-BMS, Novartis, Lundbeck, Boehringer Ingelheim, Eli Lilly, AtheroGenics, Guilford, J&J, Bayer, Merck, Fibrex, Cardax, Eisai, Abbott, Brain Pool Program (Ministry of Science & Technology, Korea)

- **Consulting:** FDA, Pfizer, Sanofi-BMS, McNeil, NPS Pharma, Bayer, Eisai, mutual funds, hedge funds

- **Speaking Bureau:** Pfizer, Sanofi-BMS

- **Patents:** British Technology Group, Novartis, Boehringer Ingelheim, Eli Lilly, Pfizer, AtheroGenics, Eisai, PAR receptors and statins

- **Unlabeled/Unapproved use:** none
Science is there, but what is missing?
Vorapaxar: Mechanism of action

- Vorapaxar:
  - First-in-class
  - Oral PAR-1 inhibitor

- Metabolism:
  - Primarily hepatic via CYP 3A4
  - Terminal half-life: ~126–269 hrs

- Prior phase 2 trials:
  - No increase in bleeding and fewer MIs
Vorapaxar Program
Evaluation of Efficacy and Safety in Acute and Chronic Atherothrombosis

Vorapaxar Program
(~38,500 pts)

NSTEACS
12,944 pts

2º Prevention
26,499 pts

TRACER

F/U: 30 days, 4,8,12 months, and 6 months thereafter

F/U 1 yr minimum

1º EP: Composite of CV death, MI, Stroke, urgent revascularization and Recurrent Ischemia w/ Rehosp

Vorapaxar
Placebo

Vorapaxar
Placebo

1º EP: Composite of CV death, MI, Stroke, and urgent revascularization
Redesigning TRACER after TRITON?

Deaths in UA/NSTEMI Patients

Number at risk
rx = Clopidogrel 5029
rx = Prasugrel 5044

0.00 0.01 0.02 0.03 0.04
fraction of patients

0 2 4 6 8 10 12 14 16
month

Serebruany, Int J Cardiol, 2015; FDA Prasugrel Review, 2009
Major Bleeding Endpoints

3-yr KM rate (%)

- Placebo
- Vorapaxar

Prior Stroke
n = 5746

- TIMI Non-CABG Major
  - ARD 2.0%
  - HR 1.87
  - P < 0.001
- ICH
  - ARD 1.5%
  - HR 2.55
  - P < 0.001
- Fatal
  - ARD 0.2%
  - HR 1.48
  - P = 0.46

No Hx of Stroke
n = 20699

- TIMI Non-CABG Major
  - ARD 0.7%
  - HR 1.35
  - P = 0.005
- ICH
  - ARD 0.2%
  - HR 1.55
  - P = 0.049
- Fatal
  - ARD 0.1%
  - HR 1.44
  - P = 0.30

Morrow et al. ACC 2012, Chicago, March 24, 2012
Background – \(1^\circ\) Efficacy Evaluation

Overall Population (\(N=26449\))

CV Death, MI, or Stroke

- Placebo: 10.5%
- Vorapaxar: 9.3%

Mean f/u: 2.5 years

Prospective Mortality

GUSTO Mod/Sev at 3 yrs
- 4.2 vs. 2.5%, HR 1.66, \(p<0.001\)

ClinicalTrials.gov NCT00526474c
Primary Efficacy Evaluation

Prior MI Cohort (N=17,779)

CV Death, MI, or Stroke

N = 17,779
Mean f/u: 2.5 years

Hazard Ratio 0.80;
95% CI 0.72 - 0.89
p < 0.001

Placebo
9.7%

Vorapaxar
8.1%

Prior MI Inclusion:
Type 1 MI >2 wks and <12 months before randomization

Scirica et al. Lancet 2012
ClinicalTrials.gov NCT00526474c
Efficacy by Time from Qual MI

**Prior MI Cohort**

**Time from qualifying MI to Randomizations**

- **< 3 months**
  - HR 0.82
  - \( p = 0.011 \)
  - Placebo: 10.4%
  - Vorapaxar: 8.9%

- **3 to 6 months**
  - HR 0.79
  - \( p = 0.023 \)
  - Placebo: 9.4%
  - Vorapaxar: 7.5%

- **>6 months**
  - HR 0.78
  - \( p = 0.026 \)
  - Placebo: 8.8%
  - Vorapaxar: 7.1%

**N =**
- Placebo: 7801
- Vorapaxar: 5151
- Placebo: 4703

Scirica et al. Lancet 2012
ClinicalTrials.gov NCT00526474c
GUSTO Moderate/Severe Bleeding and Primary Efficacy Endpoint Rates by Indication Subgroup and Thienopyridine Use in TRA2P

<table>
<thead>
<tr>
<th>subgroup</th>
<th>thienopyridine</th>
<th>N</th>
<th>primary endpoint</th>
<th>GUSTO mod/sev</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo</td>
<td>vorapaxar</td>
</tr>
<tr>
<td>MI</td>
<td>yes</td>
<td>6,207</td>
<td>6,203</td>
<td>10.6%</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>2,232</td>
<td>2,256</td>
<td>9.6%</td>
</tr>
<tr>
<td>stroke*</td>
<td>yes</td>
<td>945</td>
<td>959</td>
<td>15.0%</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>2,189</td>
<td>2,184</td>
<td>9.5%</td>
</tr>
<tr>
<td>PAD</td>
<td>yes</td>
<td>527</td>
<td>515</td>
<td>14.6%</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>1,124</td>
<td>1,108</td>
<td>11.6%</td>
</tr>
</tbody>
</table>

*includes MI and PAD strata patients with a prior history of stroke/TIA

FDA Secondary Vorapaxar Review, 2014
Inhibition of platelet aggregation

High risk of ischemic events

"Sweet spot"

High risk of bleeding events

Balancing Safety and Efficacy

Ischemic risk

Bleeding risk

Ferreiro & Angiolillo. Thromb Haemost 2010
Primary Endpoint Rates in Patients with and without GUSTO Moderate/Severe Bleeding Events in TRA2P

<table>
<thead>
<tr>
<th></th>
<th>GUSTO moderate/severe bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
</tr>
<tr>
<td>placebo</td>
<td>10.1%</td>
</tr>
<tr>
<td>vorapaxar</td>
<td>8.5%</td>
</tr>
</tbody>
</table>

FDA Secondary Vorapaxar Review, 2014
Primary Endpoint Rates by Weight < or ≥ 60 kg and Treatment in TRA2P

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Placebo</th>
<th>Vorapaxar</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 kg</td>
<td>1,852</td>
<td>8.4%</td>
<td>10.6%</td>
</tr>
<tr>
<td>≥ 60 kg</td>
<td>24,587</td>
<td>11.0%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>
Primary Endpoint Rates by Weight $< \text{ or } \geq 60 \text{ kg}$ and Treatment in TRACER

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Placebo</th>
<th>Vorapaxar</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 60 \text{ kg}$</td>
<td>1,046</td>
<td>18.2%</td>
<td>19.3%</td>
</tr>
<tr>
<td>$\geq 60 \text{ kg}$</td>
<td>11,898</td>
<td>16.9%</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

FDA Secondary Vorapaxar Review, 2014
Primary Endpoint Rates by eGFR < or ≥ 60 mL/min/1.73m² and Treatment in TRA2P

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Placebo</th>
<th>Vorapaxar</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>17,313</td>
<td>9.7%</td>
<td>7.9%</td>
</tr>
<tr>
<td>&lt;60</td>
<td>2,859</td>
<td>17.0%</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

FDA Secondary Vorapaxar Review, 2014
<table>
<thead>
<tr>
<th></th>
<th>placebo</th>
<th>vorapaxar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of CABGs</td>
<td>953</td>
<td>935</td>
</tr>
<tr>
<td>GUSTO moderate/severe bleed</td>
<td>17.0%</td>
<td>21.1%</td>
</tr>
<tr>
<td>TIMI minor/major bleed</td>
<td>8.5%</td>
<td>11.1%</td>
</tr>
<tr>
<td>TIMI major bleed</td>
<td>8.1%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.0%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Primary endpoint*</td>
<td>8.3%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Deaths</td>
<td>3.9%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

*Excluding 85 placebo and 92 vorapaxar patients with primary endpoints prior to CABG
Times to First Solid Cancer Events by Arm in TRACER

Hazard ratio 1.4 (95% CI 1.1 to 1.8, p = 0.012)
Times to First Solid Cancer Events by Arm in TRA2P

FDA Secondary Vorapaxar Review, 2014
Follow-up Rates in Patients with and without GUSTO Moderate/Severe Bleeding Events in TRA2P

<table>
<thead>
<tr>
<th></th>
<th>GUSTO moderate/severe bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
</tr>
<tr>
<td>placebo</td>
<td>96.4%</td>
</tr>
<tr>
<td>vorapaxar</td>
<td>96.6%</td>
</tr>
</tbody>
</table>
Diplopia after Vorapaxar

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Year</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing PAR-1 antagonist</td>
<td>2004</td>
<td>Unclear</td>
</tr>
<tr>
<td>Initial investment</td>
<td>2007</td>
<td>Failure</td>
</tr>
<tr>
<td>PAD Indication</td>
<td>2012</td>
<td>Success</td>
</tr>
<tr>
<td>Better Efficacy/Safety</td>
<td>2012</td>
<td>Potential Success</td>
</tr>
<tr>
<td>Sponsor commitment</td>
<td>2014</td>
<td>Failure</td>
</tr>
</tbody>
</table>
Impressions:

• Despite obvious advantages in patients undergoing heart surgery, and renal impairment, vorapaxar clinical utilization (if any) is woefully low.

• Broad FDA approved indication is still not sufficient for success

• Top problem – lack of shareholders control in trial design and marketing