Overview of the 2014 Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee Meeting About Vorapaxar

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 Patients with a history of heart disease are at increased risk for future cardiovascular events, including myocardial infarction (MI), stroke, and death resulting from cardiovascular disease. Although coronary artery disease remains the leading cause of mortality worldwide, advancements in medical therapy, particularly antithrombotic agents, have improved patient outcomes.1–4 Although the trend for MI and death after acute coronary syndrome (ACS) over the past 20 years has declined,5,6 such medical advancements are still met with discouraging rates of death and MI after revascularization.7 To this end, it is the recommendation of the American College of Cardiology and American Heart Association that all ACS patients, regardless of whether percutaneous coronary intervention was performed, be treated with dual antiplatelet therapy (DAPT) for 1 year (Class I).8 Such recommendations are based largely on results from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, which assessed aspirin versus DAPT with aspirin and clopidogrel for the reduction of ischemic end points in patients presenting with non–ST-segment–elevation ACS who did not receive percutaneous coronary intervention.9

 Atherothrombotic events under DAPT. Thrombin is one of the most potent platelet activators and acts directly on platelets through PARs. PAR-1, the highest-affinity thrombin receptor, is highly expressed in atherosclerotic plaque. In preclinical studies, vorapaxar demonstrated a >100-fold selectivity to PAR-1 over a panel of >100 receptors, ion channels, and enzymes.10–15 Vorapaxar was shown to have a significant benefit for the reduction of cardiovascular death and ischemic complications in addition to secondary prevention.12 Vorapaxar was also tested in the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial as part of adjunct therapy in the non–ST-segment–elevation ACS population.13

In this population, however, the increased risk of bleeding outweighed the potential reduction of atherothrombotic events. Thus, Merck (the sponsor) presented efficacy and safety data from both trials to the US Food and Drug Administration’s (FDA’s) Cardiovascular and Renal Drugs Advisory Committee (CRDAC) on January 15, 2014, in Silver Spring, MD. The CRDAC was asked to opine on the approvability of vorapaxar for the reduction of atherothrombotic events in patients with a history of MI, notwithstanding the concerns for the subgroup populations, which showed increased rates of intracranial hemorrhage (ICH), including patients with a previous history of stroke or body weight <60 kg.

Mechanism of Action

Platelet activation with formation of a platelet thrombus is a highly regulated physiological process that is usually triggered by disruption of the endothelial wall during physiological and pathological settings. After an initial interaction with components of the subendothelial matrix (collagen, von Willebrand factor), platelet activation is amplified by soluble agonists (ADP, thromboxane A2) that are released from platelet degranulation. Despite the use of aspirin and P2Y12 inhibitors, platelet activation is still possible and could explain the recurrence of atherothrombotic events under DAPT. Thrombin is one of the most potent platelet activators and acts directly on platelets through PARs. PAR-1, the highest-affinity thrombin receptor, is highly expressed in atherosclerotic plaque. In preclinical studies, vorapaxar demonstrated a >100-fold selectivity to PAR-1 over a panel of >100 receptors, ion channels, and enzymes.10,11,14,15

Vorapaxar is a first-in-class antiplatelet drug of the PAR-1 antagonist family that inhibits thrombin-related platelet aggregation by a mechanism distinct from aspirin and P2Y12 receptor inhibitors. It does not affect ADP-mediated platelet aggregation, coagulation parameters, or bleeding time. The sponsor-summarized data from the vorapaxar clinical development program were extensive and included data from >41,000 patients (Table 1).12,13,16–21

TRACER and TRA 2P-TIMI 50: A Tale of 2 Trials

Vorapaxar was studied in 2 phase 3 trials, TRACER and TRA 2P-TIMI 50,12,13 that were conducted with separate and distinct patient populations, indications, inclusion and exclusion criteria, and study coordination oversight.22 The Duke Clinical Research Institute coordinated the TRACER study; the TRA 2P-TIMI 50 was coordinated by the TIMI...
PK and PD assessment at doses up to 120 mg daily

Phase 2<sup>20,21</sup>

TRA-PCI (P03573) Subjects undergoing nonemergent PCI 1030

ACS (P04772) Acute treatment in NSTE-ACS population undergoing PCI 117

Stroke (P05005) Secondary prevention in stable subjects with history of ischemic stroke 90

Phase 3<sup>12,23</sup>

TRACER Acute treatment in NSTE-ACS population 12944

TRA 2<sup>P</sup>-TIMI 50 Secondary prevention in stable patients with a history of CAD, CVD, or PAD 26449

ACS indicates acute coronary syndrome; CAD, coronary artery disease; CVD, cerebrovascular disease; NSTE, non-ST-segment–elevation; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PD, pharmacodynamic; PK, pharmacokinetic; TRACER, Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome; and TRA 2<sup>P</sup>-TIMI 50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction.

This is in stark contrast to the results of TRA 2<sup>P</sup>-TIMI 50, which were used to support the proposed labeled indication for vorapaxar. Although TRACER enrolled high-risk ACS patients, TRA 2<sup>P</sup>-TIMI 50 was designed to evaluate the ability of vorapaxar to reduce secondary major cardiovascular events and urgent coronary revascularization in stable but high-risk outpatients with a history of coronary artery disease or MI, peripheral artery disease, or stroke. TRA 2<sup>P</sup>-TIMI 50 enrolled >26,000 patients from 1032 sites in 32 countries to assess the role of vorapaxar for secondary prevention. The primary efficacy end point was first occurrence of cardiovascular death, MI, stroke, or urgent coronary revascularization. The primary safety end point included GUSTO moderate or severe bleeding, although TIMI bleeding was also assessed. As with previous antiplatelet and anticoagulant trials, a net clinical outcome end point of cardiovascular death, MI, stroke, or GUSTO severe bleeding was also evaluated.

The sponsor points to January 2009 as a pivotal moment for the TRA 2<sup>P</sup>-TIMI 50 study. At that time, the joint TRACER/TRA 2<sup>P</sup>-TIMI 50 Data Safety Monitoring Board made sites aware of the increased risk of ICH with vorapaxar use in subjects with a history of stroke. On the basis of these unblinded findings, an amendment was proposed in March 2011 to exclude patients with a history of stroke. At the same time, supplementary secondary objectives (not prespecified) were outlined to assess efficacy in the following populations: (1) populations with combined coronary artery disease and peripheral artery disease, regardless of stroke history; (2) those with no stroke history; and (3) those with coronary artery disease as the qualifying condition, analyzed in all subjects compared with those without history of stroke. All randomized patients were still included in the analysis of these end points.

### Safety and Adverse Events in TRA 2<sup>P</sup>-TIMI 50

As reported in the original New England Journal of Medicine publication,<sup>12</sup> the sponsor described how vorapaxar was associated with significantly more bleeding by either GUSTO moderate/severe (4.2% versus 2.9%; HR: 1.51; 95% CI, 1.31–1.74; P<0.001) or TIMI major/minor (4.5% versus 3.0%; HR, 1.48; 95% CI, 1.29–1.70; P<0.001) compared with placebo in the overall population. Of particular concern to the CRDAC was the increase in fatal and nonfatal ICH with vorapaxar use (1.0% versus 0.6%; P<0.001).

The sponsor then presented data for the proposed label population, which excluded patients with a history of stroke or transient ischemic attack (TIA). Although not a prespecified analysis, the sponsor sought FDA approval for vorapaxar based largely on the safety results of this population (Table 2).<sup>22</sup> Specifically, the increased risk of severe bleeding, particularly fatal ICH, was substantially muted after the removal of patients with a history of stroke (Table 3). This improved the benefit-to-risk ratio of vorapaxar. Given these findings, Daniel Bloomfield, MD (vice president, Merck Clinical Research), recommended to the FDA that vorapaxar should be contraindicated in patients with a history of stroke or TIA.
The committee asked the sponsor to comment on the discrepant safety outcomes in TRACER and TRA 2P-TIMI 50, specifically why the FDA should feel comfortable with the proposed label population. Dr Kenneth Mahaffey, principal investigator for TRACER, felt that these findings could be explained primarily by the differences in patient populations. In particular, TRACER was a smaller study that comprised an older population, including many patients without previous exposure to aggressive antiplatelet therapy. Although age is known to be a predictor of stroke and ICH after ACS,24,25 Dr Mahaffey hypothesized that the naïve nature of TRACER patients to DAPT, unlike TRA 2P-TIMI 50 patients, may have played a role. These patients did not have a “stress test” for bleeding in the TRACER trial, whereas TRA 2P-TIMI 50 patients may have declared themselves at risk for bleeding before enrollment.

Additional Safety Concerns

Proposed Labeling and Time From MI

Because a TRACER patient only a few weeks out from his or her event could easily have been enrolled in TRA 2P-TIMI 50, Julia B. Lewis, MD, of the advisory committee, raised concerns about the safety and validity of the sponsor-proposed 2-week time interval from index MI until the start of vorapaxar. The sponsor pointed out that although the median time from MI until enrollment was 77 days, safety and efficacy analyses for patients enrolled at <3 months were

<table>
<thead>
<tr>
<th>End Points</th>
<th>Subjects With Events, %</th>
<th>Annualized Event Rate, %</th>
<th>Subjects With Events, n (%)</th>
<th>Annualized Event Rate, %</th>
<th>HR‡ (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GUSTO bleeding categories</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe or moderate§</td>
<td>156 (1.9)</td>
<td>2.2</td>
<td>0.8</td>
<td>231 (2.7)</td>
<td>3.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Severe</td>
<td>73 (0.9)</td>
<td>1.0</td>
<td>0.4</td>
<td>85 (1.0)</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>88 (1.0)</td>
<td>1.2</td>
<td>0.4</td>
<td>152 (1.8)</td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>CABG-related severe or moderate</td>
<td>8 (0.1)</td>
<td>0.1</td>
<td>&lt;0.1</td>
<td>6 (0.1)</td>
<td>0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td><strong>TIMI bleeding categories</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major or minor§</td>
<td>175 (2.1)</td>
<td>2.4</td>
<td>0.8</td>
<td>259 (3.1)</td>
<td>3.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Major</td>
<td>133 (1.6)</td>
<td>1.8</td>
<td>0.6</td>
<td>161 (1.9)</td>
<td>2.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Minor</td>
<td>47 (0.6)</td>
<td>0.6</td>
<td>0.2</td>
<td>105 (1.2)</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Clinically significant •</td>
<td>785 (9.3)</td>
<td>10.2</td>
<td>4.0</td>
<td>1120 (13.3)</td>
<td>14.6</td>
<td>5.9</td>
</tr>
<tr>
<td>Non–CABG-related major or minor§</td>
<td>167 (2.0)</td>
<td>2.3</td>
<td>0.8</td>
<td>251 (3.0)</td>
<td>3.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Major</td>
<td>125 (1.5)</td>
<td>1.7</td>
<td>0.6</td>
<td>153 (1.8)</td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>CABG-related major</td>
<td>8 (0.1)</td>
<td>0.1</td>
<td>&lt;0.1</td>
<td>8 (0.1)</td>
<td>0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Other categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>30 (0.4)</td>
<td>0.5</td>
<td>0.1</td>
<td>38 (0.5)</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Fatal ICH</td>
<td>8 (0.1)</td>
<td>0.1</td>
<td>&lt;0.1</td>
<td>10 (0.1)</td>
<td>0.2</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>14 (0.2)</td>
<td>0.2</td>
<td>0.1</td>
<td>14 (0.2)</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; CI, confidence interval; GUSTO, Global Utilization of Streptokinase and TPA for Occluded Arteries; HR, hazard ratio; ICH, intracranial hemorrhage; KM, Kaplan-Meier; and TIMI, Thrombolysis in Myocardial Infarction.

*KM estimate at 1080 days.
†Event rate is expressed as number of patients with events per 100 patient-years of exposure.
‡Vorapaxar vs placebo.
§Subcategories are mutually exclusive; each subject appears only in the highest-intensity subcategory observed for that subject.
||TIMI major or minor bleeding or bleeding that requires unplanned medical or surgical treatment or unplanned evaluation by a laboratory test.
Perioperative Management of Bleeding While on Vorapaxar

With a half-life of 187 hours for vorapaxar, the advisory committee inquired about drug discontinuation before surgery and how to treat bleeding events in patients while on vorapaxar. Because the trial was designed for patients to continue study medications throughout any procedure, David Morrow, MD, MPH (senior investigator, TIMI Study Group), directed the FDA’s attention to safety outcomes pertaining to coronary artery bypass graft (CABG)–related bleeding. Dr Morrow pointed out that no difference was seen in coronary artery bypass graft–related major bleeding by either GUSTO (0.1% versus 0.1%; HR, 0.84; 95% CI, 0.38–1.88; \( P = 0.68 \)) or TIMI (0.1% versus 0.1%; HR, 0.92; 95% CI, 0.43–1.97; \( P = 0.84 \)) definitions when vorapaxar was continued perioperatively. Thus, the sponsor’s final statement to the FDA on the matter was that patients should be “treated as they were treated in [the] study, and that’s to continue [vorapaxar].” These data, however, should be taken in context of the fact that only a small percentage of patients underwent coronary artery bypass graft in both arms, 175 (1.3%) and 201 (1.5%) of the total vorapaxar and placebo arms, respectively. With regard to bleeding management, the response was fairly similar. The sponsor summarized the amount and type of transfusions that occurred within 2 days of any bleeding event between the placebo and vorapaxar arms. In both the overall and proposed label population, the duration of bleeding was similar for vorapaxar and placebo (median duration: vorapaxar, 3.0 days [25th–75th percentile, 1.0–6.0 days]; placebo, 3.0 days [25th–75th percentile, 1.0–5.0 days]). Furthermore, supportive care with packed red blood cell and platelet transfusions was also similar between groups. The take-home message was to treat bleeds in patients while on vorapaxar with the same supportive care and therapy as if the patient were not receiving this therapy.

Efficacy

The overall studied population saw a 12% reduction in the primary efficacy end point (first occurrence of cardiovascular death, MI, stroke, or urgent coronary revascularization; HR, 0.88; 95% CI, 0.82–0.95; \( P = 0.001 \)). Excluding patients with a history of stroke or TIA (proposed label population) improved these results (HR, 0.86; 95% CI, 0.79–0.94; \( P < 0.001 \)). A similar reduction was seen for the key secondary end point (cardiovascular death, MI, or stroke; HR, 0.87; 95% CI, 0.80–0.94; \( P < 0.001 \)). The efficacy of the primary end point was driven primarily by a reduction in MI, which the sponsor notes was adjudicated predominantly as spontaneous type 1 in nature.26 The sponsor summarized the efficacy data from TRA 2P-TIMI 50 as follows: When added to standard of care, vorapaxar at a dose of 2.5 mg daily proved efficacious for the reduction of the primary and secondary end points in the overall studied population, the prespecified subgroups (with the exception of low body weight), and the proposed label (not a prespecified subgroup) population.

Dr Sanjay Kaul, MD (professor and attending cardiologist, UCLA School of Medicine and Cedars-Sinai Medical Center), from the advisory committee, voiced strong concern that the proposed labeled population was not 1 of the 16 prespecified subgroup populations to be analyzed and asked Dr Rose how the committee should approach this post hoc analysis, considering that the Data Safety Monitoring Board had multiple nonscheduled, unblinded analyses. Dr Rose believed that this subgroup was selected because it “did pretty well” and was not overly concerned with such an analysis. Furthermore, the 3 unplanned, unblinded Data Safety Monitoring Board analyses were to investigate the increased rates of ICH. Also responding to the appropriateness of this subgroup analysis was FDA panel member, Robert Temple, MD (deputy director for clinical science), commented to Dr Kaul that the results favor vorapaxar whether or not the subgroups were included and that “they’re leaving them [stroke group] out because they think there’s a risk” and it is “hard to say it’s not a responsible thing to do.”

The advisory committee continued deliberation as to whether the quantity of evidence was adequate to support the primary end point in the overall cohort and proposed labeled population, which represents a post hoc analysis. Dr Temple summarized how the FDA’s CRDAC typically views such cases. He stated that when a positive subgroup is found in an overall negative trial, another study is usually requested to confirm the results. However, in this case, the overall trial was positive, the proposed label population was based on a safety reference, and there was “nothing suspicious about the win.”

In conclusion, although not a prespecified subgroup, the FDA felt the concern was not as great when assessed in an overall

Table 3. Summary of ICH End Points by Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vorapaxar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N (%)</td>
<td>KM%*</td>
</tr>
<tr>
<td>Overall population</td>
<td>64/13 166 (0.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>Prior stroke history</td>
<td>22/2864 (0.8)</td>
<td>0.9</td>
</tr>
<tr>
<td>No prior stroke history‡</td>
<td>42/10 302 (0.4)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*KM estimate at 1080 days.
†Vorapaxar vs placebo.
‡Representing proposed label population. Includes subjects with transient ischemic attack.

CI indicates confidence interval; HR, hazard ratio; ICH, intracranial hemorrhage; and KM, Kaplan–Meier.
Vorapaxar Benefit–Risk
Eugene Braunwald, MD, from the TIMI Study Group, presented the benefit-to-risk profile of vorapaxar to the FDA. Pointing out the residual risk of future cardiovascular events after MI, he described the rigorous adherence of the study to contemporaneous guidelines for secondary prevention, stating the proposed label population received study medications on top of being “well treated” with aspirin (98.3%), statin (95.4%), β-blocker (85.2%), angiotensin-converting enzyme-inhibitor/angiotensin receptor blocker (78.6%), or thienopyridine (78.3%), with an average systolic blood pressure of 129 mm Hg. Dr Braunwald emphasized that the efficacy of vorapaxar for secondary prevention was seen on top of contemporary standard of care.

Understanding that any additional antiplatelet or antithrombotic agent added to current therapy would be met with the cost of increased bleeding, Dr Braunwald illustrated the net clinical benefit of vorapaxar for events considered to cause serious, irreversible harm (Figure). The true occurrence of the net clinical outcome end point in the proposed labeled population compared with placebo was 6.9% versus 8.5% (HR, 0.81; 95% CI, 0.72–0.90). Alternatively, the number needed to treat per 10,000 patient-years to prevent 1 cardiovascular death, MI, or ischemic stroke is 140, whereas the number needed to harm for the occurrence of GUSTO severe bleeding is 1798. The overall benefit ratio is touted as 71:6. In other words, vorapaxar is 12 times more likely to result in a benefit than a risk when the primary efficacy end point is compared with GUSTO major bleeding.22

Should Vorapaxar Be Avoided in Patients With Low Body Weight?
The panel spent a great deal of time discussing the labeling indication for patients with body weights <60 kg. The FDA’s clinical reviewer, Dr Rose, presented his review of the data provided to him from the Office of Clinical Pharmacology. In both the overall population and the proposed label population, vorapaxar failed to show clinical efficacy yet continued to show increased rates of moderate or severe bleeding, equating to an unfavorable benefit-to-risk ratio in patients <60 kg23 (Table 4). This was also seen for the individual component of the primary efficacy end point and rates of ICH. In conclusion, after careful review of the data provided, the recommendation of Dr Rose and the clinical pharmacology team was to avoid the use of vorapaxar in patients with body weights <60 kg. This comes as a stronger level of caution than what was proposed by the sponsor, which recommended the use of caution in this subgroup.

The FDA asked the sponsor to comment on whether vorapaxar should be contraindicated in this subgroup. Although individual contributing factors to these findings could not be teased out, it is suspected the patients with low body weights are also elderly and frail with multiple medical illnesses that place them at higher risk for bleeding and reduce the clinical efficacy. Because of the small numbers in this subgroup, the wide CIs for the HRs, and the heterogeneity of this population, the sponsor did not feel that a strong conclusion could be made. Furthermore, situations may arise in which a clinician may want to use vorapaxar in this subgroup. The sponsor prefers to keep this an individual clinician-patient decision, understanding the potential for increased bleeding, which therefore does not support a contraindication label.

Yaning Wang, PhD, speaking on behalf of the FDA’s Office of Clinical Pharmacology, strongly cautioned the advisory committee not to downplay this subgroup analysis. He called attention to the data23 in Table 5 and pointed out that safety and efficacy outcomes were similar when subgroups excluding stroke/TIA and body weight <60 kg were compared. In his opinion, the data had more evidence to support body weight restrictions than prior stroke/TIA, and “if you believe the data...
Table 4. Altered Benefit-Risk in Patients Weighing <60 kg

<table>
<thead>
<tr>
<th>Subgroup Population</th>
<th>HR (95% CI)</th>
<th>Sample Size, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO moderate or severe bleeding:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 kg overall</td>
<td>1.87 (1.19–2.94)</td>
<td>1844</td>
</tr>
<tr>
<td>&lt;60 kg proposed label</td>
<td>1.78 (0.85–3.74)</td>
<td>857</td>
</tr>
<tr>
<td>≥60 kg overall</td>
<td>1.48 (1.28–1.73)</td>
<td>24464</td>
</tr>
<tr>
<td>≥60 kg proposed label</td>
<td>1.46 (1.18–1.80)</td>
<td>15977</td>
</tr>
<tr>
<td>MACE*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 kg overall</td>
<td>1.28 (0.95–1.73)</td>
<td>1852</td>
</tr>
<tr>
<td>&lt;60 kg proposed label</td>
<td>1.07 (0.69–1.65)</td>
<td>861</td>
</tr>
<tr>
<td>≥60 kg overall</td>
<td>0.86 (0.79–0.93)</td>
<td>24546</td>
</tr>
<tr>
<td>≥60 kg proposed label</td>
<td>0.80 (0.73–0.89)</td>
<td>16012</td>
</tr>
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</table>

Cl indicates confidence interval; GUSTO, Global Utilization of Streptokinase and TPA for Occluded Arteries; and MACE, major adverse cardiac events.

*Composite of cardiovascular death, stroke, myocardial infarction, and urgent coronary revascularization.

on prior stroke, you need to believe the data on body weight restriction.”

Although the FDA agreed that more than a simple statement of caution will accompany the labeled indication for this subgroup, further details remain unsettled. Philip Sager, MD, acting chair for the panel, closed by saying that this is a complicated issue that will continue to be looked at carefully.

Questions Relevant for the Prescribing Clinician

Vorapaxar as Monotherapy or Combined With Novel P2Y12 Inhibitors?

The sponsor was asked to comment on the efficacy of vorapaxar in the absence of other antiplatelet agents, particularly aspirin or clopidogrel. The sponsor noted rates of 78% and 22% for DAPT and aspirin monotherapy, respectively, in TRA 2P-TIMI 50, with similar efficacies. However, no data are available for vorapaxar as monotherapy or for vorapaxar as second-line therapy to P2Y12 inhibitors. The take-home message was that vorapaxar is not a substitute for aspirin or P2Y12 inhibitors after MI and should be given in conjunction with standard-of-care medication.

The TRA 2P-TIMI 50 trial concluded enrollment in 2009; therefore, no data are available on the safety and efficacy of vorapaxar with either prasugrel (approved in 2009) or ticagrelor (approved in 2011). The summary recommendation was that the concomitant use of vorapaxar in patients on aspirin plus prasugrel or ticagrelor has not been studied, and current data are not sufficient to provide safety or efficacy information.

How Do You Manage Vorapaxar During ACS?

Continuation of vorapaxar during ACS when percutaneous coronary intervention is planned was discussed briefly during the review. The sponsor again pointed to the fact that TRACER and TRA 2P-TIMI 50 were designed to assess the safety and efficacy of vorapaxar during 2 separate disease presentations at different stages of the disease process. In TRACER, patients would have received loading doses of both clopidogrel and vorapaxar, in addition to parenteral anticoagulation. Furthermore, 70% of the TRACER population had no history of MI, nearly 60% of subjects were naïve to antplatelet therapy, and only 10% received DAPT before index hospitalization. This is in stark contrast to TRA 2P-TIMI 50, in which >75% were on DAPT at the time of randomization. In TRA 2P-TIMI 50, 6464 patients on vorapaxar underwent stent implantation before randomization or during the study period. Vorapaxar was not discontinued in such cases. Interestingly, no interaction was noted with increased bleeding in such patients, and perhaps even more intriguing, the risk of definite stent thrombosis was reduced with vorapaxar (1.4% versus 1.1%; HR, 0.70; 95% CI, 0.50–0.98; P=0.04). As was the response when asked to comment on perioperative management with vorapaxar, the sponsor advocates continuation of the drug during an ACS.

Panel Recommendations

After a thorough discussion about trial design, clinical and statistical conduct, and prespecified and nonprespecified subgroup analyses, including the proposed label population, the panel was asked if vorapaxar should be approved and, if so, for which populations (Table 6).

The panel voted 10 to 1 in favor of vorapaxar for the secondary prevention of atherothrombotic events in stable patients at least 2 weeks after MI or those with a history of peripheral artery disease who are also on concomitant standard therapy, including antiplatelets. Vorapaxar should not be prescribed to patients with a history of TIA/stroke. The majority of the panel congratulated the TIMI Study Group for a well-conducted trial showing strong efficacy and quite favorable benefit-to-risk ratio. Mori J. Krantz, MD, was the lone dissenter. Dr Krantz admitted that this vote was not based on lack of overall efficacy. Rather, his concerns are with the lack of efficacy for “hard end points” such as cardiovascular death and the potential for postmarketing amplification of bleeding events.

The Advisory Committee voiced a few items that they felt either were unresolved or required further investigation by the FDA before formal approval and labeling. These include concerns about the long half-life and peri procedural...
management of the drug, the lack of an established antidote, and particularly the indication for the <60-kg population because the benefit remains to be seen. Stuart Rich, MD, asked the FDA to consider a postmarketing surveillance program for the industry for such populations.

Conclusions

The vorapaxar data presented to the FDA Advisory Committee by the sponsor, on behalf of the TIMI Study Group, were both concise and robust. On May 8, 2014, the FDA followed the CRDAC recommendations and approved vorapaxar (Zontivity) with a black box warning about an increased bleeding risk in patients with a history of stroke, TIA, ICH, or active pathological bleeding. Although the indication for vorapaxar is based largely on a nonprespecified subgroup analysis, the CRDAC did not feel that this jeopardized the overall findings. The 12% reduction in the primary end point for the overall population improved to 18% in the proposed label population after exclusion of patients with a history of stroke/TIA; thus, the FDA felt that this analysis was performed in the patients’ best interests.

It remains to be seen what measure the sponsor will take to commercialize the drug and, if commercialized, how it will be adopted in clinical use for patients with ACS.

Disclosures

None.

References


Key Words: acute coronary syndrome ■ platelet aggregation inhibitors ■ thrombolytic therapy
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