Editorial

The FDA review on data quality and conduct in vorapaxar trials: Much better than in PLATO, but still not perfect

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ABSTRACT

Background/aims: Vorapaxar, a novel antiplatelet thrombin PAR-1 inhibitor, has been evaluated in TRA2P and TRACER trials. The drug is currently approved for post-myocardial infarction and peripheral artery disease indications with concomitant use of clopidogrel and/or aspirin. The FDA ruled that the overall vorapaxar data quality was acceptable, but conducted the sensitivity analyses for potential censoring. This was unusual, intriguing, and directly related to the challenged quality of ticagrelor dataset in PLATO in the previous New Drug Application for an oral antiplatelet agent submitted to the same Agency.
Methods: Hence, we compared the FDA-confirmed evidence of conduct and data quality in vorapaxar (TRA2P, and TRACER) with those of ticagrelor (PLATO) trials.
Results: The FDA provides a detailed report on information censoring, and follow-up completeness for 3 trials. TRA2P and TRACER used independent CRO for site monitoring, exhibit no heterogeneity in trial results dependent on geography, and consistent adjudication results with much less censoring than in PLATO.
Conclusion: The data quality and trial conduct in vorapaxar trials were better than testing ticagrelor in PLATO, however, there is still some room for improvement especially with regard to follow-up completeness, and less information censoring.

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1. Introduction

Vorapaxar—formerly termed SCH 530348—is a first-in-class, inhibitor of thrombin induced platelet protease-activated receptor 1 (PAR-1) [1]. The drug's Phase III program included two large outcome-driven clinical trials in patients with coronary atherothrombosis: the Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes (TRACER) trial [2] and the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Arteriosclerosis (TRA 2P-TIMI 50 or TRA2P) [3]. Importantly, among oral antiplatelet agents, vorapaxar has been approved next after ticagrelor, and both drugs were allowed for human use with controversy. In fact, vorapaxar approval was based on a TRA2P subset intention to treat population benefit (eliminating harm in post-stroke cohort), and failed TRACER, while ticagrelor approval has been granted based on a single trial (PLATO) [4], despite the furious resistance from four FDA reviewers [5,6], and some outside experts (e.g. 7–10). Herein, we compared the FDA-generated evidence with regard to trial conduct and data quality between vorapaxar and ticagrelor

New Drug Application submissions. Such a match seems important since trial primary publications never adequately report these sensitive issues [2–4], and yet, these data are exposed and analyzed in the affiliated FDA reviews [5,6,11,12] and should not be gone missing without comprehensive review.

2. TRACER

The TRACER trial randomized 12,944 patients with non-ST-elevation ACS in 37 countries around the world to receive vorapaxar or placebo on top of standard therapy with clopidogrel and aspirin [2]. As a trial requirement, the symptom onset had to be within 24 h of presentation and eligible patients had to have either elevated troponins/creatinine kinase-myoglobin (CK-MB) or new ST-segment changes as well as at least one other high-risk marker such as prior MI or revascularization, peripheral vascular disease, or diabetes. A composite of death from CV causes, MI, or stroke occurred in 822 patients in the vorapaxar group versus 910 in the placebo group (14.7% and 16.4%, respectively; hazard ratio, 0.89; 95% CI, 0.81 to 0.98; P = 0.02). Rates of moderate to severe bleeding were 7.2% in the vorapaxar group and 5.2% in the placebo group (hazard ratio, 1.35; 95% CI, 1.16 to 1.58; P < 0.001). Intracranial

hemorrhage rates were 1.1% and 0.2%, respectively (hazard ratio, 3.39; 95% CI, 1.78 to 6.45; P < 0.001) in favor of placebo. Follow-up in the trial was prematurely terminated after a safety futility review.

3. TRA2P

The pivotal study supporting approval of vorapaxar was the TRA2P trial. TRA2P was a large (26,449 subject), international, multi-center, randomized, double-blind, parallel group, cardiovascular outcomes trial in patients with a history of myocardial infarction, cerebrovascular disease, or peripheral arterial disease. Vorapaxar dosage was 2.5 mg daily, and the median duration of treatment was 823 days with follow-up to 4 years [3]. TRA2P was successful on its primary endpoint of CV death, MI, stroke, and urgent coronary revascularization. In fact, at 3 years, the primary endpoint had occurred in 1028 patients (9.3%) in the vorapaxar group and in 1176 patients (10.5%) in the placebo group (hazard ratio for the vorapaxar group, 0.87; 95% confidence interval [CI], 0.80 to 0.94; P < 0.001). Cardiovascular death, myocardial infarction, stroke, or recurrent ischemia leading to revascularization occurred in 1259 patients (11.2%) in the vorapaxar group and 1417 patients (12.4%) in the placebo group (hazard ratio, 0.88; 95% CI, 0.82 to 0.95; P = 0.001). Moderate to severe bleeding occurred in 4.2% of patients who received vorapaxar and 2.5% of those who received placebo (hazard ratio, 1.66; 95% CI, 1.43 to 1.93; P < 0.001). There was an increase in the rate of intracranial hemorrhaging in the vorapaxar group (1.0%, vs. 0.5% in the placebo group; P < 0.001). After two years, the data and safety monitoring board recommended discontinuation of the study treatment in patients with a history of stroke owing to the risk of intracranial hemorrhaging. However, both primary trial publications [2,3] were silent with regard to data quality and trials conduct.

4. PLATO

The Platelet Inhibition and Patient Outcomes (PLATO) trial randomized 18,624 patients with acute coronary syndrome to either ticagrelor plus aspirin versus clopidogrel plus aspirin [4]. The overall results indicated a significant reduction in the primary endpoint (a composite of death from vascular causes, myocardial infarction, or stroke) with ticagrelor compared to clopidogrel (9.8% vs. 11.7%, Hazard Ratio [HR] 0.84, 95% confidence interval [CI]: 0.77–0.92, P < 0.001, respectively). However, 46% (69 out of 150) of all primary endpoint events favoring ticagrelor came from just two countries (Poland and Hungary with 3933 enrolled patients, i.e. 21.1% of all study cohort), questioning the generalizability of the results of the PLATO trial to other geographical regions [7,10]. Specifically, the primary endpoint was increased in patients assigned to ticagrelor versus clopidogrel in the United States (U.S.) (HR 1.27, 95% CI: 0.92 to 1.75), Russia (HR 1.06, 95% CI: 0.67 to 1.68) and Georgia (HR 1.16, 95% CI: 0.56 to 2.37). Ironically (and somewhat disturbing) is the fact that Poland and Hungary were monitored by the study sponsor (regions showing benefit), whereas the regions showing harm with ticagrelor versus clopidogrel (U.S., Russia, and Georgia) were monitored by a third party Clinical Research Organization (CRO), Worldwide Clinical Trials (King of Prussia, PA, USA) [10]. This particular CRO has been monitoring TRA2P as well.

5. Data quality in TRACER and TRA2P

The FDA clinical reviewers judged that the datasets from both vorapaxar trials were generally of good quality [11,12]. They did find, however, that some patients discontinued early, and/or were censored on an earlier date without information available on any component of the primary endpoint. At the FDA request the vorapaxar sponsor later conducted a sensitivity analysis of 110 subjects who were censored on the last date when ascertainment of subjects' cardiovascular efficacy and safety status was made. The applicant confirmed that the primary and key secondary efficacy results were not impacted. The statistical

reviewer found one variable for capturing events' adjudication status in TRACER that was problematic. The source variable code was wrong but events were properly included in the analyses. Regarding completeness of follow-up, the primary clinical reviewers predominantly quoted the applicant's statistics, without generating own datasets. In TRA2P determining completeness of follow-up was complicated by the discontinuations of the patients with a history of stroke and who suffered a stroke during the study, and/or by a Clinical Research Form (CRF) flaw, which is described below. These stroke patients were not followed after their early termination visits, making intend-to-treat assessments impossible for the study as a whole. For the indicated subgroup (patients without a history of stroke/TIA), incomplete follow-up for withdrew consent for follow-up was about 2.4% and for lost was 0.15%, so vital status follow-up was about 97.5% complete. Because about 2.1% had vital status follow-up only, follow-up for events was about 95.3% complete by these applicant statistics. Below is the FDA Medical Team Leader analyses of follow-up for the vorapaxar trials [12]. In TRACER, about 6.3% and 5.5% of subjects in the placebo and vorapaxar arms, respectively, discontinued follow-up alive. Many of these subjects had vital status assessed; only 2.0 and 1.8% of subjects in the placebo and vorapaxar arms, respectively had no vital status available at the end of study. However, subjects who discontinued follow-up alive had no information on other study endpoints (MI, stroke, bleeding, etc.) after their last confirmed follow-up date. With regard to the completeness and quality in the TRA2P, two additional flaws were identified. First, serious adverse events (SAEs) were only to be reported until 60 days after the last dose of study drug. While this limitation is not critical for bleeding events, it is problematic for delayed SAEs, such as cancers, diplopia, and amyotrophic lateral sclerosis, that take time to develop and be detected. Second, patients who discontinued treatment were followed by phone contacts. These phone contacts consisted of a Visit case report form (CRF or screen) with fields for date of visit and type of contact (visit, phone) and possibly a patient status CRF with fields for reported status (continuing on treatment, discontinuing treatment, discontinuing study) and flags (yes/no) for adverse events, ischemic events, etc. with directions to the more detailed CRFs for the events. Unfortunately there was no date of visit field for the "Patient Status" CRF. In the data sets submitted there are examples of the last Patient Status CRF not corresponding to the last Visit phone contact. Hence, the FDA has no way of verifying from the datasets the exact last dates upon which the sites solicited events from patients whose last contacts were phone calls. Within the limitation described above, the Agency tried to characterize the completeness of follow-up for the indicated population (without a prior stroke/TIA). About 80% of vorapaxar and 82% of placebo patients without a prior stroke/TIA died on-study or had a visit with vital signs on or after the earliest last follow-up date of August 1, 2011. However, as noted above, by protocol the last contact could be a phone call in patients who discontinued treatment. About 96.5% of patients without a prior stroke/TIA died on-study or had a visit or phone contact on or after the earliest last follow-up date of August 1, 2011. The median follow-up for the 3.5% of these patients with incomplete follow-up was less than one year (0.93 year) compared to about 2.6 years for patients alive at study end with complete follow-up.

The FDA also expressed concern about the potential for informative censoring in trials of oral antiplatelet drugs because of the following potential mechanism: the new antiplatelet drug causes more bleeding that leads to discontinuation of study drug, less complete follow-up, and

Table 1
Primary endpoint rates in patients with and without GUSTO moderate/severe bleeds in TRA2P.

Arm	GUSTO moderate/severe bleed	
	No	Yes
Placebo	10.1%	37% (of 317)
Vorapaxar	8.5%	40% (of 476)