FDA Draft Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

Meeting Date: 15 January 2014

NDA: 204886

Sponsor: Merck Sharp & Dohme Corp, Inc.

Drug: ZONTIVITY (vorapaxar sulfate) 2.5mg Tablets

Indication for Use: Reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR)

Title of Study: **TRA•CER -** A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard of Care in Subjects With Acute Coronary Syndrome: Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome.

TRA 2^{o}P – TIMI 50 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 (vorapaxar) in Addition to Standard of Care in Subjects with a History of Atherosclerotic Disease: Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the vorapaxar New Drug Application (NDA) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

This document is based on the applicant's information as submitted up to 13 December 2013

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FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Room 1503), Silver Spring, MD

January 15, 2014

DRAFT POINTS TO CONSIDER

Cardiovascular and Renal Drugs Advisory Committee Questions: January 15, 2014

The Advisory Committee is asked to opine on the approvability of vorapaxar, an antagonist of the protease-activated receptor-1 (PAR-1), for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI).

The support for this claim comes primarily from TRA2P, a randomized, double-blind, placebo-controlled trial of vorapaxar 2.5 mg once daily in addition to standard therapy including other antiplatelet agents. The TRA2P study population was 26,499 patients with at least one of three atherosclerotic conditions: prior MI, prior ischemic stroke (in either case, the event occurred from 2 weeks to 12 months prior to study entry) or established peripheral arterial disease (PAD). Vorapaxar was also tested in TRACER, a randomized, double-blind, placebo-controlled trial of vorapaxar 2.5 mg daily after a 40 mg loading dose, also in addition to standard therapy including other antiplatelet agents. The TRACER study population was 12,944 patients who had acute coronary syndromes (ACS) without ST-segment elevation within 24 hours before hospital presentation.

TRACER was terminated early because of an increased rate of major bleeding, including intracranial hemorrhage (ICH), in the vorapaxar arm. Simultaneously patients with a history of stroke were terminated early in TRA2P. TRA2P was completed in the remainder of the population and the reported results show efficacy for vorapaxar: For the primary endpoint of cardiovascular (CV) death, MI, or stroke the hazard ratio was 0.87 (95% confidence interval [CI] 0.80-0.94, $p<0.001$). There was a higher rate of ICH in the vorapaxar group (1.0% vs. 0.5%, $p<0.001$).

1) Vorapaxar, like other antiplatelet and anticoagulant agents, presents a tradeoff between efficacy (reduced atherothrombotic events) and safety (increased bleeding).
   a) What is the best way to evaluate this tradeoff? Weighing subjectively separate analyses of safety and efficacy? Net clinical benefit analyses? A formal, weighted composite safety and efficacy endpoint?
   b) Is the benefit/risk evaluation favorable for vorapaxar in TRA2P? (Evaluate subpopulations in response to question 2 next.)

DRAFT POINTS TO CONSIDER (cont.)

2) The applicant's proposal is for approval in a subpopulation of the TRA2P trial, i.e., only in patients with a history of MI excluding patients with a history of stroke or TIA.
   a) Accepting subgroup analyses is fraught with dangers of over-interpretation and accepting chance variations as reality. What are valid considerations for accepting subgroup results?
   b) The applicant proposes that vorapaxar should not be used by patients with a history of stroke of any kind or TIA.
      i) Do you support this general restriction?
      ii) If use should be avoided in those with a history of ischemic stroke, is the timing of the stroke relevant? If yes, can you state a time relative to the start of treatment before which an ischemic stroke does not rule out use of vorapaxar?
      iii) Should vorapaxar be used by persons with a history of TIA?
   c) Alternative to applicant's proposal similar benefit-risk can be achieved by restricting the use of vorapaxar in patients with a history of MI weighing 60 kg or heavier. Do you support this general restriction?
   d) For what subgroups is the benefit/risk evaluation favorable for vorapaxar?
      i) Patients with a history of MI without a stroke, TIA, or ICH history as the applicant proposes?
      ii) Plus patients with PAD without a stroke, TIA, or ICH history?
      iii) Plus patients with a history of TIA?
      iv) Plus recent ACS (i.e., the TRACER population) without a stroke, TIA, or ICH history?
      v) Patients 60 kg or heavier only?

3) There was very little use of the newer approved antiplatelet agents prasugrel and ticagrelor in TRA2P.
   a) Does this affect approval?
   b) If vorapaxar is approved, how should this lack of information be expressed in labeling? As a contraindication? Only in the clinical trials section?

4) Should vorapaxar be approved? For what population?

Clinical Reviewer: Martin Rose
Application type: Standard, NDA 204886
ZONTIVITY (vorapaxar)

CLINICAL REVIEW of an NDA

Application Type	Type 1
Application Number	204886
Priority or Standard	Standard
Submit Date	(b) (4)
Received Date	(b) (4)
Date Filed	(b) (4)
Original PDUFA Goal Date	(b) (4)
Revised PDUFA Goal Date (after major amendment)	-
Division / Office	DCRP/ODE1/OND
Reviewer Names	Martin Rose, Jonathan Levine
Review Completion Date	December 16, 2013
Established Name	Vorapaxar sulfate
Trade Name	Zontivity
Therapeutic Class	Antagonist of the protease-activated receptor-1 [PAR-1, the thrombin receptor of platelets]
Applicant	Merck Sharp and Dohme Corp.
Formulation	Oral tablets – 2.5 mg
Dosing Regimen	2.5 mg once daily
Proposed Indication	"…for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR)."
Intended Population	Adults

Template Version: March 6, 2009

Clinical Reviewer: Martin Rose
Application type: Standard, NDA 204886
ZONTIVITY (vorapaxar)

Note to Readers

In this review internal hyperlinks to other parts of the review are in **bolded blue font**. A high-level summary of the efficacy and safety data is found in Section. **1.2.** Individual summaries of the efficacy and safety data are found at the beginning of Section **6** and Section **7**, respectively. Entries in the Table of Contents (below), Table of Tables (p. **5**) and Table of Figures (p. **7**) are also hyperlinked to their targets.

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Clinical Reviewer: Martin Rose
Application type: Standard, NDA 204886
ZONTIVITY (vorapaxar)

1 Recommendations / Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Vorapaxar should be approved as adjunctive therapy in patients with a history of myocardial infarction to reduce the risk of CV death, myocardial infarction, stroke and urgent coronary revascularization. This recommendation is based on the robustly positive results for the primary and key secondary endpoints of the 26,000 patient TRA 2°P RCT of vorapaxar 2.5 mg daily vs. placebo in subjects with prior MI, prior stroke or peripheral arterial disease (PAD).

1.2 Risk Benefit Assessment

Vorapaxar sulfate (this term is used interchangeably with "vorapaxar")[1] is an orally available, reversible, direct antagonist of the protease-activated-1 receptor (PAR-1). This receptor is activated by thrombin as well as other proteases, is present on platelets, and promotes platelet aggregation when activated by thrombin. The Applicant, Merck, has submitted NDA 204866, with the following proposed indication for vorapaxar:

"… for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). TRADEMARK has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR)."

1.2.1 Efficacy for the Proposed Indication

Substantial evidence of efficacy comes from a single study, the TRA 2ºP trial. This was a global, placebo-controlled, event-driven RCT conducted in 26,499 subjects with at least one of three atherosclerotic conditions: prior MI, prior ischemic stroke (in either case, the event occurred from 2 weeks to 12 months prior to study entry) or established peripheral arterial disease (PAD), but prior MI patients were to make up 70% of those enrolled. Subjects were randomized 1:1 to vorapaxar 2.5 mg once daily or placebo, with stratification by their qualifying atherosclerotic condition and by planned thienopyridine use. Subjects were to receive a background of standard care for their condition. They were followed to their last visit or telephone contact; median follow-up was 2.2 years. The primary endpoint was time to the composite of CV death, MI, stroke, or urgent coronary revascularization (UCR). The Key Secondary Endpoint was time CV death, MI or stroke. These were analyzed in all randomized subjects followed to their last contact.

The primary endpoint of time to the CV death, MI, stroke or urgent coronary revascularization (UCR) was met: 3 year KM rates of 12.4% vs. 11.2%, HR=0.88, 95% CI, 0.82-0.95, p=0.001. The key secondary endpoint of time to CV death MI or stroke was also met with a nearly identical hazard ratio (p<0.001, **Table 1**).

[1] When the free base is referenced, the term "vorapaxar free base" is used.

However, the course of the study was complicated by major safety-based changes in the study conduct that should be taken into account. These changes were recommended by the unblinded DSMB during the last year of the study in January 2011. There was substantially increased risk of intracranial hemorrhage in vorapaxar arm subjects with a prior history of stroke coupled with no observed benefit of vorapaxar for the primary endpoint in that subset. The DSMB recommended discontinuation of study treatment in subjects with a prior history of stroke or a stroke after randomization. The study leadership accepted this recommendation, and in addition, discontinued follow-up in many of the affected patients. Changes to the analysis plan relating to secondary endpoints were also made. The study continued as planned in the remaining subjects (i.e., those with no history of stroke at baseline and no stroke during the study). Study closeout commenced in August 2011.

The overall results of the study for the primary and key secondary endpoints (including all randomized patients) favored vorapaxar at the p≤0.001 level. In addition, similarly robust results favoring vorapaxar were obtained in key subgroups: all patients with no baseline history of stroke; the prior MI stratum; the pooled prior MI /PAD strata; and various subgroups of those strata with no history of stroke or stroke/TIA (**Table 1**). A benefit for vorapaxar was not shown in patients with a history of stroke (regardless of stratum)[2] or those in the isolated PAD stratum, although the results in the latter stratum favored vorapaxar numerically.

After review of the study data, the sponsor decided to narrow the proposed target population to those with a prior MI and no history of either stroke or TIA (labeled CAD, NHS/TIA and represented by the 7th row of data in **Table 1**. The analysis supporting this indication was not specified in the statistical plan.

Data on use of aspirin and other anti-platelet agents were similar in the treatment arms and was acceptably high, particularly in the sponsor's proposed label population.

In summary, the data from TRA 2°P show statistically significant results for the primary and key secondary endpoints in all of the following analyses, with p≤0.001 for all listed analyses that were performed at the end of the study:

- The overall patient population in the special ICH analysis reviewed by the DSMB in January 2011 and the same population at the end of the study
- The no stroke history population in January 2011 and again at the end of the study
- The prior MI population at the end of the study
- The Applicant's proposed label population (prior MI with no history of stroke or TIA) at the end of the study, which had the best results of any analyzed population (**Table 2**).

On the other hand, the final results for the primary and key secondary endpoints went the wrong way in the prior stroke stratum (**Table 1** and **Table 39**), and there was an excess of total deaths with vorapaxar in that stratum (81 vs. 95 in all patients followed to last visit). In the PAD stratum, which included only 14% of subjects in TRA 2ºP, there was a 5% reduction in the rate of the

[2] Subjects who met the criteria for entry into more than one atherosclerotic disease stratum were assigned to the first stratum for which they qualified in the following order: prior MI, prior stroke, and PAD. Also, some subjects had strokes more than 12 months prior to entry; these were not considered qualifying events. Consequently, 892 subjects in the pooled prior MI and PAD strata had a history of stroke.

primary endpoint with vorapaxar (p>0.5, see **Table 1**), but the results improved when prior stroke/TIA patients were removed from the analysis.

These results are sufficient to establish the effectiveness of vorapaxar for its proposed indication in patients with prior MI and support the Applicant's proposal not to include patients with prior stroke in the target population.

The Applicant has not included patients with PAD in the proposed indication. This choice is questionable and is discussed **below.**

Table 1 TRA 2°P – Primary and Key Secondary Endpoint Results in All Patients and Subgroups Based on Qualifying Event and Stroke or TIA History
ITT population, events accrued to last visit

Subgroup	Placebo (N = 13,224)	Vorapaxar (N = 13,225)	HR (95% CI)	p
	n/J (%) KM%	n/J (%) KM%		
All subjects - PEP	**1417/13224 (10.7) 12.4**	**1259/13225 (9.5) 11.2**	**0.88 (0.82 - 0.95)**	**0.001**
All subjects - KSEP	**1176/13324 (8.9) 10.5**	**1028/13225 (7.8) 9.3**	**0.87 (0.80 - 0.94)**	**<0.001**
PEP in subgroups -				-
Any history of stroke	313/2876 (10.9) 16.9	300/2870 (10.5) 15.3	0.94 (0.80 - 1.10)	0.465
CVD stratum	216/2448 (8.8) 12.1	217/2435 (8.9) 12.9	1.02 (0.84 - 1.23)	-
CAD stratum	956/8881 (10.8) 12.1	809/8898 (9.1) 10.5	0.83 (0.76 - 0.92)	<0.001
CAD, NSH	887/8583 (10.3) 11.5	757/8608 (8.8) 10.1	0.84 (0.76 - 0.93)	<0.001
CAD, NHS/TIA*	**867/8439 (10.3) 11.4**	**719/8458 (8.5) 9.8**	**0.82 (0.74 - 0.90)**	**<0.001**
CAD/PAD	1201/10776 (11.1) 12.5	1042/10790 (9.7) 11.0	0.86 (0.79 - 0.93)	<0.001
CAD/PAD, NSH	1104/10331 (10.7) 11.9	956/10343 (9.2) 10.5	0.86 (0.79 - 0.93)	<0.001
PAD stratum	245/1895 (12.9) 13.4	233/1892 (12.3) 12.7	0.95 (0.79 - 1.14)	0.567
PAD, NSH	217/1748 (12.4) 12.8	199/1735 (11.5) 11.8	0.92 (0.76 - 1.12)	0.410
PAD, NHS/TIA	206/1651 (12.5) 12.8	177/1622 (10.9) 11.1	0.87 (0.71 - 1.06)	0.167

Abbreviations: PEP= primary endpoint; KSEP= key secondary endpoint; NSH=subjects with no stroke history; CAD=coronary artery disease stratum (prior MI); CVD=cerebrovascular disease stratum (prior stroke); PAD=peripheral arterial disease stratum; CAD/PAD=pooled CAD and PAD strata; NHS/TIA= subjects with no history of stroke or TIA

* Applicant's proposed label population

Table 2 TRA 2ºP – Primary and Key Secondary Efficacy Endpoint Results in the Applicant's Proposed Label Population
(CAD NHS/TIA Population, all randomized subjects followed to last visit)

	Placebo N=8439		Vorapaxar N=8458		V vs. P HR (95% CI) IRR	p
	n (%)	KM%	n (%)	KM%		
Any Primary Efficacy Endpoint Event [1]	867 (10.3)	11.4	719 (8.5)	9.8	0.82 (0.74 - 0.90)	<0.001
CV death	96 (1.1)		82 (1.0)		*0.85*	
MI	451 (5.3)		374 (4.4)		*0.83*	
Stroke	84 (1.0)		60 (0.7)		*0.71*	
Ischemic	69 (0.8)		38 (0.4)		*0.55*	
Hemorrhagic	11 (0.1)		16 (0.2)		*1.45*	
Uncertain	4 (<0.1)		6 (0.1)		*1.50*	
UCR	236 (2.8)		203 (2.4)		*0.86*	
Any Key Secondary Efficacy Endpoint Event [2]	671 (8.0)	9.0	532 (6.3)	7.4	0.78 (0.70 - 0.88)	<0.001
CV death	101 (1.2)		84 (1.0)		*0.83*	
MI	481 (5.7)		387 (4.6)		*0.80*	
Stroke	89 (1.1)		61 (0.7)		*0.68*	
Ischemic	72 (0.9)		39 (0.5)		*0.54*	
Hemorrhagic	12 (0.1)		16 (0.2)		*1.33*	
Uncertain	5 (0.1)		6 (0.1)		*1.20*	

Abbreviations: CAH NHS/TIA=Subjects with prior MI as their qualifying condition and with no prior history of stroke or TIA; KM%= KM estimate of event rate over 1080 days; IRR=incidence rate ratio (calculated by reviewer for components of the composite endpoints, shown in italics).
1 Time to first event of composite of CV death, MI, stroke and UCR
2 Time to first event of composite of CV death, MI and stroke

Dosing regimen:

Only the proposed vorapaxar dose, 2.5 mg daily, was evaluated for efficacy. Support for the Applicant's proposed dosing regimen is supported by PK and PD information. The Applicant has demonstrated that 2.5 mg daily, but not 1 mg daily was associated with trough blood levels in a large majority of patients above 5 ng/mL, the lowest concentration associated with at least 80% inhibition of platelet aggregation induced by TRAP (Thrombin Receptor Activating Peptide). DCRP and OCP agreed with this strategy for dose selection at the EOP2 meeting (see Sec. **4.4.2**).

1.3 Safety Overview

Nearly all the clinical safety data for vorapaxar comes from the two Phase 3 CV studies, TRA•CER and TRA 2ºP. The only safety risk of substantial concern is bleeding. The Applicant presented bleeding data from TRA 2ºP as well as TRA•CER, a 13,000 patient ACS treatment study that missed its primary endpoint. There was also pooled bleeding and other AE data from the two studies, with bleeding data from the first 30 days of TRA•CER were omitted from the pool because

of the high rates of bleeding associated with interventions such as PCI and CABG in the initial hospitalization for ACS, along with associated use of injectable anticoagulants and antiplatelet agents. The data for general bleeding risk are fairly consistent across these 3 sources of information, and data from TRA 2ºP will be emphasized here.

Data for bleeding events in TRA 2ºP (all patients) from the first dose of study drug to last dose + 30 days are shown in **Table 3**. A clear increase in the rate of bleeding with vorapaxar is evident across all general bleeding categories, including the two designated major bleeding endpoints, (1) the composite of GUSTO Severe and Moderate bleeding and (2) TIMI Clinically Significant bleeding. Note all subjects in TRA 2°P are included in this analysis including those with a history of stroke, who were at substantially increased risk for ICH and fatal bleeding (driven by fatal ICH) than those with no history of stroke. In addition, patients with a history of TIA but no history of stroke had an increased rate of stroke (mostly ischemic stroke) with vorapaxar compared to placebo. In the Applicant's Proposed Label Population of subjects with a prior MI and no history of stroke or TIA, general bleeding rate data was somewhat lower than the rates for the overall to population, but vorapaxar vs. placebo hazard ratios were similar (**Table 4**). However, the rate of ICH was relatively low in the proposed label population, but was still higher with vorapaxar than placebo, although the point estimate for the hazard was closer to 1 than in the overall TRA 2ºP results and difference was not statistically significant. The rate of fatal bleeding was also low in the proposed label population.

Table 3 TRA 2°P – Analysis of Time to Bleeding Events
As-Treated Population followed from first dose to last dose + 30 days

	Placebo N=13166		**Vorapaxar N=13186**			
	n with events (%)	KM%	n with events (%)	KM%	HR (95% CI)	p
GUSTO CATEGORIES						
Severe or Moderate	258 (2.0)	2.5	424 (3.2)	4.1	1.67 (1.43 - 1.94)	<0.001
Severe	115(0.9)	1.1	168 (1.3)	1.7	1.47 (1.16 - 1.87)	0.001
Moderate	147 (1.1)	1.4	263 (2.0)	2.6	1.81 (1.48 - 2.22)	<0.001
TIMI CATEGORIES						
Major or Minor	283 (2.1)	2.7	449 (3.4)	4.3	1.61 (1.38 - 1.86)	<0.001
Clinically Significant Bleeding	1226 (9.3)	11.1	1735 (13.2)	15.7	1.46 (1.35 - 1.57)	<0.001
Major CABG-Related	11 (0.1)	0.1	10 (0.1)	0.1	0.92 (0.39 - 2.16)	0.845
OTHER CATEGORIES						
Intracranial Hemorrhage	51 (0.4)	0.5	97 (0.7)	0.9	1.91 (1.36 - 2.69)	<0.001
Fatal Bleeding	18 (0.1)	0.2	27 (0.2)	0.3	1.51 (0.83 - 2.74)	0.176

KM% over 1080 days

Table 4 TRA 2°P – Analysis of Time to Bleeding Events
As-Treated Proposed Label Population followed from first dose to last dose + 30 days

	Placebo N=13166		Vorapaxar N=13186			
	n with events (%)	KM%	n with events (%)	KM%	HR (95% CI)	p
GUSTO CATEGORIES						
Severe or Moderate	139 (1.7)	2.0	212 (2.5)	3.0	1.54 (1.24 - 1.90)	<0.001
Severe	62 (0.7)	1.0	74 (0.9)	1.1	1.20 (0.86 - 1.68)	0.287
Moderate	79 (0.9)	1.1	142 (1.7)	2.0	1.81 (1.38 - 2.38)	<0.001
TIMI CATEGORIES						
Major or Minor	159 (1.9)	2.3	237 (2.8)	3.4	1.50 (1.23 - 1.84)	<0.001
Clinically Significant Bleeding	748 (8.9)	10.2	1081 (12.8)	14.8	1.48 (1.35 - 1.63)	<0.001
Major CABG-Related	6 (0.1)	0.1	6 (0.1)	0.1	1.01 (0.33 - 3.13)	0.988
OTHER CATEGORIES						
Intracranial Hemorrhage	25 (0.3)	0.4	36 (0.4)	0.5	1.44 (0.87 - 2.40)	0.160
Fatal Bleeding	9 (0.1)	0.1	12 (0.1)	0.2	1.34 (0.56 - 3.17)	0.511

KM% over 1080 days

The findings in TRA 2°P related to a history of prior stroke and TIA are analogous to the prasugrel experience in ACS subjects. If vorapaxar is approved, it merits a contraindication in patients with a history of prior stroke or TIA, similar to prasugrel.

It is notable that hazard ratios for TIMI CABG-related bleeding are near 1.0 in the overall and Proposed Label Populations of TRA 2ºP. The ACS trial, TRA•CER, with many more CABG procedures due to the nature of the patient population, showed a similar pattern. Preclinical data suggest that vorapaxar might not increase the risk of surgical bleeding, and investigators were given the option of continuing study drug up to the time of surgery. More often than not, study drug was discontinued no later than 2 days prior to surgery. Vorapaxar vs. placebo hazard ratios for CABG bleeding were similar for patients whose study drug was stopped no more than 2 days prior to surgery compared to those whose study drug was stopped at least 3 days prior to surgery. However, our ability to write instructions for use of vorapaxar in the setting of surgery is complicated by the incomplete data regarding when other antiplatelet medication was discontinued with respect to surgery.

1.4 Risk Benefit Analyses

Risk benefit analyses were performed for both TRA 2ºP and TRA•CER by the Applicant at our request with the following specifications:

Benefit was defined as benefit for (1) fatal events, (2) serious and potentially debilitating non-fatal events and (3) total benefit (the sum of (1) and (2) with no weighting): - as follows:

- Benefit for fatal events included CV deaths other than those defined as risks (see below)
- Benefit for non-fatal serious events included non-fatal MI and non-fatal ischemic stroke

Risks were enumerated using the same paradigm as benefits, i.e., fatal risks, non-fatal serious and potentially debilitating risks, and total risks (fatal + non-fatal serious risks):

- Fatal risks included fatal ICH, fatal non-ICH bleeding events, and non-CV, non-ICH, non-bleeding deaths ("other" deaths).
- Non-fatal serious risks included non-fatal GUSTO Severe bleeding events, defined as ICH events or bleeding associated with substantial hemodynamic compromise.

Events were accrued from the first dose of study drug to the last dose + 30 days in TRA 2°P and from randomization to last visit in TRA•CER. All rates were calculated as events per 10,000 patient-years of follow-up as integers. Point estimates were used in the analyses below.

TRA 2ºP as treated-population (N=26,353)

Compared to placebo in 10,000 patient-years of follow-up, and summing benefits and risks, comparing benefits to risks, vorapaxar had the following advantages:

1. 5 fewer fatal events
2. 22 fewer non-fatal serious events, and
3. 27 fewer total fatal + non-fatal events.

However, there were 41 additional GUSTO Moderate bleeds with vorapaxar (defined as bleeding requiring transfusion, but not resulting in hemodynamic compromise).

TRA 2ºP proposed label population, as treated (N=16,856)

As one might expect, the benefit/risk profile of vorapaxar is improved in this subpopulation compared to the as-treated population. Advantages of vorapaxar were:

1. 5 fewer fatal events,
2. 45 fewer non-fatal serious events, and
3. 50 fewer total fatal + non-fatal events.

However, there were 33 additional GUSTO Moderate bleeds with vorapaxar.

TRA•CER as treated-population (N=12,887)

Benefit-risk results for the ACS treatment study TRA•CER are included because the results of Key Secondary endpoint (typical MACE, identical to the KSEP in TRA 2ºP) significantly favored vorapaxar, although the primary endpoint showed only a non-significant trend in favor of vorapaxar. Also, there was substantial overlap in the populations in the two studies, so directionally inconsistent results would seem unlikely. However, benefit-risk considerations might be different. Note that the Applicant is not seeking an indication based on the results of TRA•CER.

The benefit-risk picture for vorapaxar in this study was mixed. In 10,000 patient-years of treatment, vorapaxar use was associated with:

1. 15 ***additional*** fatal events
2. 55 ***fewer*** non-fatal serious events and
3. 40 ***fewer*** total fatal + non-fatal serious events.

Also there were 45 additional GUSTO Moderate bleeds with vorapaxar.

The consistent advantage of vorapaxar for fatal and non-fatal serious events across sub-populations in TRA 2ºP supports approval for the indication in patients with prior MI proposed by the Applicant. The mixed results in TRA•CER, with a vorapaxar showing a disadvantage for fatal events but an advantage for non-fatal serious events, is problematic for approval of an ACS acute treatment indication. The sponsor is not seeking such an indication, and this reviewer is not recommending approval for ACS.

> *Reviewer comment: We currently have no risk benefit analyses for the PAD population and its relevant subgroups. These analyses are critical for determination of whether vorapaxar should be indicated for use in patients with PAD. We have requested them from the Applicant.*

1.5 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS is recommended. A medication guide should be required with the following risk information:

- An increased risk of bleeding with vorapaxar overall;
- Contraindications in patients with prior ICH, ischemic stroke or TIA; or current overt pathological bleeding
- Discontinue treatment in the event of stroke or TIA on treatment
- Subgroups with increased risk of bleeding:
  - Elderly
  - Weight < 60 kg
  - Severe hepatic impairment
- Drug interactions (CYP 3A strong inducers and inhibitors, warfarin)

Of note, during the Mid Cycle follow-up meeting with the Applicant, DRISK staff suggested that the Sponsor might consider disseminating risk information outside of a REMS.

1.6 Recommendations for Postmarket Requirements and Commitments

No such requirements are recommended at this time.

2 Introduction and Regulatory Background

2.1 Product Information

The chemical structure of vorapaxar is depicted in **Figure 1**. Additional product information is provided in **Table 5**.

.

Figure 1 Chemical Structure of Vorapaxar

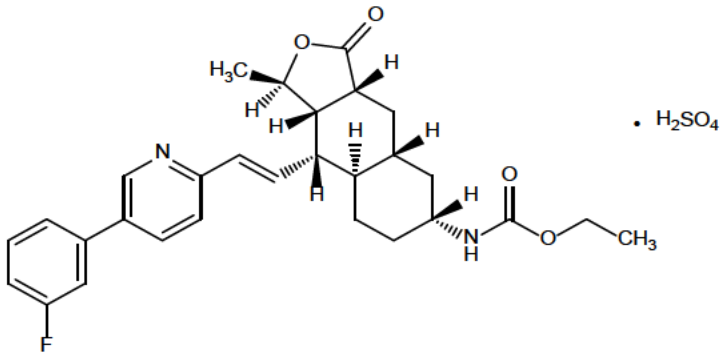


Table 5 Vorapaxar Product Information

Attribute	Description
Chemical Name	Ethyl [(1R,3aR,4aR,6R,8aR,9S,9aS)-9-{(1E)-2-[5-(3-fluoro-phenyl)pyridin-2-yl]ethen-1-yl}-1-methyl-3-oxododeca-hydronaphtho[2,3-c]furan-6-yl]carbamate sulfate.
Sponsor Code Names	SCH 530348 (Schering) and MK-5348 (Merck)
Appearance	White to off-white powder
Molecular Formula	$C_{29}H_{33}FN_2O_4 \cdot H_2SO_4$
Molecular Weight	590.7
Stereochemistry	Vorapaxar contains 7 chiral centers and theoretically has 128 stereoisomers.
Dosing Regimen	Oral, once daily
Proposed Age Group	Adults
Dosage Forms	Film-coated tablets for oral administration, 2.5 mg vorapaxar sulfate

2.2 Currently Available Treatments for Proposed Indication

2.2.1 Overview of Secondary Prevention in Patients with a History of MI

Antiplatelet therapy is a well-established component of secondary prevention in patients with a history of MI and other atherosclerotic conditions. Because the sponsor has requested an indication only for post-MI use, this section will focus on such use.

Currently Available Treatments

Aspirin is labeled in the US for several indications relevant to the proposed indication for vorapaxar:

- to reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris at dose of 75 to 325 mg daily indefinitely, and
- to reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.at a dose of 75 to 325 mg daily indefinitely.

In addition, aspirin is labeled to reduce the risk of vascular mortality in patients with a suspected acute MI at a dose of 160-162 mg daily for 30 days (with transition to chronic treatment for secondary prevention as above).

Clopidogrel at a dose of 75 mg daily is labeled for use in "…patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, Plavix has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death." However, the package insert indicates that in the CAPRIE trial that established this indication,

> "The efficacy of Plavix relative to aspirin was heterogeneous across these randomized subgroups (p=0.043). It is not clear whether this difference is real or a chance occurrence. Although the CAPRIE trial was not designed to evaluate the relative benefit of Plavix over aspirin in the individual patient subgroups, the benefit appeared to be strongest in patients who were enrolled because of peripheral vascular disease (especially those who also had a history of myocardial infarction) and weaker in stroke patients. In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, Plavix was not numerically superior to aspirin."

Clopidogrel is also labeled for use in patients with ACS in combination with aspirin. Recommending dosing of clopidogrel is a 300 mg loading dose followed by a maintenance dose of 75 mg in patients with unstable angina (UA) or non-ST elevation MI (NSTEMI). A maintenance dose of 75 mg, with or without a loading dose, is recommended for use in patients with ST elevation MI (STEMI). Labeling states that, "The optimal duration of Plavix therapy in ACS in unknown," but clopidogrel/ASA was given for 1 year tin the UA/NSTEMI trial and until hospital discharge or for 28 days, whichever occurred first, in the STEMI trial described in labeling that supported approval for use in ACS. In both of these trials, the combination of clopidogrel plus aspirin was superior to aspirin alone. About 20% if subjects in the UA/NSTEMI trial had PCI; PCI was not allowed in the NSTEMI trial. Thus, for both indications, the data suggest that dual antiplatelet therapy is superior to monotherapy with aspirin in ACS patients who did not receive PCI, although such patients are now quite uncommon.

Guidelines and use of antiplatelet therapies: Consensus guidelines from the American Heart Association and the American College of Cardiology for the secondary prevention of MI recommend the use of aspirin at a dose of 75-162 mg daily for "all patient with coronary artery disease unless contraindicated" (Class I, level of evidence A). Clopidogrel 75 mg daily is recommended as an alternative to aspirin in those who are intolerant of or allergic to aspirin (Class I, level of evidence B). Also, a P2Y12 receptor antagonist in combination with aspirin is indicated in patients after ACS or PCI with stent placement. For patients receiving a bare-metal stent or drug-eluting stent during PCI for ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for at least 12 months.(Class I, level of evidence A). For patients undergoing coronary artery bypass grafting, aspirin should be started within 6 hours after surgery to reduce saphenous vein graft closure at a dose of 100 to 325 mg daily for 1 year. Other recommendations with less compelling evidence suggest that an aspirin dose of 81 mg daily

may be preferable to higher maintenance doses after PCI and that combination therapy with both aspirin 75 to 162 mg daily and clopidogrel 75 mg daily may be considered in patients with stable coronary artery disease.(1)

2.3 Availability of Proposed Active Ingredient in the United States

Vorapaxar is not approved for use in the US. (b) (4)

2.4 Important Issues with Consideration to Related Drugs

The most important safety risk of other antiplatelet drugs is the risk of bleeding. The rate of spontaneous bleeding is elevated, as well as the rate of bleeding following tissue injury, including post-operative bleeding. In the TRITON-TIMI 38 trial, prasugrel, an approved thienopyridine irreversible P2Y12 antagonist, was associated with an increased rate of intracranial bleeding in patients with a prior history of ischemic stroke or TIA compared to clopidogrel (with a background of aspirin therapy) in patients with ACS with planned PCI; this risk resulted in a boxed warning and contraindication.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The vorapaxar development program was conducted under IND 071384. Only regulatory documents and decisions that are relevant to decision-making for the clinical portion of this NDA are described below.

An End of Phase 2 meeting was held February 27, 2007. The minutes of that meeting include the following recommendations and agreements:

- FDA indicated that it "had no major objections to Schering's dosing proposal
- The Division found that "the endpoints and study designs of the Phase 3 ACS and Secondary Prevention trials acceptable."
- The sponsor declined the Division's invitation to submit SPAs (special protocol assessments) for the Phase 3 studies, indicating that they wanted to start the studies in June of 2007 and did not want spend time on protocol negotiations.
- The Division agreed with the Sponsor's SAE reporting plans.
- The Division agreed to the Sponsor's approach to clinical exploration of the rat retinal findings (see Secs. **4.3** and **7.7.1**).
- The sample size of the Phase 3 studies should be based on the secondary endpoints. The secondary endpoint data will be critical to approval. One study in each indication could support approval with supportive Phase 2 data.

2.6 Other Relevant Background Information

2.6.1 Foreign Approvals

There are no foreign approvals.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The review of the individual Phase 3 study reports was complicated by the discontinuous nature of indexing. For example, the index for the TRA 2°P study report contained in the first electronic volume of the report (this volume was a single PDF with over 29,700 pages) did not cover the entire study report. The end of the index in volume 1 had no hyperlink to the location of the next page of the index, nor did it have any indication that where that page might be among the 30 electronic volumes of the report. Many of the key study documents, including the protocol, charters of key study committees, statistical plan, and minutes of the DSMB, were indexed in volume 10 of the report, which we learned by trial and error. The case narratives were spread over several volumes, organized by site and patient number. Each volume contained an index only for the narratives in the relevant volume; one had to guess which volume was the right place to look for a specific narrative. The Applicant responded to requests for unified indexes when asked, but useful indexes should have been provided with the original submission.

Another issue involved analysis of cause of death. There was no table describing cause of death for all deaths in the two Phase 3 trials. The Applicant indicated that they were not aware of the information in the DDeath tabulation files for each study, which included a MedDRA Preferred Term for each death that was based on information regarding cause of death provided by the investigator. Eventually a useful table of cause of death was provided for each study by the Applicant. We also created tables of cause of death using the DDeath and endpoints analysis files.

Except for the indexing issue, the NDA was organized in a reasonable manner and generally easy to understand. The hyperlinks that were present worked well.

No integrity issues were identified.

3.1.1 Dataset Quality

Datasets were generally of good quality. Some the laboratory values generated at local facilities were not associated with normal ranges, creating aberrant out of range flags. Coding for “source” of adjudication in the endpoints analysis file was flawed in TRACER: there were multiple events that were coded in a “source” variable as being “called” by the investigator but not by the CEC, yet these events were considered endpoint events in key analyses. This is inconsistent with the statistical plan, which was to count only adjudicated events for key endpoints. We later were informed that events were properly included in the analyses, but that the “source” variable code was wrong.

3.2 Compliance with Good Clinical Practices

3.2.1 Unblinding

Unused, sealed bottles of blinded study drug were opened and examined by the review team. Placebo and active vorapaxar could not be distinguished.

The TRA 2°P study report describes the following process for unblinding of the study sites:

> "Unblinding during the study was to occur only in the event of an emergency or adverse event for which it was necessary to know the study treatment to determine an appropriate course of therapy for the subject. The investigator/qualified designee was to contact the study "hotline" at TIMI to consult with a study physician about the need for unblinding. If it was agreed that the investigator/qualified designee must know the treatment assignment of an individual subject, the study hotline instructed the investigator/qualified designee to contact the IVRS for the treatment assignment.
>
> The IVRS provided the treatment assignment for only the individual subject in question after the investigator/qualified designee affirmed that the study hotline had been consulted."

The same process was used in TRA•CER.

The Applicant stated that 44 subjects (about 0.2% of those randomized) were unblinded in TRA 2°P by this process, including 19 and 25 in the placebo and vorapaxar arms, respectively. In TRA•CER, 24 subjects (about 0.2%) were unblinded by this process, including 9 and 15 in the placebo and vorapaxar arms, respectively.

> *Reviewer comment: The process could have been more rigorous because the investigator could conceivably have misrepresented whether the study physician had been consulted and agreed to the unblinding. However, the rate of unblinding in each study was low and acceptable.*

3.3 Financial Disclosures

These disclosures will be reviewed in an addendum to the review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls

The only substantial issue relating to CMC involves salt to base conversion of the drug substance. This issue is discussed in Sec. 4.4.

4.2 Clinical Microbiology

Not applicable to this submission – no clinical microbiology data were submitted.

4.3 Preclinical Pharmacology/Toxicology

Nonclinical issues identified by Dr. Harlow included the following:

- **Pre- and postnatal development findings in rats**: Dr. Harlow is recommending labeling that indicates that vorapaxar should be use during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus. This recommendation is based on the results pre-and post-natal development studies of administration of vorapaxar to gravid and nursing rat dams. These studies showed effects on peri-natal survival and body weight in pups at maternal exposures 38 times those expected at the recommended human dose (RHD). In addition, there were neurological effects consisting of impairment of startle in both sexes at 38 x the RHD and memory impairment in females at 19 x the RHD. It was not clear whether exposure in breast milk contributed to the neurological findings.

  Reviewer comment: It seems prudent to add language regarding lactation to the warning suggested by Dr. Harlow given the lack of knowledge about the effects of post-natal exposure to vorapaxar.

- **Tumorigenic findings in rats**: Male rats had no evidence of drug related tumors, but female rats had increased incidence of hepatocellular adenoma at 28 x human exposure. However, the Executive Carcinogenicity Advisory Committee (ECAC) found no evidence for carcinogenicity based on their conclusion that hepatic adenomas are a common tumor in rats, necessitating a lower p value than what was observed.
- **Retinal vacuolation in rats:** Vacuoles in the inner nuclear layer of the retina of rats without evidence of phospholipidosis or degenerative changes were observed in a 1 month study, and also seen in other 1, 3, and 6 months studies. NOAEL was about 2 x human exposure. The finding was reversible after 4 weeks of recovery and did not appear to affect retinal function. It was not seen in mice at > 300 x human exposure, in monkeys at >200 x human exposure, nor in the rat carcinogenicity studies. However, the finding in rats prompted the performance of special ophthalmic testing in humans (Sec. **4.3**).
- **Phospholipidosis in monkeys, mice, and rats:** Vacuolated macrophages and other cells with EM findings suggestive of phospholipidosis were observed in liver and small intestine of monkeys treated with vorapaxar 60 mg/kg x 3 months (> 100 x human exposure), but not at in 6 or 12 months studies at 20 mg/kg. Phospholipidosis was also observed in mice at exposures > 45 x human exposure for 3 months and in rats with > 4 x human exposure for 6 months, but not in carcinogenicity studies. Dr. Harlow believes that the most relevant finding were in monkeys, where the dose multiple was large.

Dr. Harlow's review has not yet been finalized. However, in her opinion, none of these findings should bar approval, although the developmental findings should affect labeling as discussed above.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vorapaxar is a reversible antagonist of the protease-activated receptor-1 (PAR-1). PAR-1 is a G-coupled cytoplasmic receptor found in many cell types, including platelets and vascular endothelium. Antagonism of this receptor on platelets inhibits thrombin-mediated aggregation,

although its effects on other cell types expressing PAR-1 receptors, such as vascular endothelium or neurons, are not well understood.[3]

It is not clear whether vorapaxar inhibits PAR-1 activity similarly when activated with protease enzymes other than thrombin, such as matrix metallo-protease1 (MMP-1), trypsin, or activated protein C (APC), all of which cleave and activate PAR-1's tethered ligand at different residues than does thrombin. Further, activation of PAR-1 by non-thrombin proteases may lead to different downstream effects than those associated with PAR-1 activation by thrombin. For example, thrombin-mediated activation of PAR-1 in endothelial cells causes increased vascular permeability and loss of fluid from the vascular space and has no known benefit in sepsis.(2) Therefore, its inhibition by vorapaxar may be beneficial in this setting. In contrast, APC activation of PAR-1 in endothelial cells has been shown to enhance endothelial barrier integrity (3), and is associated with protective effects in animal models of endotoxemia.(2)

In addition, there is evidence that low-level activation of PAR-1 in neurons by thrombin is neuroprotective, while high-level activation may be neurodegenerative.(4) It is not clear whether vorapaxar would interfere with the putative neuroprotective or neurodegenerative effects of neuronal PAR-1 activation.

4.4.2 Pharmacodynamics

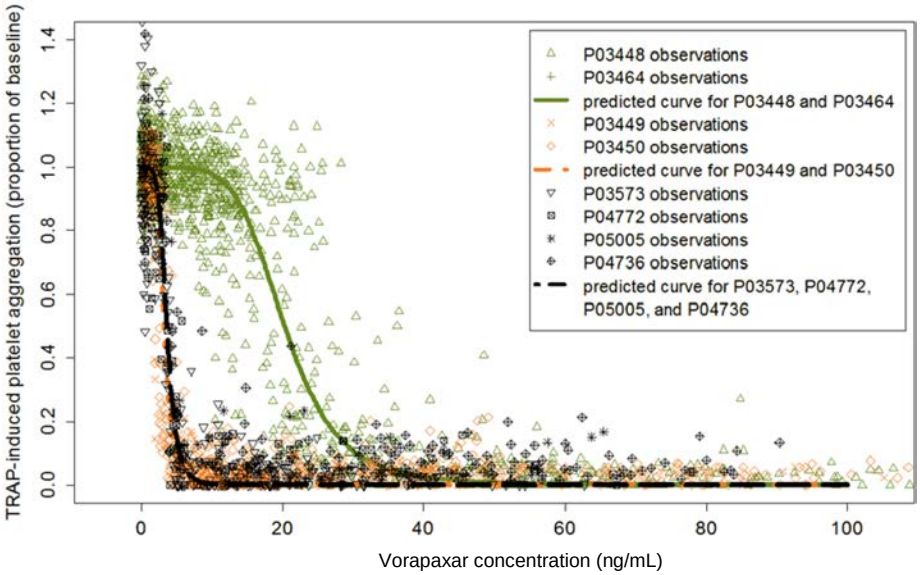
Pharmacodynamics of vorapaxar were assessed in in vitro platelet aggregation studies with stimulation by TRAP (Thrombin Receptor Activating Peptide). TRAP is a hexapeptide mimic of the PAR-1 tethered ligand that activates PAR-1 after cleavage by thrombin, and is active at sub-micromolar concentrations.

Studies using this technique show rapid onset of PD effects after a single dose of vorapaxar ≥ 3 mg and very slow recovery of platelet function after cessation of chronic dosing with doses ≥ 3 mg daily.

Studies of the concentration-response relationship for vorapaxar show large variations in the EC50 values for effects on platelet aggregation. The inter-study variability for this parameter has not been explained. The studies seem to fall into two groups, as in **Figure 2**. The studies that demonstrated a low EC50 are depicted with orange and black data points and the steeply dropping orange and black modeled curves (apparently superimposed) that hug the Y and X axes of the figure. The studies with a higher EC50 values are depicted with green data points and the green modeled curve to the right of the black curve.

[3] Activation of PAR-1 by endogenous activators differs from the usual ligand-receptor paradigm. Instead, PAR-1 has an extracellular N terminal domain (l ke a tail) that includes a potential auto-activating site, called a tethered ligand. When the tail is intact, the tethered ligand is inactive. When a piece of the tail is cleaved off at a site distal to the tethered ligand by thrombin or another activating protease, the now-shortened tail with the now exposed tethered ligand can interact with the second transcellular loop of PAR-1 on the cell surface. This activates one of several intracellular signaling mechanisms (either through G protein or β arrestin) and triggers PAR-1 effects in various tissues. Vorapaxar blocks the interaction between the exposed tethered ligand and the transcellular PAR-1 loop after cleavage of PAR-1 by thrombin, but the Sponsor did not provide information on the effects of vorapaxar when PAR-1 is activated by a non-thrombin protease.

Figure 2 Vorapaxar Concentration-Response Relationships



If the steep curve predicts response, then effective concentrations may be reached with multiple maintenance doses after a short period. However, if most patients fit the less steep curve, then a longer period of maintenance treatment time may be required to reach effective concentrations and high levels of platelet inhibition. The sponsor modeled both scenarios and generated curves for the percentage of subjects expected to reach at least 80% platelet inhibition (a target based on data for other antiplatelet agents) at day 7 and day 28 vs. daily dose of vorapaxar (**Figure 3**). The vertical dotted line represents 2.5 mg daily. For both time points, the higher curve is the low EC50 model, while the lower curve is the high EC50 model. At day 7, the low EC50 model has nearly 100% of subjects at > 80% platelet inhibition with a 2.5 mg dose. The high EC 50 model suggests that about 20% will be at or above the 80% inhibition target. At day 28, the results for the low EC50 model have not changed from day 7, but the high EC50 model indicated that about 89% of subjects will have at least 80% platelet inhibition with 2.5 mg daily. This is Sponsor's justification for the 2.5 mg daily dose. One could argue that a loading dose followed by a dose of 2.5 mg daily achieve better results in patients who fit the high EC 50 model, but that dosing regimen was not used in TRA 2°P. In any event, FDA agreed to the Sponsor's dosing strategy for TRA 2°P at the End of Phase 2 meeting.

Figure 3 Proportion of subjects achieving at least 80% inhibition of TRAP-induced platelet aggregation

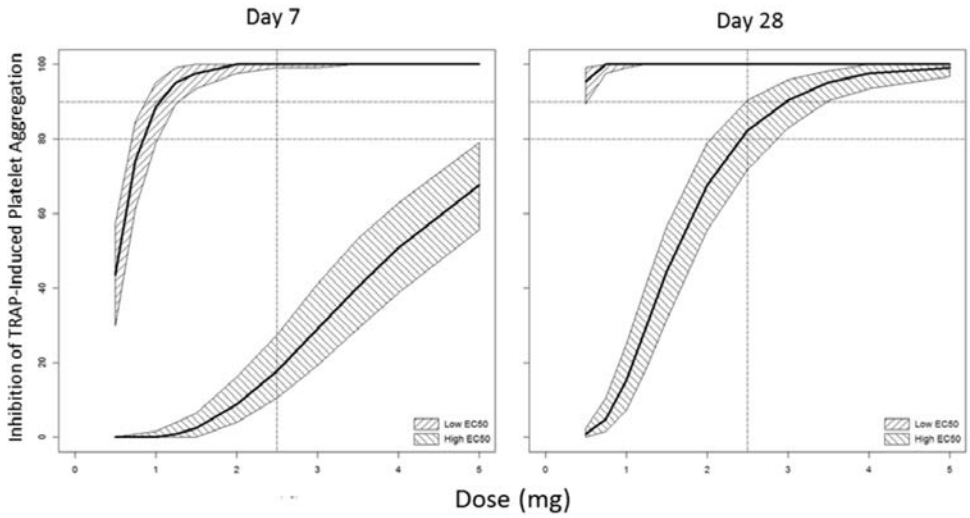


Figure 4 Onset and Offset of Platelet Inhibition with Vorapaxar

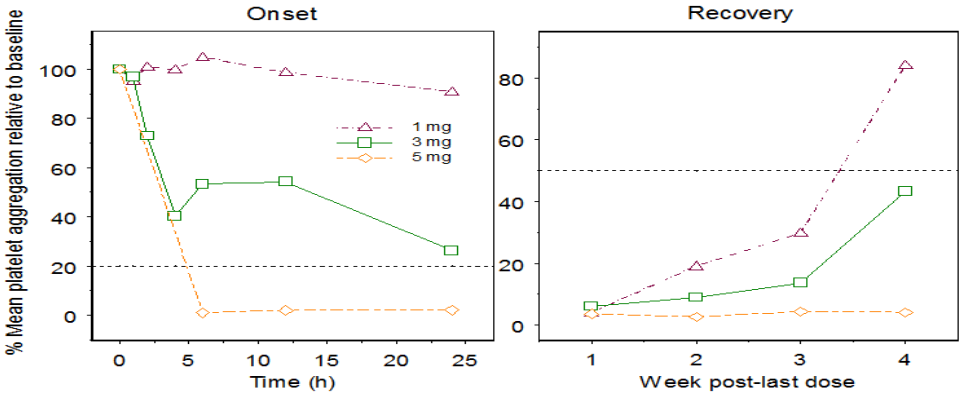


Figure 4 includes information on onset of antiplatelet effects with single doses of 1, 3,or 5 mg vorapaxar as well as offset after reaching steady state with the same doses. Offset of the effect of vorapaxar is slow. After steady state was reached at 3 mg daily, PD effect (assessed by ex-vivo 15 µM TRAP induced platelet aggregation) increased from about 5% to about 45% of pre-treatment levels four weeks after discontinuation of study drug. .

4.4.3 Pharmacokinetics

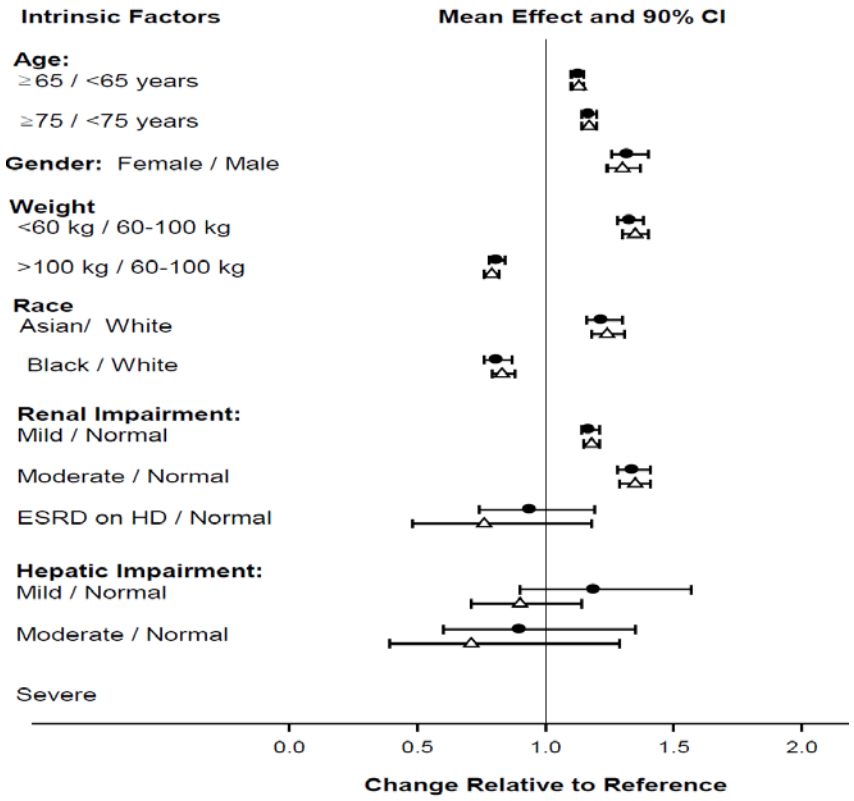
The pharmacokinetic and biopharmaceutic properties of vorapaxar are described in **Table 6**.

Table 6 Vorapaxar pharmacokinetic and biopharmaceutic properties

Absorption	Rapid, complete
Tmax	1-2 hr.
Distribution	379L
Metabolism	Extensive hepatic metabolism by 3a4, 2J2
Metabolites	
Excretion	60% stool, 25% urine (total of 85% of labeled material in 6 weeks)
Half-life	Effective: 3-4 d; terminal: 7-11 d
Dose proportionality	Slightly less than dose proportional over range of 2.5 – 40 mg.
Accumulation ratio	4.7 – 6.4
Food effect	No medically important food effect
BCS Class	II

The to-be marketed formulation is compositionally identical to the Phase 3 formulation except for a change in colorants, which did not affect dissolution.

Figure 5 Impact of Intrinsic Factors on Vorapaxar Pharmacokinetics



Source: Draft OCP Review

Impact of intrinsic factors on vorapaxar PK

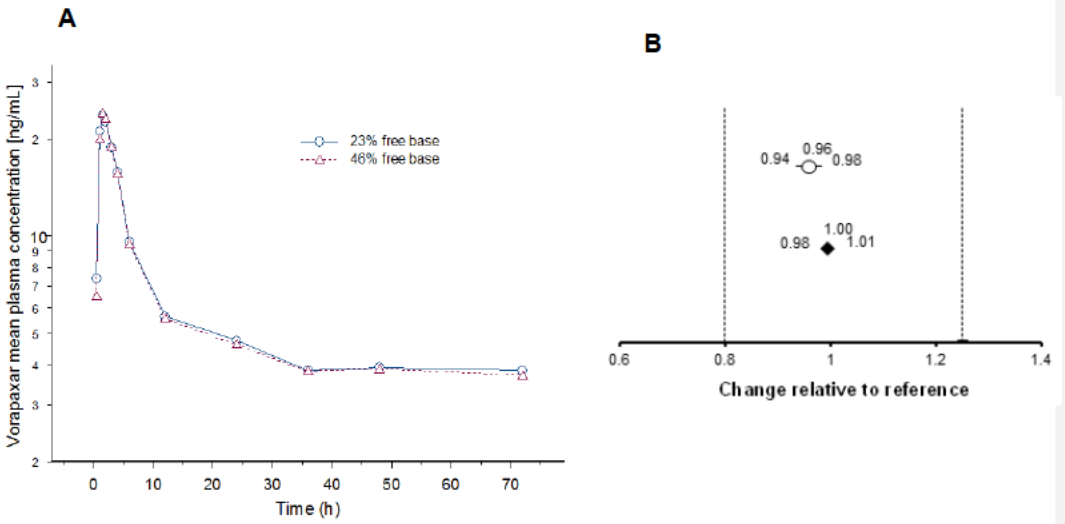
- No change in exposures with hepatic impairment
  - *Avoid use in severe hepatic impairment due to inherent risk of bleeding in that population*
- No change in exposure with renal impairment
- Avoid use in subjects with weight < 60 kg (due to demonstrated reduced efficacy and increased risk of bleeding)

Impact of extrinsic factors on vorapaxar PK

- Use with strong inhibitors or inducers of CYP3A4 is not recommended (due to doubling or halving of exposure, respectively). Mild or moderate inhibitors are not problematic and may be used.
- Co-administration with a high fat meal, antacid, or PPI had a modest impact on the rate of absorption but did not significantly affect the extent of absorption. No dose adjustments are required.

Conversion to Free Base
The vorapaxar sulfate salt spontaneously converts to the free base form during manufacturing and storage. This form would be expected to be less bioavailable than the salt. Lots of vorapaxar used in phase 3 ranged from 23% to 46% free base. The Applicant performed a BE study to compare the bioequivalence of 23% free base lot to 46% free base lot, using single doses of 2.5 mg. Results of this study in Figure 6 indicate congruence in terms of the rate and extent of absorption over 70 hours (part A) and bioequivalence for Cmax and AUC (Part B open circle and filled diamond, respectively).

Figure 6 BE study of 23% Free Base Lot vs. 46% Free Base Lot



4.4.4 Exposure-Response Modeling

See discussion in Sec. 4.4.2 for the Applicant's PD modeling that supports the proposed dosing regimen.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 7 Major Clinical Trials Supporting Safety and Efficacy of Vorapaxar for Secondary Prevention in Patients Prior MI

STUDY	Indication	Goal	Phase
STUDIES SUPPORTING EFFICACY			
TRA 2ºP	Prevention of CV events in patients with prior MI, prior stroke or PAD when added to standard care	See indication	3
TRA•CER	Prevention of CV events in patient with ACS when added to standard care	See indication	3
STUDIES SUPPORTING SAFETY			
TRA 2ºP	(see above)	See indication	3
TRA•CER	(see above)	See indication	3
OUTCOMES STUDIES SUPPORTING DOSING REGIMEN *			
TRA 2ºP			3
TRA•CER			3

*See Sec. **4.4.2** for a summary of PK/PD modeling supporting the dosing regimen.

5.2 Review Strategy

The clinical review of efficacy was performed by one reviewer (MR) and the review of safety by two reviewers (JL and MR).

The efficacy review focuses primarily on the TRA 2ºP, the only controlled trial powered to evaluate the clinical efficacy of vorapaxar for its intended indication. Efficacy is supported by the results of TRA•CER, a trial in patients with ACS which failed to demonstrate the efficacy of vorapaxar for the designated primary endpoint, but did show a statistically significant benefit of vorapaxar for typical MACE events, probably a more biologically reasonable endpoint than the one selected by the sponsor as the primary endpoint. The safety review focuses primarily on the two data from TRA 2ºP, but also includes data form TRA•CER. However, safety data from TRA 2°P alone is sufficient to support the a substantive review.

5.3 Discussion of Individual Studies/Clinical Trials

The evidence for the efficacy of vorapaxar for its proposed indication is based primarily on the results of the TRA 2ºP study, described immediately below.

5.3.1 Protocol P04737 - Secondary Prevention of Atherothrombotic Ischemic Events Patients with Atherosclerotic Disease

Protocol name: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study To Evaluate The Safety And Efficacy Of Sch 530348 (Vorapaxar) In Addition To Standard Of Care In Subjects With A History Of Atherosclerotic Disease: Thrombin Receptor Antagonist In Secondary Prevention Of Atherothrombotic Ischemic Events (TRA 2ºP – TIMI 50)

5.3.1.1 Study Design and Objectives

TRA 2ºP was a randomized, parallel-group, placebo-controlled, double-blind, multicenter, event-driven superiority trial of vorapaxar 2.5 mg given orally once daily. The primary objective was to determine whether the efficacy of vorapaxar is superior to placebo for reducing time to the composite of CV death, stroke, MI, or UCR in subjects with arteriosclerotic disease of the heart, CNS or peripheral vasculature treated with standard care.

5.3.1.2 Geographic Scope

TRA 2ºP was conducted at 1032 sites in 32 countries on 6 continents, which were the basis of the 7 study regions. About 22% of subjects were from the US, 30% were from North America (US, Canada and Puerto Rico), and another 42% were from "Europe 1", an administrative region comprised of countries in Western Europe as well as Israel and South Africa. Regional enrollment was well-balanced between the two treatment arms (see **Table 85**).

5.3.1.3 Study Duration/Dates

The first patient was enrolled on September 26, 2007, and enrollment was closed on November 12, 2009. The last patient contact was on December 23, 2011. Database lock was on January 9, 2012.

Durations of treatment and follow-up were well-balanced in the treatment arms. Treatment duration ranged from 1 to 1461 days (4.00 years), with a median of about 825 days (2.26 years). Follow-up duration ranged from 1 to 1471 days (4.03 years), with a median of about 906 days (2.48 years).

5.3.1.4 Patients

Patients who met each of the inclusion criteria below could enroll:

1. Subject may be of either sex and any race, and must be at least 18 years old.
2. Subject must have evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems as follows:
    a. Coronary artery disease (CAD) as indicated by a history of presumed spontaneous MI (hospitalized with final diagnosis of MI, excluding periprocedural or definite secondary MI [e.g., due to profound anemia or hypertensive emergency, troponin increase in sepsis]) ≥2 weeks but ≤12 months prior to enrollment, or

   b. Ischemic (presumed thrombotic) cerebrovascular disease (CVD) as indicated by a history of ischemic stroke (hospitalized with final diagnosis of nonhemorrhagic stroke [includes completion of a standard evaluation for stroke in an acute care facility or stroke clinic without hospital admission]) ≥2 weeks but ≤12 months prior, or
   c. Peripheral arterial disease (PAD) as indicated by a history of intermittent claudication and
      i. a resting ankle/brachial index (ABI) of <0.85, or
      ii. amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia
3. Subjects were required to be able and willing to give appropriate informed consent.
4. A woman of child-bearing potential who is currently sexually active were required to agree to use a medically accepted method of contraception prior to screening, while receiving protocol-specified medication, and for 2 months after stopping the medication. Highly effective methods of birth control were defined as those that result in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as hormonal implants, injectables, combined oral contraceptives, hormonal intrauterine devices, sexual abstinence, or surgical sterilization (e.g., vasectomy of male partner).
5. A woman of child-bearing potential who is not currently sexually active must agree to use a medically accepted method of contraception should she become sexually active while participating in the study.

Patients who met any one or more of the following study-specific criteria were excluded:

1. clinically unstable at the time of enrollment
2. any planned coronary revascularization or peripheral intervention
3. concurrent or anticipated treatment with warfarin (or derivatives, e.g., phenprocoumon), oral factor Xa inhibitor, or oral direct thrombin inhibitor after enrollment
   (NOTE: If a subject was taking warfarin during determination of eligibility, and the investigator was willing to stop the subject's treatment with warfarin immediately [following all recommendations of GCP associated with such a decision], and the subject was not otherwise disqualified from participation, then the subject could receive randomized assignment of study drug and participate per protocol. A subject who was not using warfarin/derivatives and for whom use was not anticipated, but who subsequently requires warfarin/derivatives after randomized assignment of study drug may continue treatment with warfarin/derivatives and randomized study drug, except under the circumstances described in **Section 7.3.3** of the protocol.)
4. concurrent or anticipated treatment with a potent inducer (e.g., rifampin) or potent inhibitor (e.g., ketoconazole, erythromycin) of CYP3A4 isoenzymes (a more detailed list will be supplied in separate instructions to the investigator)
   (NOTE: A subject who was not using a potent CYP3A4 inducer or potent inhibitor and/or for whom such therapy was not anticipated, but who subsequently requires such therapy after randomized assignment of study drug might receive such therapy pursuant to the protocol.
5. history of a bleeding diathesis, or evidence of active abnormal bleeding within 30 days before enrollment
6. history at any time of intracranial hemorrhage (except “microhemorrhage” [e.g., as detected on T2-weighted MRI {magnetic resonance imaging}]), intracranial or spinal cord surgery, or a central nervous system tumor or aneurysm

7. documented sustained severe hypertension (systolic blood pressure >200 mmHg or diastolic blood pressure >110 mmHg) at enrollment or within the previous 10 days
8. severe valvular heart disease, as defined by the American College of Cardiology/American Heart Association
9. history within 2 weeks prior to enrollment of major surgery other than mentioned above or of ischemic (presumed thrombotic) stroke
10. known platelet count <100,000/mm^3 within 30 days before enrollment
11. known active hepatobiliary disease, or known unexplained persistent increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) activity to two times or more the upper limit of the reference range (upper limit of "normal" [≥ 2xULN])

5.3.1.5 **Randomization and Treatments**

After meeting the study enrollment criteria, eligible subjects were randomized to treatment with vorapaxar, given as one 2.5 mg film-coated, immediate release tablet daily (without regard to meals) or matching placebo. No other vorapaxar dosing regimen was allowed.

Randomization was 1:1 in blocks of 4. A telephonic IVRS was used for randomization, which was stratified by –

1. qualifying condition for enrollment according to the following hierarchy -
   1.1. CAD (recent MI),
   1.2. CVD (recent ischemic stroke), or
   1.3. PAD.

(If a subject met the criteria for more than one of these conditions, he or she was assigned to the stratum for first condition in the hierarchy that was met); and

2. planned treatment with a thienopyridine (being taken or added at enrollment vs. not taken or added)

Study drug was supplied in uniquely numbered treatment kits in small boxes with sufficient tablets (always in bottles of 70) to last until the next visit; time between visits varied from 1 to 6 months. The kits were assigned in a blinded fashion by the IVRS system at each visit. From the site's standpoint, any remaining kit in stock that was of the appropriate size might be assigned to any given patient at a given visit. Staff at the site were to key into the telephone the kit number provided by the IVRS system as a quality check. A fax with the assigned kit number was also sent to the site. Bar codes were not used to identify kit numbers. Kit numbers were not re-entered into the CRF when bottles were returned.

5.3.1.5.1 Duration of Treatment and Follow-up

Except as provided below and in Sec. **6.1.9.1** (regarding discontinuation of treatment and in many cases, discontinuation of follow-up of subjects with a history of stroke) treatment with blinded study drug was to continue until the final study visit or telephone contact, which was to occur following attainment of the target number of endpoint events. Patients could withdraw from treatment at their discretion, but would have been followed up as described below unless they explicitly withdrew from follow-up as well as from treatment.

In addition, the protocol indicated that double-blind treatment was to be discontinued as follows:

Study treatment “may be discontinued” for the following reasons:

- life-threatening or other serious adverse event
- failure to comply with the dosing, evaluations, or other requirements of the study
- unusual or excessive bleeding / signs or symptoms of abnormal bleeding from any source that cannot be controlled without discontinuation of the study drug

Study treatment “should be discontinued” for the following reasons:

- if the blind is broken for a subject at the request of the investigator/qualified designee
- pregnancy
- requirement for concurrent therapy with aspirin plus a thienopyridine plus warfarin
- requirement for therapy with a potent inducer or potent inhibitor of CYP3A4 for a period >4 weeks. A subject who was not using a potent CYP3A4 inducer or potent inhibitor at enrollment and/or for whom such therapy was not anticipated, but who subsequently required such therapy after randomized assignment of study drug was to have treatment with randomized study drug temporarily interrupted or permanently discontinued as follows.
    - Potent CYP3A4 Inducer: Continue treatment with randomized study drug concurrently until therapy with the inducer ends, or until therapy with the potent inducer extends beyond 4 weeks, at which point, discontinue treatment with randomized study drug.
    - Potent CYP3A4 Inhibitor: Interrupt treatment with randomized study drug until therapy with the potent inhibitor ends, or until therapy with the potent inhibitor extends beyond 4 weeks, at which point, discontinue treatment with randomized study drug.

Note that discontinuation was not required for the occurrence of an efficacy endpoint.

If a subject's study treatment was discontinued early for any reason, the subject was to to:

- return for a discontinuation visit, and
- continue to participate in the study, without taking study medication, via telephone contacts with the investigator or qualified designee and be evaluated through study completion, unless the subject withdrew consent for follow-up.

If a subject discontinued study participation; i.e., withdrew consent for follow-up:

- while taking study medication, the subject was to return for a final evaluation visit, or
- after (1) receiving randomized treatment assignment but before taking the first dose, or (2) after previously discontinuing treatment, the investigator or qualified designee was to collect information on suspected efficacy endpoint and bleeding events that may have occurred since the last contact.

Subjects who discontinued treatment or follow-up were not replaced.

5.3.1.5.2 Special Dosing Procedures

There were no special dosing procedures other than those described in the previous section. The Applicant notes that, "Results of the three Phase 2 studies demonstrated no clinically meaningful incremental risk of bleeding relative to placebo, even in surgical situations such as CABG." Thus, the Applicant suggested that study treatment be continued in the event of trauma, surgery, or invasive procedures.

Subjects were to be instructed that if they missed a dose or forget to take a dose, they should simply take the next daily dose as scheduled.

Reviewer comment: The recommendation regarding missed doses makes sense in light of the long PK and even longer PD half-life of vorapaxar.

5.3.1.5.3 Concomitant Medications

All concomitant medications were to be recorded in the CRF. Other than medications mentioned in the exclusion criteria (vitamin K antagonists, factor Xa and IIa antagonists, and potent inducers or inhibitors of CYP3A4, see Sec. **5.3.1.4**), there were no prohibited concomitant medications.

5.3.1.6 Blinding

The Applicant prepared the randomization schemes and provided them to the IVRS vendor. The IVRS vendor was not to disclose information for any subject unless disclosure was required for proper care of the subject. The following process was described for emergency unblinding for individual subjects:

"The investigator/qualified designee was to contact the study "hotline" at TIMI to consult with a study physician about the need for unblinding. If it was agreed that the investigator/qualified designee must know the treatment assignment of an individual subject, the study hotline instructed the investigator/qualified designee to contact the IVRS for the treatment assignment. The IVRS provided the treatment assignment for only the individual subject in question after the investigator/qualified designee affirmed that the study hotline had been consulted."

Copies of the randomization scheme were also provided to the following persons within Merck:

- Clinical supply staff responsible for packaging and shipping study drug
- The administrative head of Drug Safety Surveillance

The Applicant asserts that all copies of these randomization schemes were protected by standard operating procedures of the Sponsor and the IVRS vendor, and the schemes were not disclosed until after study completion and closure of the data base.

Reviewer comment: It's not clear to me why the head of Drug Safety would need the randomization code during the trial. In this study, the IVRS vendor provided treatment assignment information when such information was urgently needed by the sites to appropriately manage subjects. During the trial, safety staff should ordinarily be blinded in order to evaluate AEs in an unbiased way Other than drug supply staff and firewalled statisticians preparing materials for the DSMB, no other persons within a Sponsor's organization ordinarily have a need for the randomization code. Good practice is to restrict availability of the code to persons who need it to perform their duties. The Applicant should explain the rationale for this aspect of its blinding process.

5.3.1.7 **Study Plan and Procedures**

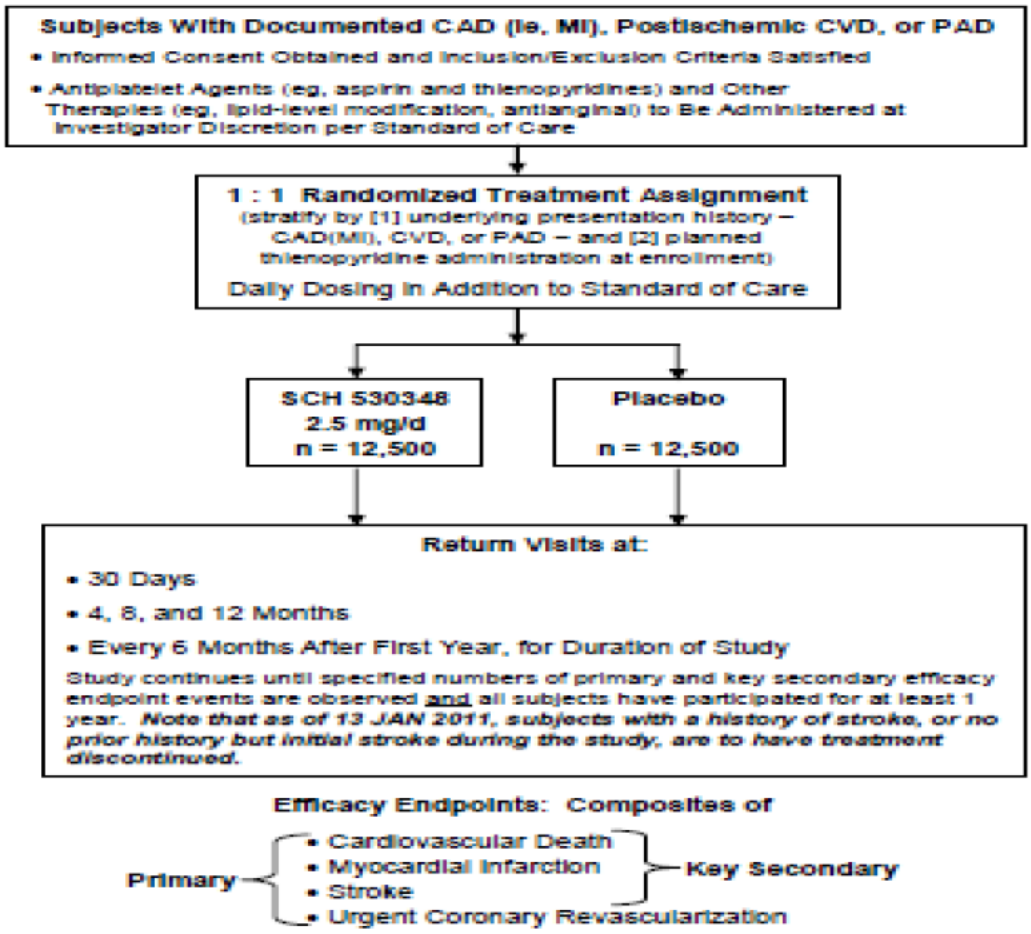
5.3.1.7.1 Study Visits and Information Collected

Screening could occur up to 10 days prior to randomization. After obtaining informed consent and determination of eligibility based on history, physical exam (including ankle-brachial index), ECG and clinical laboratory studies, patients were randomized to study treatment and given study drug. Blood for biomarkers (all subjects) and genomic studies (at selected sites, with additional informed consent) was also collected at screening or soon afterwards. Subsequent study visits were at 30 days, 4 months, 8 months, 12 months, and then every 6 months until study completion.

There were visits for early discontinuation of study drug and for completion of the study pursuant to the Executive Committee's recommendation to close the trial. Patients who discontinued study drug early were encouraged to remain in the trial. After an in-person early discontinuation visit subjects had telephone contacts on the same schedule as the visits for those who continued treatment.

Figure 7 provides an overview of the study procedures; see **Table 86** for additional detail.

Figure 7 Study Flow Diagram



5.3.1.8 Efficacy Endpoints

Unless otherwise specified, for the events described below only adjudicated events were counted, and the event collection window was from randomization to the last visit, which may have been an in-person or telephone visit.

5.3.1.8.1 Primary Endpoint

The primary efficacy outcome was time to the first occurrence of the composite of CV death, MI, stroke, MI or urgent coronary revascularization. For definitions of these events, see Sec. 5.3.1.12.

5.3.1.8.2 Secondary Endpoints

The key secondary endpoint was the composite of time to the first occurrence of CV death, MI or stroke.

Other secondary efficacy endpoints included several additional composite endpoints as well as their individual components. These were to be evaluated in an alpha-conserving hierarchy that started with (1) the primary endpoint and (2) the and key secondary endpoint:

3. all-cause death, MI, stroke, and urgent coronary revascularization
4. cardiovascular death and MI
5. cardiovascular death, MI, stroke, urgent coronary revascularization, or urgent hospitalization for vascular cause of ischemic nature
6. all-cause death, MI, stroke, any revascularization (including amputation for ischemic limb)
7. cardiovascular death, MI, stroke, any revascularization (including amputation for ischemic limb), or urgent hospitalization for vascular cause of ischemic nature
8. the individual components of the composite primary efficacy endpoint -
   a) cardiovascular death
   b) MI
   c) stroke
   d) urgent coronary revascularization
9. all-cause death

Secondary endpoints above were specified in the original version of the protocol. After the DSMB recommended that patients with a history of stroke should be discontinued from study drug, the following additional secondary endpoints were added:

1. cardiovascular death, MI, stroke, and urgent coronary revascularization
2. cardiovascular death, MI, and stroke

These were assessed in each of the following subsets of subjects:

1. CAD/PAD: subjects who received randomized treatment assignment and whose qualifying condition was either CAD or PAD, regardless of stroke history
2. NSH (No Stroke History): subjects who received randomized treatment assignment and did NOT have a documented prior history of stroke
3. CAD: subjects who received randomized treatment assignment and whose qualifying condition was CAD analyzed in (a) all of these subjects, regardless of stroke history, and (b) those subjects without a documented prior history of stroke

5.3.1.9 Safety Endpoints

Specific safety objectives, in relative order of importance, include time to event analyses of evaluation of -

1. The composite of moderate and severe bleeding events according to the GUSTO (**G**lobal **U**tilization of **S**treptokinase and **T**issue Plasminogen Activator for **O**ccluded Arteries cooperative group) classification
2. "clinically significant bleeding," defined as TIMI (**T**hrombolysis **i**n **M**yocardial **I**nfarction Study Group) major or TIMI minor bleeding, or bleeding that requires unplanned medical

treatment, surgical treatment, or laboratory evaluation even if it does not meet the criteria for TIMI major or TIMI minor bleeding

Exploratory safety endpoints include the following:

1. GUSTO severe bleeding events
2. All TIMI major and minor bleeding events
3. Non-CABG TIMI major and minor bleeding events
4. Major bleeding events defined according to International Society of Thrombosis and Haemostasis (ISTH)
5. "Net Clinical Outcome": the composite of cardiovascular death, MI, stroke, urgent coronary revascularization, GUSTO severe and moderate bleeding
6. Bleeding events that do not meet the TIMI criteria for major or minor
   a) TIMI bleeding requiring medical attention
   b) bleeding not meeting any TIMI definition and are at least GUSTO mild)
7. In subjects undergoing CABG while still receiving study drug:
   a) TIMI major CABG related
   b) GUSTO severe CABG related
   c) incidence of any blood product transfusion (e.g. red blood cell, platelet)
   d) incidence of packed red blood cell transfusion
   e) incidence of platelet transfusion
   f) bleeding assessed
      i. by chest-tube drainage (in ml) through 8 hours after surgery, through 24 hours after surgery and by total drainage; and
      ii. by need for re-operation for bleeding..
8. Intracranial hemorrhage
   a) intracerebral hemorrhage
   b) subarachnoid hemorrhage
   c) subdural/epidural hemorrhage

5.3.1.10 **Safety Procedures**

Adverse Events

Adverse events were to be elicited through general questioning, such as, "How have you been feeling since your last visit?" The sites were explicitly instructed not to ask about any specific AE.

There was an eCRF module for AEs other than bleeding and a separate module for bleeding events, which were not to be considered AE's. Other endpoint events were also not to be captured as AEs, and were not reported as such. For a list of events that were not to be reported as AEs, see below .

Investigators were not to grade bleeding events for severity because they would be sent for adjudication. The bleeding event module captured data needed to grade bleeding events by the GUSTO, ISTH and TIMI scales.

Generally, results of laboratory tests or other procedures were to be interpreted as an adverse event if they represent a "clinically relevant" change or finding. Also, the protocol specified that the following laboratory results were to be captured as AEs:

- decrease from baseline in platelet count by ≥50%, or to a value <100,000/mm^3
- platelet counts <50,000/mm3 require reporting as a serious adverse event
- increase from baseline in ALT or AST activity to a value ≥3 x ULN
- increase from baseline in total bilirubin concentration to a value ≥1.5 x ULN

AEs were graded for severity as follows:

- **Mild:** awareness of sign, symptom, or event, but easily tolerated;
- **Moderate:** discomfort enough to cause interference with usual activity and may warrant intervention;
- **Severe:** incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention;
- **Life-Threatening:** immediate risk of death

AEs were assessed for causality as follows:

- **Unlikely related:** no temporal association, or the cause of the event has been identified, or the drug, biological, or device cannot be implicated;
- **Possibly related:** temporal association, but other etiologies are likely to be the cause; however, involvement of the drug, biological, or device cannot be excluded;
- **Probably related:** temporal association, other etiologies are possible, but unlikely.

Serious adverse events were defined as any adverse drug experience that results in any of the following:

- death (but see below)
- life-threatening AE (i.e., one that places the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurs)
- persistent or significant disability/incapacity
- requires in-patient hospitalization (i.e., admission), or prolongs hospitalization
- congenital anomaly or birth defect, or
- important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs, unless explicitly exempted (see below), were to be entered into the eCRF within 1 working day of when the investigator or qualified designee became aware of the event. This triggered notification of the appropriate Sponsor contacts. There also were to be reported to IRBs or equivalent bodies as required by local laws.

Exempted events that were not to be reported as SAEs were:

- death from any cause
- MI
- stroke (including primary hemorrhagic stroke and ischemic [thrombotic] stroke with hemorrhagic conversion)

- any revascularization (egg, urgent coronary revascularization, amputation for ischemic limb)
- hospitalization for vascular cause of ischemic nature
- any bleeding

Data regarding all deaths were to be entered in the eCRF death module.

Serious and non-serious AEs were coded using MedDRA 14.0.

Reviewer comment: The exemption of death from AE reporting is inconsistent with the definition of SAE in the protocol; there may have been confusion at the sites about this. However, as long as all deaths were recorded in the database and are represented accurately without undercounts or duplicate counts in the study report and ISS, this is not a material issue. The applicant represents that death data are based on the death/survival page in the CRF.

5.3.1.11 Additional data to be collected

Other types of data were collected in optional substudies at interested sites:

- pharmacokinetics,
- pharmacodynamics, including potential assessment of dozens of markers of –
  - inflammation and atherogenesis
  - endothelial function
  - thrombosis
  - oxidative stress
  - ischemia/necrosis
  - hemodynamic stress
  - metabolic/lipid dysregulation
  - renal dysfunction and
  - platelet and myeloid-cell activation,
- pharmacogenomics (relating to PAR-1 polymorphism)
- ocular safety of vorapaxar (Protocol P05183, discussed in Sec **7.7.1**).

5.3.1.12 Endpoint Definitions

The following definitions in the Clinical Endpoint Committee (CEC) charter (July 2011 version) were used in assessing endpoints.

Myocardial infarction was based on clinical context:

A. For patients with no recent revascularization in whom biomarkers were never elevated or have been documented to return to normal after a qualifying (or recent) MI, criteria (1) & (2) or criterion (3) or criterion (4) must be met:

1) Typical cardiac biomarker rise and/or fall with the following degrees of elevation accepted as biochemical evidence of myocardial necrosis:
   a) Troponin T or I: maximal concentration greater than the MI decision limit; (or)
   b) CK-MB: maximal concentration greater than the ULN; **AND**
2) At least 1 of the following additional supportive criteria:

a) Ischemic discomfort at rest lasting ≥10 minutes; or
b) ECG changes indicative of ischemia (ST elevation ≥0.1 mV or ST depression ≥0.05 mV, or new T-wave inversions); **OR**

3) Development of new, abnormal Q waves (≥30 msec in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction; **OR**

4) Pathologic findings of an acute MI.

B. For patients with no recent revascularization in whom biomarkers from a qualifying (or recent) MI remain elevated, criteria (1) and (2), or criterion (3), or criterion (4) must be met:

1) Cardiac biomarker re-elevation defined as:
   a) Increase by at least 20% of the previous value; and
   b) Documentation that the biomarker assayed was decreasing prior to the suspected new MI; **AND**
2) At least 1 of the following additional supportive criteria:
   a) Ischemic discomfort at rest lasting ≥10 minutes; or
   b) ECG changes indicative of ischemia (ST elevation ≥0.1 mV or ST depression ≥0.05 mV, or new T-wave inversions); **OR**

3) Development of new, abnormal Q waves (≥30 msec in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction; **OR**

4) New elevation of ST-segments ≥ 0.1 mV in ≥ 2 contiguous precordial or adjacent limb leads AND at least one of the following:
   a) Ischemic discomfort at rest lasting ≥ 20 minutes; or
   b) Ischemia-mediated new hemodynamic decompensation requiring pharmacologic or mechanical support; or
   c) Angiographic evidence of acute coronary occlusion

C. For patients who have a PCI, within 24 hours there is either:
1) CK-MB >3× ULN and, if the pre-PCI CK-MB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI; or
2) Pathologic findings of an acute MI.

(Note: symptoms were not required in either of these cases)

D. Within 24 hours after CABG a patient must have had EITHER:
1) CK-MB >5× ULN and, if the pre-CABG CK-MB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI; **AND**

2) At least one of the following supportive criteria:
   a) Development of new, abnormal Q waves (≥30 msec in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction, or

b) Angiographically documented new graft or native coronary occlusion, or
c) Imaging evidence of new loss of viable myocardium

OR

3) Pathologic findings of an acute MI.

Note: symptoms were not required. If cardiac troponin measurements were re the only cardiac biomarker data available, they could have been used by the CEC, along with the ECG and clinical scenario, in the adjudication of suspected MI after revascularization (PCI or CABG).

Myocardial infarctions were also classified according to the following universal definition of MI criteria:

Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.

Type 2: MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.

Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Type 4a: MI associated with PCI.

Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy.

Type 5: MI associated with CABG.

Reviewer comment: These definitions are similar in many respects, but not identical to those in the 2007 Universal Definition of MI.(5) They are adequate for use in this study. Note that the 2007 Universal Definition document was published in 3 major cardiology journals about 1 to 2 months after the first study patient was randomized in TRA 2ºP.

Urgent Coronary Revascularization was defined as ischemic discomfort or equivalent meeting the following criteria:

1. lasting ≥ 10 minutes at rest, or repeated episodes at rest lasting ≥ 5 minutes, considered to be myocardial ischemia upon final diagnosis

AND

2. prompting coronary revascularization performed during an unscheduled visit to healthcare facility or during an unplanned hospitalization for these symptoms, or revascularization which was either done emergently or not previously planned during the course of the

hospitalization. Attempted revascularization procedures, even if not successful, will be counted. Potential ischemic events meeting the criteria for myocardial infarction will not be adjudicated as urgent coronary revascularization.

Stroke was defined as an acute focal neurological deficit of sudden onset,
a) that is not reversible within 24 hours or results in death (in <24 hrs) and is not due to an identifiable non-vascular cause (i.e. brain tumor, trauma), orb) that resolves in <24 hrs and is accompanied by clear evidence of a new stroke on cerebral imaging.

Stroke was to be sub-classified into one of the following 4 groups:

- Non-hemorrhagic Cerebral Infarction: Stroke without focal collections of intracerebral blood on a brain imaging. This category will be sub-classified into suspected embolic vs. other.
- Non-hemorrhagic Infarction with Hemorrhagic Conversion: Cerebral infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage. Hemorrhagic conversion usually occurs on the cortical surface. Hemorrhagic conversion in the deeper brain requires evidence of non- hemorrhagic infarction in the same vascular territory. Microhemorrhages evident on MRI, whether in the cortex or deep brain structures, are not considered to be consistent with a hemorrhagic conversion endpoint.
- Primary Hemorrhagic
  - Intracerebral Hemorrhage - Stroke with focal collections of intracerebral blood seen on a brain image (CT or MRI) or a postmortem examination, not likely to represent hemorrhagic conversion. Primary hemorrhages cause hematomas which are usually easily discriminated by their subcortical location and rounded or elliptical shape. Microhemorrhages incidentally discovered on brain imaging in the absence of associated symptoms will not be considered to be a primary intracranial hemorrhage endpoint.
  - Subarachnoid hemorrhage - High density fluid collection in subarachnoid space on brain images or blood in the subarachnoid space on autopsy
- Uncertain - Any stroke without brain image (CT or MRI) or autopsy documentation of type, or if tests are inconclusive

Subdural hematoma will not be classified as a stroke but will be classified as a bleeding event (intracranial hemorrhage). Intracerebral microhemorrhages will be classified in a separate category for analysis. Microhemorrhage is defined as rounded foci of <10mm that appear hypointense and that are distinct from other causes of signal loss on gradient-echo MRI sequences (e.g. vascular flow voids, leptomeningeal hemasidarosis, or non-hemorrhagic subcortical mineralization).

Transient ischemic attack is defined by both:

1. an acute focal neurological deficit ending lasting <24 hours, and not due to an identifiable non-vascular cause (i.e. brain tumor, trauma), and
2. absence of new infarct on brain imaging (if obtained)

5.3.1.13 Adjudication of Endpoints

An independent Clinical Endpoint Committee (CEC), which operated under a procedures manual (also called a “charter”), was created to adjudicate the endpoints described below. The CEC

served the TRA 2ºP and TRA•CER studies, although there was one "branch" of the CEC for each study. The adjudicated endpoints and classifications in TRA 2ºP were:

- Death
  - Cardiovascular
  - Non-cardiovascular
  - Unknown
- Myocardial Infarction
  - Non-procedural
  - Peri-PCI
  - Peri-CABG
- Stroke
  - Hemorrhagic
  - Non-hemorrhagic
- Ischemia leading to Urgent Coronary Revascularization
- Coronary Ischemia Requiring Hospitalization
- Urgent Hospitalization for Vascular Cause of Ischemic Nature
- Coronary Stent Thrombosis
- Bleeding
  - TIMI Classification
  - GUSTO Classification
  - ISTH Major Bleeding Classification

5.3.1.13.1 CEC structure and responsibilities

Adjudication for TRA 2ºP was coordinated by the TIMI study group in Boston, while coordination for TRA•CER has handled by the Duke Clinical Research Institute (DCRI). TIMI was responsible for selecting members and the chair of its branch of the CEC. The CEC chair was responsible for overall quality control and training of members. A Coordinator was responsible for day to day operations, such as preparing documents for review by the members. The CEC members were responsible for review of endpoints.

5.3.1.13.2 Ascertainment of events for adjudication

Suspected events were identified systematically by a computer program that queried data fields on the eCRF determined to be CEC critical variables. This program was called the CEC "trigger" program. This program was run on study data as they were entered or updated from the eCRF or queries.

The initial set of triggers was based on the trial protocol, eCRF, and general CEC experience in prior ACS trials. However, the development of clinical trial triggers was to be an iterative process with the possibility that the triggers may be revised during the course of the trial. The specific triggers were documented in a separate document.

Once all eCRF data fields necessary for CEC review had all outstanding data queries resolved, the case was administratively reviewed for completeness and then adjudicated.

Adjudication packages were to include:

1) appropriate adjudication pages
2) data worksheet including entry forms
3) overall subject summary
4) appropriate eCRF pages (or data summary), including narratives
5) relevant laboratory data, imaging, procedural reports, and ECGs.

5.3.1.13.3 Adjudication procedures

Adjudication packages were randomly assigned to two physician members of the CEC, who reviewed them independently. If they concurred, the case was considered complete. If they did not concur, or at the discretion of a reviewer, the case was sent to at least one additional reviewer for a final adjudication. Copies of all signed adjudication forms were kept. A log was kept.

Five percent of randomly selected cases were sent for QC review by a second set of reviewers (of unstated size) who reviewed the cases without knowledge of the original reviews. The Coordinator compared the two rounds of reviews. Discrepancies between the reviews were handled as follows. Disagreements regarding whether an event occurred were consider "major" disagreement. These were openly compared and discussed by the entire committee. "Minor" disagreements were those that where there was agreement on whether an event occurred, but disagreement regarding its type of the evidence. These were reviewed by the CEC Coordinator, or if necessary, the Chair. In the case of "compelling" evidence that the original adjudication was in error and the QC review was correct, the adjudication result was changed. A random sample of events underwent QC review by the CEC Phase II committee.

Reviewer comment: These processes seem adequate on their face.

5.3.1.14 Statistical Plan

5.3.1.14.1 History of the Statistical Plan

There are two versions of the statistical plan, which was termed the Data Analysis Plan (DAP). Dates of these plans, along with major study milestones, are provided in **Table 8.**

Table 8 TRA 2ºP – History of the DAP and Other Relevant Events

SAP Version or Relevant Event	Date	Comments
First patient randomized	9/26/2007	-
1st DSMB meeting with data review	2/11/2008	Minutes indicate there were no safety concerns
Enrollment ends in PAD stratum	5/12/2009	Enrollment continues in other 2 strata
Enrollment ends in CVD stratum	7/31/2009	Enrollment continues in CAD stratum
Original DAP	11/03/2009	See text
Study enrollment closed	11/12/2009	--
DSMB meets to review report of planned interim analysis	2/24/2010	DSMB recommended that the study should continue as planned
Second unscheduled DSMB meeting to discuss ICH events	5/2011	DSMB recommended discontinuation of patients with history of stroke to Study Chair (E. Braunwald) on 1/8/2011
Study Chair notifies sites to discontinue subjects with history of stroke	1/13/2011	--
Amended DAP finalized	7/22/2011	See text
Last subject contact	12/23/2011	--
Database lock	01/09/2012	--

5.3.1.14.2 Original DAP

The discussion below describes the original DAP, which was finalized on November 3, 2009.

5.3.1.14.2.1 Sample Size

This study was planned as the only Phase 3 trial for a secondary prevention indication. The statistical assumptions were:

- Based on prior data from CAPRIE and CHARISMA, the placebo arm rates of the primary efficacy endpoint (time from randomization to CV death, MI, stroke or urgent coronary revascularization) and the key secondary efficacy endpoint (time from randomization to CV death, MI or stroke) would be 8% and 4% at one year, respectively.
- The would be a 15% reduction in risk for each endpoint with vorapaxar 1% loss to follow-up
- Accounting for dropouts (rate not specified), 9750 subjects per arm (with a total of 2279 primary endpoint events and 1322 key secondary endpoint events in the combined arms) would be required to detect the expected risk reduction at the 0.05 level of alpha with 98% power for the primary endpoint and 85% power for the key secondary endpoint.
- The original DAP allowed for a blinded assessment of the number of accumulated primary and key secondary endpoint and consequent increase of the sample size up to 13,500/arm if needed to maintain power.

During the study, a blinded assessment of event rates prior to closure of enrollment led to the expansion of the expected enrollment to 25,000 (12,500/arm) with an increase to 1400 key secondary endpoints. It was also stipulated that each subject who did not drop out would participate for a minimum of 1 year.

The Applicant intended the study to have the following make-up of subjects in the 3 qualifying categories of arteriosclerotic disease: 70% CAD, 15% CVD (cerebrovascular disease), and 15% CAD. The Executive Committee could cut off enrollment of any one or more of these categories to achieve this end.

5.3.1.14.2.2 *Efficacy Variables*

Only adjudicated events would be counted in the final study analysis. The efficacy analyses were in the all randomized patients population using a Cox proportional hazards model with covariates of treatment and the stratification factors: type of qualifying arteriosclerotic disease and planned thienopyridine use (yes or no). Events for the ITT analyses were collected from randomization through the last visit or contact.

The proportionality assumption of the Cox model for the primary and key secondary endpoints would be assessed by testing interactions between treatment and follow-up time in the Cox model at the 5% level. If the assumption was not satisfied, the estimate of the HR "will be interpreted as an average treatment effect over the time range of the study."

Multiplicity was handled as follows: The primary endpoint was analyzed at with an alpha of 0.05 level. If that analysis was successful, the key secondary endpoint was analyzed at the 0.05 level.

However, after describing that process, the protocol states,

> Other secondary efficacy endpoints will be tested only if the primary efficacy endpoint is significant. If the primary hypothesis is found to be significant, each of the other secondary efficacy endpoints will be tested sequentially at alpha level of 0.05 in the order listed previously. Testing will continue until a non-significant result is found.

*Reviewer comment: The statement in the indented text immediately above seems inconsistent with the text immediately above the indented text because it suggests testing of the "other" secondary endpoints will be performed without regard to the results of the key secondary endpoint analysis. Indeed, this language was modified in the Amended DAP (see Sec. **5.3.1.14.2.5**.)*

The "other" secondary endpoints were:

(1) all-cause death, MI, stroke, and urgent coronary revascularization

(2) cardiovascular death and MI
(3) cardiovascular death, MI, stroke, urgent coronary revascularization, or urgent hospitalization for vascular cause of ischemic nature
(4) all-cause death, MI, stroke, any revascularization (including amputation for ischemic limb)
(5) cardiovascular death, MI, stroke, any revascularization (including amputation for ischemic limb), or urgent hospitalization for vascular cause of ischemic nature
(6) the individual components of the composite primary efficacy endpoint
    (a) cardiovascular death
    (b) MI
    (c) stroke
    (d) urgent coronary revascularization
(7) all-cause death

There was also a series of exploratory efficacy endpoints:

1. all-cause death, MI, and stroke in subjects undergoing PCI during participation in the study
2. all-cause death, MI, and stroke in subjects undergoing CABG during participation in the study
3. cardiovascular death, MI, stroke and urgent coronary revascularization in association with use of thienopyridine (regardless of aspirin use)
4. cardiovascular death, MI and stroke in association with use of thienopyridine (regardless of aspirin use)
5. cardiovascular death, MI, stroke and urgent coronary revascularization in subjects taking aspirin but not thienopyridine
6. cardiovascular death, MI, and stroke in subjects taking aspirin but not thienopyridine

The DAP indicates that these exploratory endpoints are “supportive” and that “no additional multiplicity adjustment will be applied.”

The DAP specified that efficacy would be explored in the following subgroups of patients:

- Sex
- Age: <65 vs. ≥65 and <75 vs. ≥75
- Race: Caucasian, vs. non-Caucasian
- Body weight: <median vs. ≥median
- Stratification factor of atherosclerosis history at time of enrollment: CAD, CVD, PAD
- Planned use of thienopyridine
- Aspirin use
- Geographic Regions
- History of diabetes mellitus
- Prior stroke
- Prior MI
- Prior ACS (MI or hospitalization for unstable angina)
- Renal insufficiency

- Tobacco use
- Lipid medication
- Statin therapy

Reviewer comment: The list of subgroups above is from the final DAP. It differs slightly from the one in the original DAP only in that in the original DAP, aspirin use was stratified by dose (none, <100 mg, ≥ 100 mg) and the first row was "gender", not "sex".

5.3.1.14.2.3 *Safety Variables*

Safety endpoints were analyzed in the "as treated" population in time to event analyses. The two major safety endpoints matched those specified in the protocol: (1) the composite of GUSTO moderate and severe events and (2) "clinically significant bleeding," defined as TIMI minor or major bleeding or bleeding requiring unplanned medical or surgical treatment or laboratory evaluation (see Sec. **5.3.1.9**.).

Exploratory safety variables included:

- GUSTO Severe bleeding events
- all TIMI Major and TIMI Minor bleeding events
- non-CABG TIMI Major and Minor bleeding events
- Major bleeding events defined according to the International Society on Thrombosis and Haemostasis
- Net Clinical Outcome – the composite of CV death, MI, stroke, urgent coronary revascularization, GUSTO severe bleeding, or GUSTO moderate bleeding
- bleeding events that did not meet the criteria for TIMI Major or TIMI Minor bleeding, and
    - required medical attention (required unplanned medical or surgical treatment or unplanned laboratory evaluation)
    - did not meet any TIMI definition (did not require medical attention) , but were at least GUSTO Mild
- intracranial hemorrhage
    - intracerebral hemorrhage
    - subarachnoid hemorrhage
    - epidural/subdural hemorrhage
- in subjects who underwent CABG while still receiving study drug --
    - GUSTO Severe CABG-related bleeding events
    - TIMI Major CABG-related bleeding events
    - incidence of any blood product transfusion (e.g., red blood cell, platelet)
    - incidence of PRBC transfusion
    - incidence of platelet transfusion
    - bleeding assessed by -
        - chest-tube drainage (mL) through 8 hours and 24 hours after surgery, and in total
        - need for re-operation for bleeding

5.3.1.14.2.4 *Interim Analysis*

There was a formal interim analysis of the primary endpoint and key secondary endpoint planned when half the target number of primary endpoint events had occurred, using the same Cox model as the final primary endpoint analysis and counting only adjudicated events. A supportive analysis was planned using adjudicated and non-adjudicated events. The DSMB could recommend stopping the study if the one-sided p for the primary endpoint analysis was < 0.003. The impact of the interim look on the final p for success in the superiority analysis for the primary endpoint and key secondary endpoint would be a reduction of the two sided p to 0.049 from 0.05.

The interim analysis was performed by an independent statistical group at DCRI in an unblinded fashion. The study report indicates that the data were supplied only to the DSMB. The data did not meet the target for early stopping of the study due to efficacy, and the study continued (see Sec. **6.1.9.1** for additional information).

5.3.1.14.2.5 *Amended DAP*

The second and final version of the DAP was finalized on July 22, 2011, after the interim analysis and also after the study changes of January 2011 relating to and increased risk of ICH in subjects randomized to vorapaxar with a history of stroke (see Sec. **6.1.9.1**).

Changes to the DAP made at this time included:

- A description of the events of January 2011 referenced immediately above and described in Sec. **6.1.9.1**;
- Addition of Supplementary Secondary Objectives/Endpoints (outside the hierarchical analysis) related to efficacy in subsets of patents of based on stroke history, as follows
    - evaluation of time the following two composites -
        1. cardiovascular death, MI, stroke, and urgent coronary revascularization, and
        2. cardiovascular death, MI, and stroke

        in each of the following subsets of subjects:

        1. CAD/PAD: subjects who received randomized treatment assignment and whose qualifying condition was either CAD or PAD, regardless of stroke history,
        2. NSH (No Stroke History): subjects who received randomized treatment assignment and did NOT have a documented prior history of stroke prior to randomization, and
        3. CAD: subjects who received randomized treatment assignment and whose qualifying condition was CAD, analyzed in (a) all of these subjects, regardless of stroke history, and (b) those subjects without a documented prior history of stroke prior to randomization:

- Modification of the fifth “other secondary endpoint” to read

the individual components -

- cardiovascular death
- MI
- urgent coronary revascularization
- all-cause death
- stroke

Reviewer comment: In the initial DAP, the effective order of these endpoints (which are part of a hierarchy of endpoints that might conceivably be proposed for labeling) was:

- *cardiovascular death*
- *MI*
- *stroke*
- *urgent coronary revascularization*
- *all-cause death*

This change was made after patients with a history of stroke were removed from the study at the recommendation of the DSMB. This change in the order of secondary endpoint analysis hierarchy would likely affect alpha error because the sponsor probably suspected the reason for the DSMB's recommendation. However, because the findings for CV death were not significant, thus terminating the hierarchical analysis at that point, this issue is moot.

- Addition of on-treatment analysis for primary and key secondary efficacy endpoints, with on-treatment defined as first dose to last dose + 3 days.
- Addition of TIMI major CABG related bleeding, GUSTO severe CABG related bleeding and intracranial hemorrhage exploratory safety endpoints.
- Revision of the multiplicity section to clarify the hierarchy for testing the hypotheses to clarify that the list of secondary endpoints would be tested only if the results for the key secondary endpoint were positive.

5.3.1.15 **Study Committees**

The study protocol described the following committee structure:

Steering Committee (SC): This was a committee comprising the National Lead Investigators from the participating countries and academic experts in the several disciplines included in the study (e.g., cardiovascular medicine, vascular neurology). The committee was created to provide clinical guidance on implementation and conduct of the study, and on interpretation of results. The Committee chair was the study chair, Dr. Eugene Braunwald.

Executive Committee (EC): The Executive Committee was a subset of the Steering Committee. This committee was also chaired by Dr. Braunwald. It was responsible for the overall design, conduct, and supervision of the study, including the development of the protocol and protocol amendments. It was responsible for reviewing the progress of the study at regular intervals to ensure subject safety and study integrity, and made all final recommendations regarding study status (e.g., modification). In particular, the Executive Committee was responsible to the DSMB (see below) for –

- monitoring study conduct, and collection and quality of the data
- reviewing blinded DSMB reports of aggregated data
- reviewing and then accepting, rejecting, or modifying recommendations of the DSMB.
- implementing protocol changes if in accord with recommendations of the DSMB
- communicating accepted DSMB-recommended changes in the conduct of the study to investigators

- Operations Committee (OC): The OC was a small group of EC members, including representatives of the sponsor and CRO, tasked with "ensuring that study execution and management were of the highest quality." It met every 2 weeks to discuss and report on the conduct of the study.

The three members of this powerful committee included two physicians from the TIMI group: Dr. Braunwald and Dr. David Morrow, who was the study's Principal Investigator, as well as Dr. John Strony of Merck, the study's responsible Medical Officer.

Data and Safety Monitoring Board (DSMB): A DSMB (common to TRA 2ºP and TRA•CER) was established pursuant to a charter to monitor the progress of the studies and ensure that the safety of subjects. The DSMB members were selected by Dr. Braunwald and Dr. Robert Harrington (the study chair for TRA•CER). When the DSMB was considering TRA 2ºP , it was chaired by Dr. Robert Frye, a cardiologist from the Mayo Clinic; when it met to consider TRA•CER, it was chaired by Dr. Freek Verheught, a cardiologist from the Netherlands. There were two additional cardiologists, one neurologist, and one statistician (Dr. Kent Baily, Mayo Clinic).

Specifically, the DSMB was tasked to --

- review the protocol and any amendment,
- review safety monitoring procedures,
- review periodically the accumulating safety data and evaluate any adverse effects of treatment,
- perform one prespecified interim efficacy analysis
- advise the Study Chairs regarding the continuing safety of current and anticipated participants, and
- evaluate the continuing validity and scientific merit of the studies.

The DSMB received from an independent statistical group periodic aggregated safety reports that were partially blinded – results separated by treatment, but treatment not identified – but could (and did) receive fully unblinded results upon request.

All recommendations of the DSMB were made in writing to the respective Study Chairs, or to both Study Chairs if appropriate. Unblinded results were not to be released to the Sponsor or any one related to the conduct of either trial before trial data base lock.

Clinical Endpoint Committee (CEC): The composition and functions of the CEC are described above in Section **5.3.1.13.**

Independent Statistical Group: The independent statistical group for the current study was provided by the Duke Clinical Research Institute (DCRI), led by Kerry Lee, PhD, Director of Statistics at DCRI. The independent statistical group was responsible for the following:

- preparing and distributing partially blinded safety reports to the DSMB, and blinded reports if requested by the DSMB,
- preparing and distributing blinded safety reports to the Study Chair in advance of DSMB review,
- preparing and distributing the pre-specified interim efficacy analysis report to the DSMB and,

- in conjunction with the DSMB Chair, preparing the summary notes of each DSMB meeting or conference call

The Thrombolysis in Myocardial Infarction Study Group (TIMI) of Brigham and Women's Hospital and the Harvard Medical School, an academic research organization, served as the study coordinating center for TRA 2ºP. TIMI provided intellectual and support services in connection with the design and operation of the study. DCRI served as the study coordinating center for TRA•CER and had an analogous role in that study.

5.3.1.16 Protocol Amendments

The original protocol was finalized and dated 31 May 2007. Subsequent General amendments (i.e., those that were not country-specific) are discussed below.

Table 9 TRA 2ºP Protocol Amendments Applicable to the US

Amendment No..	Date	Description
1 (Genera)l	21 Jan 2009	Provided for stopping enrollment in CAD, CVD and PAD strata when enrollment in those strata reached 70%, 15%, and 15%, respectively, of the overall target; modified dosing procedures to accommodate enrollment at selected sites into Protocol 05183, the ocular safety substudy; provided for reassessment of sample size; included additional information on inclusion criteria, baseline data collection, and collection of concomitant medication data; removed requirement for strict compliance with treatment schedule at the 30 day visit; provided guidance on assessment of stroke, and added two exploratory safety endpoints.
2 (General)	23 March 2009	Increased sample size to about 25,000 from 19,500; increased minimum number of key secondary endpoints to 1400 from 1322 on the basis of blinded evaluation of accrued data; provided for a later reassessment of sample size up to 27,000.
3 (General)	10 March 2011	This amendment followed the revisions to the study triggered by the recommendation of the DSMB dated 8 Jan 2008 to discontinue subjects with a history of stroke. Changes to the study conduct, protocol and statistical plan made in connection with that recommendation are extensive and are discussed in Sec. **6.1.9.1**.

The protocol amendment xx (date) was a response to a letter to xx from the DSMB recommending major changes to the protocol related to the observed increased risk of intracranial hemorrhage, especially in subjects with a prior history of stroke. This protocol amendment was based on an unscheduled, unblinded analysis of the study data. This protocol amendment is discussed more fully in Sec**. 0**.

5.3.2 Supporting Study: TRA•CER

TRA•CER refers to a global study entitled, A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard of Care in Subjects With Acute Coronary Syndrome: Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (Protocol No. P04736).

5.3.2.1 Design of TRA•CER and Contrasts with TRA 2ºP

The two studies overlapped substantially in timing and had many important features in common. Similarities and differences between TRA 2°P and TRA•CER in terms of design features and enrollment data are shown in the following table.

Table 10 Features of TRA 2°P and TRA•CER

	TRA 2ºP	TRA•CER
Basic design	Randomized, double-blind, placebo-controlled, event-driven, parallel trial	Same
Primary objective	Demonstrate superiority of vorapaxar to placebo when added to standard of care for reduction in the rate of primary endpoint events (CV death, MI, stroke, urgent coronary revascularization) in patients with established CAD, ischemic CVD, or PAD	Demonstrate superiority of vorapaxar to placebo when added to standard of care for reduction in the rate of primary endpoint events (CV death, MI, stroke, recurrent ischemia with rehospitalization, urgent coronary revascularization) in patients with non-ST segment elevation MI or UA.
Patients	Adults (≥18 yrs.) with prior MI (2 weeks to 12 months prior to entry) or prior ischemic stroke (in same time frame as MI) or established PAD Key exclusions included clinical instability and specified disease- or treatment-based risk factors for bleeding, including prior ICH, or planned coronary revascularization	Adults with non-ST segment elevation ACS and one or more of these CV risk factors: • Age ≥ 55 y • Prior history of MI, PCI, or CABG • Pharmacologically treated DM • PAD Key exclusions included specified disease or treatment-based risk factors for bleeding, including prior ICH; or thrombotic stroke within 2 weeks of entry
Geographic scope	6 continents, 32 countries, 1034 sites	6 continents, 36 countries, 818 sites
Planned sample size	Up to 27,000	12,500
Enrolled	26,449	12,994
Event target	2279	2334
Vorapaxar dose	2.5 mg po once daily	40 mg oral loading dose followed by 2.5 mg po once daily
Control agent and dose	Matching placebo	Same
Planned follow-up	To final study visit, with timing based on attainment of event target, regardless of treatment status	Same
Primary endpoint/Key secondary endpoint	Composite of CV death, MI, stroke and urgent coronary revascularization / Composite of CV death, MI and stroke	Composite of CV death, MI, stroke, recurrent ischemia with rehospitalization and urgent coronary revascularization / Composite of CV death, MI and stroke

	TRA 2ºP	TRA•CER
Primary endpoint analysis	Superiority to placebo for time to first-occurring component of the primary endpoint	Same
Primary safety endpoint analysis	Time to first of component of GUSTO moderate or severe bleeding or clinically significant bleeding as defined in the protocol	Same as TRA 2°P. Safety procedures were also similar to those in TRA 2°P.
Important endpoints adjudicated?	Yes. The same clinical endpoints committee charter was used for both TRA 2°P and TRA•CER, but staff were different	Yes. See entry for TRA 2°P.
Planned Interim Analysis?	Yes, at 50% of event target	Same
PK/PD data collected?	Yes	Yes
First patient entered	Dec 19, 2006	Dec 18, 2007
Last patient entered	November 12, 2009	Jun 4, 2010 (except China) Nov. 30, 2010 (China)
Last patient contact	December 23, 2011	Jul 25, 2011
Median F/U	2.2 yrs.	1.1 yr
Administrative Structure	Study Chair, Executive Committee, Steering Committee, DSMB, Clinical Events Committee for adjudication, Principal Investigator	Same. The DSMB was shared with TRA 2°P. The CEC charter was shared with TRA 2°P, but the CEC members were unique to each trial.
Primary Academic Research Organization	TIMI	DCRI

5.3.2.1.1 Additional TRA•CER design information

If a an event triggering a UCR or an RIR met the criteria for MI, it was classified only as an MI. If an event met the criteria for both RIR and UCR, it was classified only as a UCR.

5.3.2.2 Efficacy Results of TRA•CER

Efficacy results of TRA•CER, a study in patients with ACS, are provided in this section. The reader desiring to understand the primary data supporting the efficacy of vorapaxar for its target indication of secondary prevention may elect to go directly to Section 6, which contains the results of the single definitive study, TRA 2ºP. Safety results of both TRA•CER and TRA 2ºP are discussed in Section 7.

5.3.2.2.1 Demographics

A total of 12,944 subjects were randomized, 6471 to placebo and 6473 to vorapaxar. Demographic and risk factor data for the ITT population (i.e., all randomized subjects) are provided here.

The treatment arms in the ITT population were quite well balanced at baseline in terms of demographic features (**Table 11**) vital signs and physical measurements (

Table 12), and medical history and risk factors (**Table 83**). There were no notable imbalances. Each arm had a median age of 64 years, with 17% in each arm with age ≥ 75 years. Women comprised 28% of subjects in each arm. Non-whites made up 14% and 15% of subjects cases in the vorapaxar (labeled as SCH 530348 in the Applicant's tables) and placebo arms, respectively.

The percentage of subjects with a prior history of ischemic stroke was low and balanced between the two arms at 4% in each arm. The percentage of subjects with a prior history of TIA was likewise low and well balanced at about 2.6% and 2.4% in the vorapaxar and placebo arms, respectively (**Table 83**). This may have contributed to lower rate of ICH in TRA•CER than in TRA 2ºP. In the latter trial, about 22% of subjects in each arm had a prior history of stroke and 2% had a prior history of TIA without stroke. The treatment arms in TRA•CER were similar in terms of the distribution of NYHA functional class, Killip class, and Canadian Cardiovascular Society class for angina, with the majority of subjects having no symptoms or limitations of activity (data not shown).

Likewise, the number of subjects randomized in the various geographic regions was similar between the two arms. About 22% of subjects in each arm were from the US (**Table 84**).

Table 11 TRA•CER – Demographic Features

Characteristic	Placebo (n = 6471)	SCH 530348 (n = 6473)	Total (n = 12944)
Age (y)			
Mean (SD)	64.4 (9.98)	64.4 (9.95)	64.4 (9.96)
Median	64.0	64.0	64.0
25th to 75th Percentile	58 – 72	58 – 71	58 – 72
Min-Max	29 – 94	31 – 94	29 – 94
Age (n (%))			
<65 y	3369 (52.1)	3390 (52.4)	6759 (52.2)
65-<75 y	2006 (31.0)	1973 (30.5)	3979 (30.7)
≥75 y	1096 (16.9)	1110 (17.1)	2206 (17.0)
Sex (n (%))			
Female	1822 (28.2)	1810 (28.0)	3632 (28.1)
Male	4649 (71.8)	4663 (72.0)	9312 (71.9)
Race (n (%))			
White	5510 (85.1)	5529 (85.4)	11039 (85.3)
Non-white	943 (14.6)	927 (14.3)	1870 (14.4)
American Indian / Alaskan Native	16 (0.2)	19 (0.3)	35 (0.3)
Asian	533 (8.2)	523 (8.1)	1056 (8.2)
Black / African American	161 (2.5)	151 (2.3)	312 (2.4)
Multiracial	213 (3.3)	222 (3.4)	435 (3.4)
Native Hawaiian / Pacific Islander	20 (0.3)	12 (0.2)	32 (0.2)
Missing	18 (0.3)	17 (0.3)	35 (0.3)
Ethnicity (n (%))[a]			
Chinese	136 (2.1)	137 (2.1)	273 (2.1)
Hispanic/Latino	532 (8.2)	557 (8.6)	1089 (8.4)
Japanese	145 (2.2)	136 (2.1)	281 (2.2)
Korean	65 (1.0)	64 (1.0)	129 (1.0)
Taiwanese	111 (1.7)	107 (1.7)	218 (1.7)
Other	5336 (82.5)	5311 (82.0)	10647 (82.3)
Missing	17 (0.3)	30 (0.5)	47 (0.4)

Table 12 TRA•CER – Vital Signs and Physical Measurements

Characteristic	Placebo (n = 6471)	SCH 530348 (n = 6473)	Total (n = 12944)
Weight (kg)	(n = 6641)	(n = 6444)	(n = 12885)
Mean (SD)	82.25 (17.66)	82.66 (18.12)	82.45 (17.89)
Median	80.00	80.35	80.00
25th to 75th Percentile	70.0 – 92.0	70.0 – 93.0	70.0 – 92.4
Min-Max	27.0 – 181.0	31.8 – 190.3	27.0 – 190.3
Missing	30	29	59
Weight (n(%))			
< 60 kg	493 (7.6)	494 (7.6)	987 (7.6)
≥60 kg	5948 (91.9)	5950 (91.9)	11898 (91.9)
Missing	30 (0.5)	29 (0.4)	59 (0.5)
Height (cm)	(n = 6431)	(n = 6431)	(n = 12862)
Mean (SD)	169.74 (9.60)	169.78 (9.64)	169.76 (9.62)
Median	170.00	170.00	170.00
25th to 75th Percentile	163.0 – 176.0	164.0 – 177.0	163.0 – 176.5
Min-Max	95.0 – 200.6	109.2 – 200.7	95.0 – 200.7
Missing	40	42	82
Calculated Body Mass Index (kg/m^2)[b]	(n = 6426)	(n = 6426)	(n = 12852)
Mean (SD)	28.44 (5.16)	28.57 (5.34)	28.51 (5.25)
Median	27.70	27.80	27.70
25th to 75th Percentile	25.0 – 31.1	25.0 – 31.2	25.0 – 31.2
Min-Max	13.8 – 62.6	13.8 – 74.3	13.8 – 74.3
Missing	45	47	92
Heart Rate (beats/min)	(n = 6435)	(n = 6419)	(n = 12854)
Mean (SD)	70.9 (13.24)	70.8 (13.07)	70.9 (13.15)
Median	70.0	70.0	70.0
25th to 75th Percentile	61 – 79	61 – 79	61 – 79
Min-Max	40 – 163	34 – 142	34 – 163
Missing	36	54	90
Systolic Blood Pressure (mm Hg)	(n = 6435)	(n = 6419)	(n = 12854)
Mean (SD)	131.8 (20.83)	132.0 (20.67)	131.9 (20.75)
Median	130.0	130.0	130.0
25th to 75th Percentile	117 – 145	118 – 145	117 – 145
Min-Max	73 – 247	76 – 230	73 – 247
Missing	36	54	90

(table continued)

Diastolic Blood Pressure (mm Hg)	(n = 6435)	(n = 6419)	(n = 12854)
Mean (SD)	75.0 (12.48)	74.8 (12.42)	74.9 (12.45)
Median	75.0	75.0	75.0
25th to 75th Percentile	66 – 82	66 – 82	66 – 82
Min-Max	32 – 137	31 – 164	31 – 164
Missing	36	54	90
Waist Circumference (cm)	(n = 5749)	(n = 5726)	(n = 11475)
Mean (SD)	100.36 (14.09)	100.61 (14.18)	100.49 (14.13)
Median	100.00	100.00	100.00
25th to 75th percentile	91.0 – 109.0	91.4 – 109.0	91.4 – 109.0
Min-Max	51.0 – 175.0	53.0 – 210.8	51.0 – 210.8
Missing	722	747	1469

5.3.2.2.2 Subject Disposition

Of the 12,944 randomized subjects, 30 assigned to placebo and 27 assigned to vorapaxar never received treatment, leaving 6441 subjects who received treatment in the placebo arm and 6446 in the vorapaxar arm.

Information regarding patients who discontinued treatment and/or follow-up during the trial is provided in **Table 13.**

Table 13 TRA•CER – Subject Disposition

ITT Population/Treated Population

	PLACEBO N=6471 n (%)	VORAPAXAR N=6473 n (%)
Never received study treatment	30 (0.5)	27 (0.4)
Received study treatment	6441 (99.5)	6446 (99.6)
The denominator for percentages below this row is the number of patients who received study treatment in the respective arm.		
Treated until death or study end	4715 (73.2)	4628 (71.8)
Died on Treatment	156 (2.4)	153 (2.4)
Completed study therapy	4559 (70.8)	4475 (69.4)
Total treated who failed to complete	1726 (26.8)	1818 (28.2)
AE, Bleeding, or Efficacy Event	489 (7.6)	649 (10.1)
Subject requested to withdraw from treatment	865 (13.4)	858 (13.3)
Non-compliance	287 (4.5)	232 (3.6)

Did not have disease of interest	65 (1.0)	56 (0.9)
FOLLOW-UP AT STUDY COMPLETION:		
Completed Final Study Visit	5732 (89.0)	5780 (89.7)
Death before Final Study Visit during follow-up	300 (4.7)	314 (4.9)
Prematurely discontinued follow-up	409 (6.3)	352 (5.5)
Withdrew consent for follow-up	315 (4.9)	266 (4.1)
Lost to follow-up	94 (1.5)	86 (1.3)
Among those who prematurely discontinued follow-up --		
Only vital status assessed	279 (4.3)	233 (3.6)
Died	13 (0.2)	16 (0.2)
Alive	266 (4.1)	217 (3.4)
No vital status available	130 (2.0)	119 (1.8)

Source: Study report Display A-1.4

Of treated subjects, slightly more completed therapy in the placebo arm (73.2% vs. 71.8%). The difference was due primarily to the excess of subjects who discontinued treatment for an adverse event, bleeding, or an efficacy event in the vorapaxar arm, largely due to bleeding events (see Sec. **7.4.1**).

Follow-up of subjects was reasonably good. About 6.3% and 5.5% of subjects in the placebo and vorapaxar arms, respectively, discontinued follow-up alive. However, 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. However, subjects who discontinued follow-up alive had no information on other study endpoints (MI, stroke, bleeding, etc.) after their last follow-up date.

5.3.2.2.3 Analysis of Efficacy Endpoints

The primary endpoint in TRA•CER was the time to the primary endpoint, which was the first event of CV death, MI, stroke, RIR (recurrent ischemia with rehospitalization) or UCR (urgent coronary revascularization).

Results for the analysis of the primary efficacy endpoint are displayed in the first data row in **Table 14** Other data rows show results for all cause death and the key secondary endpoint, time to the composite of CV death/MI/stroke. Data for components of the composite endpoints are also displayed (only for events counted as primary endpoint events).

Table 14 TRA•CER – Key Efficacy Results

ITT Population

	Placebo N=6471		Vorapaxar N=6473		V vs. P HR (95% CI)	p (not adjusted)
Parameter	n (%)	KM Rate at 730 d	n (%)	KM Rate at 730 d		

Primary Endpoint [1] CV death MI Stroke Ischemic Hemorrhagic Uncertain RIR UCR	1102 (17.0) 122 (1.9) 668 (10.3) 89 (1.4) 82 (1.3) 6 (0.1) 1 (<0.1) 53 (0.8) 170 (2.6)	19.9	1031 (15.9) 115 (1.8) 596 (9.2) 83 (1.3) 63 (1.0) 19 (0.3) 1 (<0.1) 60 (0.9%) 177 (2.7)	18.5	0.92 (0.85-1.01)	0.072
Key Secondary Endpoint [2] CV death MI Stroke Ischemic Hemorrhagic Uncertain	910 (14.1) 127 (2.0) 692 (10.7) 91 (1.4) 84 (1.3) 6 (0.1) 1 (<0.1)	16.4	822 (12.7) 122 (1.9) 614 (9.5) 86 (1.3) 66 (1.0) 19 (0.3) 1 (<0.1)	14.7	0.89 (0.81-0.98)	0.018
All-Cause Death	318 (4.9)	6.1	334 (5.2)	6.5	1.05 (0.90-1.23)	0.515

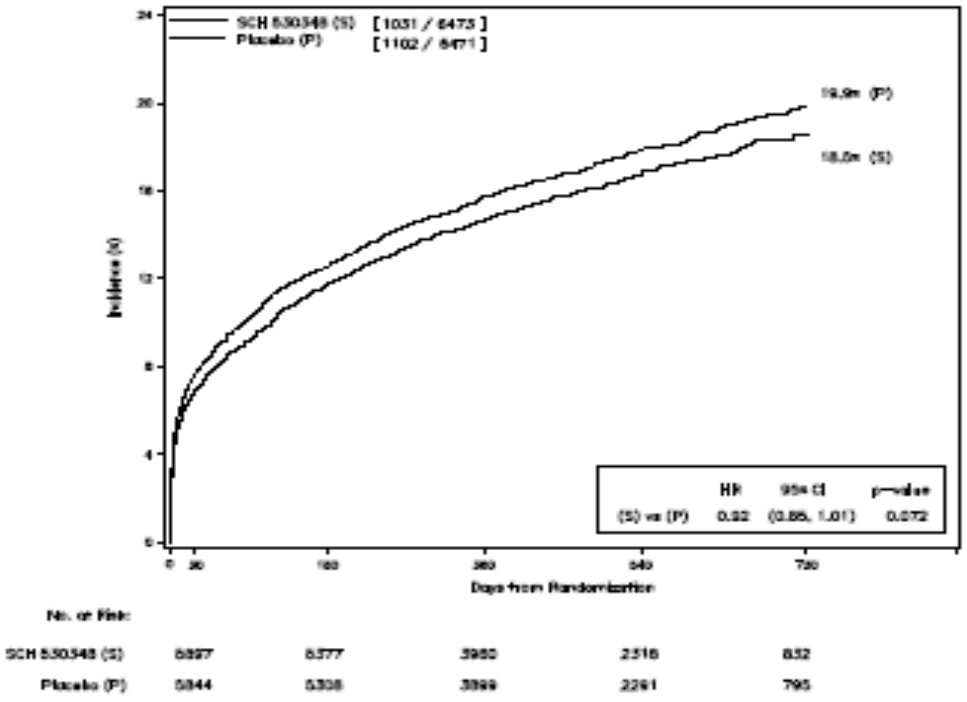
1 Primary Endpoint: Time to first of CV death, MI, stroke, recurrent ischemia with rehospitalization (RIR) or urgent coronary revascularization (UCR)
2. Key Secondary Endpoint: Time to first of CV death, MI or stroke

The primary endpoint numerically favored vorapaxar, but the results were not statistically significant. However, the key secondary endpoint, which included all the events in primary endpoint except those that were triggered by a decision of a health care provider (i.e., the key secondary endpoint excluded urgent coronary revascularization and recurrent ischemia requiring rehospitalization, but did include CV death, MI and stroke), was statistically significant in favor of vorapaxar.

Rates of the components of MACE (CV death, MI and stroke) in the Primary and Key Secondary Endpoints favored vorapaxar. However, hemorrhage stroke favored placebo, while ischemic stroke favored vorapaxar. Rates of RIR and UCR in the Primary Endpoint favored placebo.

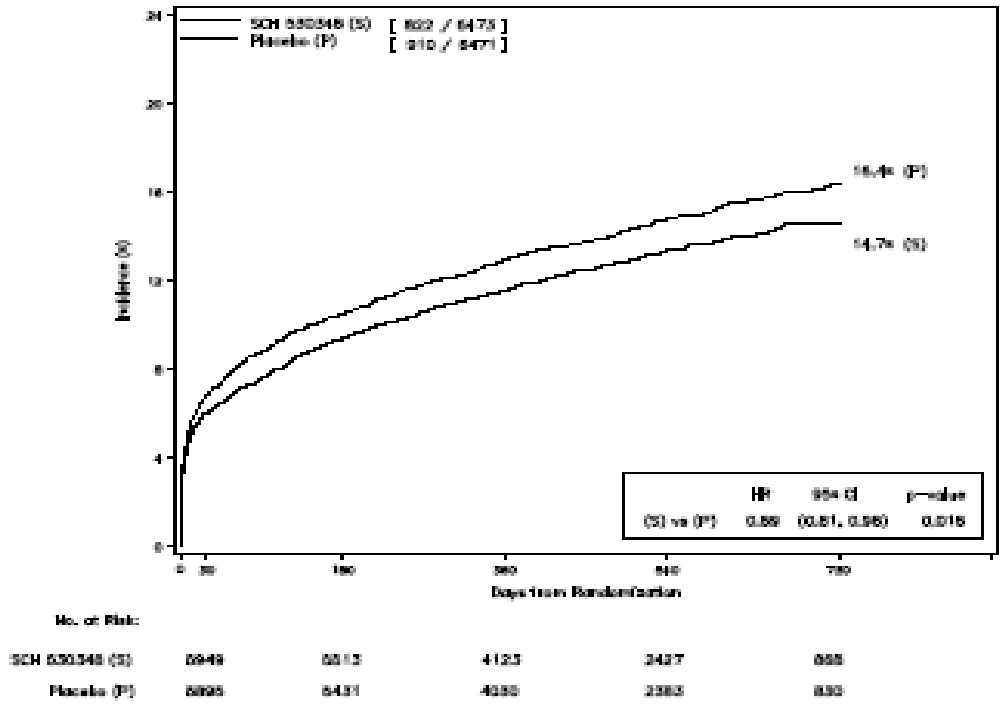
The Kaplan-Meier curves for time to first primary efficacy event and the first key secondary endpoint are shown in Error! Reference source not found. and Error! Reference source not found..

Figure 8 TRA•CER – Time To First Primary Efficacy Endpoint Event
(ITT Population, Randomization to Last Visit)



No. at Risk:					
SCH 530348 (S)	6897	6377	3960	2516	852
Placebo (P)	6844	6308	3899	2261	795

Figure 9 TRA•CER – Time to First Key Secondary Efficacy Endpoint Event



Additional Endpoints

Table 15 is a display of rates of secondary endpoints. Of the individual endpoints, all-cause death, UCR and RIR numerically favored placebo, while MI and total stroke numerically favored vorapaxar. The difference in rates was statistically significant for MI, which was the most frequent of the secondary endpoints. All cause slightly favored placebo. All of the compound endpoints included MI and favored vorapaxar.

Table 15 TRA•CER – Rates Of Secondary Efficacy Endpoints
(ITT Population)

Endpoints	Placebo (n = 6471) Subjects With Events (%)	Placebo (n = 6471) KM%[c]	SCH 530348 (n = 6473) Subjects With Events (%)	SCH 530348 (n = 6473) KM%[c]	Hazard Ratio[a,b] (95% Confidence Interval)	P Value[b]
CV Death / MI / Stroke / UCR	1065 (16.5%)	19.2%	983 (15.2%)	17.5%	0.91 (0.84-1.00)	0.038
CV Death / MI	834 (12.9%)	14.9%	755 (11.7%)	13.5%	0.90 (0.81-0.99)	0.027
All-Cause Death / MI / Stroke / RIR / UCR	1180 (18.2%)	21.5%	1129 (17.4%)	20.6%	0.94 (0.87-1.03)	0.174
All-Cause Death / MI / Stroke / UCR	1143 (17.7%)	20.8%	1081 (16.7%)	19.6%	0.93 (0.86-1.02)	0.108
CV Death	207 (3.2%)	3.8%	208 (3.2%)	3.8%	1.00 (0.83-1.22)	0.963
MI	698 (10.8%)	12.5%	621 (9.6%)	11.1%	0.88 (0.79-0.98)	0.021
RIR	69 (1.1%)	1.5%	79 (1.2%)	1.6%	1.14 (0.83-1.58)	0.418
UCR	189 (2.9%)	3.5%	203 (3.1%)	3.8%	1.07 (0.88-1.31)	0.493
All-Cause Death	318 (4.9%)	6.1%	334 (5.2%)	6.5%	1.05 (0.90-1.23)	0.515
Stroke	103 (1.6%)	2.1%	96 (1.5%)	1.9%	0.93 (0.70-1.23)	0.606

Table 16 is a display of rates of myocardial infarction by type, using the classification system of the Second Universal Definition of MI. Of the 1319 subjects with an MI, 61% were Type 1 (spontaneous) and another 26& were Type 4a (associated with PCI). Rates for both of these types favored vorapaxar; the difference was largest for the Type 1 events (incidence of 6.8% vs. 5.6%)

Table 16 TRA•CER – Rates of Myocardial Infarction by Type
(ITT Population)

Endpoints	Placebo (n = 6471) Subjects With Events (%)	SCH 530348 (n = 6473) Subjects With Events (%)
Myocardial Infarction	698	621
Type 1, spontaneous	440 (6.8%)	365 (5.6%)
Type 2, secondary	24 (0.4%)	35 (0.5%)
Type 3, with sudden death	2 (<0.1%)	0
Type 4a, associated with PCI	180 (2.8%)	163 (2.5%)
Type 4b, associated with stent thrombosis	40 (0.6%)	36 (0.6%)
Type 5, associated with CABG	12 (0.2%)	20 (0.3%)
Missing	0	2 (<0.1%)

A total of 7075 subjects received a coronary stent during their index hospitalization for ACS. Rates of stent thrombosis are shown in Table 17. Overall rates and rates in the subjects who received a drug-eluting stent numerically favored placebo. Rates in those who received a bare metal stent favored vorapaxar, but no differences were statistically significant.

Table 17 TRA•CER – Rates of ARC-Defined Stent Thrombosis

Adjudicated Stent Thrombosis[c]	Placebo Subjects With Events (%)	Placebo KM%[d]	SCH 530348 Subjects With Events (%)	SCH 530348 KM%[d]	Hazard Ratio[a,b] (95% Confidence Interval)	P Value[b]
Subjects Receiving Any Stent	(n = 3526)	-	(n = 3549)	-	-	-
Definite	47 (1.3)	1.4	50 (1.4)	1.5	1.06 (0.71-1.58)	0.772
Definite or Probable	54 (1.5)	1.7	61 (1.7)	1.8	1.12 (0.78-1.62)	0.530
Definite, Probable, or Possible	82 (2.4)	2.7	96 (2.7)	3.0	1.13 (0.84-1.52)	0.409
Subjects Receiving a Bare Metal Stent	(n = 1636)	-	(n = 1732)	-	-	-
Definite	30 (1.8)	1.8	27 (1.6)	1.7	0.85 (0.51-1.44)	0.551
Definite or Probable	37 (2.3)	2.4	33 (1.9)	2.0	0.84 (0.53-1.35)	0.472
Definite, Probable, or Possible	51 (3.1)	3.4	53 (3.1)	3.4	0.98 (0.67-1.44)	0.920
Subjects Receiving a Drug Eluting Stent	(n = 2042)	-	(n = 1973)	-	-	-
Definite	23 (1.1)	1.2	29 (1.5)	1.6	1.32 (0.77-2.29)	0.316
Definite or Probable	23 (1.1)	1.2	34 (1.7)	1.8	1.55 (0.91-2.63)	0.105
Definite, Probable, or Possible	40 (2.0)	2.3	50 (2.5)	2.9	1.30 (0.86-1.97)	0.218

KM rates through 720 days.

Rates of stroke (by type) and TIA are shown in Table 18 for the overall population and in Table 19 in subjects with or without a prior stroke or TIA. In the overall population both total stroke and total TIA rates numerically favored vorapaxar. The rate of ischemic stroke numerically favored vorapaxar but the rate of hemorrhagic stroke favored placebo. In the small subset of those with a prior stroke or TIA (about 6% of subjects), subjects in the two treatment arms had similar rates of stroke (both ischemic and hemorrhagic). In the much larger subset of those without a prior history of stroke or TIA, the rates of total stroke, stroke and TIA favored vorapaxar, but the rate of hemorrhagic stroke favored placebo. As expected, the rate of stroke was substantially higher in those with a prior history of stroke or TIA than in those without such a history. However, unlike in TRA 2°P, the rate of hemorrhagic stroke was significantly higher with vorapaxar than with placebo in subjects without a prior history of stroke or TIA.

Table 18 TRA•CER – Rates of Stroke and TIA

Event	Number (%) of Subjects				Hazard Ratio[a,b] (95% Confidence Interval)
	Placebo (n = 6471)	Event Rate[c]	SCH 530348 (n = 6473)	Event Rate[c]	
Any Stroke	103 (1.6)	1.2%	96 (1.5)	1.1%	0.93 (0.70-1.23)
Ischemic (non-hemorrhagic) Stroke	93 (1.4)	1.1%	74 (1.1)	0.9%	0.79 (0.59-1.08)
Hemorrhagic Stroke	8 (0.1)	0.1%	22 (0.3)	0.3%	2.73 (1.22-6.14)
Ischemic Stroke With Hemorrhagic Conversion	5 (0.1)	0.1%	3 (<0.1)	<0.1%	0.60 (0.14-2.50)
Primary Intracerebral Hemorrhage	3 (<0.1)	<0.1%	16 (0.2)	0.2%	5.29 (1.54-18.15)
Subarachnoid Hemorrhage	0	-	3 (<0.1)	<0.1%	-
Uncertain	3 (<0.1)	<0.1%	1 (<0.1)	<0.1%	0.33 (0.03-3.19)
Any Transient Ischemic Attack	35 (0.5)	0.4%	24 (0.4)	0.3%	0.68 (0.41-1.15)
Hospitalized	27 (0.4)	0.3%	20 (0.3)	0.2%	1.39 (0.76-2.55)
Not Hospitalized	8 (0.1)	0.1%	4 (0.1)	<0.1%	0.69 (0.21-2.30)

Table 19 TRA•CER – Rates of Stroke and TIA by Prior History of Stroke or TIA

Event	Number (%) of Subjects				Hazard Ratio[b,c] (95% Confidence Interval)
	Placebo (n = 6471)	Event Rate[d]	SCH 530348 (n = 6473)	Event Rate[d]	
Subjects With History of Prior Stroke or TIA	393	-	420	-	-
Any Stroke	17 (4.3)	3.5%	17 (4.0)	3.3%	0.93 (0.47 - 1.83)
Ischemic (non-hemorrhagic) Stroke	16 (4.1)	3.3%	15 (3.6)	2.9%	0.88 (0.44 - 1.80)
Hemorrhagic Stroke[a]	2 (0.5)	0.4%	2 (0.5)	0.4%	0.96 (0.13 - 6.94)
Uncertain	0	-	0	-	-
Transient Ischemic Attack	7 (1.8)	1.5%	2 (0.5)	0.4%	0.24 (0.05 - 1.17)
Subjects Without History of Prior Stroke or TIA	6074	-	6050	-	-
Any Stroke	86 (1.4)	1.1%	79 (1.3)	1.0%	0.92 (0.68 - 1.24)
Ischemic (non-hemorrhagic) Stroke	77 (1.3)	1.0%	59 (1.0)	0.7%	0.76 (0.54 - 1.07)
Hemorrhagic Stroke[a]	6 (0.1)	0.1%	20 (0.3)	0.2%	3.32 (1.33 – 8.27)
Uncertain	3 (<0.1)	<0.1%	1 (<0.1)	<0.1%	0.34 (0.03 - 3.23)
Transient Ischemic Attack	28 (0.5)	0.3%	22 (0.4)	0.3%	0.79 (0.45 - 1.37)

5.3.2.2.4 Subgroups

Forest plots of HR for vorapaxar vs. placebo in various subgroups of subjects are shown in **Table 20** for the primary endpoint. In general, the data for the key secondary endpoint appear similar (data not shown). **Table 21** provides information on subgroup by treatment interactions with a $p < 0.15$ for either of these endpoints.

The interaction with thienopyridine use, while not statistically significant, is notable and in the expected direction; i.e., vorapaxar has a greater beneficial effect in subjects who did not use clopidogrel than in those who did. The interaction with aspirin use is much weaker (p=0.963 and p=0.696 for the primary and key secondary endpoints, respectively), but very few subjects did not use aspirin.

Table 20 TRA•CER –Treatment by Subgroup Interactions for the Primary Endpoint

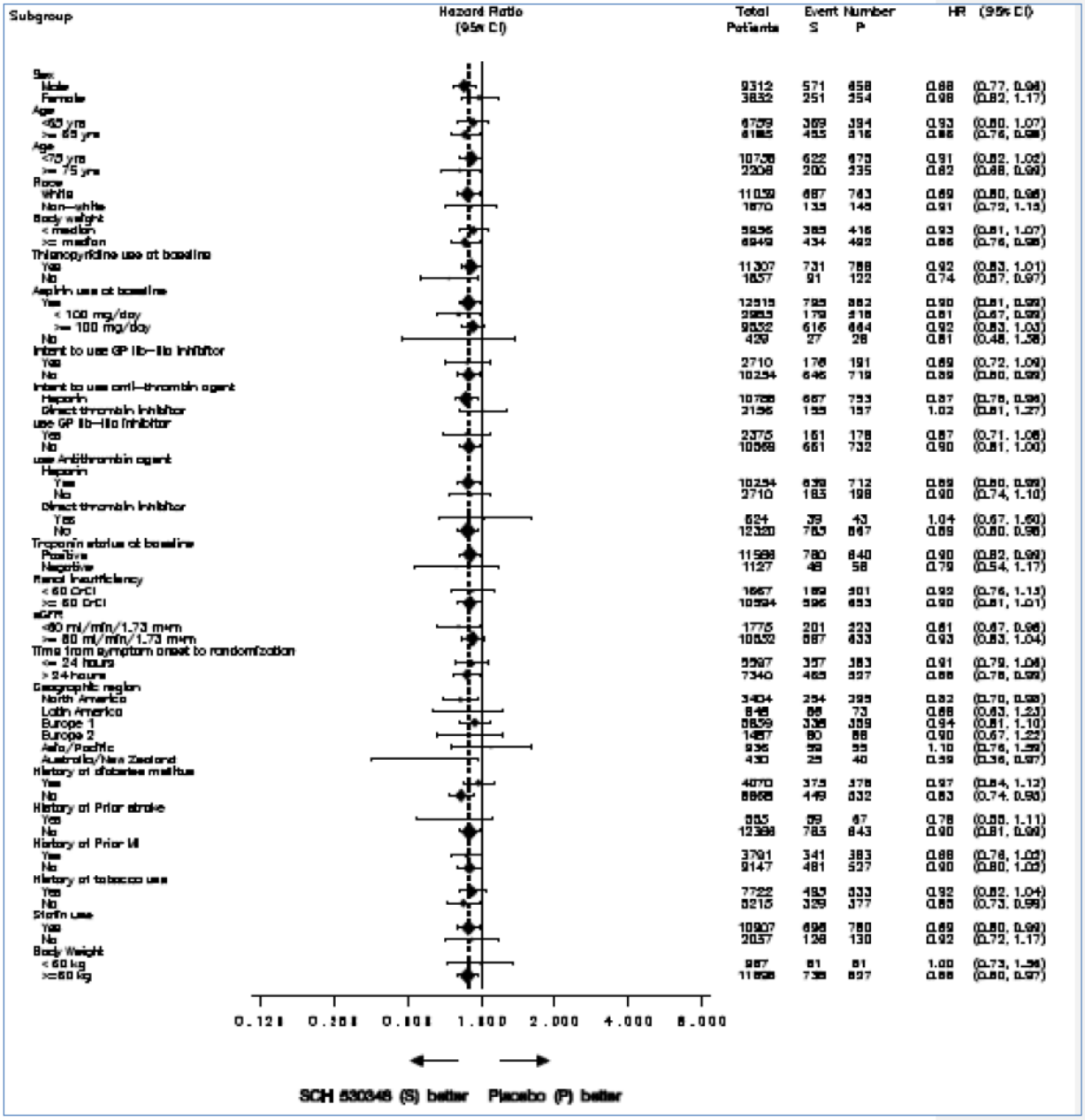


Table 21 TRA•CER – Treatment by Subgroup Interactions with p<0.15 for the Primary or Key Secondary Endpoints

Subgroup	End-point	Placebo (N = 6471) n/J (%) KM%	Vorapaxar (N = 6473) n/J (%) KM%	HR (95% CI)	Interaction p
eGFR: <60 [a]	PEP	241/859 (28.1%) 32.0%	218/916 (23.8%) 27.5%	0.81 (0.67 - 0.97)	0.105
≥60 [a]		791/5283 (15.0%) 17.4%	770/5249 (14.7%) 17.1%	0.97 (0.88 - 1.07)	
eGFR: <60 [a]	KSEP	223/859 (26.0%) 29.3%	201/916 (21.9%) 25.5%	0.81 (0.67 - 0.98)	0.263
≥60 [a]		633/5283 (12.0%) 14.1%	587/5249 (11.2%) 12.9%	0.93 (0.83 - 1.04)	
Diabetes: Yes	PEP	435/2030 (21.4%) 26.3%	426/2040 (20.9%) 25.0%	0.96 (0.84 - 1.10)	0.405
No		667/4439 (15.0%) 17.0%	605/4429 (13.7%) 15.6%	0.90 (0.80 - 1.00)	
Diabetes: Yes	KSEP	378/2030 (18.6%) 23.0%	373/2040 (18.3%) 21.7%	0.97 (0.84 - 1.12)	0.099
No		532/4439 (12.0%) 13.5%	449/4429 (10.1%) 11.5%	0.83 (0.74 - 0.95)	
Thienopyridine use at baseline: Yes	PEP	957/5639 (17.0%) 19.8%	918/5668 (16.2%) 18.8%	0.95 (0.87 - 1.04)	0.127
No		145/832 (17.4%) 20.4%	113/805 (14.0%) 16.3%	0.77 (0.60 - 0.99)	
Thienopyridine use at baseline: Yes	KSEP	788/5639 (14.0%) 16.3%	731/5668 (12.9%) 14.9%	0.92 (0.83 - 1.01)	0.152
No		122/832 (14.7%) 17.5%	91/805 (11.3%) 13.0%	0.74 (0.57 - 0.97)	
Intent to use AT [b] agent: Heparin	PEP	914/5373 (17.0%) 19.8%	829/5415 (15.3%) 17.8%	0.89 (0.81 - 0.97)	0.044
Direct thrombin inhibitor		188/1098 (17.1%) 19.9%	202/1058 (19.1%) 22.1%	1.11 (0.91 - 1.36)	
Intent to use AT agent: Heparin	KSEP	753/5373 (14.0%) 16.4%	667/5415 (12.3%) 14.2%	0.87 (0.78 - 0.96)	0.211
Direct thrombin inhibitor		157/1098 (14.3%) 16.7%	155/1058 (14.7%) 16.8%	1.02 (0.81 - 1.27)	

Abbreviations: PEP=Primary endpoint; KSEP=Key secondary endpoint; KM%: KM rate at 24 months
a mL/min/1.73 m^2 BSA – MDRD method
b AT=Antithrombotic

6 Review of Efficacy

Efficacy Summary

Substantial evidence of efficacy comes from a single study, the TRA 2ºP trial. This was a global, placebo-controlled, event-driven RCT conducted in 26,499 subjects with at least one of three atherosclerotic conditions: prior MI, prior ischemic stroke (in either case, the event occurred from 2 weeks to 12 months prior to study entry) or established peripheral arterial disease (PAD). Study enrollment was intended to be unequal in these 3 subgroups, with a target of 70% of subjects in the prior MI (CAD) stratum and 15% in each of the prior stroke (CVD) and PAD strata. Subjects were randomized 1:1 to vorapaxar 2.5 mg once daily or placebo, with stratification by their qualifying atherosclerotic condition and by planned thienopyridine use. Subjects were to receive a background of standard care for their condition. They were followed to their last visit or telephone contact; median follow-up was 2.2 years. The primary endpoint was time to the composite of CV death, MI, stroke, or urgent coronary revascularization (UCR). The Key Secondary Endpoint was time CV death, MI or stroke. These were to be analyzed in all randomized subjects followed to their last study visit or telephone contact.

The primary endpoint key secondary endpoints were met (see **Table 1**). However, the course of the study was complicated by major safety-based changes in the study protocol in the last year of the study. These resulted from recommendations regarding study conduct that were made by the DSMB in January 2011 (when about 90% of the targeted number primary of endpoint events had occurred) and promptly implemented by the study leadership.

These changes were precipitated by an unscheduled and unblinded interim analysis of the study by the DSMB to evaluate an observed increased rate of intracranial hemorrhage (ICH) in vorapaxar arm subjects. The analysis revealed an about 3X risk of ICH in vorapaxar arm subjects with a history of stroke at baseline compared to placebo, coupled with no evidence of overall benefit for the primary endpoint for vorapaxar in that population. In subjects without a history of stoke, the overall rate of ICH was appreciably lower and the imbalance of ICH events disfavoring vorapaxar appeared less pronounced than in the prior stroke subset. In addition, the primary and key secondary endpoint data in the subjects without a history of stoke favored vorapaxar, with statistically significant results, as did these analyses in the entire patient population. Accordingly, the DSMB recommended discontinuation of study drug in all subjects with either a history of stroke at baseline or a stroke after randomization, and continuation in the study for other subjects.

This recommendation was implemented by the study leadership through a communication to the sites sent on January 13, 2011. About 3600 of the >4500 subjects who discontinued study drug as a result of this communication also had their final study contact alive within a few weeks, but some were followed off study drug to the end of the study or until they died. The study continued as planned in the remaining subjects (i.e., those with no history of stroke at baseline and no stroke during the study). Study closeout commenced in August 2011.

Data lock and analysis of the study results occurred in January 2012. The overall results of the study for the primary and key secondary endpoints (including all randomized patients) favored vorapaxar at the p≤0.001 level. In addition, similarly robust results favoring vorapaxar were obtained in key subgroups: all patients with no baseline history of stroke; the prior MI stratum; the pooled prior MI /PAD strata; and various subgroups of those strata with no history of stroke or stroke/TIA (**Table 1**). A benefit for vorapaxar was not shown in patients with a history of stroke (regardless of stratum)[4] or those in the isolated PAD stratum.

Apparently after review of the study data, the sponsor decided to narrow the proposed target population to those with a prior MI and no history of either stroke or TIA (labeled CAD, NHS/TIA and represented by the 7th row of data in **Table 1**. The analysis supporting this indication was not specified in the statistical plan. Of note, the DSMB interim analysis of the primary endpoint that led to the recommendation to discontinue treatment in the patients with a prior history of stroke also significantly favored vorapaxar in the overall population. For all analyses at the study end, the results for the key secondary endpoint (typical MACE) closely tracked the primary endpoint. In all subgroups where vorapaxar appeared effective, the results were driven by a reduction in the rate of MI. Data for total stroke, ischemic stroke, CV death, and UCR also favored vorapaxar numerically (see **Table 2** for results in the sponsor's proposed label population).

Data on use of aspirin and other anti-platelet agents were similar in the treatment arms and was acceptably high, particularly in the sponsor's proposed label population, in which at baseline about 98% of subjects were receiving aspirin, 78% were receiving a thienopyridine, and 77% were receiving both aspirin and a thienopyridine. In the overall population, where use of dual antiplatelet therapy would be expected to be lower due to lack of data supporting use of dual antiplatelet therapy in subjects with prior stroke or PAD, analogous data were 94%, 62%, and 57%, respectively. In both populations mentioned above, over 99% of subjects were receiving at least one antiplatelet agent at baseline, which includes a few percent receiving either cilostazol or dipyridamole and very limited use of prasugrel. There was no use of ticagrelor.

In summary, the data from TRA 2°P show statistically significant results for the primary and key secondary endpoints in all of the following analyses, with p≤0.001 for analyses performed at the end of the study below:

- The overall patient population in the special ICH analysis reviewed by the DSMB in January 2011 and the same population at the end of the study
- The no stroke history population in January 2011 and again at the end of the study
- The prior MI population at the end of the study
- The Applicant's proposed label population (prior MI with no history of stroke or TIA) at the end of the study, which had the best results of any analyzed population (**Table 2**).

On the other hand, the final results for the primary and key secondary endpoints went the wrong way in the prior stroke stratum (**Table 1** and **Table 39**), and there was an excess of total deaths with vorapaxar in that stratum (81 vs. 95 in all patients followed to last visit). In the PAD stratum, which included only 12% of subjects in TRA 2ºP, there was a 5% reduction in the rate of the

[4] Subjects who met the criteria for entry into more than one atherosclerotic disease stratum were assigned to the first stratum for which they qualified in the following order: prior MI, prior stroke, and PAD. Also, some subjects had strokes more than 12 months prior to entry; these were not considered qualifying events. Consequently, 892 subjects in the pooled prior MI and PAD strata had a history of stroke.

primary endpoint with vorapaxar (p>0.5)). These results for vorapaxar improved somewhat when subjects with prior stroke or TIA were excluded, yielding a 13% reduction in the rate of the primary endpoint (p=0.17, see **Table 1**).

These results are sufficient to establish the effectiveness of vorapaxar for its proposed indication in patients with prior MI and support the Applicant's proposal not to include prior stroke in the indication. Note that the Applicant's proposed indication does not include patients with PAD. This choice is debatable and is discussed **below**.

Table 22 TRA 2°P – Primary and Key Secondary Endpoint Results in All Patients and Subgroups Based on Qualifying Event and Stroke or TIA History
ITT population, events accrued to last visit

Subgroup	Placebo (N = 13,224)			Vorapaxar (N = 13,225)			HR (95% CI)	p
	n/J	(%)	KM%	n/J	(%)	KM%		
All subjects - PEP	**1417/13224**	**(10.7)**	**12.4**	**1259/13225**	**(9.5)**	**11.2**	**0.88 (0.82 - 0.95)**	**0.001**
All subjects - KSEP	**1176/13324**	**(8.9)**	**10.5**	**1028/13225**	**(7.8)**	**9.3**	**0.87 (0.80 - 0.94)**	**<0.001**
PEP in subgroups -								-
Any history of stroke	313/2876	(10.9)	16.9	300/2870	(10.5)	15.3	0.94 (0.80 - 1.10)	0.465
CVD stratum	216/2448	(8.8)	12.1	217/2435	(8.9)	12.9	1.02 (0.84 - 1.23)	-
CAD stratum	956/8881	(10.8)	12.1	809/8898	(9.1)	10.5	0.83 (0.76 - 0.92)	<0.001
CAD, NSH	887/8583	(10.3)	11.5	757/8608	(8.8)	10.1	0.84 (0.76 - 0.93)	<0.001
CAD, NHS/TIA*	**867/8439**	**(10.3)**	**11.4**	**719/8458**	**(8.5)**	**9.8**	**0.82 (0.74 - 0.90)**	**<0.001**
CAD/PAD	1201/10776	(11.1)	12.5	1042/10790	(9.7)	11.0	0.86 (0.79 - 0.93)	<0.001
CAD/PAD, NSH	1104/10331	(10.7)	11.9	956/10343	(9.2)	10.5	0.86 (0.79 - 0.93)	<0.001
PAD stratum	245/1895	(12.9)	13.4	233/1892	(12.3)	12.7	0.95 (0.79 - 1.14)	0.567
PAD, NSH	217/1748	(12.4)	12.8	199/1735	(11.5)	11.8	0.92 (0.76 - 1.12)	0.410
PAD, NHS/TIA	206/1651	(12.5)	12.8	177/1622	(10.9)	11.1	0.87 (0.71 - 1.06)	0.167

Abbreviations: PEP= primary endpoint; KSEP= key secondary endpoint; NSH=subjects with no stroke history; CAD=coronary artery disease stratum (prior MI); CVD=cerebrovascular disease stratum (prior stroke); PAD=peripheral arterial disease stratum; CAD/PAD=pooled CAD and PAD strata; NHS/TIA=subjects with no history of stroke or TIA
* Applicant's proposed label population

Table 23 TRA 2°P – Primary and Key Secondary Efficacy Endpoint Results in the Applicant's Proposed Label Population
(CAD NHS/TIA Population, all randomized subjects followed to last visit)

	Placebo N=8439		Vorapaxar N=8458		V vs. P HR (95% CI) IRR	p
	n (%)	KM%	n (%)	KM%		
Any Primary Efficacy Endpoint Event [1]	867 (10.3)	11.4	719 (8.5)	9.8	0.82 (0.74 - 0.90)	<0.001
CV death	96 (1.1)		82 (1.0)		*0.85*	
MI	451 (5.3)		374 (4.4)		*0.83*	
Stroke	84 (1.0)		60 (0.7)		*0.71*	

	Placebo N=8439		Vorapaxar N=8458		V vs. P HR (95% CI)	p
Ischemic	69 (0.8)		38 (0.4)		*0.55*	
Hemorrhagic	11 (0.1)		16 (0.2)		*1.45*	
Uncertain	4 (<0.1)		6 (0.1)		*1.50*	
UCR	236 (2.8)		203 (2.4)		*0.86*	
Any Key Secondary Efficacy Endpoint Event [2]	671 (8.0)	9.0	532 (6.3)	7.4	0.78 (0.70 - 0.88)	<0.001
CV death	101 (1.2)		84 (1.0)		*0.83*	
MI	481 (5.7)		387 (4.6)		*0.80*	
Stroke	89 (1.1)		61 (0.7)		*0.68*	
Ischemic	72 (0.9)		39 (0.5)		*0.54*	
Hemorrhagic	12 (0.1)		16 (0.2)		*1.33*	
Uncertain	5 (0.1)		6 (0.1)		*1.20*	

Abbreviations: CAH NHS/TIA=Subjects with prior MI as their qualifying condition and with no prior history of stroke or TIA; KM%= KM estimate of event rate over 1080 days; IRR=incidence rate ratio (calculated by reviewer for components of the composite endpoints, shown in italics).
1 Time to first event of composite of CV death, MI, stroke and UCR
2 Time to first event of composite of CV death, MI and stroke

Dosing regimen:

Support for the Applicant's proposed dosing regimen of 2.5 mg once daily is supported by the following information:

The sponsor selected a pharmacodynamic goal of at least 80% of TRAP induced platelet aggregation 5 for vorapaxar based on preclinical data for abciximab from a dog model of platelet induced coronary occlusion showing that at least 80% blockade of GP IIb/IIa was necessary to prevent or reverse occlusion The Applicant also cited clinical data with eptifibitide that indicated that an effective dose of this product was one that induced > 80% inhibition of ADP- and TRAP-induced platelet aggregation.

The Applicant cites 5 multiple dose clinical Phase 1 or 2 PD studies (P03450, P03448, P03573, P04772, and P05005) in which 2.5 mg daily was the lowest multiple dose associated with a "consistently high proportion" of subjects "achieving ≥80% inhibition of TRAP-induced platelet aggregation within one week of initiation of dosing."

Modeling of integrated PK/PD data from the 5 multiple dose studies mentioned above and 2 single dose studies (P03449, P03464) was performed to provide additional information on dose response. The data indicate that the vorapaxar blood levels necessary to achieve 70% to 90% inhibition of TRAP-induced platelet aggregation are quite similar and about 5 ng/mL. Data regarding day 7 trough blood levels in Phase 2 and Phase 3 studies for doses of 0.5, 1, 2.5 and 5 mg daily indicate that 2.5 mg daily is the lowest of these doses associated with a lower boundary

[5] TRAP (thrombin receptor-activating peptide) is a synthetic hexapeptide corresponding to AA 42-47 of thrombin. It is a mimetic of a portion of the PAR-1 tethered ligand that is exposed by cleavage of the PAR-1 tail by thrombin and is a PAR-1 direct agonist.

of the 95% CI ≥ 5 ng/mL. Data for the two lower doses suggests that a non-trivial percentage of subject will have trough levels on Day 7 that are >5 ng/mL.

The apparent goal of achieving 80% inhibition of TRAP induced platelet aggregation within one week of starting therapy is reasonable for treatment of a stable post-MI patient already taking at least one and probably two other antiplatelet agents. OCP agrees with Sponsor's dose selection.

6.1 Indication

The Applicant's proposed indication is:

TRADEMARK (vorapaxar sulfate), an antagonist of the protease-activated receptor-1 (PAR-1), is indicated for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). TRADEMARK has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).

6.1.1 Methods

The Applicant provided an ISE, but did not pool the results of TRA 2ºP and TRA•CER. The designs of the two studies have already been described. Because the results of TRA•CER are not useful to shape efficacy labeling in the US, only the results of TRA 2ºP are discussed here. The efficacy results of TRA•CER are found at the end of the preceding section starting on page **71**.

6.1.2 Demographics

Baseline data for demographic and disease-related parameters are displayed in **Table 24** for the ITT population (N=26,449).

As expected in a study of this size, the treatment arms were well balanced for all important demographic and prevalent disease-specific features, as well the stratification factors: study-qualifying conditions and planned use of thienopyridines (yes or no). . About 65% of subjects in each arm were male. The mean age in both arms was 69 years. About 67%, 18% and 14% of subjects in each arm qualified in the basis of CAD, CVD, and PAD, respectively. Thienopyridine therapy (either already started at randomization or intended) was planned in about 58% in each arm. In each arm, median age was 67 years, 25% of subjects were women, 87% were white and 14% were Hispanic/Latino. Weight, height, and BMI were similar in each arm.

Table 24 TRA 2ºP – Baseline Demographics and Disease-Related Parameters
(ITT population)

Characteristic	Placebo N=13,224	Vorapaxar N=13,225	Total N=26,449
Gender			
Female, N (%)	3172 (24.0)	3154 (23.8)	6326 (23.9)
Age, years, %			
Median	61.0	61.0	61.0
<65	8273 (62.6)	8188 (61.9)	16461 (62.2)

≤65 to <75	3445 (26.1)	3523 (26.6)	6968 (26.3)
≥75	1506 (11.4)	1514 (11.4)	3020 (11.4)
Race, N (%)			
White	11524 (87.1)	11562 (87.4)	23086 (87.3)
Black/African American	350 (2.6)	339 (2.6)	689 (2.6)
Asian	606 (4.6)	588 (4.4)	1194 (4.5)
American Indian / Alaska Native	30 (0.2)	19 (0.1)	49 (0.2)
Native Hawaiian/Pacific Islander	15 (<0.1)	14 (0.1)	29 (0.1)
Missing	5 (<0.1)	7 (0.1)	12 (<0.1)
Ethnicity, N (%)			
Hispanic or Latino	1836(13.9)	1857(14.0)	3693(14.0)
Body metrics, Mean (SD)			
Weight (kg)	82.75 (17.27)	82.29 (16.88)	82.52 (17.08)
Height (cm)	170.63 (9.57)	170.56 (9.58)	170.60 (9.58)
BMI	28.32 (5.0)	28.19 (4.9)	28.26 (4.9)
Cigarette Use			
Current smoker	2750 (20.8)	2748 (20.8)	5498 (20.8)
Past smoker	6534 (49.4)	6563 (49.6)	13097 (49.5)
Prior TIA			
Yes	543 (4.1)	577 (4.4)	1120 (4.2)
No prior stroke	253 (1.9)	269 (2.0)	522 (2.0)
Prior Stroke, N (%)			
Yes	2876(21.7)	2870 (21.7)	5746 (21.7)
Hemorrhagic	5 (<0.1)	7 (0.1)	12 (<0.1)
Non-hemorrhagic	2713 (20.5)	2701 (20.4)	5414 (20.5)
Unknown	158 (1.2)	162 (1.2)	320 (1.2)
Prior Percutaneous Carotid Intervention			
Yes	149 (1.1)	117 (0.9)	266 (1.0)
Prior Carotid Endarterectomy			
Yes	352 (2.7)	350 (2.6)	702 (2.7)
Hypertension, N (%)	4092 (30.9)	4178 (31.6)	8270 (31.3)
Yes	7962 (87.3)	7954 (87.6)	15916 (87.4)

Diabetes mellitus, N (%)			
Yes	3356 (25.4)	3368 (25.5)	6724 (25.4)
Family history of premature CAD, N (%)			
Yes	3953 (29.9)	4005 (30.3)	7958 (30.1)
Prior MI, N (%)			
Yes	9586 (72.5)	9570 (72.4)	19156 (72.4)
Prior PCI			
Yes	7652 (57.9)	7600 (57.5)	15252 (57.7)
Prior CABG			
Yes	1749 (13.2)	1776 (13.4)	3525 (13.3)
Prior Peripheral Artery Revascularization			
Yes	1417 (10.7)	1404 (10.6)	2821 (10.7)
Prior Amputation Related to Limb Ischemia			
Yes	107 (0.8)	124 (0.9)	231 (0.9)
History of Renal Disease			
Yes	696 (5.3)	727 (5.5)	1423 (5.4)
Estimated eGFR by MDRD at Baseline			
<60 mL/min, n(%)	1735 (13.1)	1803 (13.6)	3538 (13.4)
Hepatic Function at Baseline			
ALT ≥2xULN	237/12968 (1.8)	263/12961 (2.0)	500/25929 (1.9)
AST ≥2xULN	120/13005 (0.9)	117/12996 (0.9)	237/26001 (0.9)
Alkaline Phosphatase ≥2xULN	30/13055 (0.2)	24/13059 (0.2)	54/26114 (0.2)
GGT ≥2xULN	782/13052 (6.0)	768/13056 (5.9)	1550/26108 (5.9)
Total Bilirubin ≥1.5xULN	69/13042 (0.5)	83/13044 (0.6)	152/26086 (0.6)
Baseline Ocular History			
Diabetic Retinopathy	291 (2.2)	297 (2.2)	588 (2.2)
Glaucoma	341 (2.6)	333 (2.5)	674 (2.5)
Macular Degeneration	130 (1.0)	108 (0.8)	238 (0.9)
High Intraocular Pressure	182 (1.4)	169 (1.3)	351 (1.3)

An analysis of medications received prior to baseline reveals no imbalances between the groups in the use of any of the classes of medications expected to be used by the enrolled patients. Other than antiplatelet medications, used by > 99% of subjects (see **Table 25**), common medication

classes (>20% of subjects), were, in descending order of use, statins, beta blockers, ACE inhibitors, and proton pump inhibitors (**Table 26**).

Table 25 TRA 2ºP – Concomitant Antiplatelet/Anticoagulant Medications Received at Baseline

ITT population

Medication N (%)	Placebo N= 13224	Vorapaxar N = 13225	Total N = 26449
Any Antiplatelet Agent (including aspirin)	13100 (99.1)	13129 (99.3)	26229 (99.2)
Aspirin – any dose	12363 (93.5)	12371 (93.5)	24734 (93.5)
<100 mg/d	4847 (36.7)	4866 (36.8)	9713 (36.7)
100-162 mg/d	5541 (41.9)	5520 (41.7)	11061 (41.8)
>162-325 mg/d	1911 (14.5)	1919 (14.5)	3830 (14.5)
>325 mg/d	55 (0.4)	53 (0.4)	108 (0.4)
Dose missing	9 (0.1)	13 (0.1)	22 (0.1)
Clopidogrel – any dose	8124 (61.4)	8076 (61.1)	16200 (61.2)
75 mg/d	8052 (60.9)	7999 (60.5)	16051 (60.7)
150 mg/d	59 (0.4)	50 (0.4)	109 (0.4)
Other dose	12 (0.1)	27 (0.2)	39 (0.1)
Dose missing	1 (<0.1)	0	1 (<0.1)
Any Ticlopidine	99 (0.7)	110 (0.8)	209 (0.8)
Any Prasugrel	18 (0.1)	22 (0.2)	40 (0.2)
Any Thienopyridine or Ticagrelor (a)	8238 (62.3)	8204 (62.0)	16442 (62.2)
Any Dipyridamole	543 (4.1)	539 (4.1)	1082 (4.1)
Any Cilostazol	315 (2.4)	287 (2.2)	602 (2.3)
Any Antiplatelet Agent Other Than Aspirin or Clopidogrel (b)	101 (0.8)	104 (0.8)	205 (0.8)
Aspirin Only	4121 (31.2)	4197 (31.7)	8318 (31.4)
Aspirin Plus Either a Thienopyridine or Ticagrelor	7569 (57.2)	7504 (56.7)	15073 (57.0)
Aspirin Plus Any Other Antiplatelet Agent	8242 (62.3)	8174 (61.8)	16416 (62.1)
Any Vitamin K Antagonist	12 (0.1)	16 (0.1)	28 (0.1)
Warfarin	9 (0.1)	9 (0.1)	18 (0.1)

a. “Thienopyridines” were defined as clopidogrel, prasugrel, ticlopidine and ticagrelor, but no subject received ticagrelor.
b. Subjects were not taking either aspirin or clopidogrel

Table 26 TRA 2ºP – Other Concomitant Medications Received at Baseline
ITT population

Medication N (%)	Placebo N= 13224	Vorapaxar N = 13225	Total N = 26449
Any Systemic Beta-adrenergic Antagonist	9232 (69.8)	9128 (69.0)	18360 (69.4)
Any ACE Inhibitor or Combination	7953 (60.1)	7852 (59.4)	15805 (59.8)
Any ARB or combination	2123 (16.1)	2051 (15.5)	4174 (15.8)
Any Statin	11927 (90.2)	11810 (89.3)	23737 (89.7)
Simvastatin	5139 (38.9)	5180 (39.2)	10319 (39.0)
Atorvastatin	4664 (35.3)	4636 (35.1)	9300 (35.2)
Rosuvastatin	1148 (8.7)	1108 (8.4)	2256 (8.5)
Any Proton Pump Inhibitor	3241 (24.5)	3245 (24.5)	6486 (24.5)
Any H2-Receptor Antagonist	664 (5.0)	635 (4.8)	1299 (4.9)

Use of dual antiplatelet therapy and other potentially life-saving classes of drugs were higher in the proposed label population (**Table 27** and **Table 28**) than in the ITT population

Table 27 TRA 2ºP – Concomitant Antiplatelet/Anticoagulant Medications Received at Baseline

Proposed Label Population – Subjects with CAD as the Qualifying Condition at Entry and No History of Stroke/TIA Prior to Randomization

Medication N (%)	Placebo N=8439	Vorapaxar N=8458	Total N=16897
Any Antiplatelet Agent (including aspirin)	8398 (99.5)	8437 (99.8)	16835 (99.6)
Aspirin – any dose	8298 (98.3)	8315 (98.3)	16613 (98.3)
<100 mg/d	3323 (39.4)	3349 (39.6)	6672 (39.5)
100-162 mg/d	3661 (43.4)	3653 (43.2)	7314 (43.3)
>162-325 mg/d	1280 (15.2)	1279 (15.1)	2559 (15.1)
>325 mg/d	33 (0.4)	34 (0.4)	67 (0.4)
Dose missing	1 (<0.1)	0	1 (<0.1)
Clopidogrel – any dose	6572 (77.9)	6538 (77.3)	13110 (77.6)
75 mg/d	6521 (77.3)	6483 (76.6)	13004 (77.0)
150 mg/d	44 (0.5)	39 (0.5)	83 (0.5)
Other dose	7 (0.1)	16 (0.2)	23 (0.1)
Dose missing	-	-	-
Any Ticlopidine	44 (0.5)	48 (0.6)	92 (0.5)
Any Prasugrel	17 (0.2)	21 (0.2)	38 (0.2)
Any Thienopyridine (a)	6631 (78.6)	6604 (78.1)	13235 (78.3)
Any Dipyridamole	2 (<0.1)	8 (0.1)	10 (0.1)
Any Cilostazol	29 (0.3)	16 (0.2)	45 (0.3)
Any Antiplatelet Agent without either Aspirin or Clopidogrel (b)	2 (<0.1)	8 (0.1)	10 (0.1)
Aspirin Only	1754 (20.8)	1822 (21.5)	3576 (21.2)
Aspirin Plus a Thienopyridine	6531 (77.4)	6482 (76.6)	13013 (77.0)
Aspirin Plus Any Other Antiplatelet Agent	6544 (77.5)	6493 (76.8)	13037 (77.2)
Any Vitamin K Antagonist	4 (<0.1)	7 (0.1)	11 (0.1)
Warfarin	3 (<0.1)	5 (0.1)	8 (<0.1)
Any Antithrombin Agent (c)	20 (0.2)	21 (0.2)	41 (0.2)

a. Thienopyridines by definition include clopidogrel, prasugrel, ticlopidine and ticagrelor, but there is no evidence for use of ticagrelor in this study
b. Subjects took an antiplatelet agent but were not taking either aspirin or clopidogrel
c. Includes unfractionated or low molecular weight heparin, fondaparinux, and direct thrombin inhibitors

Table 28 TRA 2ºP – Other Concomitant Medications Received at Baseline
Proposed Label Population – Subjects with CAD as the Qualifying Condition at Entry and No History of Stroke/TIA Prior to Randomization

Medication N (%)	Placebo N=8439	Vorapaxar N=8458	Total N=16897
Any Systemic Beta-adrenergic Antagonist	7209 (85.4)	7194 (85.1)	14403 (85.2)
Any ACE Inhibitor or Combination	5586 (66.2)	5586 (66.0)	11172 (66.1)
Any ARB or combination	1105 (13.1)	1002 (11.8)	2107 (12.5)
Any Statin	8086 (95.8)	8031 (95.0)	16117 (95.4)
Simvastatin	3297 (39.1)	3366 (39.8)	6663 (39.4)
Atorvastatin	3367 (39.9)	3315 (39.2)	6682 (39.5)
Rosuvastatin	787 (9.3)	778 (9.2)	1565 (9.3)
Any Proton Pump Inhibitor	2168 (25.7)	2183 (25.8)	4351 (25.8)
Any H2-Receptor Antagonist	421 (5.0)	398 (4.7)	819 (4.8)

6.1.3 Subject Disposition and Compliance with Study Drug

6.1.3.1 Disposition

Table 29 provides information on subjects who discontinued treatment and those who discontinued follow-up prior to the end of the study. Note that most subjects who discontinued treatment as a result of the recommendation of the DSMB to discontinue study therapy in all subjects with a history of stroke at baseline or during the study also discontinued follow-up at this time under the amended protocol, but were classified as completing follow-up.

Table 29 TRA 2°P – Subject Disposition

ITT Population

	PLACEBO n (%)	VORAPAXAR n (%)
Randomized	13224 (100)	13225 (100)
Never received study treatment	58 (0.4)	39 (0.3)
Received study treatment	13166 (99.6)	13186 (99.7)
Completed treatment	7970 (60.3)	7779 (58.8)
Had history of stroke and discontinued treatment per recommendation of DSMB	2248 (17.0)	2262 (17.1)
Discontinued treatment early for other reason:	2948 (22.3)	3145 (23.8)
AE, Bleeding, or Efficacy event	1299 (9.8)	1381 (10.4)
AEs other than bleeding	960 (7.3)	926 (7.0)
Bleeding events	234 (1.8)	401 (3.0)
Efficacy events	105 (0.8)	54 (0.4)
Withdrew consent to study treatment	1211 (9.2)	1257 (9.5)
Did not meet protocol eligibility	48 (0.4)	42 (0.3)
Non-compliance	297 (2.2)	355 (2.7)
Required prohibited medication	57 (0.4)	67 (0.5)
Other/missing	36 (0.3)	43 (0.3)
FOLLOW-UP AT STUDY COMPLETION:		
Completed the Study (1),(5)	11103	11140
Discontinued follow-up per amended protocol in connection with discontinuation of treatment per recommendation of DSMB (5)	1820	1813
Completed the Study (2)	12932 (97.8)	12953 (97.9)
Completed Final Study Visit (3)	12696 (96.0)	12728 (96.2)
Only vital status assessed	236 (1.8)	225 (1.7)
Died	25 (0.2)	22 (0.2)
Alive	211 (1.6)	203 (1.5)
Prematurely discontinued follow-up	292 (2.2)	272 (2.1)
Withdrew consent for follow-up	277 (2.1)	255 (1.9)
Lost to follow-up	15 (0.1)	17 (0.1)
All deaths (4)	589 (4.5)	556 (4.2)

Source: Study report Display A-1.4
(1) Followed to study termination or died during study.
(2) Sponsor's analysis: subjects in (1) plus subjects who discontinued follow-up in connection with discontinuation of treatment per the recommendation of the DSMB
(3) Includes subjects who discontinued follow-up in connection with discontinuation of treatment per the recommendation of the DSMB
(4) All known deaths, including those who only had vital status assessed. Those who died during follow-up are counted as completing the study; those whose deaths were ascertained in a vital status report after discontinuation of follow-up are not counted as completing the study.
(5) Reviewer's estimate based on number of prior stroke stratum subjects who "completed "the study alive between 1/13/2011 (the date that study leadership decided to discontinue follow-up in patients with a baseline history of stroke) and 7/31/2011 (one day before study close-out began).

6.1.3.2 Compliance with Study Drug

Table 30 is a display of compliance with study drug as determined by counts of returned tablets About 88% to 89% of subjects had > 90% compliance as assessed in this manner.

Table 30 Compliance with Study Drug by Counts of Returned Tablets

	Placebo n (%)	Vorapaxar N (%)
Any exposure	13166 (100)	13186 (100)
Percent compliance		
≤10%	5 (<0.1)	3 (<0.1)
>10%-20%	4 (<0.1)	3 (<0.1)
>20%-30%	8 (0.1)	7 (0.1)
>30%-40%	11 (0.1)	20 (0.2)
>40%-50%	28 (0.2)	42 (0.3)
>50%-60%	46 (0.3)	49 (0.4)
>60%-70%	84 (0.6)	99 (0.8)
>70%-80%	232 (1.8)	261 (2.0)
>80%-90%	808 (6.1)	801 (6.1)
>90%	11712 (89.0)	11655 (88.4)
Replacement (a)	226 (1.7)	245 (1.9)
Indeterminate (b)	2 (<0.1)	1 (<0.1)

(a) Extent of Exposure for subjects who were assigned replacement kit (s) could not be determined.
(b) When total dispensed quantity < total returned quantity.

6.1.3.3 Analysis Populations

Analysis populations for the TRA 2ºP efficacy analyses of the overall study population are shown in **Table 31**.

Table 31 TRA 2ºP – Overall Efficacy Analysis Populations

Population [1]	Placebo n (%)	Vorapaxar n (%)	Total n (%)
ITT (All randomized)	13,224	13,225	26,449
As-Treated	13,166	13,186	26,352

1 ITT Population – All randomized patients ; As-Treated Population – Randomized patients who took at least one dose of study drug; this is also the safety population

In addition, efficacy analyses were performed in key subsets of subjects pursuant to changes in the protocol and DAP made in response to the recommendation of the DSMB to discontinue treatment in subjects with a history of stroke. In decreasing order of size, these subsets were the::

- No Stroke History (NSH) population, ITT N=20,699; As-Treated N=20,633
- Post MI NSH population, ITT N=17,191; As-Treated N=17,147

One additional population used to evaluate efficacy and safety represents an important post-hoc subset of subjects:

- The Proposed Label Population (CAD stratum with no history of stroke or TIA), ITT N=16,897; As-Treated N=16,856

This last population, which comprises 95% of the CAD stratum, is the Applicant's proposed target population. The Applicant's rationale for limiting use to this population is that it might be difficult for a physician to distinguish between a prior stroke and a prior TIA, and it would more prudent to simply exclude patients with either from treatment with vorapaxar because of the risk of intracranial hemorrhage.

6.1.4 Analysis of Primary Endpoint and Key Secondary Endpoint

The primary efficacy endpoint was time to the first event in the composite of CV death, MI, stroke (all types) and UCR, and was assessed in the ITT population, with events counted from randomization to the last visit. The Key secondary endpoint was similar, but omitted UCR from the composite. The occurrence of UCR, unlike the other components of the primary endpoint, is dependent on a therapeutic decision by a physician. This would be expected to create a source of noise, possible reducing the ability to discriminate between an active drug and placebo. Indeed, in TRA2°P the Key Secondary efficacy endpoint, typical MACE, had a lower HR than the Primary Endpoint overall and in most subsets. This was also so in TRA•CER, where the primary endpoint had two components that were dependent on a physician's therapeutic decision, and where typical MACE was the Key Secondary endpoint (for results of TRA•CER see **Table 14**). However, in each study, the difference in the HR between the Primary and Key Secondary Endpoints was not large.

Table 32 TRA 2ºP – Primary and Key Secondary Efficacy Endpoint Results
Time to first event (Adjudicated data, ITT Population)

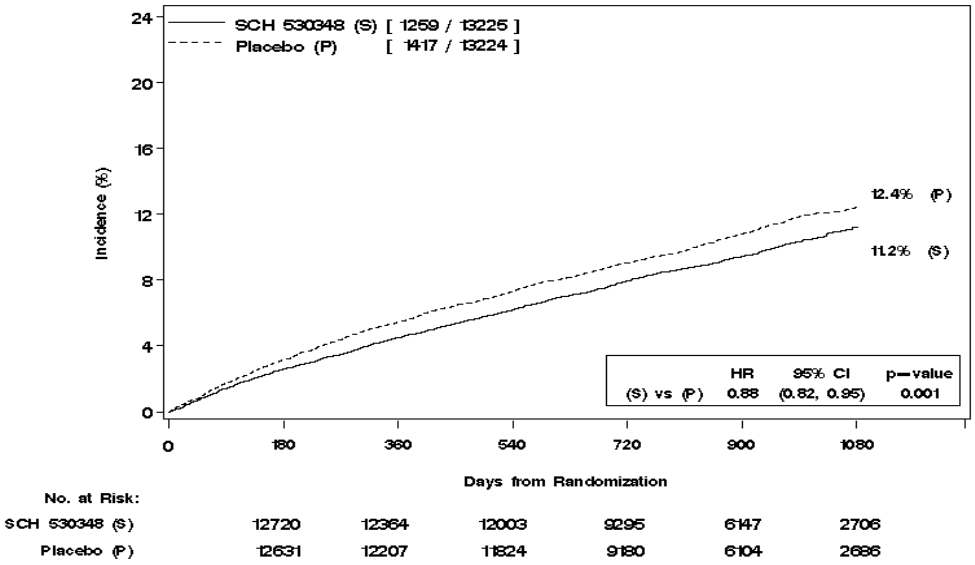
	Placebo N=13,224		Vorapaxar (N=13,225)		V vs. P HR (95% CI)	p
	n (%)	%/yr	n (%)	%/yr		
Any Primary Efficacy Endpoint Event [1]	1417 (10.7)	4.6	1259 (9.5)	4.1	0.88 (0.82 - 0.95)	0.001
CV death	199 (1.5)		172 (1.3)			
MI	629 (4.8)		536 (4.1)			
Stroke	297 (2.2)		297 (2.2)			
Ischemic	256 (1.9)		210 (1.6)			
Hemorrhagic	27 (0.2)		67 (0.5)			
Uncertain	14 (0.1)		20 (0.2)			
UCR	292 (2.2)		254 (1.9)			
Any Key Secondary Efficacy Endpoint Event [2]	1176 (8.9)	3.8	1028 (7.8)	3.3	0.87 (0.80 - 0.94)	<0.001
CV death	207 (1.6)		175 (1.3)			
MI	665 (5.0)		554 (4.2)			
Stroke	304 (2.3)		299 (2.3)			
Ischemic	260 (2.0)		212 (1.6)			
Hemorrhagic	28 (0.2)		67 (0.5)			
Uncertain	16 (0.1)		20 (0.2)			

1 Composite of CV death, MI, stroke and UCR
2 Composite of CV death, MI and stroke

The beneficial effect of vorapaxar on both these endpoints appears to be primarily driven by a reduction in the rate of MI. There was also a roughly similar relative reduction in the rate of ischemic stroke, but it was offset in absolute terms by an increase in the rate of hemorrhagic stroke, leaving the overall results for stroke neutral in the component analyses of both endpoints. There modest advantages with vorapaxar for CV death in both analyses and for UCR in the primary endpoint analysis.

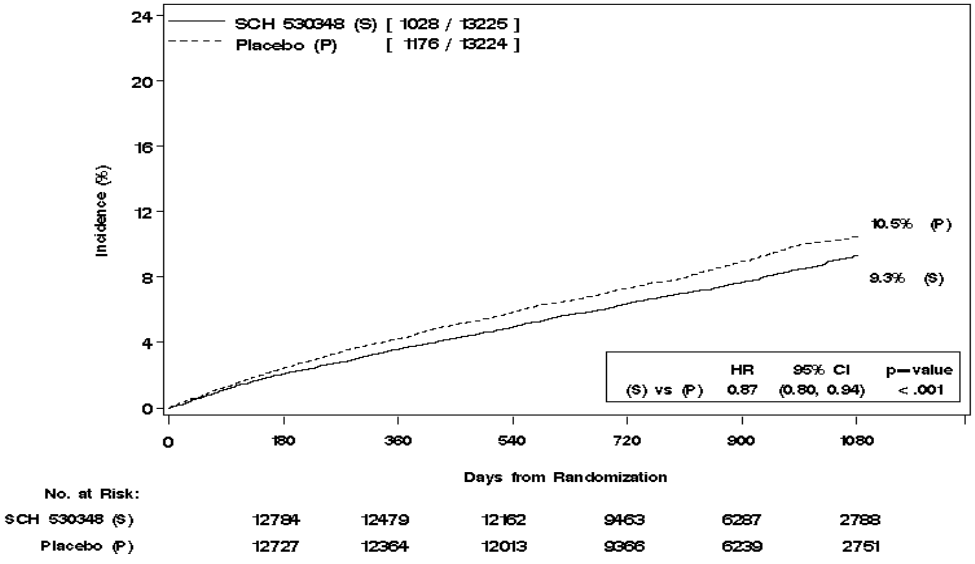
KM plots for the time to the first Primary and Key Secondary endpoint events are displayed in **Figure 10** and **Figure 11**, respectively.

Figure 10 TRA 2ºP - Time to First Primary Efficacy Endpoint Event



No. at Risk:						
SCH 530348 (S)	12720	12364	12003	9295	6147	2706
Placebo (P)	12631	12207	11824	9180	6104	2686

Figure 11 TRA 2ºP - Time to First Key Secondary Efficacy Endpoint Event



No. at Risk:						
SCH 530348 (S)	12784	12479	12162	9463	6287	2788
Placebo (P)	12727	12364	12013	9366	6239	2751

In both curves, divergence is gradual. In each case, the curves appear to reach a maximum absolute divergence of about 1.2% over 3 years.

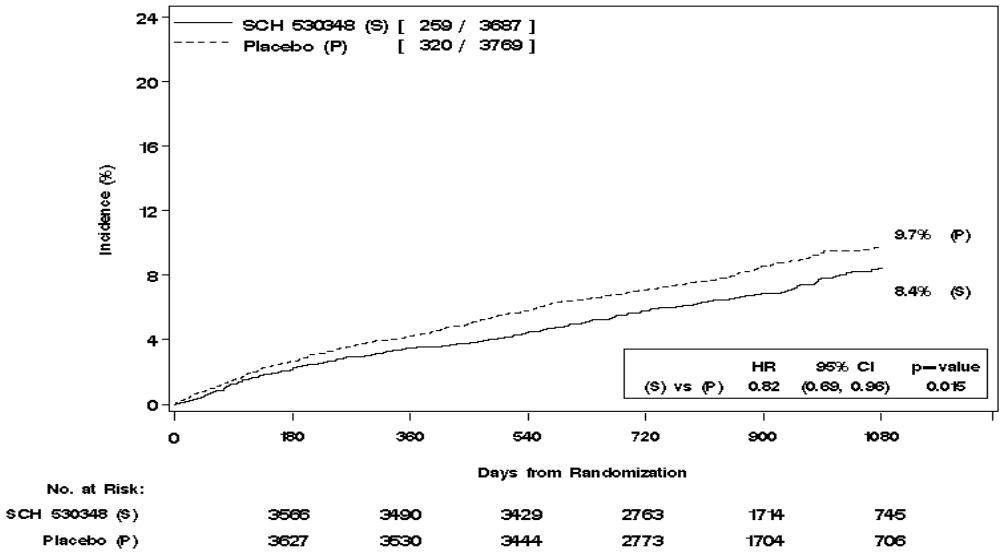
Hazard ratios for the as-treated analyses of the Primary and Key Secondary endpoints (i.e., on treatment, counting events from first dose of study drug to last dose + 3 days) do not differ materially from the ITT analyses, and do not show the often-observed pattern of better results for treatment vs. placebo than the ITT analysis. For the Primary endpoint, there were 1178 vs. 1046 events cases in the placebo and vorapaxar arms respectively, yielding KM estimates (over 1080 days) of 11.3% and 10.4%, with an HR of 0.89 (0.82, 0.97; p=0.007). Analogous data for the Key Secondary endpoint were 953 vs. 835 events, with KM estimates of 9.3% and 8.4%, and an HR of 0.88 (0.80, 0.97; p=0.008).

The sponsor performed analyses of the Key secondary endpoint in subgroups of the proposed label population (i.e., those with a prior MI and no prior history of stroke or TIA) based on the time from the qualifying MI to randomization: <3 months, 3 to 6 months, and >6 months. KM curves for these analyses are displayed in Error! Reference source not found.

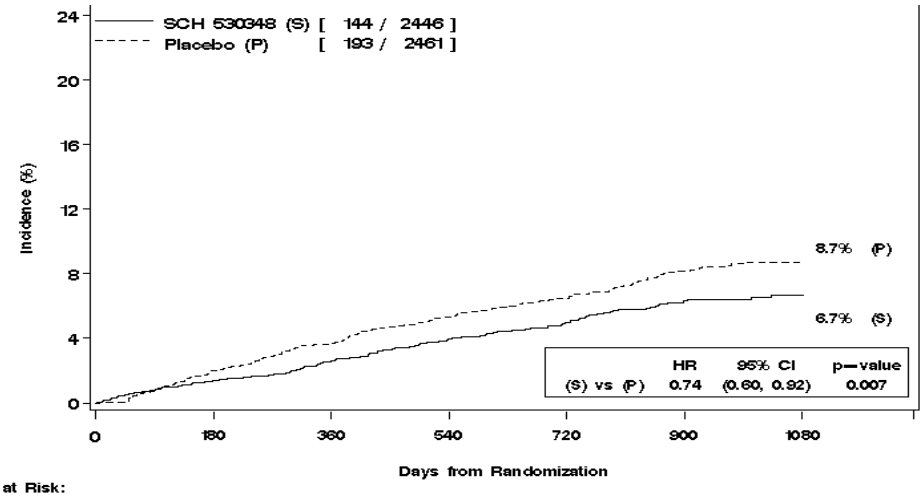
Figure 12 KM Estimate of Time to the First Occurrence of Key Secondary Efficacy Endpoint by the Time of Qualifying MI to Randomization (Δ time)

ITT Population

A – Subjects with Δ time <3 months

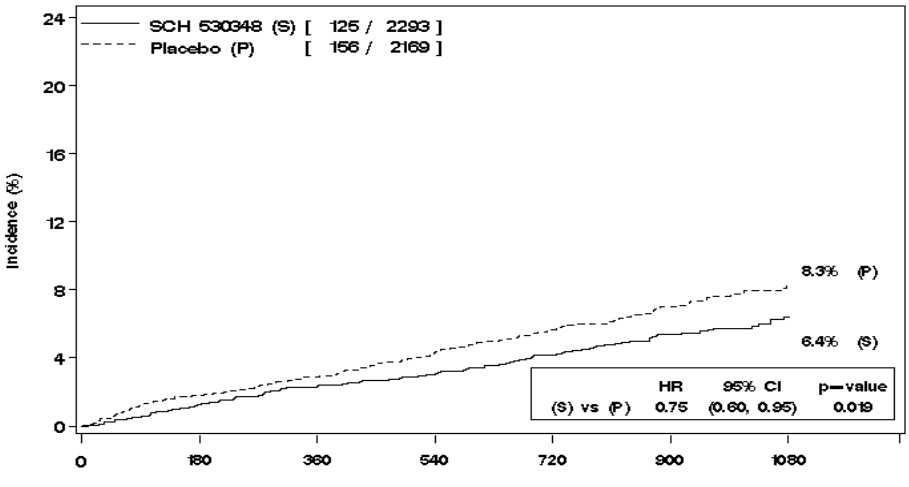


B – Subjects with Δ time from 3 to 6 months



No. at Risk:						
SCH 530348 (S)	2390	2339	2276	1801	1137	513
Placebo (P)	2379	2315	2258	1807	1169	554

C – Subjects with Δ time >6 months



No. at Risk:						
SCH 530348 (S)	2239	2207	2181	1797	1268	575
Placebo (P)	2110	2075	2032	1674	1205	555

Source: CSR Figures 8 – 10.

All 3 plots show a statistically significant benefit for vorapaxar over placebo. Curve A (subjects who were randomized < 3 months after an MI) had highest (i.e., least favorable for vorapaxar) HR. This was the largest of the time-based subgroups. The curves for each treatment arm are very

close together until about 6 months after randomization, when they begin to diverge and both curves become less steep. The other two plots were associated with associated with similar hazard ratios near 0.75, with earlier divergence of the treatment arms and less steep curves from randomization than A. The pattern of better results for vorapaxar with later entry into the study suggests that its effects may not be as great early after an MI, perhaps because there are patients are likely to have additional events soon after an MI regardless of the intensity of treatment. However, this does not necessarily mean that vorapaxar therapy should be delayed until at least 3 months after an MI.

6.1.5 Other Efficacy Endpoints

6.1.5.1 Death

Table 33 includes information on all deaths in the study database, regardless of timing. All rows numerically favor vorapaxar.

Table 33 TRA 2ºP – All-Cause Deaths
Adjudicated endpoints, ITT Population

	Placebo N=13,224 n (%)	Vorapaxar N=13,225 n (%)
All deaths in any period	610 (4.6)	580 (4.4)
All deaths from randomization to the ast visit (i.e., the ITT analysis)	565 (4.3)	540 (4.1)
All deaths after the last visit	45 (0.3)	40 (0.3)

Table 34 is a display of results in the ITT population for secondary endpoint data, including all-cause death and CV death, and non-CV death. As noted above, all-cause death and CV death favor apixaban, while non-CV death favors placebo. None of the differences between the study arms in the rates of death were statistically significant. Additional information on deaths is found in the Safety review in Sec. 7.3.

Table 34 TRA 2ºP – Secondary Endpoints
Adjudicated endpoints, ITT Pop, Randomization to Last Visit

Endpoint	Placebo N=13,224		Vorapaxar (N=13,225)		V vs. P HR (95% CI)	p
	n (%)	%/yr	n (%)	%/yr		
All-cause death	565 (4.3)	1.8	540 (4.1)	1.7	0.95 (0.85 - 1.07)	0.411
CV death	319 (2.4)	1.0	285 (2.2)	0.9	0.89 (0.76 - 1.04)	0.151
Non-CV death (by subtraction)	246 (1.9)	-	255 (1.9)	-	-	-
MI	673 (5.1)	2.1	564 (4.3)	1.8	0.83 (0.74 - 0.93)	0.001
Stroke	324 (2.5)	1.0	315 (2.4)	1.0	0.97 (0.83 - 1.14)	0.733
UCR	316 (2.4)	1.0	279 (2.1)	0.9	0.88 (0.75 - 1.03)	0.108
UH-VCIN	646 (4.9)	2.1	539 (4.1)	1.7	0.83 (0.74 - 0.93)	0.001
Any Revasc	1768 (13.5)	6.0	1583 (12.0)	5.3	0.89 (0.83 - 0.95)	<0.001
All-Cause Death / MI / Stroke / UCR	1614 (12.2)	5.3	1481 (11.2)	4.8	0.91 (0.85-0.98)	0.009
CV Death / MI	913 (6.9)	2.9	789 (6.0)	2.5	0.86 (0.78 - 0.94)	0.002
CV Death / MI / Stroke / UCR/UH-VCIN	1681 (12.7)	9.0	1481 (11.2)	8.2	0.87 (0.81 - 0.93)	<0.001
All-Cause death/MI/Stroke/Any Revasc	2594 (19.6)	9.0	2395 (18.1)	18.1	0.91 (0.86 - 0.96)	0.001
CV Death / MI / Stroke / Any Revasc /UH-VCIN	2542 (19.2)	8.9	2314 (17.5)	17.5	0.90 (0.85 - 0.95)	<0.001

Abbreviations: CV = cardiovascular; MI = myocardial infarction; Revasc = revascularization; UCR = urgent coronary revascularization; UH-VCIN = urgent hospitalization for vascular cause of ischemic nature.

6.1.5.2 Other Secondary Endpoints

Data for other pre-specified secondary from the original statistical plan are displayed in **Table 34** below the rows with death data. These endpoints include the individual components of the primary and secondary endpoints, analyzed without regard to occurrence of other endpoints. Also included are additional endpoints relating to ischemic events: urgent hospitalization for vascular cause of ischemic nature (UH-VCIN) and any revascularization procedure, which included any arterial revascularization procedure and also amputation of an ischemic limb. Several additional composite endpoints were also analyzed; all of these included MI and either CV death or all-cause death.

Of the individual components of the primary endpoint, only the results for MI significantly favored vorapaxar. All of the composite endpoint secondary endpoints significantly favored vorapaxar, as did the results for any revascularization and UH-VCIN. .

The prespecified hierarchical analysis plan stipulated that analysis of endpoints would be performed in the order below after the Primary endpoint and the Key Secondary endpoint (each of those two endpoints favored vorapaxar with p<0.05) until a non-statistically significant result (p≥0.05) was obtained. Statistically significant results are indicated with a check mark; the first non-significant result (for CV death) is indicated by "✗";for endpoints lower in the hierarchy than CV death, symbols are in parentheses:

1. ✓ all-cause death, MI, stroke, and urgent coronary revascularization
2. ✓ CV death and MI
3. ✓ CV death, MI, stroke, urgent coronary revascularization, or urgent hospitalization for vascular cause of ischemic nature
4. ✓ all-cause death, MI, stroke, any revascularization (including amputation for ischemic limb)
5. ✓ CV death, MI, stroke, any revascularization (including amputation for ischemic limb), or urgent hospitalization for vascular cause of ischemic nature
6. the following individual components of the primary endpoint –
   a. ✗ cardiovascular death
   b. MI (✓)
   c. stroke (✗)
   d. urgent coronary revascularization (✗)
7. all-cause death (✗)

Note that all the above endpoints were fully analyzed, including those below CV death in the hierarchy.

6.1.5.3 Additional Endpoints

Rankin score was assessed in all patients with a prior history of stroke at baseline. Any patient with a new focal neurological defect was evaluated for Rankin score at presentation, hospital discharge, 90-120 days after onset, and at each subsequent patient visit.

Data for change in Rankin Score are provided in Table 35. Although there were fewer subjects with strokes in the vorapaxar arm, the rate of fatal stroke (Rankin score =6) with vorapaxar was about double the rate with placebo (12.8% of those with strokes vs. 6.7%). This is consistent with the expectation that hemorrhagic strokes, which were substantially more common in the vorapaxar arm than in the placebo arm, tend to be more serious than ischemic strokes. On the other hand, other metrics of Rankin score change were similar in the two arms.

Table 35 TRA 2°P – Rankin Scores for Subjects with Adjudicated Stroke During the Study

Modified Rankin Score	Placebo n/N (%)	Vorapaxar n/N (%)
Died as result of stroke (Score = 6)	22/326 (6.7)	41/321 (12.8)
At any assessment following a stroke		
Increased ≥ 2 from score before	187/326 (57.4)	183/321 (57.0)

Modified Rankin Score	Placebo n/N (%)	Vorapaxar n/N (%)
stroke		
Score of 0 or 1 before stroke increased to 2 to 6 after stroke (no disability to disability or dead)	183/291 (62.9)	177/267 (66.3)
Score of 0 to 2 before stroke increased to 3 to 6 after stroke (independent to dependent or dead)	168/291 (57.7)	50/267 (56.2)
At final assessment		
Increased ≥ 2 from score before stroke	113/326 (34.7)	99/321 (30.8)
Score of 0 or 1 before stroke increased to 2 to 6 after stroke (no disability to disability or dead)	115/291 (39.5)	100/267 (37.5)
Score of 0 to 2 before stroke increased to 3 to 6 after stroke (independent to dependent or dead)	92/291 (31.6)	82/267 (30.7)

Note: Scores are as follows:
0 = no symptom
1 = no significant disability, despite symptom(s)
2 = slight disability, but still independent
3 = moderate disability
4 = moderately severe disability
5 = severe disability
6 = death

Changes from baseline in Fontaine Classification of PAD symptoms in subjects with PAD at entry are summarized in **Table 36**. In general, increases in Fontaine class (i.e., clinical worsening) of more than one level were uncommon. Results for worsening in Fontaine class consistently favored vorapaxar numerically, but differences between the treatment arms were uniformly small.

Reviewer comment: Vorapaxar was developed to prevent adverse CV outcomes in patients with PAD, prior stroke and prior MI, not as a symptomatic treatment for PAD.

Table 36 TRA 2°P – Worsening from Baseline in Fontaine Class for Subjects with Peripheral Arterial Disease

Change in Fontaine Score Classification	Placebo n/N (%)	Vorapaxar n/N (%)
At any assessment after baseline		
Class I-III at baseline and increased ≥1 class	242/1874 (12.9)	207/1859 (11.1)
Class I-IIb at baseline and Increased ≥2 classes	56/1828 (3.1)	47/1814 (2.6)

Change in Fontaine Score Classification	Placebo n/N (%)	Vorapaxar n/N (%)
Class I-III at baseline and increased to class III or IV	26/1874 (1.4)	25/1859 (1.3)
At final assessment		
Class I-III at baseline and increased ≥1 class	201/1874 (10.7)	169/1859 (9.1)
Class I-IIb at baseline and Increased ≥2 classes	46/1828 (2.5)	38/1814 (2.1)
Class I-III at baseline and increased to class III or IV	22/1874 (1.2)	17/1859 (0.9)

Class levels are as follows
I = asymptomatic
IIa = intermittent claudication walking >200 m
IIb = intermittent claudication walking <200 m
III = pain at rest or at night
IV = ulceration, necrosis, or gangrene

Table 37 is a display of the rates of ARC-defined stent thrombosis in patients in the post-MI stratum with no prior history of stroke or TIA who received a coronary stent prior to randomization or during the study. The data indicate that very few patients received a stent during the study period. It is not clear if stents inserted “before randomization" include only stents inserted during an index hospitalization for MI. Results favor vorapaxar over placebo in all data rows. Data for the ITT population include a modestly increased number of patients with stents in the placebo and vorapaxar arms (about 11% -13% more) and hazard ratios that are slightly less favorable for vorapaxar, ranging from 0.71 to 0.84 in the various data rows (data not shown).

Table 37 TRA 2°P - ARC Coronary Stent Thrombosis in Subjects Undergoing PCI with Stent Implantation Prior to or During the Study

Proposed label population

	Placebo N=13224	Vorapaxar N=13225	HR (95% CI)	p
Subjects receiving any stent prior to randomization	N=6340 n (%)	N=6334 n (%)	-	-
Definite	78 (1.2)	55 (0.9)	0.70 (0.50 - 1.00)	0.047
Definite or probable	85 (1.3)	62 (1.0)	0.73 (0.53 - 1.01)	0.058
Definite, probable or possible	143 (2.3)	112 (1.8)	0.78 (0.61 - 1.00)	0.052
Subjects receiving any stent prior to randomization or during the study	N=6460 n (%)	N=6464 n (%)		
Definite	80 (1.2)	56 (0.9)	0.70 (0.50 - 0.98	0.040
Definite or probable	87 (1.3)	63 (1.0)	0.72 (0.52 - 1.00)	0.050
Definite, probable or possible	145 (2.2)	113 (1.7)	0.78 (0.61 - 0.99)	0.045

6.1.6 Subpopulations

6.1.6.1 Subpopulations of the global study population

Results for the Primary efficacy endpoint and Key Secondary efficacy endpoint were analyzed in various subgroups of patients, based on geographic region, demographic factors, disease-related factors, and prior medication use. For all subgroups of substantial size (i.e., > 15% of the patient population), the HR for vorapaxar vs. placebo was <1.0 (**Table 38** and **Table 39**). The sole exception was the stroke primary enrollment stratum, which included 18% of subjects and had an HR of 1.02.

Table 38 Primary Efficacy Endpoint Results by Subgroup

ITT Population

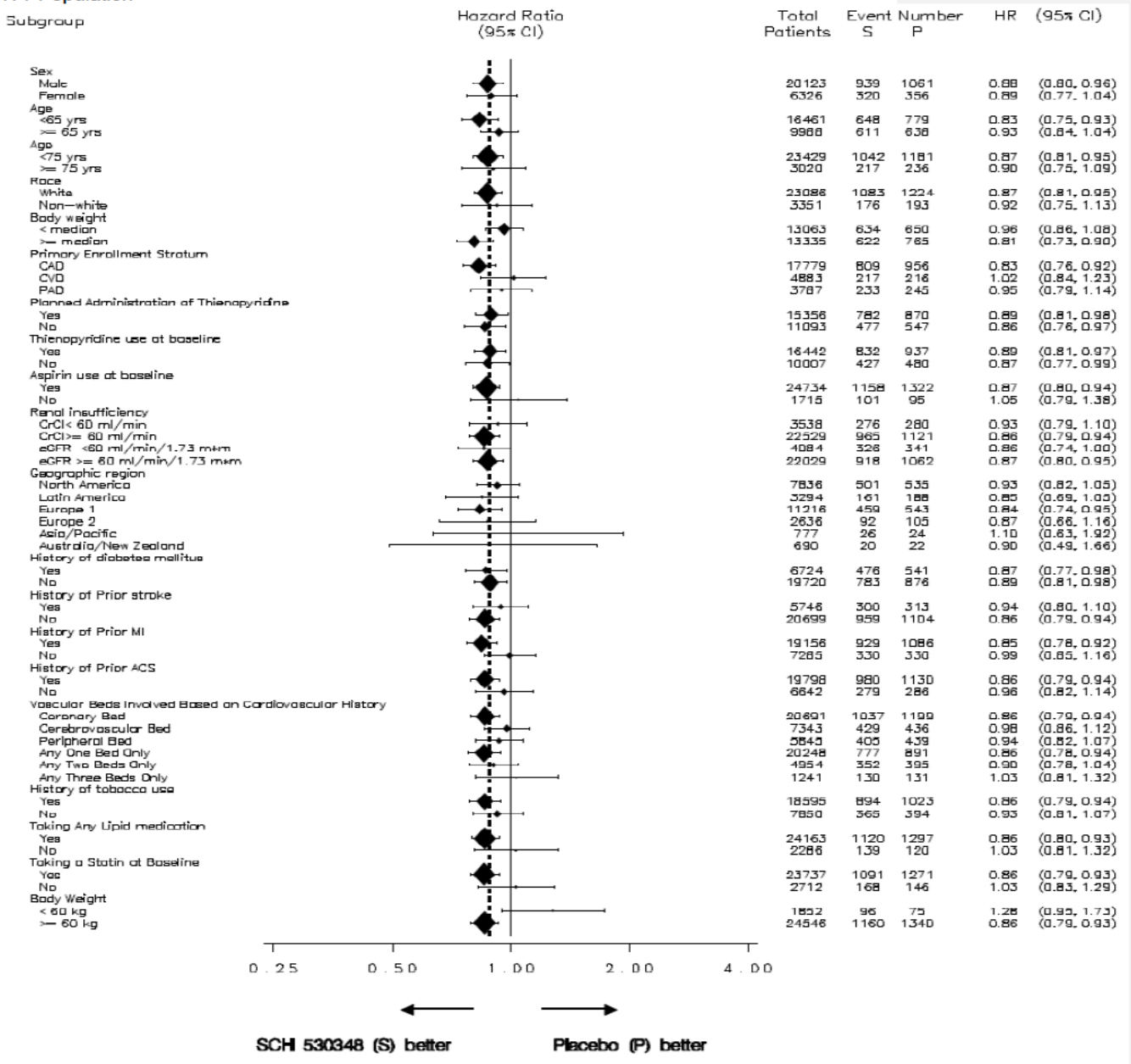


Table 39 Key Secondary Efficacy Endpoint Results by Subgroup

ITT Population

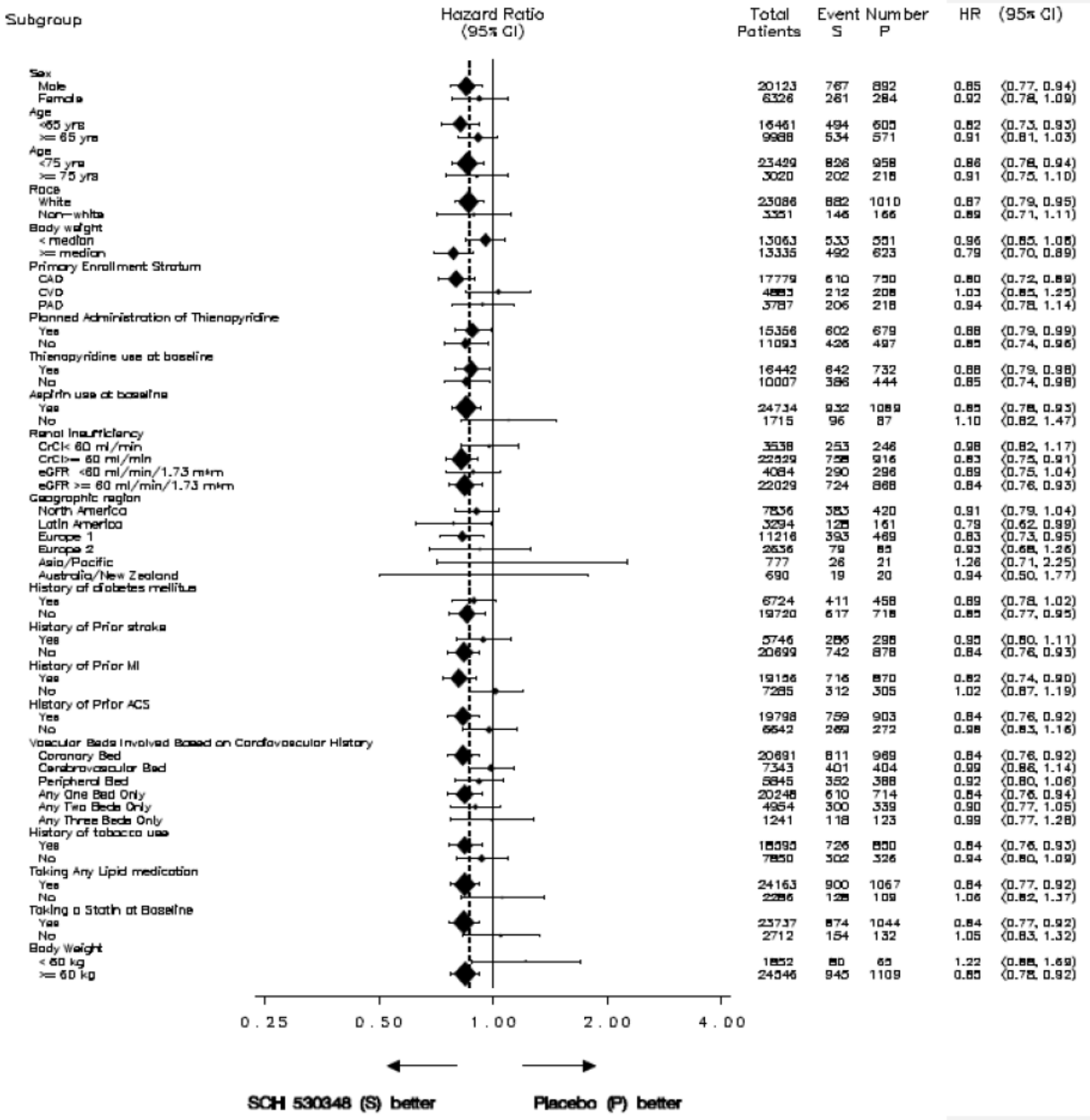


Table 40 provides information on treatment by subgroup interactions with p values ≤ 0.15 for either the Primary or Key Secondary endpoint analyses.

Table 40 TRA 2°P – Treatment by Subgroup Interactions with p≤0.15 for the Primary or Key Secondary Endpoints

Subgroup	End-point	Placebo (N = 13,224) n/J (%) KM%	Vorapaxar (N = 13,225) n/J (%) KM%	HR (95% CI)	Interaction p
Age <65	PEP	779/8273 (9.4) 10.6	648/8188 (7.9) 9.3	0.83 (0.75, 0.93)	0.145
≥65		638/4951 (12.9) 15.3	611/5037 (12.1) 14.3	0.93 (0.84, 1.04)	
Age <65	KSEP	605/8273 (7.3) 8.5	494/8188 (6.0) 7.3	0.82 (0.73 - 0.93)	0.215
≥65		571/4951 (11.5) 13.8	534/5037 (10.6) 12.6	0.91 (0.81 - 1.03)	
Weight < median	PEP	650/6489 (10.0) 12.0	634/6574 (9.6) 11.8	0.96 (0.86, 1.08)	0.024
≥ median		765/6703 (11.4) 12.9	622/6632 (9.4) 10.7	0.81 (0.73 - 0.90)	
Weight < median	KSEP	551/6489 (8.5) 10.4	533/6574 (8.1) 10.1	0.96 (0.85 - 1.08)	0.024
≥ median		623/6703 (9.3) 10.6	492/6632 (7.4) 8.6	0.79 (0.70 - 0.89)	
Weight <60 kg	PEP	75/921 (8.1) 9.6	96/931 (10.3) 13.6	1.28 (0.95 - 1.73)	0.012
≥60 kg		1340/12271 (10.9) 12.6	1160/12275 (9.5) 11.1	0.86 (0.79 - 0.93)	
Weight <60 kg	KSEP	65/921 (7.1) 8.4	80/931 (8.6) 11.5	1.22 (0.88 - 1.69)	0.058
≥60 kg		1109/12271 (9.0) 10.6	945/12275 (7.7) 9.2	0.85 (0.78 - 0.92)	
Primary Stratum: MI	PEP	956/8881 (10.8) 12.1	809/8898 (9.1) 10.5	0.83 (0.76 - 0.92)	0.128
Stroke		216/2448 (8.8) 12.1	217/2435 (8.9) 12.9	1.02 (0.84 - 1.23)	
PAD		245/1895 (12.9) 13.4	233/1892 (12.3) 12.7	0.95 (0.79 - 1.14)	
Primary Stratum: MI	KSEP	750/8881 (8.4) 9.7	610/8898 (6.9) 8.1	0.80 (0.72 - 0.89)	0.058
Stroke		208/2448 (8.5) 11.7	212/2435 (8.7) 13.0	1.03 (0.85 - 1.25)	
PAD		218/1895 (11.5) 11.9	206/1892 (10.9) 11.3	0.94 (0.78 - 1.14)	

Aspirin use at BL? Yes	PEP	1322/12363 (10.7) 12.3	1158/12371 (9.4) 11.0	0.87 (0.80 - 0.94)	0.192
No		95/861 (11.0) 13.9	101/854 (11.8) 14.9	1.05 (0.79 - 1.38)	
Aspirin use at BL? Yes	KSEP	1089/12363 (8.8) 10.3	932/12371 (7.5) 9.0	0.85 (0.78 - 0.93)	0.092
No		87/861 (10.1) 12.7	96/854 (11.2) 14.1	1.10 (0.82 - 1.47)	
Statin use at BL? Yes	PEP	1271/11927 (10.7) 12.2	1091/11810 (9.2) 10.8	0.86 (0.79 - 0.93)	0.096
No		146/1297 (11.3) 14.5	168/1415 (11.9) 15.0	1.03 (0.83 - 1.29)	
Statin use at BL? Yes	KSEP	1044/11927 (8.8) 10.2	874/11810 (7.4) 8.8	0.84 (0.77 - 0.92)	0.056
No		132/1297 (10.2) 13.4	154/1415 (10.9) 14.1	1.05 (0.83 - 1.32)	

KM% is a 720 day estimate.
a Per 1.72 m^2 BSA – MDRD method
b AT=Antithrombotic
b PEP=Primary endpoint
c KSEP=Key secondary endpoint
Trends for treatment by subgroup interactions were observed for subgroups based on:

- Primary stratum at entry, with the prior MI stratum showing the greatest beneficial effect of vorapaxar and the prior stroke stratum showing a small net detrimental effect; results for the PAD stratum were intermediate.
- Weight, with lighter subjects receiving less benefit from vorapaxar than heavier ones. This effect was most evident in those with weight < 60 kg, but was also observed in those with weight < the median (81 kg).
- Age, with persons with age < 65 receiving less benefit from vorapaxar than those with age ≥65. However, when the much smaller subgroup of those ≥ 75 (n=~1500/arm) was compared those <75, the HRs for vorapaxar vs. placebo did not differ markedly similar (0.90 vs. 0.87).
- Aspirin use at baseline, with no use (<900 subjects/arm) being associated with an HR of 1.05. This seems counter-intuitive, and may be a chance result in a very small subset of the population
- Statin use at baseline, with no use (~1300-1400 subjects/arm) being associated with an HR of 1.03.

Other subgroups based on factors closely related to those described above also showed trends or p<0.05 for interactions. For example, the results in subgroups based on prior history of MI (yes or no) had an interaction p of 0.077 with the Primary endpoint.

One subgroup pair as notably missing from the list of those with interaction trends: those using thienopyridines at baseline (yes or no). Users and non-users had similar results for the Primary endpoint and also for the Key Secondary endpoint, although the relative benefit of vorapaxar was slightly larger in those with no thienopyridine use at baseline, as one might expect (**Table 41**). A nearly identical pattern of results was seen in the subgroups based on planned thienopyridine use during the study (data not shown).

Table 41 TRA 2°P – Effect of Thienopyridine use at Baseline on Results of the Primary and Key Secondary Endpoints

Subgroup	End-point	Placebo (N = 13,224)	Vorapaxar (N = 13,225)	HR (95% CI)	Interaction p
		n/J (%) KM%	n/J (%) KM%		
Use: YES	PEP	937/8238 (11.4) 12.9	832/8204 (10.1) 11.7	0.89 (0.81-0.97)	0.869
NO		480/4986 (9.6) 11.6	427/5021 (8.5) 10.5	0.87 (0.77-0.99)	
Use: YES	KSEP	732/8238 (8.9) 10.3	642/8204 (7.8) 9.2	0.88 (0.79-0.98)	0.760
NO		444/4986 8.9) 10.8	386/5021 (7.7) 9.6	0.85 (0.74-0.98)	

Abbreviations: PEP=Primary endpoint; KSEP=Key secondary endpoint

6.1.6.2 Additional Analyses Related to History of Qualifying Events and TIA History

As noted in Sec. **5.3.1.14.2.5**, new analyses were added to the statistical plan in 2011 in connection with the decision to discontinue study drug in subjects with a history of stroke. These included analysis of the Primary and Key Secondary endpoints in the following populations:

- CAD/PAD: subjects who received randomized treatment assignment and whose qualifying condition was either CAD or PAD, regardless of stroke history,
- NSH (No Stroke History): subjects who received randomized treatment assignment and did NOT have a documented prior history of stroke prior to randomization, and
- CAD: subjects who received randomized treatment assignment and whose qualifying condition was CAD (i.e., those with a prior MI),--

analyzed in (a) all of these subjects, regardless of stroke history, and (b) those subjects without a documented prior history of stroke prior to randomization. In addition, several post-hoc analyses of interest were performed and are described below.

Results for the Primary and Key Secondary endpoints in various populations based on qualifying condition and stroke history are provided in **Table 42**. The all subjects ITT analysis and all subgroup analyses in the table other than those for subjects with a history of stroke significantly favored vorapaxar, with the most favorable analyses being those for the CAD (prior MI) population with no history of either stroke or TIA. Note that the "history of stroke" category in the table includes subjects with stroke as the qualifying event and also those in other qualifying event strata with a history of stroke at randomization.

Table 42 TRA 2°P – Results for the Primary and Key Secondary Endpoints in Subgroups Based on Qualifying Event and Stroke or TIA History

ITT Population

Subgroup	End-point	Placebo (N = 13,224) n/J (%) KM%	Vorapaxar (N = 13,225) n/J (%) KM%	HR (95% CI)	p
All subjects	PEP	1417/13224 (10.7) 12.4	1259/13225 (9.5) 11.2	0.88 (0.82 – 0.95)	0.001
All subjects	KSEP	1176/13224 (8.9) 10.5	1028/13225 (7.8) 9.3	0.87 (0.80 – 0.94)	<0.001
History of stroke	PEP	313/2876 (10.9) 16.9	300/2870 (10.5) 15.3	0.94 (0.80 - 1.10)	0.465
History of stroke	KSEP	298/2876 (10.4) 16.4	286/2870 (10.0) 15.2	0.95 (0.80 - 1.11)	0.505
NSH	PEP	1104/10344 (10.7) 11.8	959/10355 (9.3) 10.6	0.86 (0.79 – 0.94)	<0.001
NSH	KSEP	878/10344 (8.5) 9.6	742/10355 (7.2) 8.3	0.84 (0.76 – 0.93)	<0.001
CAD, NSH	PEP	887/8583 (10.3) 11.5	757/8608 (8.8) 10.1	0.84 (0.76 – 0.93)	<0.001
CAD, NSH	KSEP	687/8583 (8.0) 9.1	564/8608 (6.5) 7.7	0.81 (0.73 – 0.91)	<0.001
CAD, NHS/TIA	PEP	867/8439 (10.3) 11.4	719/8458 (8.5) 9.8	0.82 (0.74 - 0.90)	<0.001
CAD, NHS/TIA	KSEP	671/8439 (8.0) 9.0	532/8458 (6.3) 7.4	0.78 (0.70 - 0.88)	<0.001
CAD/PAD,	PEP	1201/10776 (11.1) 12.5	1042/10790 (9.7) 11.0	0.86 (0.79 - 0.93)	<0.001
CAD/PAD	KSEP	968/10776 (9.0) 10.2	816/10790 (7.6) 8.8	0.83 (0.76 - 0.92)	<0.001
CAD/PAD, NHS	PEP	1104/10331 (10.7) 11.9	956/10343 (9.2) 10.5	0.86 (0.79 - 0.93)	<0.001
CAD/PAD, NHS	KSEP	878/10331 (8.5) 9.6	739/10343 (7.1) 8.3	0.84 (0.76 - 0.92)	<0.001
PAD	PEP	245/1895 (12.9) 13.4	233/1892 (12.3) 12.7	0.95 (0.79 - 1.14)	0.567
PAD	KSEP	218/1895 (11.5) 11.9	206/1892 (10.9) 11.3	0.94 (0.78 - 1.14)	0.532
PAD, NSH	PEP	217/1748 (12.4) 12.8	199/1735 (11.5) 11.8	0.92 (0.76 - 1.12)	0.410
PAD, NSH	KSEP	191/1748 (10.9) 11.2	175/1735 (10.1) 10.4	0.92 (0.75 - 1.13)	0.432
PAD, NHS/TIA	PEP	206/1651 (12.5) 12.8	177/1622 (10.9) 11.1	0.87 (0.71 - 1.06)	0.167
PAD, NHS/TIA	KSEP	180/1651 (10.9) 11.1	156/1622 (9.6) 9.8	0.88 (0.71 - 1.09)	0.229

Abbreviations: NSH=subjects with no stroke history; CAD=coronary artery disease stratum; PAD=peripheral arterial disease stratum; CAD/PAD=pooled CAD and PAD strata NHS/TIA=subjects with no history of stroke or TIA; PEP=Primary endpoint; KSEP=Key Secondary endpoint

The analysis of any of NHS/TIA populations was not included in any version of the protocol or revised statistical plan. Thus, the analyses of these populations and the decision to make the CAD NSH/TIA population the sole indicated population in the Applicant's proposed labeling seems likely to have been made after review of the study data. The Applicant suggests that the decision to exclude patients with a prior history of TIA from the labeled indication was based on the inability of a prescriber to know with certainty that a prior neurological event was a stroke or TIA, so the best course of action would be to exclude those with a history of either event. It is thus appropriate to further explore the data for the NHS/TIA population.

Note that the best results among the subgroups in **Table 42** are in the Applicant's proposed label population. However, there are other populations with good results, but only those that include the

large prior MI population have statistically significant results The results are robustly positive for the CAD/PAD population overall and the subset of this population with no stroke history (p <0.001 for both analyses). The results in the overall PAD population alone favor vorapaxar (HR=0.87), but the results are not statistically significant. When prior stroke subjects and then prior stroke/TIA are removed from the analysis, the HR falls to 0.92 and then 0.87, not too much worse than the best analysis in the proposed label population. However the results are still not statistically significant. Notably, the PAD population is just 14% of the overall population, about 1/5 the size of the prior MI population. TRA 2°P was powered to show efficacy of vorapaxar in the entire population, and was clearly not designed to show efficacy in a 14% subset of that population.

Thus, there is an argument that subjects with PAD and no history of stroke or TIA should be included in the indication for use. However, we do not have detailed risk benefit information in that population. We have requested such information from the Applicant.

Table 43 and **Table 44** are displays of stroke and TIA rate in the ITT population subsets of those with a baseline history of stroke (with our without a history of TIA) and those with a history of stroke or TIA, respectively. **Table 45** displays analogous data for the ITT population with a history of TIA but without a stroke history, obtained by subtraction of data in the two tables. Finally, **Table 51** is a display of analogous data from the ITT population without a history of stroke, TIA or both.

Table 43 TRA 2°P – Number of Subjects with Stroke or Transient Ischemic Attack in Subjects with History of Stroke

ITT Population

	Placebo N=2876 n (%)	Vorapaxar N=2870 n (%)	V vs. P HR (95% CI)
Any Stroke	175 (6.1)	192 (6.7)	1.10 (0.89 - 1.34)
Ischemic	158 (5.5)	141 (4.9)	0.89 (0.71 - 1.11)
Hemorrhagic	11 (0.4)	47 (1.6)	4.30 (2.23 - 8.29)
Uncertain	10 (0.3)	10 (0.3)	0.98 (0.41 - 2.37)
TIA	104 (3.6)	69 (2.4)	0.66 (0.49 - 0.89)

Table 44 TRA 2°P – Number of Subjects with Stroke or Transient Ischemic Attack in Subjects with History of Stroke or TIA

ITT Population

	Placebo N=3120 n (%)	Vorapaxar N=3139 n (%)	V vs. P HR (95 CI)
Any Stroke	179 (5.7)	217 (6.9)	1.21 (0.99 - 1.48)
Ischemic	161 (5.1)	163 (5.2)	1.01 (0.81 - 1.25)
Hemorrhagic	12 (0.4)	49 (1.6)	4.10 (2.18 - 7.72
Uncertain	10 (0.3)	11 (0.4)	1.08 (0.46 - 2.55)
TIA	115 (3.7)	73 (2.3)	0.63 (0.47 - 0.84)

Table 45 TRA 2°P – Number of Subjects with Stroke or Transient Ischemic Attack in Subjects with History of TIA but not Stroke

ITT Population

	Placebo N=244 n (%)	Vorapaxar N=269 n (%)	V vs. P Incidence Rate Ratio
Any Stroke	4 (1.6)	25 (9.3)	5.7
Ischemic	3 (1.2)	22 (8.2)	6.7
Hemorrhagic	1 (0.4)	2 (0.7)	1.8
Uncertain	0	1 (0.4)	--
TIA	11 (4.5)	4 (1.5)	0.3

Data obtained by subtracting patient and event counts in **Table 44** from those in **Table 43** and calculation of incidence rate ratios.

Table 46 TRA 2°P – Number of Subjects with Stroke or Transient Ischemic Attack in Subjects Without a History of Stroke or TIA

ITT Population

	Placebo N=10091 n (%)	Vorapaxar N=10084 n (%)	V vs. P HR (95% CI)
Any Stroke	145 (1.4)	98 (1.0)	0.67 (0.52 - 0.87)
Ischemic	118 (1.2)	69 (0.7)	0.58 (0.43 - 0.78)
Hemorrhagic	19 (0.2)	24 (0.2)	1.26 (0.69 - 2.30)
Uncertain	9 (0.1)	9 (0.1)	1.00 (0.40 - 2.51)
TIA	55 (0.5)	48 (0.5)	0.88 (0.59 - 1.29)

The data for subjects with a history of stroke (without regard to TIA history), or a history of TIA without a stroke suggest the following:

- In subjects with a history of stroke with or without TIA:
  - the rate of ischemic stroke numerically favored vorapaxar,
  - the rate of hemorrhage stroke strongly favored placebo
  - the rate of TIA favored vorapaxar
- In subjects with a history of stroke or TIA or with both:
  - the rate of ischemic stroke was similar in the treatment arms
  - the rate of hemorrhagic stroke strongly favored placebo
  - the rate of TIA favored vorapaxar
- In the small subset of subjects with a history of TIA but not stroke:
  - the rate of ischemic stroke strongly favored placebo
  - few subjects had hemorrhagic stroke.

  - the rate of TIA favored vorapaxar y
- In subjects without a history of stroke or TIA:
  - the rate of ischemic stroke was low compared to those with a history of stroke or TIA and favored vorapaxar
  - the rate of hemorrhagic stroke was low and favored placebo, but the observed increase in risk with vorapaxar was modest
  - The rate of TIA was low and numerically favored vorapaxar, but the difference in rates was small

Reviewer comment: The results in the subset of subjects with a TIA history but not a stroke history seem counterintuitive with regard to the effects of vorapaxar on ischemic stroke rate. In subjects with and without a prior stroke, vorapaxar appeared to have a favorable effect on ischemic stroke. Note that subjects with a history of hemorrhagic stroke were excluded from the study, so one would expect most prior strokes to have been ischemic. It is thus hard to understand how in those with TIA without a prior stroke vorapaxar would increase the rate of ischemic stroke. The observed increased rate of this event in the TIA history only subset could be a chance effect. However, a warning against its use in anyone who has had a TIA may be justified if the drug is approved.

Table 47 is a display of results for the Key Secondary endpoint and its components in the ITT and NSH populations that is formatted to understand the effects of deletion of patients with a prior history of stroke on the KSEP and its components. As one would expect, the major contributor to the reduction in HR for vorapaxar vs. placebo when prior stroke subjects are deleted from the analysis is an improvement in the vorapaxar vs. placebo incidence rate ratio (IRR) for stroke. The IRR does not change notably for CV death or MI.

Table 47 TRA 2°P – Comparison of Key Secondary Endpoint Results in ITT and NSH Populations

Population, Treatment (N)	KSEP n (%)	HR V vs. P	CV death n (%)	IRR	MI n (%)	IRR	Stroke n (%)	IRR
ITT, Placebo (13224)	1176 (8.9)	0.87	207 (1.6)	0.85	665 (5.0)	0.83	304 (2.3)	0.98
ITT, Vorapaxar (13225)	1028 (7.8)		175 (1.3)		554 (4.2)		299 (2.3)	
NSH, Placebo (10344)	878 (8.5)	0.84	167 (1.6)	0.84	578 (5.6)	0.84	133 (1.3)	0.86
NSH, Vorapaxar (10355)	742 (7.2)		140 (1.3)		488 (4.7)		114 (1.1)	

Abbreviations: KSEP=Key Secondary endpoint; IRR=Incidence Rate Ration; UCR=Urgent coronary revascularization; ITT= Intent to treat; NSH=no stroke history at baseline
Component counts include only events contributing to the KSEP
Percentages are n of patients with events/N

Information on rates of the Primary and Key Secondary endpoints and their components are displayed in Table 48 for the proposed label population, which is restricted to subjects who qualified for the study with a prior history of MI and who had no baseline history of stroke or TIA

(the CAD NHS/TIA population). The results for both composite endpoints significantly favored vorapaxar. Incidence rate ratios were calculated for the components of the two composite endpoints. MI (the most frequently observed event in these analyses), total stroke, ischemic stroke, UCR and CV death favored vorapaxar. Only hemorrhagic stroke and stroke of uncertain cause favored placebo. The greatest beneficial effect of vorapaxar in terms of risk reduction was on ischemic stroke, followed by total stroke, MI and CV death.

Table 48 TRA 2ºP – Primary and Key Secondary Efficacy Endpoint Results in the CAD NHS/TIA Population

	Placebo N=8439		Vorapaxar N=8458		V vs. P HR (95% CI) IRR	p
	n (%)	KM%	n (%)	KM%		
Any Primary Efficacy Endpoint Event [1]	867 (10.3)	11.4	719 (8.5)	9.8	0.82 (0.74 - 0.90)	<0.001
CV death	96 (1.1)		82 (1.0)		0.85	
MI	451 (5.3)		374 (4.4)		0.83	
Stroke	84 (1.0)		60 (0.7)		0.71	
Ischemic	69 (0.8)		38 (0.4)		0.55	
Hemorrhagic	11 (0.1)		16 (0.2)		1.45	
Uncertain	4 (<0.1)		6 (0.1)		1.50	
UCR	236 (2.8)		203 (2.4)		0.86	
Any Key Secondary Efficacy Endpoint Event [2]	671 (8.0)	9.0	532 (6.3)	7.4	0.78 (0.70 - 0.88)	<0.001
CV death	101 (1.2)		84 (1.0)		0.83	
MI	481 (5.7)		387 (4.6)		0.80	
Stroke	89 (1.1)		61 (0.7)		0.68	
Ischemic	72 (0.9)		39 (0.5)		0.54	
Hemorrhagic	12 (0.1)		16 (0.2)		1.33	
Uncertain	5 (0.1)		6 (0.1)		1.20	

Abbreviations: CAH NHS/TIA=Subjects with prior MI as their qualifying condition and with no prior history of stroke or TIA; KM%= KM estimate of event rate over 1080 days; IRR=incidence rate ratio (calculated by reviewer for components of the composite endpoints).
1 Time to first event of composite of CV death, MI, stroke and UCR
2 Time to first event of composite of CV death, MI and stroke

There is evidence for an interaction between time the time of prior stroke to an intervention that might increase the risk of hemorrhagic stroke.. For example, labeling for alteplase (TPA) includes the following contraindication:

> "Activase therapy in patients with acute ischemic stroke is contraindicated in the following situations because of an increased risk of bleeding, which could result in significant disability or death: ….

> Recent (within 3 months) intracranial or intraspinal surgery, serious head trauma, or previous stroke" (emphasis added).

The Applicant examined the effect of the timing of prior history of stroke (considering the most recent stroke) with respect to randomization on the rate of the Key Secondary Endpoint in subjects in the prior stroke stratum. The following subsets of subjects were examined: those with prior stroke < 3 months before randomization, those with a stroke 3 to 6 months before randomization and those with a stroke > 6 months before randomization. Results for the comparison between vorapaxar and placebo for the Key Secondary Endpoint (without breakdown of the type of event) are provided in **Table 49**.

Table 49 Effect of Timing of Prior Stroke on Rate of Key Secondary Endpoint [1]
Subjects in CVD (prior stroke) stratum, stratified by time of most recent stroke to randomization

Time from most recent stroke to randomization	Placebo		Vorapaxar		V vs. P HR (95% CI)	p
	n/J (%)	KM%	n/J (%)	KM%		
< 3 months	107/1243 (8.6)	11.9%	115/1255 (9.2)	14.4%	1.06 (0.82 – 1.38)	0.66
3 to 6 months	55/733 (7.5)	9.9%	62/706 (8.8)	13.8%	1.20 (0.83 – 1.72)	0.33
> 6 months	45/442 (10.6)	14.7%	31/446 (7.0)	10.1%	0.67 (0.43 – 1.06)	0.09

1 Time to first event of composite of CV death, MI and stroke
Source: Applicant's KM curves with annotations, Figures E-2.18 to E-2.20 (without data on nature of event)

The observed data above suggest that in those with their most recent stroke ≤ 6 months prior to randomization in the prior stroke stratum in TRA 2°P, there was no benefit of vorapaxar for the Key Secondary Endpoint. However, there was a strong trend for a benefit in the subgroup with their most recent stroke more than 6 months prior to randomization.

However, there are reasons to be skeptical of the seemingly beneficial profile of vorapaxar in those with their most recent stroke more than 6 months prior to randomization. This subgroup is considerably smaller than the others, and even though the HR for the Key Secondary Endpoint was 0.67 in this subgroup, the 95% CI was wide and crossed 1.0. In addition, the rate of events in the placebo arm of this timing subgroup was higher than either of the other two timing subgroups. This is the opposite of what one would expect and is inconsistent with the vorapaxar arm data, which show a step-wise reduction in the event rate as the time from prior stroke to randomization increases, rather than the "V" shaped pattern in the placebo arm.

Finally, the data from the TRITON-TIMI 38 trial of prasugrel vs. clopidogrel in subjects with ACS raise concerns. That study showed an increased rate of stroke in subjects in the prasugrel arm compared to control in the subset of subjects with a prior history of stroke. The data for timing of the prior event with respect to randomization (which was a binary choice on the CRF: either less than one year prior or ≥ 1 year prior) suggest that the increased relative risk of stroke with prasugrel vs. control (about 3.5 to 1) was similar in those with prior stroke < 1 year before

randomization and those with prior stoke ≥ 1 year before randomization, although the absolute rates of stroke in both arms were higher in those with more recent prior stroke and the total number of strokes in the prior stroke population was small (14).[6] This relationship may also hold for vorapaxar, even though vorapaxar and prasugrel affect different receptors on platelets and the populations in TRITON and TRA 2°P differed.

> *Reviewer comment: Given the factors noted above, it seems prudent to assume that the risk of CV events in subjects with a prior history of stroke treated with vorapaxar may remain elevated even if the most recent stroke was more than 6 months prior to the start of treatment.*

6.1.6.3 **Efficacy in US patients only**

Key efficacy results for the US ITT and CAD NHS/TIA populations are shown in **Table 50**. Hazard ratios for the Primary endpoint, Key Secondary endpoint and all-cause mortality US results were directionally similar in pattern to the global results (compare to **Table 32** and **Table 34**).

[6] Incidence rates for ICH and ischemic stroke during the study (prasugrel vs. control) with median treatment of 14.5 months were: in subjects with prior stroke < 1 year before randomization: ICH 1/17 vs. 0/20, ischemic stroke 3/17 vs. 1/20; in those with stroke ≥ 1 year prior to randomization: ICH 4/164 vs. 0/140, ischemic stroke 4/164 vs. 1/140.

Table 50 TRA 2ºP - US Patients – Key Efficacy Results
ITT Population and Proposed Label Populations, followed to last visit
(Includes US and Puerto Rico)

	Placebo		Vorapaxar		HR (95% CI)
Analysis	n (%)	KM%	n (%)	KM%	
ITT POPULATION	**N=2971**		**N=2973**		
Primary Efficacy Endpoint	443 (14.9)	16.8	427 (14,4)	16.0	0.95 (0.83 - 1.00)
Key Secondary Endpoint	342 (11.5)	13.2	315 (10.6)	12.2	0.91 (0.78 – 1.06)
All-cause Mortality	161 (5.4)	-	142 (4.8)	-	-
CAD NHS/TIA POPULATION*	**N=1904**		**N=1923**		
Primary Efficacy Endpoint	277 (14.5)	15.8	251 (13.1)	14.8	0.88 (0.74 – 1.05)
Key Secondary Endpoint	200 (10.5)	11.6	165 (8.6)	10.0	0.81 (0.66 – 0.99)
All-Cause Mortality	67 (4.1)	-	55 (2.9)	-	-

* Prior MI stratum with no history of prior stroke or TIA. This is the proposed label population
KM% is 3 year estimate

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dosing regimen of vorapaxar was evaluated in TRA 2ºP, the primary study supporting efficacy for the proposed indication – 2.5 mg orally once daily.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Kaplan Meier curve for time to the Key Secondary efficacy endpoint in TRA 2ºP suggests that efficacy is maintained with continued treatment for up to 3 years (**Figure 9**). **Table 51** is a display of cumulative KM rates over time for the secondary endpoint. Rates in the treatment arms are already diverging at 30 days after randomization. The difference between the arms in favor of vorapaxar reached 1% by 540 days (1.5 years) and reached a maximum extent of divergence of 1.2% at 900 days (2.5 years), which was maintained to 1080 days (3 years). Note that the Key Secondary endpoint data were selected for display in lieu of the Primary endpoint because the final HR was slightly lower for this endpoint than for the primary. These data suggest that efficacy was maintained for at least 1.5 years and possibly considerably longer. There is no way of knowing whether the difference in event rates between vorapaxar and placebo would be maintained or lost if study drug were discontinued after the point that the curves for the two treatment arms stopped diverging.

Table 51 TRA 2ºP – Key Secondary Endpoint Results by Days from Randomization
ITT Population

	Placebo (N=13,224)			Vorapaxar (N=13,225)		
Event Window (days after randomization)	KM %	N with events	N at risk	KM %	N with events	N at risk
0 – 30	0.5%	66	13107	0.4%	47	13138
0 – 180	2.4%	321	12727	2.1%	274	12784
0 – 360	4.2%	552	12364	3.6%	469	12479
0 – 540	5.9%	761	12013	4.9%	644	12162
0 – 720	7.3%	935	9366	6.4%	814	9463
0 – 900	8.9%	1072	6239	7.7%	926	6287
0 – 1080	10.5%	1153	2751	9.3%	1008	2788

KM% is cumulative at each time point
N at risk was assessed on the last day of each event window.

6.1.9 Additional Efficacy Issues/Analyses

6.1.9.1 Protocol Amendment: Discontinuation of Subjects with a History of Stroke and Related Analyses

General Amendment 3 of the TRA 2ºP protocol, dated March 10, 2011 was the result of the events and planned analyses of the final study results triggered by a letter dated January 8, 2011 from the DSMB to the study chair recommending that study drug should be discontinued subjects with a history of stroke, including those who experienced a stroke after randomization, while the study should proceed as planned for other subjects. Many of the events described in the amendment had already occurred by the time the protocol was amended.

Relevant text in the letter from the DSMB Chair is reproduced below:

"The combined Data Safety and Monitoring Board (DSMB) of the
TRA•CER and TRA2P – TIMI 50 studies met face-to-face January 8,
2011. After considering all data of both trials the DSMB recommends the following:

1. Discontinuation of study drug in subjects with a history of stroke in the TRA2P -TIMI 50 trial and continuation of the study drug as planned in all other subjects in TRA2P-TIMI 50. Discontinuation of study drug in subjects with prior stroke in TRA2P – TIMI 50 includes stroke occurring pre and post randomization.
2. Discontinuation of study drug in all subjects in TRA•CER, and close-out of the trial."

Reviewer comment: The discussion here will focus in TRA 2ºP.[7]

The Board's recommendation regarding TRA 2ºP was based on its ongoing, unblinded follow-up of bleeding data, including intracranial hemorrhage (ICH) in both TRA 2ºP and TRA•CER.

Information from the DSMB minutes regarding the number ICH events in the TRA 2ºP treatment arms over the course of the study is shown in **Table 52.** For brevity, only the total enrolled and number of ICH events in each arm is provided; randomization was 1:1 and the N in each treatment arm was similar at each meeting. There were 8 regularly scheduled meetings and 3 additional unscheduled meetings, noted by (a) in first column, that were called by the DSMB chair to evaluate accrued cases of ICH. Meeting 1 was to some extent an organizational meeting; no study data were provided in the meeting minutes.

Table 52 TRA 2ºP DSMB Meeting Minutes: Intracranial Hemorrhage (ICH) – "Best Available" Data by Treatment

Meeting No.	Date	Total N	Patients with ICH – Vorapaxar n	Patients with ICH – Placebo n
1	2/11/2008	-	-	-
2	5/9/2008	2725	No data	No data
3 (a)	9/11/2008	6481	3	3
4	2/12/2009	>15,000	9	9
5	5/25/2009	>19,000	19	13
6	9/30/2009	< 25,000	27	17
7	2/24/2010	26,449	47	30
8	6/26/2010	26,449	61	42
9 (b)	10/20/2010	26,448	(b)	(b)
10 (a)	12/15/2010	-	No data	No data
11 (a, c)	1/8/2011	26,448	90	50

(a) Unscheduled meeting called to evaluate cases of ICH
(b) No data were provided on the number of ICH events. HR (V vs. P) was 1.39 (0.89, 2.18) for adjudicated data.
(c) Adjudicated data for ICH: 51 vs. 39 cases in the vorapaxar and placebo arms, respectively.

There was an excess of ICH events in the vorapaxar arm by Meeting 5 in May, 2009. The divergence in the count of ICH events became more prominent at the next meeting in September 2009 and remained prominent through the end of the study.

[7] The DSMB's recommendation to close out TRA•CER was made on the same day they recommended discontinuation of study drug in prior stroke patients in TRA 2ºP. The TRA•CER recommendation was based on the facts that the study had nearly reached its event target and did not have statistically significant results for the primary endpoint.

At Meeting 7 in February 2010 when the formal interim analysis results were discussed, the DSMB minutes note that in the subset of subjects with a prior history of stroke the rates of ICH were 1.3% vs. 0.8% in the vorapaxar and placebo arms, respectively. In analogous subjects without a prior history of stroke the ICH rates were 0.3% vs. 0.2%. Results for the primary endpoint were as follows: There were 768 adjudicated primary endpoint events. KM event rates were 4.0% and 3.3% in the placebo and vorapaxar arms, respectively (HR=0.90, 95% CI: 0.78, 1.03, p=0.133). The Board determined that the study should continue as planned.

At Meeting 8 in June 2010, the minutes indicate that there were 20 vs. 8 fatal ICH events in the vorapaxar and placebo arms, respectively.

Meeting 9 in October 2010 was the last scheduled meeting. The number of ICH events was not provided in the minutes. However, the minutes state that the hazard ratio for ICH (vorapaxar vs. placebo) was 1.39 (CI, 0.89, 2.18, (Percentage level of CI not given)) for adjudicated data. The minutes state "The Board suggests closely monitor the study and continuing review ICH events [sic]."

Meeting 10 was an unscheduled telephonic meeting on December 15, 2010 held because of "increased ICH cases" reported to the TRA 2ºP DSMB Chair by the TRA 2ºP Study PI. There were no data provided in the minutes, which indicate that the Board planned a subsequent face-to-face meeting shortly to discuss ICH.

Meeting 11 occurred a few weeks later on January 8, 2011. It was noted that, "This meeting is triggered by an increased number of intracranial hemorrhage recently (17 new cases since the last DSMB meeting on Oct. 2010)." A relatively rich set of unblinded data, including primary endpoint event rates with components, bleeding rates, and ICH rates, was prepared for this meeting. Data for event rates by treatment arm in subsets of patients based on prior stroke history were also provided. The data indicated the following:

- The adjudicated primary endpoint data favored vorapaxar: 726 vs. 848 events (total of 1574), HR=0.85 (0.77, 0.94), with 89% of target endpoint events accrued and 80% of these adjudicated; "best available" primary endpoint data, with a total of 2011 events, were consistent with adjudicated data in terms of HR.
- Each adjudicated component of the primary endpoint numerically favored vorapaxar, with MI having the most favorable results:
    - CV death: 183 vs. 212
    - MI: 382 vs. 461
    - Stroke: 250 vs. 257
    - Urgent coronary revascularization: 228 vs. 277
- There was excess bleeding in the vorapaxar arm: for adjudicated GUSTO severe bleeding, the HR=1.50 (1.16, 1.94); results for TIMI major bleeding were directionally similar.
- ICH also favored placebo: 51 vs. 39 adjudicated events, HR = 1.31 (0.86, 1.98). For best available data, there were 90 vs. 50 events, HR= 1.80 (1.27, 2.54). Most of the ICH cases were determined to be intracerebral hemorrhage.
    - In subjects with a baseline history of ischemic stroke (total N=4881; best available data), the count of ICH events was 49 (1.78%) vs. 18, (0.6%), HR=2.71 (1.58, 4.65). Overall mortality was similar between the 2 arms, 101 (3.6%) vs. 100 (3.5%),

HR=1.00. There were 236 (8.3%) vs. 251 (8.8%) primary endpoint events in the two arms (HR= 0.94 (0.78, 1.12).

- In subjects with no stroke history (N=21567), there were 46 (0.4%) vs. 34 (0.3%) events, HR=1.28 (0.81, 2.03). Mortality was similar in the two arms: 257 (2.5%) vs. 276 (2.7%), HR=0.93 (0.70, 1.1). Data on primary endpoint counts in each of the two arms were not provided, but the total count was 1524 primary endpoint events and the HR between the treatment arms was 0.86 (0.77, 0.95), favoring vorapaxar.

Reviewer comment: The above data are from the 11th DSMB meeting minutes; data tables prepared by DCRI and provided in the NDA have minor but unimportant differences from the above data.

The Board additionally noted the following:

- The overall data indicated an advantage for vorapaxar over placebo for the primary endpoint, and numerical advantages for MI, stroke, CV death and all-cause death, suggesting that the trial should continue
- Data in patients with a history of stroke showed no efficacy benefit to compensate for the increased risk of ICH
- The Board concluded that patients with a stroke prior to or after randomization should discontinue study treatment. The study should continue in other subjects without further modification to the protocol.

As noted earlier, on January 8, 2010, the Board communicated its recommendations to the study chair, Eugene Braunwald, who served as chair of the Steering Committee, as well as the 3-person Executive Committee. The latter group had responsibility for reviewing, evaluating, and implementing recommendations of the DSMB through protocol changes and communications to investigators. The Executive Committee and the Sponsor accepted the recommendations of the DSMB, and began communications to implement the recommendations to the sites on January 13, 2013. The protocol was later changed to reflect the changes described below:

The essence of these communications was as follows:

- Regarding study drug:
  - All patients with a prior history of stroke or a stroke after randomization (including those in the CAD and PAD strata) were to discontinue study drug immediately
  - Other patients were to continue study drug
- Regarding follow-up:
  - Subjects in the CVS (stroke) stratum taking study drug on Jan 13, 2013, but with no stroke after randomization were to have their final study visit ASAP. The sites were instructed record in the CRF spontaneously reported “serious medical events” up to 60 days after discontinuing study drug, but the site did not reach out to these patients after the final visit.
  - Subjects in the CVS stratum taking study drug on Jan 13, 2013, but with a stroke after randomization, were have an early discontinuation of study drug visit and a telephone follow-up at the end of the study.
  - Subjects in the CVS stratum who discontinued treatment before Jan 13, 2013 and those who never took study drug who had no stroke after randomization were have a final telephone contact ASAP. The sites were instructed record in the CRF

spontaneously reported “serious medical events” up to 60 days after discontinuing study drug, but the site did not reach out to these patients after the final telephone call.

- Subjects in the CVS stratum who discontinued treatment before Jan 13, 2013 and those who never took study drug and had a stroke after randomizations were have a final telephone contact at the end of the study.
- Subjects in the CAD or PAD strata with no prior history of stroke and no stroke after randomization who were taking study drug on Jan 13, 2011 were to continue study visits per protocol.
- Subjects in the CAD or PAD strata with either a prior history of stroke or a stroke after randomization who discontinued study drug before Jan 13, 2011 or who never took study drug, and were still being followed were to have continued telephone contacts per protocol. .

Reviewer comment: The minutes of DSMB meetings suggest that the DSMB did its job of protecting study subjects and to the extent possible, the integrity and power of the study. The recommendations in the Jan 8. 2011 letter to the study chair seem reasonable. Note the DSMB's recommendations in the letter regarding TRA 2ºP concerned only discontinuation of study drug; the recommendations do not mention follow-up at all. Also, no rationale for the recommendations was provided in the letter.

The decisions of the Executive Committee and the Sponsor to discontinue treatment in subjects with a history of stroke before or after randomization also seem reasonable. However, the follow-up rules had the effect of cutting off follow-up for most patients at high risk of stroke who might have contributed events to the primary endpoint analysis, while continuing to follow-up patients who could no longer contribute events to the primary endpoint analysis because they already had had a stroke after randomization. It is notable the long terminal half-life of vorapaxar and slow offset of effect would have increased the risk of bleeding for many days after the last dose of study drug. While capturing these post-discontinuation events might have affected the study outcome, the effect would likely have been very small. While vorapaxar increases the risk of ICH, it seems to reduce the risk of ischemic stroke somewhat. Most importantly, the study data supported removal of patients with a prior history of stroke from treatment because of a demonstrated increase the risk of ICH in the vorapaxar arm. Continuing to follow those patients might result in more ICH events in the vorapaxar arm, thus reinforcing the existence of a risk that was already quite clear. However, once the DSMB recommended withdrawal of study drug from patients with a history of stroke in January 2011, it would have been quite clear to the study team that if vorapaxar were to be approved eventually, its labeling would be very likely to warn against or contraindicate use in patients with a prior history of stroke, like the labeling of prasugrel, which had been approved in July 2009. Continued follow-up of subjects of with a stroke history but without a stroke after randomization would only confound the study's ability to provide information the effects of vorapaxar in patients without a stroke history, including those in the proposed labeled population. It is also reassuring that despite the increased rate of ICH in the vorapaxar arm, there was a numerical benefit for total stroke for vorapaxar in the scheduled interim analysis, at the time of the DSMB's subsequent review of the data that led to the recommendation regarding patients with a history of stroke, and again in the final study analysis.

7 Review of Safety

Safety Summary

Nearly all the clinical safety data for vorapaxar comes from the two Phase 3 CV studies, TRA•CER and TRA 2ºP. The only safety risk of substantial concern is bleeding. The Applicant presented bleeding data from TRA 2ºP as well as TRA•CER, a 13,000 patient ACS treatment study that missed its primary endpoint. There was also pooled bleeding and other AE data from the two studies, with bleeding data from the first 30 days of TRA•CER were omitted from the pool because of the high rates of bleeding associated with interventions such as PCI and CABG in the initial hospitalization for ACS, along with associated use of injectable anticoagulants and antiplatelet agents. The data for general bleeding risk are fairly consistent across these 3 sources of information, and data from TRA 2ºP will be emphasized here.

Data for bleeding events in TRA 2ºP (all patients) from the first dose of study drug to last dose + 30 days are shown in **Table 3**. A clear increase in the rate of bleeding with vorapaxar is evident across all general bleeding categories, including the two designated major bleeding endpoints, (1) the composite of GUSTO Severe and Moderate bleeding and (2) TIMI Clinically Significant bleeding. Note all subjects in TRA 2°P are included in this analysis including those with a history of stroke, who were at substantially increased risk for ICH and fatal bleeding (driven by fatal ICH) than those with no history of stroke. In addition, patients with a history of TIA but no history of stroke had an increased rate of stroke (mostly ischemic stroke) with vorapaxar compared to placebo. In the Applicant's Proposed Label Population of subjects with a prior MI and no history of stroke or TIA, general bleeding rate data was somewhat lower than the rates for the overall to population, but vorapaxar vs. placebo hazard ratios were similar (**Table 4**). However, the rate of ICH was relatively low in the proposed label population, but was still higher with vorapaxar than placebo, although the point estimate for the hazard was closer to 1 than in the overall TRA 2ºP results and difference was not statistically significant. The rate of fatal bleeding was also low in the proposed label population.

Table 53 TRA 2°P – Analysis of Time to Bleeding Events
As-Treated Population followed from first dose to last dose + 30 days

	Placebo N=13166		Vorapaxar N=13186			
	n with events (%)	KM%	n with events (%)	KM%	HR (95% CI)	p
GUSTO CATEGORIES						
Severe or Moderate	258 (2.0)	2.5	424 (3.2)	4.1	1.67 (1.43 - 1.94)	<0.001
Severe	115(0.9)	1.1	168 (1.3)	1.7	1.47 (1.16 - 1.87)	0.001
Moderate	147 (1.1)	1.4	263 (2.0)	2.6	1.81 (1.48 - 2.22)	<0.001
TIMI CATEGORIES						
Major or Minor	283 (2.1)	2.7	449 (3.4)	4.3	1.61 (1.38 - 1.86)	<0.001
Clinically Significant Bleeding	1226 (9.3)	11.1	1735 (13.2)	15.7	1.46 (1.35 - 1.57)	<0.001
Major CABG-Related	11 (0.1)	0.1	10 (0.1)	0.1	0.92 (0.39 - 2.16)	0.845
OTHER CATEGORIES						
Intracranial Hemorrhage	51 (0.4)	0.5	97 (0.7)	0.9	1.91 (1.36 - 2.69)	<0.001
Fatal Bleeding	18 (0.1)	0.2	27 (0.2)	0.3	1.51 (0.83 - 2.74)	0.176

KM% over 1080 days

Table 54 TRA 2°P – Analysis of Time to Bleeding Events
As-Treated Proposed Label Population followed from first dose to last dose + 30 days

	Placebo N=13166		Vorapaxar N=13186			
	n with events (%)	**KM%**	**n with events (%)**	**KM%**	**HR (95% CI)**	**p**
GUSTO CATEGORIES						
Severe or Moderate	139 (1.7)	2.0	212 (2.5)	3.0	1.54 (1.24 - 1.90)	<0.001
Severe	62 (0.7)	1.0	74 (0.9)	1.1	1.20 (0.86 - 1.68)	0.287
Moderate	79 (0.9)	1.1	142 (1.7)	2.0	1.81 (1.38 - 2.38)	<0.001
TIMI CATEGORIES						
Major or Minor	159 (1.9)	2.3	237 (2.8)	3.4	1.50 (1.23 - 1.84)	<0.001
Clinically Significant Bleeding	748 (8.9)	10.2	1081 (12.8)	14.8	1.48 (1.35 - 1.63)	<0.001
Major CABG-Related	6 (0.1)	0.1	6 (0.1)	0.1	1.01 (0.33 - 3.13)	0.988
OTHER CATEGORIES						
Intracranial Hemorrhage	25 (0.3)	0.4	36 (0.4)	0.5	1.44 (0.87 - 2.40)	0.160
Fatal Bleeding	9 (0.1)	0.1	12 (0.1)	0.2	1.34 (0.56 - 3.17)	0.511

KM% over 1080 days

The findings in TRA 2°P related to a history of prior stroke and TIA are analogous to the prasugrel experience in ACS subjects. If vorapaxar is approved, it merits a contraindication in patients with a history of prior stroke or TIA, similar to prasugrel.

It is notable that hazard ratios for TIMI CABG-related bleeding are near 1.0 in the overall and Proposed Label Populations of TRA 2ºP. The ACS trial, TRA•CER, with many more CABG procedures due to the nature of the patient population, showed a similar pattern. Preclinical data

suggest that vorapaxar might not increase the risk of surgical bleeding, and investigators were given the option of continuing study drug up to the time of surgery. More often than not, study drug was discontinued no later than 2 days prior to surgery. Vorapaxar vs. placebo hazard ratios for CABG bleeding were similar for patients whose study drug was stopped no more than 2 days prior to surgery compared to those whose study drug was stopped at least 3 days prior to surgery. However, our ability to write instructions for use of vorapaxar in the setting of surgery is complicated by the incomplete data regarding when other antiplatelet medication was discontinued with respect to surgery.

In both TRA 2°P and TRA•CER, there was a slight excess of adjudicated non-Cardiovascular death. This seemed to driven by an excess of death related to solid tumors, although the number of AEs related to solid tumors was higher in only TRA•CER (see **Table 59** and **Table 63**). However, overall death in the secondary prevention trial TRA 2°P numerically favored vorapaxar.

7.1 Methods of Safety Analysis

7.1.1 Overall Analysis Scheme

The Applicant's summary of clinical safety (SCS) includes information from two Phase 3 outcomes trials with a total of 43,208 treated subjects (21,575 placebo, 21,630 vorapaxar). The two studies were TRA 2ºP, a secondary prevention study subjects in with recent MI, recent stroke, or peripheral arterial disease, and TRA•CER, a study in subjects with NSTEMI ACS.

The two studies were analyzed individually and together. For analysis of bleeding events, the Applicant created a "Chronic Pool" from which included (1) the entirety of TRA 2°P bleeding information and (2) TRA•CER bleeding information excluding the first 30 days after randomization, when bleeding risk would be expected to be higher than during the rest of trial due to the use of multiple antithrombotic drugs in the hospital, invasive cardiac procedures. For analyses of non-bleeding events, the trials were pooled without exclusion of safety information.

Information from Phase 1 and Phase 2 studies was provided, but the amount of exposure in those trials is dwarfed by the Phase 3 information (see xx). In addition, there was a small ocular safety study imbedded in TRA 2°P (see xx).

For a discussion of prospectively specified safety endpoints in the TRA 2°P, which were all related to bleeding, see Sec. **5.3.1.9**. Safety procedures in TRA 2°P are described in Sec. **5.3.1.10**.

Reviewer Comment: The Phase 3 pooling strategy is reasonable and was agreed to by FDA at the pre-NDA stage. Notably, TRA 2°P, with more than 13,000 subjects and over 25,000 patient-years of exposure in each of the vorapaxar and placebo treatment arms, has sufficient exposure to support an NDA by itself.

The study design and safety monitoring plans of both trials were similar and appropriate for large antithrombotic trials.

Table 55 Patients Exposed in Studies of Vorapaxar Included in the Safety Summaries

Study or Grouping	Placebo N (Median exposure)	Vorapaxar N (Median Exposure)	Total N
TRA 2°P Proposed Label Population	8412 (907)	8444 (966)	16856
TRA 2°P All subjects	13166 (905)	13186 (906)	26352
TRA•CER All subjects	6441 (481)	6446 (482)	12887
POOLED PHASE 3 [1]	19607	19632	39239
PHASE 2 (3 studies)	308 (see text)	929 (see text)	1237
PHASE 1 (21 studies)	-	1060 (see text)	1060
ALL STUDIES [2]	19915	21621	41536

Exposure time is measured in days.
[1] Pooled Phase 3 bleeding data, but not data for non-bleeding AEs, exclude the first 30 days of treatment in TRA•CER due to the expected high rate of bleeding during that period in patients with ACS. Patients in TRA•CER who were treated for ≤30 days are thus excluded completely from the pool.
[2] Total for all studies includes all patients in TRA•CER.

The placebo-controlled Phase 2 studies included 2 studies in patients with ACS (1147 subjects in all, with loading doses as high as 40 mg and daily maintenance doses as high as 2.5 mg) and one study in 90 patients who had had a stroke and were treated with vorapaxar doses as high as 2.5 mg daily. In each the Phase 2 studies drug was to be administered for 60 days. More than 80% of subjects received at least 55 days of study treatment, and exposure was similar in the treatment arms. Data from these studies were not pooled for the safety analysis.

A total of 1215 subjects were included in Phase 1 studies, 1060 of whom received vorapaxar. There were 105 randomized to placebo and 130 randomized to other therapy; some subjects received more than one treatment. Exposure in 9 of the 21 Phase 1 studies ranged from a single dose to 7 days; the latter include vorapaxar doses as high as 7.5 mg daily. Some of the studies had loading doses or final doses as high as 40 mg daily. One of the two remaining studies had 21 days of dosing at a rate of 2.5 mg daily and an ocular safety study included patients with 1, 2, or 3 months of dosing at a rate of 2.5 mg po once daily. All or nearly all subjects completed treatment in each of the studies. Six of the studies were biopharmaceutic studies and were not pooled. Data from the other 15 studies (clinical pharmacology studies) were pooled for safety analysis.

Thus, 91% of subjects exposed to vorapaxar were in TRA 2°P or TRA•CER. Because persons were treated for a median of more than 2 years and one year, respectively in those trials, the two Phase 3 trials provide more than 91% of the of the total explore to vorapaxar. Consequently, results of the Phase 3 trials, and TRA 2°P in particular, will be the focus of this review.

The duration and extent of exposure in the vorapaxar clinical program is adequate for review, even if only TRA 2°P is considered.

7.1.1. Studies/Clinical Trials Used to Evaluate Safety

The Applicant's primary safety sources are TRA 2ºP (P0437) and TRA•CER (P0436). The trials are described in **Sec 5.3.1** Protocol P04737 and **Sec 5.3.2** (TRA•CER). The reviewer's safety analysis focused primarily on data in TRA 2ºP (rather than TRA•CER). Both trials assessed the same safety endpoint, however TRA 2ºP contained twice the number of subjects, treated subjects about one year longer, and treated the target population of post-MI patients, while TRA•CER involved ACS subjects, who would be expected to have a higher rate of bleeding during the early stages of treatment. Nonetheless, exposure in TRA•CER was substantial and patients were treated sufficiently long after their MI so that period of exposure after MI overlapped extensively with the exposure period in TRAP. Analysis of TRA•CER thus should be part of the safety evaluation.

7.1.2 Categorization of Adverse Events

Study procedures regarding AEs were similar in TRA 2°P and TRA•CER. Adverse events were coded and grouped into preferred terms by System Organ Class (SOC) using the Medical Dictionary of Regulatory Activities (MedDRA) version 14.0 for TRA•CER and MedDRA version 14.1 for TRA 2ºP and the Applicant's integrated summaries. The Applicant reports that the variable AETERM in the AE dataset contains verbatim terms, while AEDECODE is the assigned Preferred Term (PT).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

See **Methods**.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Dosing in the Phase 3 studies was entirely at the rate of 2.5 mg po daily. The size of the as-treated population is only a few patients shy of the ITT population in each of the two Phase 3 studies, so the demographics can be assumed to similar.

7.2.2 Explorations for Dose Response

This is discussed in Sec **6.1.7**.

7.2.3 Special Animal and/or In Vitro Testing

Non-clinical testing was adequate to explore potential adverse reactions. There is a brief summary in **Sec 4.3**. See Dr. Harlow's PT review for more information.

7.2.4 Routine Clinical Testing

At each visit, ascertainment of clinical events for adjudication was done and is described in **Sec 5.3.1.7.1**. At each study visit, blood for a CBC and typical renal and liver function test was drawn. At the first visit, last visit and yearly in between, additional safety testing (an "extended safety panel" was performed. ECGs were obtained on the same schedule as the extended safety panel.

7.2.5 Metabolic, Clearance, and Interaction Workup

This was summarized in Section 4.4 Clinical Pharmacology

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The identification of AEs in TRA 2ºP appeared to be reasonable. The SAEs specific for this drug class are included in those that were adjudicated and those methods have been discussed. . The only potential safety risk other than bleeding identified before the start of the Phase 3 program was ocular toxicity, which was evaluated in TRA 2°P in a substudy (see xx).

Note that bleeding and all efficacy endpoints (MI, stroke, and death from any cause) were not considered to be adverse events. Non-bleeding AEs are termed "other" adverse events by the Applicant.

7.3 Deaths

Mortality data were analyzed separately in the two Phase 3 studies.

7.3.1 TRA 2°P

Mortality was an efficacy endpoint, so it is discussed in **Sec 6.1.5.1**, where data on CV death and all-cause death from randomization to the last visit are presented. However, the discussion there has no information on specific cause of death other than ICH; such information is provided below.

Death during the period of the first dose of study drug to last dose + 60 days is summarized below. This is intended to capture deaths that might reasonably be associated with study drug, given the long elimination half-life of vorapaxar and the tendency of investigators to discontinue or interrupt study drug in subjects who become critically ill.

There were 3 potential sources of death information in the case record: (1) the death/survival page ("death page"), (2) specific event pages (stroke, cardiac ischemia, bleeding events, and non-bleeding ("other") AEs, and (3) the adjudication results. Information on these pages follows:

1. The death page was to be completed for each death. It had check boxes for CV and non-CV death, pull-down menus with check boxes for various causes of CV death as well as free text fields where other causes of CV or non-CV death could be entered, and also extended narrative fields.
2. The individual event pages had a check box for fatal results of the event, along with a reminder to complete the death page.
3. All deaths were to be adjudicated centrally, but the adjudication results were often of limited value in understanding cause of death. All deaths were adjudicated as either "fatal bleeding" or "not fatal bleeding." In addition, cause of death was adjudicated as cardiovascular, non-cardiovascular or "unknown." Death was to be classified as unknown only if there was no information regarding the facts of death. If the death was considered either unknown or non-cardiovascular, there was no further specificity as to cause. If a death was adjudicated as a CV death, it was further classified to one of four categories:

    - Sudden CV death - witnessed
    - Sudden CV death - unwitnessed
    - Unwitnessed CV death
    - Non-sudden CV death

    Beyond these broad categories, there was no further classification of cause of death.

Table 56 provides information on the source of death information and cause of death during treatment (here defined as first dose to last dose + 60 days). Adjudication results are not incorporated into this analysis.

Table 56 Deaths on Treatment
Treated patients followed to last dose + 60 days

	Placebo N=13166 n (%)	Vorapaxar N=13186 n (%)
DEATHS FROM DEATH / SURVIVAL PAGE (Total deaths)	368 (2.8)	349 (2.6)
DEATHS FROM INDIVIDUAL CRF PAGES	274 (2.1)	263 (2.0)
ADVERSE EVENT PAGE	172 (1.3)	174 (1.3)
BLEEDING PAGE	24 (0.2)	38 (0.3)
MI PAGE	83 (0.6)	56 (0.4)
STROKE PAGE	25 (0.2)	36 (0.3)
TOTAL NUMBER OF DEATHS FROM DEATH / SURVIVAL PAGE AND NOT IN INDIVIDUAL CRF PAGE	94 (0.7)	86 (0.7)
ADVERSE EVENT	2 (<0.1)	1 (<0.1)
CLINICAL EVENT EFFICACY/SAFETY ENDPOINT	21 (0.2)	23 (0.2)
PROCEDURE-RELATED COMPLICATIONS	-	-
DISEASE-RELATED COMPLICATIONS	23 (0.2)	13 (0.1)
OTHER	42 (0.3)	41 (0.3)
MISSING	6 (<0.1)	8 (0.1)

There were more deaths with placebo on treatment than with vorapaxar (368 vs. 349). Fatal MIs substantially favored vorapaxar, while fatal strokes and fatal bleeding (not necessarily mutually exclusive) favored placebo, based on the dedicated pages for those events. Fatal “adverse events” (here denoting non-bleeding AEs, but not otherwise explained in this table) were similar in the two arms. The 5 rows in the table immediately above “MISSING” regarding deaths that were noted only on the death page correspond to mutually exclusive check box categories on that page.

Table 57 TRA 2°P – Adjudicated Deaths in Treated Patients
Treated patients followed as indicated

	Deaths to last dose + 60 days		Deaths to last visit*	
	PLACEBO N=13166 n (%)	VORAPAXAR N=13186 n (%)	PLACEBO N=13166 n (%)	VORAPAXAR N=13186 n (%)
ALL DEATHS	368 (2.8)	349 (2.6)	565 (4.3)	536 (4.1)
CV DEATHS	241 (1.8)	209 (1.6)	319 (2.4)	283 (2.1)
FATAL BLEEDING	11 (0.1)	25 (0.2)	16 (0.1)	31 (0.2)
NON-CV DEATHS	127 (1.0)	140 (1.1)	246 (1.9)	253 (1.9)
FATAL BLEEDING	9 (0.1)	4 (<0.1)	11 (0.1)	7 (0.1)

*An additional 43 and 39 treated patients in the placebo and vorapaxar arms respectively, died after their last visit but before database lock.
Source: Reviewer analysis of Applicant dataset P04737 ENDPTS.XPT & Applicant analysis

Table 57 displays adjudication results for deaths on treatment, with deaths captured to last dose + 60 days or to the last study visit. With follow-up to last dose + 60 days, all cause death and CV death favor vorapaxar, while non-CV death favors placebo, 127 to 140. The difference at last dose + 60 days appears to be driven by deaths due to solid tumors (39 vs. 56, based on the investigator's assessment of cause of death; data not shown for this subgroup). There were 8 deaths due to hematologic malignancy or dysplasia in each arm. By the last study visit, the number of deaths was considerably larger in each arm. All cause death and CV death still favor vorapaxar, while non-CV death is similar (246 vs. 253). Note that the breakdown for CV and non-CV death and death related to neoplasms is somewhat different when the investigator's classification of death is used (**Table 58**). For more information on deaths due to neoplasms, see **Table 59.**

As noted above, the cause of death was to have been noted on the death page by the investigator. We asked the Applicant to perform an analysis of the MedDRA terms were assigned by the Applicant to each death based on the free text and pull-down menu information on the death page form (**Table 58**). Note that rows for each MedDRA System Organ Class (SOC) include all deaths with terms in that SOC, but rows for individual High Level Group Terms (HLGTs) are included only for HLGTs with at least 10 deaths in either treatment arm. Percentage rates appear to be based on the randomized population, although the death count includes treated patients only (N=13166 and 13186 for placebo and vorapaxar, respectively). The difference in rates between the TRA 2°P methods of calculation, if any, would be no be expected to be no more than 0.1% for any event.

Table 58 TRA 2°P - Deaths on Treatment by SOC and HLGT
Includes all deaths to last dose + 60 days in all SOCs each and each HLGT with at least 10 deaths in either treatment arm (Investigator information)

SOC HLGT	Placebo N=13224 n (%)	Vorapaxar N=13225 n (%)
ALL DEATHS	367 (2.8)	349 (2.6)
CARDIOVASCULAR DEATHS (per Investigator)	**193 (1.5)**	**185 (1.4)**
CARDIAC DISORDERS	124 (0.9)	95 (0.7)
CARDIAC ARRHYTHMIAS	28 (0.2)	25 (0.2)
CORONARY ARTERY DISORDERS	58 (0.4)	38 (0.3)
HEART FAILURES	35 (0.3)	29 (0.2)
GASTROINTESTINAL DISORDERS	1 (<0.1)	1 (<0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	43 (0.3)	45 (0.3)
FATAL OUTCOMES	43 (0.3)	42 (0.3)
INFECTIONS AND INFESTATIONS	1 (<0.1)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (<0.1)	6 (<0.1)
METABOLISM AND NUTRITION DISORDERS	0	1 (<0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	1 (<0.1)	3 (<0.1)
NERVOUS SYSTEM DISORDERS	10 (0.1)	18 (0.1)
CENTRAL NERVOUS SYSTEM VASCULAR DISORDERS	10 (0.1)	18 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	7 (0.1)	4 (<0.1)
VASCULAR DISORDERS	5 (<0.1)	12 (0.1)
NON-CARDIOVASCULAR DEATHS (per Investigator)	**168 (1.3)**	**162 (1.2)**
CARDIAC DISORDERS	3 (<0.1)	1 (<0.1)
GASTROINTESTINAL DISORDERS	4 (<0.1)	7 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	36 (0.3)	29 (0.2)
FATAL OUTCOMES	30 (0.2)	24 (0.2)
HEPATOBILIARY DISORDERS	4 (<0.1)	2 (<0.1)
INFECTIONS AND INFESTATIONS	34 (0.3)	32 (0.2)
INFECTIONS - PATHOGEN UNSPECIFIED	33 (0.2)	29 (0.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	41 (0.3)	44 (0.3)
RESPIRATORY AND MEDIASTINAL NEOPLASMS MALIGNANT AND UNSPECIFIED	16 (0.1)	19 (0.1)
NERVOUS SYSTEM DISORDERS	11 (0.1)	14 (0.1)
CENTRAL NERVOUS SYSTEM VASCULAR DISORDERS	10 (0.1)	12 (0.1)
PSYCHIATRIC DISORDERS	2 (<0.1)	6 (<0.1)
RENAL AND URINARY DISORDERS	8 (0.1)	4 (<0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	12 (0.1)	12 (0.1)
SOCIAL CIRCUMSTANCES	0	1 (<0.1)
VASCULAR DISORDERS	4 (<0.1)	0
MISSING	6 (<0.1)	2 (<0.1)

As expected from the efficacy results, CV deaths favored vorapaxar. Most deaths classified as Cardiovascular by the investigator were from the cardiac disorders SOC. All common HLGTs in the SOC, including cardiac arrhythmias, coronary artery disorders and heart failure, favored

vorapaxar. As one might expect from the efficacy results, the HLGT for CNS vascular disorders, which includes all strokes as well any intracranial hemorrhage, favored placebo.

Non-CV death overall also slightly favored vorapaxar in this analysis. Some deaths in the CNS vascular disorders HGLT were considered non-CV deaths, and like in CV deaths, this category favored placebo, although less strongly. Deaths in the Psychiatric Disorders SOC favored placebo (2 vs. 6). All these deaths were completed suicides. However, as noted below, the data in TRACER for a related event favored vorapaxar.

Lastly, FDA analyzed all deaths in the database in all treated subjects to try to better understand the modest excess of deaths in the vorapaxar arm in subjects with non-CV death in **Table 57**. This excess appears to be driven by deaths in the Neoplasms SOC. Deaths attributed to solid tumors and hematologic cancers and dysplasias are summarized in **Table 59**.

Table 59 TRA 2ºP – All Deaths in Treated Patients Attributed to Conditions with Preferred Terms in the Neoplasms SOC

	Placebo (N=13166) n (%)	**Vorapaxar** (N=13186) n (%)
Solid tumors	97 (0.7)	111 (0.8)
Hematologic malignancies and dysplasias	10 (0.1)	7 (0.1)

Data here are drawn from 1190 deaths occurring during or "after" the study with cause of death information.
Source: Reviewer analysis of Applicant dataset P04737 DDEATH.XPT

The modest excess of deaths due to malignancy here occurred despite the overall data for serious AEs in the Neoplasms Benign, Malignant and Unspecified SOC, which slightly favored vorapaxar (484 (3.7%) vs. 471 (3.6%) subjects).

7.3.2 TRA•CER

Table 60 is a display of all deaths during the study (randomization to last visit) that provides information on the source of death information. It is similar in format to **Table 56** but covers a different accrual period. Unlike TRA 2°P, in TRA•CER the overall mortality results favored the placebo arm.

Table 61 is a display of adjudicated deaths in treated subjects, both on treatment (to last dose + 60 days) and followed to the last visit. Here, there is no difference in the rate of CV death and a slight excess of non-CV death and overall death with vorapaxar on treatment, and an excess of deaths in the vorapaxar arm in all analyses at the end of the study. Unlike in TRA 2°P, where the rate of fatal bleeding favored vorapaxar in adjudicated non-CV death, but favors placebo in CV death, in TRA•CER fatal bleeding notably favors placebo for both CV and non-CV death.

Table 60 TRA•CER – Deaths During the Study
ITT Population followed from randomization to last visit

	PLACEBO N=6471 n (%)	VORAPAXAR N=6473 n (%)
DEATHS FROM DEATH / SURVIVAL PAGE (All deaths)	319 (5.0)	338 (5.2)
DEATHS FROM INDIVIDUAL CRF PAGE	253 (3.9)	258 (4.0)
ADVERSE EVENT	177 (2.7)	175 (2.7)
BLEEDING	24 (0.4)	33 (0.5)
MI	77 (1.2)	71 (1.1)
STROKE	21 (0.3)	22 (0.3)
DEATHS FROM DEATH / SURVIVAL PAGE AND NOT IN INDIVIDUAL CRF PAGE	66 (1.0)	80 (1.2)
ADVERSE EVENT	1 (<0.1)	1 (<0.1)
CLINICAL EVENT EFFICACY/SAFETY ENDPOINT	15 (0.2)	15 (0.2)
PROCEDURE-RELATED COMPLICATIONS	2 (<0.1)	3 (<0.1)
DISEASE-RELATED COMPLICATIONS	14 (0.2)	18 (0.3)
OTHER	24 (0.4)	33 (0.5)
MISSING	10 (0.2)	10 (0.2)

Note: A table of deaths during treatment was not provided in this format.

Table 61 TRA•CER – Adjudicated Deaths in Treated Patients
Treated patients followed as indicated

	Deaths to last dose + 60 days		Deaths to last visit	
	PLACEBO N=6441 n (%)	VORAPAXAR N=6446 n (%)	PLACEBO N=6441 n (%)	VORAPAXAR N=6446 n (%)
ALL DEATHS	231 (3.6)	238 (3.7)	315 (4.9)	333 (5.2)
CV DEATHS	174 (2.7)	174 (2.7)	205 (3.2)	208 (3.2)
FATAL BLEEDING	7 (0.1)	15 (0.2)	9 (0.1)	16 (0.2)
NON-CV DEATHS	57 (0.9)	64 (1.0)	110 (1.7)	125 (1.9)
FATAL BLEEDING	5 (0.1)	13 (0.2)	7 (0.1)	14 (0.2)

Table 62 TRA•CER - Deaths from Randomization to Last Dose + 60 Days by SOC and HLGT

Includes All Deaths in Each SOC and all HLGTs with at least 10 deaths in either treatment arm

SOC HLGT	Placebo N=6471 n (%)	Vorapaxar N=6473 n (%)
ALL DEATHS	232 (3.6)	240 (3.7)
CARDIOVASCULAR DEATHS (per Investigator)	169 (2.6)	164 (2.5)
CARDIAC DISORDERS	121 (1.9)	108 (1.7)
CARDIAC ARRHYTHMIAS	28 (0.4)	26 (0.4)
CORONARY ARTERY DISORDERS	30 (0.5)	31 (0.5)
HEART FAILURES	52 (0.8)	50 (0.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	24 (0.4)	30 (0.5)
FATAL OUTCOMES	23 (0.4)	26 (0.4)
INFECTIONS AND INFESTATIONS	1 (<0.1)	2 (<0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	9 (0.1)	5 (0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	0	1 (<0.1)
NERVOUS SYSTEM DISORDERS	8 (0.1)	7 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (<0.1)	4 (0.1)
VASCULAR DISORDERS	4 (0.1)	7 (0.1)
NON-CARDIOVASCULAR DEATHS (per Investigator)	63 (1.0)	76 (1.2)
CARDIAC DISORDERS	1 (<0.1)	1 (<0.1)
GASTROINTESTINAL DISORDERS	3 (<0.1)	3 (<0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	11 (0.2)	18 (0.3)
FATAL OUTCOMES	6 (0.1)	13 (0.2)
HEPATOBILIARY DISORDERS	0	1 (<0.1)
IMMUNE SYSTEM DISORDERS	0	1 (<0.1)
INFECTIONS AND INFESTATIONS	19 (0.3)	13 (0.2)
INFECTIONS - PATHOGEN UNSPECIFIED	18 (0.3)	13 (0.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (0.1)	0
METABOLISM AND NUTRITION DISORDERS	1 (<0.1)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	8 (0.1)	9 (0.1)
NERVOUS SYSTEM DISORDERS	3 (<0.1)	10 (0.2)
CENTRAL NERVOUS SYSTEM VASCULAR DISORDERS	3 (<0.1)	10 (0.2)
PSYCHIATRIC DISORDERS	2 (<0.1)	1 (<0.1)
RENAL AND URINARY DISORDERS	2 (<0.1)	5 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8 (0.1)	12 (0.2)
VASCULAR DISORDERS	1 (<0.1)	2 (<0.1)

As in TRA 2ºP, there was a modest excess of deaths in the vorapaxar arm in subjects with adjudicated non-CV death (Table 61). We performed an analysis of the cause of death

information in the DDEATH file. As in TRA 2ºP, the excess deaths appear to be driven by deaths associated with terms in the Neoplasms SOC (**Table 63**).

Table 63 TRA•CER – All Deaths in Treated Patients Attributed to Conditions with Preferred Terms in the Neoplasms SOC

	Placebo (N=6441) n (%)	**Vorapaxar** (N=6446) n (%)
Solid tumors	18 (0.3)	27 (0.4)
Hematologic malignancies and dysplasias	1 (<0.1)	0

Data here are drawn from 661 deaths with cause of death information occurring during or "after" the study.
Source: Applicant dataset P04736 DDEATH.XPT

Unlike TRA 2ºP, in TRA•CER serious AEs collected to the last study visit with terms in the Neoplasms SOC favored placebo (110 (1.7%) vs. 134 (2.1%) subjects).

7.4 Bleeding

7.4.1 Bleeding in TRA 2°P

7.4.1.1 Key Bleeding-Related Endpoints

Bleeding data from TRA 2°P are emphasized here. For bleeding information from TRA•CER, see Sec.

Bleeding is directly related to the pharmacologic activity of vorapaxar and is the primary safety concern. Bleeding was not considered an AE in either TRA 2°P or TRA•CER. Information on bleeding events was collected in a special bleeding event module of the eCRF.

Several bleeding endpoints were specified as secondary endpoints in the trial. These included:

1. The composite of moderate and/or severe bleeding events according to the GUSTO classification, and
2. "Clinically significant bleeding," defined as TIMI major or TIMI minor bleeding, or bleeding that requires unplanned medical treatment, surgical treatment, or laboratory evaluation even if it does not meet the criteria for TIMI major or TIMI minor bleeding

Additional pre-specified, exploratory bleeding endpoints included:

1. severe bleeding events according to the GUSTO criteria
2. all major and minor bleeding events, according to the TIMI classification
3. non-CABG TIMI major and minor bleeding events

4. major bleeding defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria
5. "Net Clinical Outcome," defined as the composite of cardiovascular death, MI stroke, urgent coronary revascularization, GUSTO moderate bleeding, GUSTO severe bleeding
6. bleeding events that do not meet the TIMI criteria for major or minor
7. in subjects undergoing CABG at any time while still receiving study drug
    a. incidence of blood product transfusions (e.g., red blood cell, platelet)
    b. bleeding assessed (1) by chest-tube drainage (a) through 8 hours after surgery and (b) total drainage, and (2) by need for reoperation for bleeding

The amended statistical plan describes the analyses above and additional safety variables relating to bleeding, some of which overlap with those above:

1. in subjects undergoing CABG while still receiving study drug:
    a. TIMI major CABG related
    b. GUSTO severe CABG related
    c. incidence of any blood product transfusion (e.g. red blood cell, platelet)
    d. incidence of packed red blood cell transfusion
    e. incidence of platelet transfusion
    f. bleeding assessed (1) by chest-tube drainage (in ml) (a) through 8 hours and 24 hours after surgery, (b) total drainage and (2) by need for re-operation for bleeding.
2. Intracranial hemorrhage
    a. Intracerebral hemorrhage
    b. Subarachnoid hemorrhage
    c. Subdural/epidural

The final protocol states only that safety analyses will be performed in the as-treated population. However, the amended statistical plan also indicates that safety analyses will be performed in the as-treated population, but adds that time-to-event analyses of safety events will count events from randomization to the event of interest, with censoring at death or last-follow-up. The study report primary presentation of time to event bleeding event information (Table 69 in the CSR) is consistent with the statistical plan, and data from that analysis is proposed by the Applicant in labeling. However, this ITT-like analysis would be expected to reduce any treatment-related differences in outcomes due to extensive time off treatment for some patients. Consequently, an on-treatment analysis seems more appropriate. Due to the long half-life of vorapaxar, an observation period from first dose to last +30 days is reasonable. **Table 64** provides the data generated by the Applicant in response to our request for such an on-treatment analysis of bleeding.

Table 64 TRA 2°P – Analysis of Time to Bleeding Events
As-Treated Population followed from first dose to last dose + 30 days

	Placebo N=13166		Vorapaxar N=13186			
	n with events (%)	KM%	n with events (%)	KM%	HR (95% CI)	p
GUSTO CATEGORIES						
Severe or Moderate	258 (2.0)	2.5	424 (3.2)	4.1	1.67 (1.43 - 1.94)	<0.001
Severe	115(0.9)	1.1	168 (1.3)	1.7	1.47 (1.16 - 1.87)	0.001
Moderate	147 (1.1)	1.4	263 (2.0)	2.6	1.81 (1.48 - 2.22)	<0.001
Severe or Moderate CABG-Related	10 (0.1)	0.1	9 (0.1)	0.1	0.91 (0.37 - 2.24)	0.835
TIMI CATEGORIES						
Major or Minor	283 (2.1)	2.7	449 (3.4)	4.3	1.61 (1.38 - 1.86)	<0.001
Major	202 (1.5)	1.9	288 (2.2)	2.8	1.44 (1.20 - 1.72)	<0.001
Minor	84 (0.6)	0.8	170 (1.3)	1.6	2.05 (1.58 - 2.66)	<0.001
Clinically Significant Bleeding	1226 (9.3)	11.1	1735 (13.2)	15.7	1.46 (1.35 - 1.57)	<0.001
Non CABG-Related Major or Minor	272 (2.1)	2.6	439 (3.3)	4.2	1.63 (1.40 - 1.90)	<0.001
Major	191 (1.5)	1.8	278 (2.1)	2.7	1.47 (1.22 - 1.77)	<0.001
Major CABG-Related	11 (0.1)	0.1	10 (0.1)	0.1	0.92 (0.39 - 2.16)	0.845
OTHER CATEGORIES						
ISTH Major	392 (3.0)	3.6	607 (4.6)	5.8	1.57 (1.38 - 1.79)	<0.001
Intracranial Hemorrhage	51 (0.4)	0.5	97 (0.7)	0.9	1.91 (1.36 - 2.69)	<0.001
Fatal Bleeding	18 (0.1)	0.2	27 (0.2)	0.3	1.51 (0.83 - 2.74)	0.176
Net Clinical Outcome (1)	1416 (10.8)	13.1	1371 (10.4)	12.9	0.97 (0.90 - 1.05)	0.489

KM% over 1080 days
(1) Composite of primary endpoint events, gusto severe and gusto moderate bleeding

Results for both of the two pre-specified “secondary” bleeding endpoints (the major safety analyses, (1) the composite of GUSTO Severe and Moderate bleeding and (2) TIMI Clinically Significant bleeding) favored placebo over vorapaxar with p <0.001, as did most of the pre-specified bleeding parameters.

However, GUSTO and TIMI CABG bleeding rates both favored vorapaxar over placebo, although the difference in rates between the treatment arms was not statistically significant in either analysis.

7.4.1.2 Location-Specific Bleeding

Table 65 is a display of CEC-adjudicated GUSTO moderate or severe bleeding during the study by MedDRA system organ class (SOC) and preferred term (PT). For each SOC, the two most frequently reported PTs for vorapaxar are listed, along with any PT with 10 or more events in either arm and PTs of special interest. The most commonly affected SOC was Gastrointestinal Disorders, followed by Nervous System Disorders (due primarily to ICH) and Injury, Poisoning and

Procedural Complications. Epistaxis, the most commonly reported bleeding event regardless of severity (see **Table 66**), was not frequently reported as a GUSTO moderate or severe bleed.

Table 65 TRA 2ºP – Subjects with GUSTO Severe or Moderate Bleeding from Randomization to Last Visit by Organ System and Preferred Term

SYSTEM ORGAN CLASS PREFERRED TERM	**Placebo** N=13166 n (%)	**Vorapaxar** N=13186 n (%)
ANY GUSTO MODERATE OR SEVERE BLEED	**313 (2.4)**	**471 (3.6)**
NO SOC OR PT SPECIFIED	1 (<0.1)	5 (<0.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	7 (0.1)	7 (0.1)
ANEMIA	0	3 (<0.1)
HAEMORRHAGIC DIATHESIS	4 (<0.1)	4 (<0.1)
CARDIAC DISORDERS	3 (<0.1)	7 (0.1)
CARDIAC TAMPONADE	2 (<0.1)	0
PERICARDIAL HAEMORRHAGE	1 (<0.1)	7 (0.1)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (<0.1)	2 (<0.1)
GASTROINTESTINAL ARTEROVENOUS MALFORMATION	1 (<0.1)	1 (<0.1)
HAEMORRHAGIC ATEROVENOUS MALFORMATION	0	1 (<0.1)
GASTROINTESTINAL DISORDERS	144 (1.1)	194 (1.5)
GASTROINTESTINAL HAEMORRHAGE	31 (0.2)	51 (0.4)
HAEMATEMESIS	14 (0.1)	17 (0.1)
HAEMATOCHEZIA	13 (0.1)	5 (<0.1)
MELAENA	38 (0.3)	59 (0.4)
RECTAL HAEMORRHAGE	20 (0.2)	21 (0.2)
UPPER GI HAEMORRHAGE	12 (0.1)	12 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6 (<0.1)	6 (<0.1)
CATHETER SITE HAEMORRHAGE	3 (<0.1)	2 (<0.1)
CATHETER SITE HAEMATOMA	1 (<0.1)	4 (<0.1)
INFECTIONS AND INFESTATIONS	1 (<0.1)	0
GASTROENTERITIS	1 (<0.1)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	66 (0.5)	91 (0.7)
OPERATIVE HAEMORRHAGE	21 (0.2)	25 (0.2)
POST PROCEDURAL HAEMORRHAGE	25 (0.2)	37 (0.3)
SUBDURAL HAEMATOMA	11 (0.1)	12 (0.1)
SUBDURAL HAEMORRHAGE	0	2 (<0.1)
TRAUMATIC INTRACRANIAL HAEMORRHAGE	0	1 (<0.1)
INVESTIGATIONS	4 (<0.1)	5 (<0.1)
HAEMOGLOBIN DECREASED	2 (<0.1)	1 (<0.1)
OCCULT BLOOD POSITIVE	2 (<0.1)	3 (<0.1)
METABOLISM AND NUTRITION DISORDERS	0	1 (<0.1)
HAEMOSIDEROSIS	0	1 (<0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (<0.1)	3 (<0.1)
TUMOUR HAEMORRHAGE	2 (<0.1)	3 (<0.1)

SYSTEM ORGAN CLASS PREFERRED TERM	**Placebo** N=13166 n (%)	**Vorapaxar** N=13186 n (%)
NERVOUS SYSTEM DISORDERS	49 (0.4)	91 (0.7)
HAEMORRHAGE INTRACRANIAL	42 (0.3)	71 (0.5)
HAEMORRHAGIC TRANSFORMATION STROKE	1 (<0.1)	6 (<0.1)
RENAL AND URINARY DISORDERS	10 (0.1)	17 (0.1)
HAEMATURIA	9 (0.1)	14 (0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (<0.1)	9 (0.1)
MENORRHAGIA	1 (<0.1)	3 (<0.1)
MENSTRUAL DISORDER	1 (<0.1)	2 (<0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8 (0.1)	20 (0.2)
EPISTAXIS	2 (<0.1)	10 (0.1)
HAEMOPTYSIS	1 (<0.1)	4 (<0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	5 (<0.1)
ECCHYMOSIS	0	3 (<0.1)
INCREASED TENDENCY TO BRUISE	0	1 (<0.1)
SKIN HAEMORRHAGE	0	1 (<0.1)
SURGICAL AND MEDICAL PROCEDURES	1 (<0.1)	3 (<0.1)
ABDOMINAL OPERATION	0	1 (<0.1)
PROSTATECTOMY	0	1 (<0.1)
SURGERY	1 (<0.1)	1 (<0.1)
VASCULAR DISORDERS	25 (0.2)	41 (0.3)
HAEMATOMA	3 (<0.1)	17 (0.1)
HAEMORRHAGE	15 (0.1)	15 (0.1)

Table 66 is a display of treatment-emergent bleeding regardless of severity by MedDRA SOC and PT. For each SOC organ system, the most frequent PT for vorapaxar is listed as well as bleeding PTs reported for more than 10 subjects in either arm. Bleeding with vorapaxar was most frequent in the Respiratory, Thoracic and Mediastinal Disorders SOC. The most commonly reported bleeding PT with vorapaxar was epistaxis. Bleeding in the Gastrointestinal Disorders SOC affected 3.7% vs. 5.6% of subjects in the placebo and vorapaxar arms, respectively.

Table 66 TRA 2ºP – Subjects with Treatment-Emergent Bleeding Events Regardless of Severity by System Organ Class and Preferred Term

Event accrued from randomization to last dose + 1 day

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo N=13166 n (%)	Vorapaxar N=13186 n (%)
ANY SYSTEM ORGAN CLASS	**2260 (17.2)**	**3211 (24.4)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	40 (0.3)	69 (0.5)
ANAEMIA	4 (<0.1)	11 (0.1)
HAEMORRHAGIC DIATHESIS	30 (0.2)	52 (0.4)
CARDIAC DISORDERS	2 (<0.1)	5 (<0.1)
PERICARDIAL HAEMORRHAGE	1 (<0.1)	4 (<0.1)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (<0.1)	4 (<0.1)
GASTROINTESTINAL ARTERIOVENOUS MALFORMATION	1 (<0.1)	1 (<0.1)

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo N=13166 n (%)	Vorapaxar N=13186 n (%)
EAR AND LABYRINTH DISORDERS	9 (0.1)	10 (0.1)
EAR HAEMORRHAGE	9 (0.1)	10 (0.1)
ENDOCRINE DISORDERS	0	1 (<0.1)
ADRENAL HAEMORRHAGE	0	1 (<0.1)
EYE DISORDERS	97 (0.7)	134 (1.0)
CONJUNCTIVAL HAEMORRHAGE	33 (0.3)	65 (0.5)
EYE HAEMORRHAGE	45 (0.3)	43 (0.3)
VITREOUS HAEMORRHAGE	10 (0.1)	6 (<0.1)
GASTROINTESTINAL DISORDERS	492 (3.7)	742 (5.6)
GASTROINTESTINAL HAEMORRHAGE	32 (0.2)	68 (0.5)
GINGIVAL BLEEDING	60 (0.5)	131 (1.0)
HAEMATEMESIS	21 (0.2)	37 (0.3)
HAEMATOCHEZIA	52 (0.4)	49 (0.4)
HAEMORRHOIDAL HAEMORRHAGE	79 (0.6)	96 (0.7)
MELAENA	68 (0.5)	114 (0.9)
RECTAL HAEMORRHAGE	132 (1.0)	176 (1.3)
RETROPERITONEAL HAEMORRHAGE	1 (<0.1)	10 (0.1)
UPPER GASTROINTESTINAL HAEMORRHAGE	17 (0.1)	15 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	68 (0.5)	72 (0.5)
CATHETER SITE HAEMORRHAGE	37 (0.3)	29 (0.2)
CATHETER SITE HAEMATOMA	20 (0.2)	20 (0.2)
INJECTION SITE HAEMORRHAGE	3 (<0.1)	10 (0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	526 (4.0)	646 (4.9)
CONTUSION	296 (2.2)	386 (2.9)
LACERATION	42 (0.3))	40 (0.3
OPERATIVE HAEMORRHAGE	37 (0.3)	33 (0.3)
PERIORBITAL HAEMATOMA	10 (0.1)	6 (<0.1)
POST PROCEDURAL HAEMORRHAGE	42 (0.3)	54 (0.4)
SUBCUTANEOUS HAEMATOMA	11 (0.1))	10 (0.1)
SUBDURAL HAEMATOMA	7 (0.1)	11 (0.1)
WOUND HAEMORRHAGE	49 (0.4)	85 (0.6)
INVESTIGATIONS	39 (0.3)	58 (0.4)
BLOOD URINE PRESENT	6 (<0.1)	15 (0.1)
OCCULT BLOOD POSITIVE	22 (0.2)	27 (0.2)
METABOLISM AND NUTRITION DISORDERS	0	1 (<0.1)
HAEMOSIDEROSIS	0	1 (<0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	4 (<0.1)	8 (0.1)
TUMOUR HAEMORRHAGE	2 (<0.1)	3 (<0.1)
NERVOUS SYSTEM DISORDERS	37 (0.3)	75 (0.6)
HAEMORRHAGE INTRACRANIAL	32 (0.2)	59 (0.4)
RENAL AND URINARY DISORDERS	278 (2.1)	367 (2.8)
HAEMATURIA	265 (2.0)	343 (2.6)
HAEMORRHAGE URINARY TRACT	14 (0.1)	25 (0.2)

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo N=13166 n (%)	Vorapaxar N=13186 n (%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	66 (0.5)	93 (0.7)
GENITAL HAEMORRHAGE	16 (0.1)	13 (0.1)
MENORRHAGIA	11 (0.1)	23 (0.2)
MENSTRUAL DISORDER	10 (0.1)	11 (0.1)
POSTMENOPAUSAL HAEMORRHAGE	12 (0.1)	13 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	472 (3.6)	908 (6.9)
EPISTAXIS	412 (3.1)	821 (6.2)
HAEMOPTYSIS	47 (0.4)	68 (0.5)
PHARYNGEAL HAEMORRHAGE	12 (0.1)	23 (0.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	324 (2.5)	523 (4.0)
ECCHYMOSIS	43 (0.3)	74 (0.6)
INCREASED TENDENCY TO BRUISE	190 (1.4)	311 (2.4)
PETECHIAE	8 (0.1)	17 (0.1)
SKIN HAEMORRHAGE	83 (0.6)	126 (1.0)
SURGICAL AND MEDICAL PROCEDURES	7 (0.1)	6 (<0.1)
TOOTH EXTRACTION	3 (<0.1)	2 (<0.1)
VASCULAR DISORDERS	231 (1.8)	376 (2.9)
HAEMATOMA	177 (1.3)	272 (2.1)
HAEMORRHAGE	48 (0.4)	93 (0.7)

Includes organ system preferred term with the most events in the vorapaxar arm and any term with more than 10 events in either arm.

7.4.1.3 Intracranial Hemorrhage

ICH, including hemorrhagic stroke, is universally considered among the most serious types of bleeding and is placed in the most serious category of bleeding in all major bleeding classification systems. As discussed at length in the efficacy section of this review, there were more ICH events with vorapaxar than with placebo. **Table 67** is a display of the count of ICH events by treatment arm with information on type, location and outcomes. In general, the excess of ICH events in the vorapaxar arm was more marked for spontaneous intraparenchymal events than for other types of events. The relative risk for fatal vs. non-fatal ICH events was similar for vorapaxar vs. placebo.

Table 67 TRA 2ºP – Patients with ICH Events from Randomization through Last Visit

	Placebo N=13166		Vorapaxar N=13186	
	n	(%)	n	(%)
Total Intracranial Hemorrhage	**44**	**(0.33)**	**90**	**(0.68)**
Location				
Subdural with No Other Extension	9	(0.07)	12	(0.09)

Subdural with Other Extension	8	(0.06)	8	(0.06)
Intraparenchymal with no Other Location	16	(0.12)	41	(0.31)
Intraparenchymal with Intraventricular Extension	3	(0.02)	16	(0.12)
Intraparenchymal and Subarachnoid Only	2	(0.02)	3	(0.02)
Intraventricular with No Other Extension	0		4	(0.03)
Intraventricular and Subarachnoid Only	2	(0.02)	2	(0.02)
Subarachnoid with No Other Location	2	(0.02)	3	(0.02)
Epidural with No Other Location	0		0	
Unknown	2	(0.02)	1	(<0.01)
Cause				
Spontaneous	12	(0.09)	54	(0.41)
-- Without Stroke	4	(0.03)	10	(0.08)
-- With Stroke	8	(0.06)	44	(0.33)
-- Hemorrhagic Conversion	0		2	(0.02)
-- Primary ICH	7	(0.05)	41	(0.31)
-- Subarachnoid Hemorrhage	1	(<0.01)	1	(<0.01)
Traumatic	19	(0.14)	21	(0.16)
Surgery/Procedure	1	(<0.01)	2	(0.02)
Mass/Tumor	2	(0.02)	2	(0.02)
Intracranial Vascular	3	(0.02)	2	(0.02)
Fibrinolysis	3	(0.02)	2	(0.02)
Other	8	(0.06)	12	(0.09)
ICH Outcome				
Fatal	8	(0.06)	19	(0.14)
Non-Fatal	35	(0.27)	68	(0.52)
ICH Contributing to Death	1	(<0.01)	3	(0.02)

"ICH contributing to death" signifies that death resulted from a complication of ICH such as sepsis rather than as a direct result of the neurological insult.

7.4.1.4 **Subgroup Analysis – Proposed Label Population**

The Sponsor's proposed label population (PLP) is persons with a prior MI but without a history of stroke or TIA. **Table 68** is a display of bleeding rates in this subgroup with event accrual from first dose to last dose + 30 days.

In general, more severe types of GUSTO and TIMI bleeding were lower in the as-treated PLP than in the overall as-treated population (compare **Table 68** to **Table 64**). The hazard ratio for both

GUSTO severe and GUSTO moderate bleeding was reduced (i.e., became for favorable for vorapaxar) in the PLP. There was also a reduction in the rate of ICH and fatal bleeding in the PLP accompanied by an improvement in the HR for ICH from 1.91 (95% CI, 1.36 - 2.69) in the overall population to 1.44 (0.87 - 2.40) in the proposed label population. The HR for fatal bleeding was also more favorable for vorapaxar in the PLP compared to the overall population, as were the results for the Applicant's Net Clinical Outcome analysis (i.e., the composite of CV death, MI, stroke, urgent coronary revascularization, GUSTO severe, and GUSTO moderate bleeding).

Table 68 TRA 2°P – Analysis of Time to Bleeding Events
Proposed Label Population followed from first dose to last dose + 30 days

	PLACEBO N=13166		VORAPAXAR N=13186			
	n with events (%)	KM%	n with events (%)	KM%	HR (95% CI)	p
GUSTO CATEGORIES						
Severe or Moderate	139 (1.7)	2.0	212 (2.5)	3.0	1.54 (1.24 - 1.90)	<0.001
Severe	62 (0.7)	1.0	74 (0.9)	1.1	1.20 (0.86 - 1.68)	0.287
Moderate	79 (0.9)	1.1	142 (1.7)	2.0	1.81 (1.38 - 2.38)	<0.001
Severe or Moderate CABG-Related	6 (0.1)	0.1	5 (0.1)	0.1	0.84 (0.26 - 2.76)	0.775
TIMI CATEGORIES						
Major or Minor	159 (1.9)	2.3	237 (2.8)	3.4	1.50 (1.23 - 1.84)	<0.001
Major	120 (1.4)	1.7	146 (1.7)	2.1	1.22 (0.96 - 1.56)	0.102
Minor	40 (0.5)	0.6	96 (1.1)	1.3	2.41 (1.67 - 3.49)	<0.001
Clinically Significant Bleeding (1)	748 (8.9)	10.2	1081 (12.8)	14.8	1.48 (1.35 - 1.63)	<0.001
Non CABG-Related Major or Minor	153 (1.8)	2.2	231 (2.7)	3.3	1.52 (1.24 - 1.87)	<0.001
Major	114 (1.4)	1.6	140 (1.7)	2.1	1.23 (0.96 - 1.58)	0.095
Major CABG-Related	6 (0.1)	0.1	6 (0.1)	0.1	1.01 (0.33 - 3.13)	0.988
OTHER CATEGORIES						
ISTH Major	213 (2.5)	3.0	322 (3.8)	4.6	1.53 (1.28 - 1.81)	<0.001
Intracranial Hemorrhage	25 (0.3)	0.4	36 (0.4)	0.5	1.44 (0.87 - 2.40)	0.160
Fatal Bleeding	9 (0.1)	0.1	12 (0.1)	0.2	1.34 (0.56 - 3.17)	0.511
Net Clinical Outcome (2)	879 (10.4)	12.3	802 (9.5)	11.5	0.91 (0.83 - 1.00)	0.055

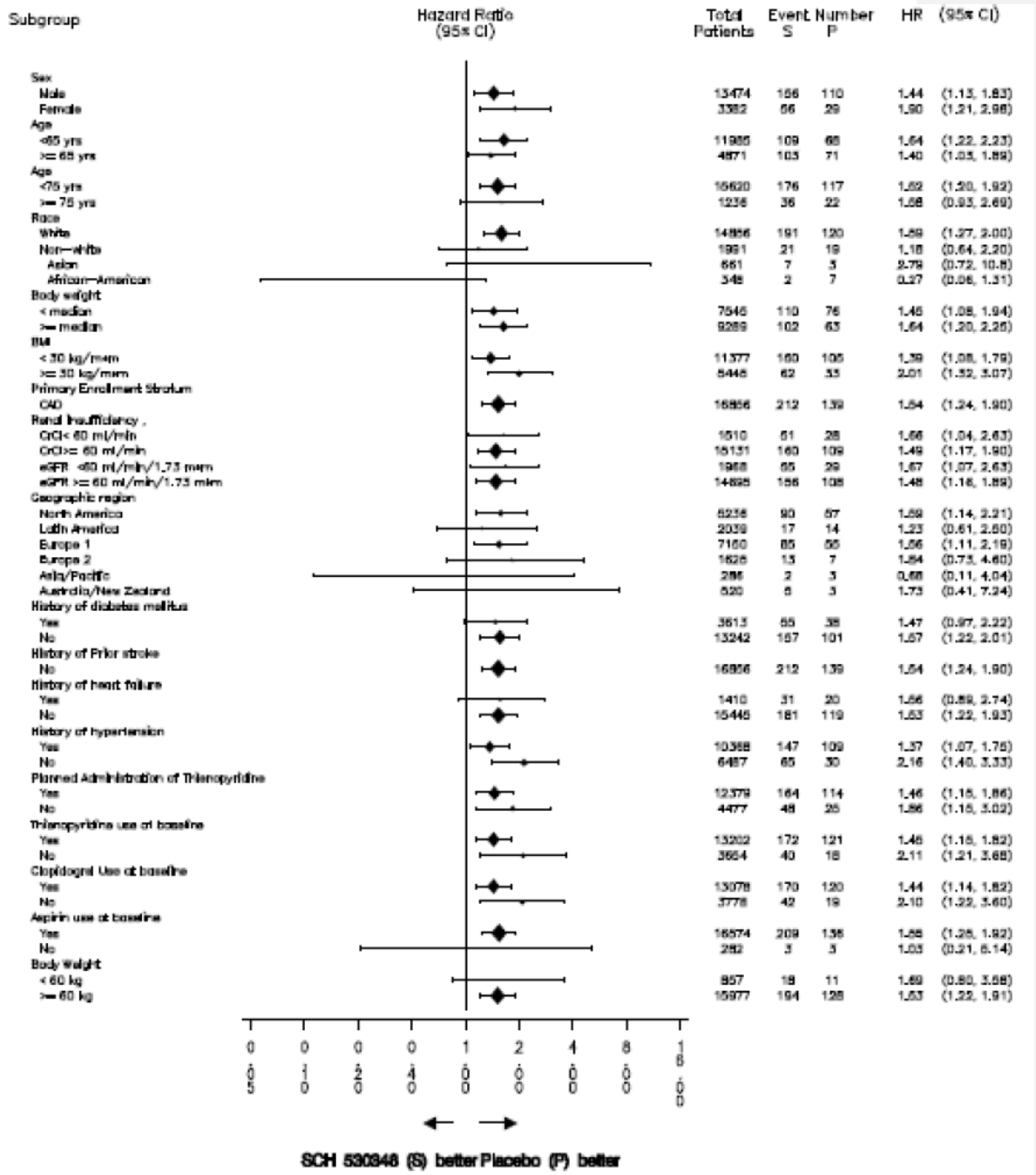
KM% over 1080 days
(1) TIMI Major or Minor bleeding, or bleeding that requires unplanned medical or surgical treatment, or unplanned evaluation via laboratory test.
(2) This is a measure of clinical burden. It is a composite of the following components: CV death, MI, stroke, UCR, GUSTO moderate bleeding, GUSTO severe bleeding.

Figure 13 is a display of GUSTO Severe or Moderate bleeding in subgroups of the Proposed Label population. Results across subgroups are reasonably consistent. There was no increase in the bleeding risk with vorapaxar compared to placebo in subjects aged ≥ 65 years compared to younger subjects, those with weight below the median compared to heavier subjects, or those with planned or baseline thienopyridine use compared to those with no such use. North American results were similar to the overall results. However, the risk of bleeding with vorapaxar compared to placebo was somewhat higher in women than men.

Figure 13 TRA 2°P - GUSTO Severe or Moderate Bleeding in the Proposed Label Population by Subgroup

Events accrued from first dose to last dose plus 30 days

(see next page)


Subgroup
Hazard Ratio (95% CI)
Total Patients
Event Number S
Event Number P
HR
(95% CI)
Sex
Male 13474 156 110 1.44 (1.13, 1.83)
Female 3382 56 29 1.90 (1.21, 2.98)
Age
<65 yrs 11985 109 68 1.64 (1.22, 2.23)
>= 65 yrs 4871 103 71 1.40 (1.03, 1.89)
Age
<75 yrs 15620 176 117 1.52 (1.20, 1.92)
>= 75 yrs 1236 36 22 1.58 (0.93, 2.69)
Race
White 14896 191 120 1.59 (1.27, 2.00)
Non-white 1961 21 19 1.18 (0.64, 2.20)
Asian 661 7 5 2.79 (0.72, 10.8)
African-American 348 2 7 0.27 (0.06, 1.31)
Body weight
< median 7546 110 76 1.46 (1.08, 1.94)
>= median 9289 102 63 1.64 (1.20, 2.25)
Bmi
< 30 kg/mxm 11377 160 105 1.39 (1.08, 1.79)
>= 30 kg/mxm 5446 62 33 2.01 (1.32, 3.07)
Primary Enrollment Stratum
CAD 16856 212 139 1.54 (1.24, 1.90)
Renal Insufficiency
CrCl< 60 ml/min 1510 51 28 1.66 (1.04, 2.63)
CrCl>= 60 ml/min 16131 160 109 1.49 (1.17, 1.90)
eGFR <60 ml/min/1.73 mxm 1958 65 29 1.67 (1.07, 2.63)
eGFR >= 60 ml/min/1.73 mlm 14695 156 108 1.48 (1.16, 1.89)
Geographic region
North America 5236 90 57 1.59 (1.14, 2.21)
Latin America 2039 17 14 1.23 (0.61, 2.50)
Europe 1 7160 85 55 1.56 (1.11, 2.19)
Europe 2 1626 13 7 1.84 (0.75, 4.50)
Asia/Pacific 286 2 3 0.68 (0.11, 4.04)
Australia/New Zealand 520 5 3 1.73 (0.41, 7.24)
History of diabetes mellitus
Yes 3613 65 38 1.47 (0.97, 2.22)
No 13242 157 101 1.57 (1.22, 2.01)
History of Prior stroke
No 16856 212 139 1.54 (1.24, 1.90)
History of heart failure
Yes 1410 31 20 1.56 (0.89, 2.74)
No 15446 181 119 1.53 (1.22, 1.93)
History of hypertension
Yes 10368 147 109 1.37 (1.07, 1.76)
No 6487 65 30 2.16 (1.40, 3.33)
Planned Administration of Thienopyridine
Yes 12379 164 114 1.46 (1.15, 1.86)
No 4477 48 25 1.86 (1.15, 3.02)
Thienopyridine use at baseline
Yes 13202 172 121 1.46 (1.15, 1.82)
No 3654 40 18 2.11 (1.21, 3.68)
Clopidogrel Use at baseline
Yes 13078 170 120 1.44 (1.14, 1.82)
No 3778 42 19 2.10 (1.22, 3.60)
Aspirin use at baseline
Yes 16574 209 138 1.55 (1.25, 1.92)
No 282 3 3 1.03 (0.21, 5.14)
Body Weight
< 60 kg 857 18 11 1.69 (0.80, 3.58)
>= 60 kg 15977 194 128 1.53 (1.22, 1.91)
0.05
0.10
0.20
0.40
1.00
2.00
4.00
8.00
16.00
SCH 530348 (S) better Placebo (P) better

7.4.1.5 Bleeding in the US

Data for key bleeding endpoints in US subjects are limited to the event accrual period from randomization through last visit, rather than to last dose or last dose + 30 days. This would be expected to reduce the hazard ratio somewhat for vorapaxar vs. placebo compare to accrual periods based on treatment. For example, in the overall as treated population, the KM rates and the hazard ratio (vorapaxar vs. placebo) for Gusto Severe/Moderate bleeding were as 3.3% vs. 2.2% and 1.52, respectively when events were accrued from randomization to last visit. When events were accrued from first dose to last dose + 30 days, KM rates and the HR were 4.1% vs. 2.5% and 1.67, respectively.

Table 69 Key Bleeding Endpoints in US Patients
As-Treated Population, Randomization to Last Visit

Endpoints	Placebo (N = 2960)			Vorapaxar (n = 2961)			Hazard Ratio (95% CI
	Subjects With Events	(%)	KM%	Subjects With Events	(%)	KM%	
GUSTO CATEGORIES							
Severe or Moderate	124	(4.2%)	4.8%	182	(6.1%)	7.2%	1.48 (1.18 - 1.86)
Severe	48	(1.6%)	1.9%	56	(1.9%)	2.3%	0.85 (0.58 - 1.25)
TIMI CATEGORIES							
Major or Minor	136	(4.6%)	5.2%	173	(5.8%)	6.9%	1.28 (1.02 - 1.60)
Major	92	(3.1%)	3.5%	92	(3.1%)	3.7%	1.00 (0.75 - 1.33)
Clinically Significant	468	(15.8%)	17.4%	596	(20.1%)	22.2%	1.31 (1.16 - 1.48)
Major CABG Related	8	(0.3%)	0.3%	5	(0.2%)	0.2%	0.62 (0.20 - 1.89)
OTHER CATEGORIES							
Intracranial Hemorrhage	24	(0.8%)	1.0%	19	(0.6%)	0.8%	0.79 (0.43 - 1.43)
Fatal Bleeding	9	(0.3%)	0.4%	10	(0.3%)	0.5%	1.10 (0.45 - 2.71)

Safety findings for the more common bleeding events in the US are directionally consistent with global findings. The analysis may be confounded somewhat by the accrual period used for the US analysis.

7.4.2 Bleeding in TRA•CER

Results for key bleeding endpoints are shown in **Table 70**. Only the Applicant's preferred analysis, which would be expected to reduce the magnitude of the hazard ratio for vorapaxar vs. placebo, is available. As expected in an ACS trial, KM bleeding rates in both arms tend to be higher than in TRA 2°P (contrast with **Table 64**), even though for TRACER the KM estimates are over 720 days, while for TRA 2°P, they are over 1080 days. As in TRA 2°P, vorapaxar use in TRA•CER was associated with increased bleeding compared to placebo, but the increase was not as marked for

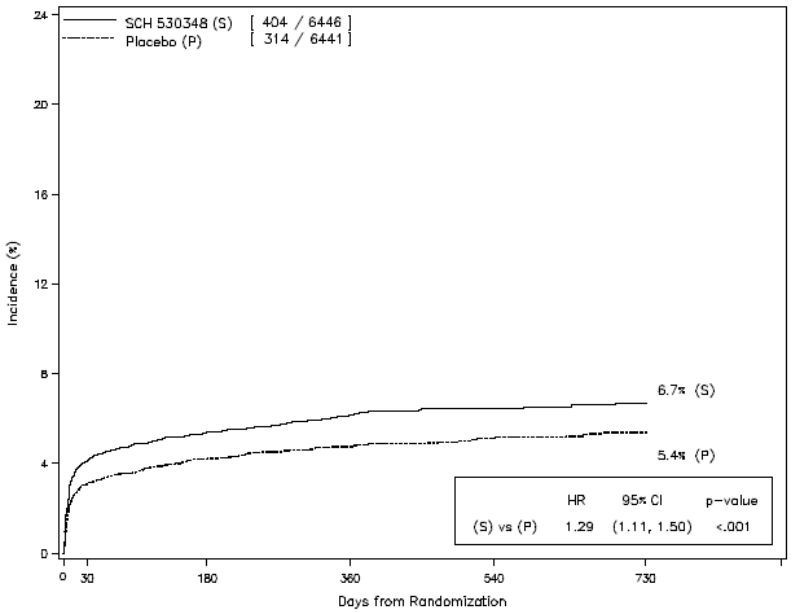
CABG-related bleeding. A KM plot of time to GUSTO Severe or Moderate Bleeding in TRA•CER shows the expected high early rate of bleeding in patients with ACS (**Figure 14**).

Table 70 TRA•CER Time to Event for Key Bleeding Endpoints
As Treated Population, Randomization to Last Visit

Endpoints	Placebo (n = 6441) Subjects With Events (%)	KM%	Vorapaxar (n = 6446) Subjects With Events (%)	KM%	Hazard Ratio (95% CI	P
GUSTO CATEGORIES						
Severe or Moderate	332 (5.2)	5.8	449 (7.0)	7.6	1.36 (1.18 – 1.57)	<0.001
Severe	106 (1.6)	1.9	172 (2.7)	3.0	1.62 (1.27 – 2.06)	<0.001
Moderate	236 (3.7)	4.1	296 (4.6)	5.0	1.26 (1.06 – 1.49)	0.009
TIMI CATEGORIES						
Major or Minor	248 (3.9)	4.4	375 (5.8)	6.5	1.52 (1.29 – 1.78)	<0.001
Major	162 (2.5)	2.9	242 (3.8)	4.1	1.49 (1.22 – 1.82)	<0.001
Minor	92 (1.4)	1.6	144 (2.2)	2.6	1.56 (1.20 – 2.03)	<0.001
Clinically Significant	813 (12.6)	14.6	1128 (17.5)	19.5	1.41 (1.29 – 1.54)	<0.001
OTHER CATEGORIES						
NonCABG-Related Major or Minor	182 (2.8)	3.3	292 (4.5)	5.2	1.61 (1.34 – 1.94)	<0.001
NonCABG-Related Major	95 (1.5)	1.8	157 (2.4)	2.8	1.65 (1.28 – 2.13)	<0.001
NonCABG-Related Minor	92 (1.4)	1.6	144 (2.2)	2.6	1.56 (1.20 – 2.03)	<0.001
CABG-Related Major	68 (1.1)	1.2	89 (1.4)	1.4	1.31 (0.95 – 1.79)	0.098
Intracranial Hemorrhage	19 (0.3)	0.4	48 (0.7)	1.0	2.52 (1.48 – 4.29)	<0.001
Fatal ICH	6 (0.1)	0.2	13 (0.2)	0.3	2.15 (0.82 - 5.66)	0.120
Fatal Bleeding	16 (0.2)	0.3	29 (0.4)	0.5	1.81 (0.98 – 3.34)	0.056

KM estimate at 720 days

Figure 14 TRA•CER – KM Plot of Time to GUSTO Severe or Moderate Bleeding
As Treated Population, Randomization to Last Visit



No. at Risk:

SCH 530348 (S)	6014	5665	4267	2533	901
Placebo (P)	6051	5695	4299	2584	915

7.4.3 CABG-Related Bleeding

TIMI CABG-related bleeding is the only bleeding parameter that was specifically designed to capture bleeding events associated with CABG. It was defined as follows in the CEC Manual of Operations:

"Major: Any hemorrhage that meets any of the following criteria:
a. Fatal bleeding (i.e., bleeding that directly results in death), r
b. Peri-operative intracranial bleeding*, r
c. Re-operation following closure of the sternotomy incision for the purpose of controlling bleeding,
d. Transfusion** of >=5 units of whole blood or PRBCs within a 48 hour period, or
e. Chest tube output >2 L within a 24 hour period….

* In light of the increased sensitivity of brain imaging for microhemorrhages of uncertain clinical significance, brain imaging with an incidental finding of microhemorrage in the absence of attributable clinical symptoms/findings will not be considered to meet the protocol definition of intracranial hemorrhage. Intracerebral microhemorrhages will rather be classified in a separate category for analysis.

** Cell saver transfusion will not be counted in calculations of blood products."

This section will focus on TIMI Major CABG-related bleeding in TRA 2ºP and TRA•CER.

7.4.3.1 TRA 2ºP

A total of 319 subjects in TRA 2ºP underwent CABG surgery from randomization to last visit. Results for TIMI Major CABG related bleeding and CABG related Fatal Bleeding [8] are displayed in **Table 71**.

Table 71 TRA 2ºP – CABG Related Bleeding

Bleeding Parameter	Timing of CABG vs. study milestone	Placebo n/N (%)	Vorapaxar n/N (%)	HR (95% CI)
TIMI Major CR	CABG from randomization to last visit	13/230 (5.7)	12/189 (6.3)	1.1 (0.5-2.3)
CR Fatal Bleeding	CABG from randomization to last visit	1/230 (0.4)	0	-
TIMI Major CR	CABG from 1st dose to last dose + 3 days[1]	8/159 (5.0)	10/146 (6.8)	1.2 (0.5-3.1)
TIMI Major CR	Treatment interrupted before CABG [2]	0/31	2/36 (5.6)	-
TIMI Major CR	Treatment not interrupted before CABG [3]	8/126 (6.3)	6/104 (5.8)	-

Abbreviations: CR = CABG related
1 "Last dose" means last recorded dose of study drug without regard to interruptions
2 Defined as an interruption of study treatment > 2 days prior to CABG in subjects who did not permanently discontinue study drug prior to CABG
3 Defined as continuation of study drug up to at least 2 days prior to CABG in subjects who did not permanently discontinue study drug prior to CABG

The data suggest that the Applicant's treatment strategy of allowing investigators to continue study drug up to and even through CABG surgery did not greatly increase risk of bleeding. While the comparison of subjects who interrupted treatment prior to CABG vs. those who did not is not a randomized comparison, and we have not yet analyzed information on the use of other antiplatelet drugs in the peri-operative period, it may be appropriate to continue vorapaxar up within several days of surgery, even though blood levels in the operative period would be expected to be little changed from steady state levels.

7.4.3.2 TRA•CER

TRA•CER was an ACS study, and CABG was performed at a substantially higher rate than in TRA 2ºP. **Table 72** is a display of CABG related bleeding parameters.

[8] Defined as a "CEC adjudicated fatal bleeding event occurred within 7 days from CABG. The subject should also have major bleeding events associated with the CABG surgery itself such as TIMI major CABG related bleeding or GUSTO Severe bleeding within 48 hours of CABG."

Table 72 TRA•CER – CABG Related Bleeding

Bleeding Parameter	Timing of CABG vs. study milestone	Placebo n/N (%)	Vorapaxar n/N (%)	HR (95% CI)
TIMI Major CR	CABG from randomization to last visit	68/949 (7.2)	89/931 (9.6)	1.35 (098-1.85)
CR Fatal Bleeding	CABG from randomization to last visit	2/949 (0.2)	0	-
TIMI Major CR	Treatment interrupted or discontinued before CABG [1]	22/264 (8.3)	32/299 (10.7)	1.29 (0.75-2.21)
TIMI Major CR	Treatment not interrupted or discontinued before CABG [3]	46/685 (6.7)	57/632 (9.0)	1.36 (0.92-2.00)

Abbreviations: CR = CABG related
1 "Last dose" means last recorded dose of study drug without regard to interruptions
2 Defined as an interruption of study treatment > 2 days prior to CABG in subjects who did not permanently discontinue study drug prior to CABG
3 Defined as continuation of study drug up to at least 2 days prior to CABG in subjects who did not permanently discontinue study drug prior to CABG

Reviewer comment: CABG related bleeding data from in TRA•CER also may support the Applicant's dosing strategy. However, before such a strategy can be described in labeling, more information is needed.

7.5 Discontinuations for Adverse Events

7.5.1 TRA 2°P

Data on discontinuation of treatment for adverse events are presented separately for bleeding events and non-bleeding events.

Table 73 provides a summary of subjects who discontinued treatment for bleeding events by treatment arm, System Organ Class (SOC) and Preferred Term (PT) in the overall as-treated population. Note that only PTs associated with at least 10 discontinued subjects in either arm are listed, but all subjects who discontinued for bleeding are counted in the first row of data. As expected, rates of discontinuation for bleeding were higher in the vorapaxar arm overall and in each SOC represented in the table. Gastrointestinal Disorders was the SOC with largest number of discontinuations for bleeding, but the PT associated with the most discontinuations for bleeding was epistaxis.

In the proposed label population, the pattern of discontinuations for bleeding was similar to that in the overall population. A total of 146 (1.7%) and 246 (2.9%) subjects in the placebo and vorapaxar arms respectively, discontinued for bleeding. As in the overall study population, the SOC and PT associated with the most discontinuations for bleeding were Gastrointestinal Disorders and epistaxis, respectively (data not shown).

Table 73 TRA 2°P - Summary of Subjects who Discontinued Treatment for Bleeding Events by SOC and PT

As-Treated Population (Includes only PTs with at least 10 discontinuations in either arm)

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=13166) n (%)	Vorapaxar (N=13186) n (%)
SUBJECTS IN ANY SOC	**234 (1.8)**	**401 (3.0)**
GASTROINTESTINAL DISORDERS	82 (0.6)	122 (0.9)
GASTROINTESTINAL HAEMORRHAGE	11 (0.1)	17 (0.1)
HAEMATEMESIS	7 (0.1)	10 (0.1)
HAEMORRHOIDAL HAEMORRHAGE	7 (0.1)	12 (0.1)
MELAENA	15 (0.1)	30 (0.2)
RECTAL HAEMORRHAGE	18 (0.1)	24 (0.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	20 (0.2)	43 (0.3)
CONTUSION	8 (0.1)	18 (0.1)
NERVOUS SYSTEM DISORDERS	22 (0.2)	53 (0.4)
HAEMORRHAGE INTRACRANIAL	19 (0.1)	40 (0.3)
RENAL AND URINARY DISORDERS	19 (0.1)	26 (0.2)
HAEMATURIA	18 (0.1)	25 (0.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	32 (0.2)	66 (0.5)
EPISTAXIS	23 (0.2)	57 (0.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	15 (0.1)	37 (0.3)
INCREASED TENDENCY TO BRUISE	6 (<0.1)	23 (0.2)
SKIN HAEMORRHAGE	5 (<0.1)	11 (0.1)
VASCULAR DISORDERS	22 (0.2)	27 (0.2)
HAEMATOMA	9 (0.1)	10 (0.1)
HAEMORRHAGE	10 (0.1)	15 (0.1)

Data on discontinuations for non-bleeding adverse events are summarized in **Table 74**. Non-bleeding PTs that notably favored placebo include, not surprisingly, anemia and iron deficiency anemia. Other AEs with results favoring placebo included vertigo (4 vs. 12 subjects in the placebo and vorapaxar arms respectively), ALS (1 vs. 3 subjects) and “upper motor neurone lesion” (primary lateral sclerosis, 0 vs. 1 subject).

Table 74 TRA 2°P - Summary of Subjects who Discontinued Treatment for Other (Non-Bleeding) Adverse Events by SOC and PT

As-Treated Population (Includes only PTs with at least 5 discontinuations in either arm, rare AEs that are sometimes drug related, and other AEs that are related to those qualifying for inclusion in the table)

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=13166) n (%)	Vorapaxar (N=13186) n (%)
SUBJECTS REPORTING ANY ADVERSE EVENT	**960 (7.3)**	**926 (7.0)**
BLOOD AND LYMPHATIC SYSTEM	43 (0.3)	69 (0.5)
ANAEMIA	18 (0.1)	43 (0.3)
IRON DEFICIENCY ANAEMIA	1 (<0.1)	5 (<0.1)
PANCYTOPENIA	3 (<0.1)	0
THROMBOCYTOPENIA	15 (0.1)	9 (0.1)
THROMBOTIC THROMBOCYTOPENIC PURPURA	1 (<0.1)	0
CARDIAC DISORDERS	111 (0.8)	99 (0.8)
ATRIAL FIBRILLATION	55 (0.4)	58 (0.4)
ATRIAL FLUTTER	4 (<0.1)	2 (<0.1)
CARDIAC FAILURE	15 (0.1)	12 (0.1)
CARDIAC FAILURE CONGESTIVE	6 (<0.1)	3 (<0.1)
CARDIAC FAILURE CHRONIC	1 (<0.1)	0
PALPITATIONS	5 (<0.1)	3 (<0.1)
VENTRICULAR FIBRILLATION	5 (<0.1)	3 (<0.1)
VENTRICULAR ARRHYTHMIA	1 (<0.1)	0
VENTRICULAR TACHYCARDIA	1 (<0.1)	0
CARDIO-RESPIRATORY) ARREST	1 (<0.1)	1 (<0.1
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	4 (<0.1)
EAR AND LABYRINTH DISORDERS	6 (<0.1)	14 (0.1)
VERTIGO	4 (<0.1)	12 (0.1)
ENDOCRINE DISORDERS	1 (<0.1)	2 (<0.1)
EYE DISORDERS	14 (0.1)	13 (0.1)
VISION BLURRED)	5 (<0.1)	2 (<0.1)
VISUAL ACUITY REDUCED	0	2 (<0.1)
VISUAL IMPAIRMENT	2 (<0.1)	0
GASTROINTESTINAL DISORDERS	125 (0.9)	114 (0.9)
ABDOMINAL DISCOMFORT	10 (0.1)	4 (<0.1)
ABDOMINAL PAIN	7 (0.1)	9 (0.1)
ABDOMINAL PAIN UPPER	9 (0.1)	12 (0.1)
DIARRHOEA	18 (0.1)	12 (0.1)
DYSPEPSIA	6 (<0.1)	5 (<0.1)

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=13166) n (%)	Vorapaxar (N=13186) n (%)
GASTRIC ULCER	1 (<0.1)	5 (<0.1)
DUODENAL ULCER	2 (<0.1)	0
DUODENITIS	0	1 (<0.1)
GASTRITIS	3 (<0.1)	6 (<0.1)
GASTRIC ULCER PERFORATION	1 (<0.1)	0
GASTROOESOPHAGEAL REFLUX DISEASE	1 (<0.1)	4 (<0.1)
NAUSEA	24 (0.2)	20 (0.2)
PANCREATITIS ACUTE	5 (<0.1)	2 (<0.1)
PANCREATITIS	2 (<0.1)	3 (<0.1)
PEPTIC ULCER	1 (<0.1)	1 (<0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	53 (0.4)	51 (0.4)
ASTHENIA	7 (0.1)	5 (<0.1)
FATIGUE	15 (0.1)	13 (0.1)
MALAISE	5 (<0.1)	4 (<0.1)
NON-CARDIAC CHEST PAIN	6 (<0.1)	3 (<0.1)
HEPATOBILIARY DISORDERS	13 (0.1)	13 (0.1)
HEPATIC FAILURE	1 (<0.1)	1 (<0.1)
HEPATIC FUNCTION ABNORMAL	0	2 (<0.1)
HEPATIC STEATOSIS	1 (<0.1)	1 (<0.1)
HEPATITIS	1 (<0.1)	1 (<0.1)
HEPATITIS ALCOHOLIC	1 (<0.1)	0
HEPATITIS TOXIC	1 (<0.1)	0
HEPATOTOXICITY	1 (<0.1)	0
HYPERTRANSAMINASAEMIA	0	1 (<0.1)
ISCHAEMIC HEPATITIS	1 (<0.1)	0
LIVER DISORDER	2 (<0.1)	1 (<0.1)
IMMUNE SYSTEM DISORDERS	8 (0.1)	6 (<0.1)
INFECTIONS AND INFESTATIONS	55 (0.4)	61 (0.5)
PNEUMONIA	11 (0.1)	12 (0.1)
SEPSIS	5 (<0.1)	5 (<0.1)
SEPTIC SHOCK	5 (<0.1)	3 (<0.1)
URINARY TRACT INFECTION	2 (<0.1)	5 (<0.1)
UROSEPSIS	1 (<0.1)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	26 (0.2)	16 (0.1)
FALL	6 (<0.1)	2 (<0.1)
FEMUR FRACTURE	5 (<0.1)	1 (<0.1)
INVESTIGATIONS	98 (0.7)	90 (0.7)
ALANINE AMINOTRANSFERASE INCREASED	10 (0.1)	7 (0.1)
ASPARTATE AMINOTRANSFERASE ABNORMAL	1 (<0.1)	0

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=13166) n (%)	Vorapaxar (N=13186) n (%)
ASPARTATE AMINOTRANSFERASE INCREASED	5 (<0.1)	8 (0.1)
BLOOD ALKALINE PHOSPHATASE INCREASED	2 (<0.1)	3 (<0.1)
BLOOD BILIRUBIN INCREASED	3 (<0.1)	0
BLOOD CREATINE PHOSPHOKINASE INCREASED	9 (0.1)	7 (0.1)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	9 (0.1)	10 (0.1)
HEPATIC ENZYME INCREASED	21 (0.2)	15 (0.1)
LIVER FUNCTION TEST ABNORMAL	15 (0.1)	11 (0.1)
PLATELET COUNT DECREASED	7 (0.1)	5 (<0.1)
TRANSAMINASES ABNORMAL	0	1 (<0.1)
TRANSAMINASES INCREASED	8 (0.1)	14 (0.1)
METABOLISM AND NUTRITION DISORDERS	11 (0.1)	9 (0.1)
NEOPLASMS, MALIGNANT BENIGN & UNSPECIFIED	157 (1.2)	153 (1.0)
LUNG CARCINOMA CELL TYPE UNSPECIFIED STAGE IV	0	2 (<0.1)
LUNG NEOPLASM	0	2 (<0.1)
LUNG NEOPLASM MALIGNANT	11 (0.1)	12 (0.1)
LUNG SQUAMOUS CELL CARCINOMA STAGE I	0	1 (<0.1)
LUNG SQUAMOUS CELL CARCINOMA STAGE	4 (<0.1)	0
NON-SMALL CELL LUNG CANCER	2 (<0.1)	1 (<0.1)
NON-SMALL CELL LUNG CANCER METASTATIC	0	1 (<0.1)
NON-SMALL CELL LUNG CANCER STAGE IV	1 (<0.1)	0
PANCREATIC CARCINOMA	7 (0.1)	4 (<0.1)
PANCREATIC CARCINOMA METASTATIC	7 (0.1)	7 (0.1)
SMALL CELL CARCINOMA	0	1 (<0.1)
SMALL CELL LUNG CANCER METASTATIC	1 (<0.1)	0
SMALL CELL LUNG CANCER STAGE UNSPECIFIED	2 (<0.1)	4 (<0.1)
NERVOUS SYSTEM DISORDERS	92 (0.7)	104 (0.8)
AMYOTROPHIC LATERAL SCLEROSIS	1 (<0.1)	3 (<0.1)
COGNITIVE DISORDER	2 (<0.1)	1 (<0.1)
DEMENTIA	1 (<0.1)	6 (<0.1)
DEMENTIA ALZHEIMER'S TYPE	1 (<0.1)	2 (<0.1)
HEADACHE	29 (0.2)	25 (0.2)
SYNCOPE	5 (<0.1)	5 (<0.1)
UPPER MOTOR NEURONE LESION	0	1 (<0.1)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	3 (<0.1)	2 (<0.1)
PSYCHIATRIC DISORDERS	43 (0.3)	45 (0.3)
DEPRESSION	13 (0.1)	7 (0.1)
DEPRESSIVE SYMPTOM	0	1 (<0.1)
INITIAL INSOMNIA	0	1 (<0.1)
INSOMNIA	13 (0.1)	7 (0.1)
RENAL AND URINARY DISORDERS	24 (0.2)	28 (0.2)

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=13166) n (%)	Vorapaxar (N=13186) n (%)
RENAL FAILURE	4 (<0.1)	11 (0.1)
RENAL FAILURE ACUTE	8 (0.1)	3 (<0.1)
RENAL FAILURE CHRONIC	4 (<0.1)	0
RENAL IMPAIRMENT	0	4 (<0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	12 (0.1)	8 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	53 (0.4)	32 (0.2)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	6 (<0.1)	4 (<0.1)
PULMONARY EMBOLISM	16 (0.1)	10 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	71 (0.5)	65 (0.5)
PRURITUS	14 (0.1)	6 (<0.1)
PRURITUS GENERALISED	2 (<0.1)	2 (<0.1)
RASH	20 (0.2)	23 (0.2)
SURGICAL AND MEDICAL PROCEDURES	0	1 (<0.1)
VASCULAR DISORDERS	29 (0.2)	23 (0.2)
DEEP VEIN THROMBOSIS	8 (0.1))	5 (<0.1
HYPERTENSION	5 (<0.1)	3 (<0.1)
THROMBOSIS	1 (<0.1)	1 (<0.1)
VARICOSE VEIN	0	1 (<0.1)
VEIN PAIN	0	1 (<0.1)
VENOUS THROMBOSIS	0	1 (<0.1)

7.5.2 TRA•CER

Bleeding led to discontinuation of treatment in 125 (1.9%) vs. 255 (4.0%) subjects in the placebo and vorapaxar arms, respectively in TRA•CER. Discontinuation was most commonly due to bleeding in the GI Disorders SOC, affecting 51 (0.8%) vs. 75 (1.2%) of subjects in the placebo and vorapaxar arms, respectively. The single most common bleeding Preferred Term associated in the vorapaxar arm leading to discontinuation was epistaxis: 13 (0.2%) vs. 33 (0.5%) subjects in the placebo and vorapaxar arms, respectively. However, if terms generally associated with lower GI bleeding evident in the stool are summed (assuming one term per subject), the composite includes 22 (0.3%) vs. 48 (0.7%) subjects (data not shown).

Table 75 is a display of non-bleeding AEs leading to discontinuation in at least 5 subjects in either treatment arm. Anemia and rash were notably more common with vorapaxar.

Table 75 TRA•CER - Summary of Subjects who Discontinued Treatment for Other (Non-Bleeding) Adverse Events by SOC and PT

System Organ Class and Adverse Events	Placebo (n = 6441)	SCH 530348 (n = 6446)
SUBJECTS REPORTING ANY ADVERSE EVENT	**348 (5.4)**	**407 (6.3)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
ANAEMIA	8 (0.1)	20 (0.3)
THROMBOCYTOPENIA	8 (0.1)	4 (0.1)
CARDIAC DISORDERS		
ATRIAL FIBRILLATION	22 (0.3)	29 (0.4)
CARDIAC FAILURE	15 (0.2)	11 (0.2)
CARDIOGENIC SHOCK	11 (0.2)	5 (0.1)
VENTRICULAR FIBRILLATION	5 (0.1)	1 (<0.1)
GASTROINTESTINAL DISORDERS		
ABDOMINAL DISCOMFORT	5 (0.1)	0
ABDOMINAL PAIN UPPER	1 (<0.1)	5 (0.1)
DIARRHOEA	6 (0.1)	6 (0.1)
NAUSEA	15 (0.2)	12 (0.2)
VOMITING	2 (<0.1)	5 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	3 (<0.1)	5 (0.1)
OEDEMA PERIPHERAL	0	5 (0.1)
INFECTIONS AND INFESTATIONS		
SEPTIC SHOCK	6 (0.1)	2 (<0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
COLON CANCER	3 (<0.1)	8 (0.1)
NERVOUS SYSTEM DISORDERS		
DIZZINESS	9 (0.1)	7 (0.1)
HEADACHE	6 (0.1)	4 (0.1)
PSYCHIATRIC DISORDERS		
CONFUSIONAL STATE	1 (<0.1)	5 (0.1)
RENAL AND URINARY DISORDERS		
RENAL FAILURE	8 (0.1)	3 (<0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
PULMONARY EMBOLISM	8 (0.1)	10 (0.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
RASH	10 (0.2)	20 (0.3)
VASCULAR DISORDERS		
DEEP VEIN THROMBOSIS	4 (0.1)	5 (0.1)

7.6 Serious Adverse Events

7.6.1 TRA 2°P

Table 76 is a display of serious non-bleeding adverse events, including those associated with at least 20 subjects in either treatment arm and less common SAEs of special interest.

Table 76 TRA 2°P - Summary of Subjects with Serious Non-Bleeding Adverse Events by SOC and PT

As-Treated Population, Events Accrued from First Dose to Last Dose + 30 Days
(PT rows are limited to those associated with at least 20 subjects in either treatment arm or also less common AEs of special interest, but exclude myocardial infarction and stroke)

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=13166) n (%)	Vorapaxar (N=13186) n (%)
SUBJECTS IN ANY SOC	3027 (23.0)	3024 (22.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	40 (0.3)	84 (0.6)
ANAEMIA	7 (0.1)	34 (0.3)
THROMBOCYTOPENIA	20 (0.2)	16 (0.1)
NEUTROPENIA	1 (<0.1))	1 (<0.1
PANCYTOPENIA	2 (<0.1)	0
CARDIAC DISORDERS	502 (3.8)	521 (4.0)
ATRIAL FIBRILLATION	95 (0.7)	120 (0.9)
ATRIAL FLUTTER	16 (0.1)	28 (0.2)
ATRIAL TACHYCARDIA	3 (<0.1)	0
CARDIAC FAILURE	147 (1.1)	152 (1.2)
CARDIAC FAILURE CONGESTIVE	70 (0.5)	77 (0.6)
ATRIOVENTRICULAR BLOCK	3 (<0.1)	3 (<0.1)
ATRIOVENTRICULAR BLOCK COMPLETE	13 (0.1)	18 (0.1)
ATRIOVENTRICULAR BLOCK FIRST DEGREE	0	1 (<0.1)
ATRIOVENTRICULAR BLOCK SECOND DEGREE	6 (<0.1)	4 (<0.1)
BIFASCICULAR BLOCK	1 (<0.1)	0
BRADYCARDIA	25 (0.2)	17 (0.1)
BUNDLE BRANCH BLOCK RIGHT	2 (<0.1)	0
BUNDLE BRANCH BLOCK LEFT	2 (<0.1)	0
VENTRICULAR TACHYCARDIA	33 (0.3)	33 (0.3)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	2 (<0.1)	7 (0.1)
EAR AND LABYRINTH DISORDERS	15 (0.1)	20 (0.2)
VERTIGO	15 (0.1)	20 (0.2)
ENDOCRINE DISORDERS	13 (0.1)	10 (0.1)
EYE DISORDERS	29 (0.2)	24 (0.2)
AMAUROSIS	0	1 (<0.1)
BLINDNESS UNILATERAL	1 (<0.1)	0

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=13166) n (%)	Vorapaxar (N=13186) n (%)
CATARACT	13 (0.1)	10 (0.1)
CORNEAL OEDEMA	1 (<0.1)	0
DIABETIC RETINOPATHY	1 (<0.1)	1 (<0.1)
ENDOCRINE OPHTHALMOPATHY	0	1 (<0.1)
GLAUCOMA	3 (<0.1)	0
LACRIMATION INCREASED	0	1 (<0.1)
MACULAR DEGENERATION	0	1 (<0.1)
MACULAR FIBROSIS	1 (<0.1)	0
MACULAR HOLE	0	1 (<0.1)
OPTIC ISCHAEMIC NEUROPATHY	1 (<0.1)	0
OPTIC NEUROPATHY 1	(<0.1)	0
POSTERIOR CAPSULE OPACIFICATION	1 (<0.1)	0
RETINAL ARTERY THROMBOSIS	0 1	(<0.1)
RETINAL DETACHMENT	5 (<0.1)	3 (<0.1)
RETINAL VEIN OCCLUSION	0	1 (<0.1)
RETINAL VEIN THROMBOSIS	0	1 (<0.1)
ULCERATIVE KERATITIS	1 (<0.1)	0
VISION BLURRED	0	1 (<0.1)
VISUAL IMPAIRMENT	0	1 (<0.1)
GASTROINTESTINAL DISORDERS	309 (2.3)	313 (2.4)
GASTRITIS	24 (0.2))	26 (0.2
GASTROOESOPHAGEAL REFLUX DISEASE	30 (0.2)	22 (0.2)
INGUINAL HERNIA	34 (0.3)	38 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**511 (3.9)**	**500 (3.8)**
NON-CARDIAC CHEST PAIN	433 (3.3)	415 (3.1)
HEPATOBILIARY DISORDERS	102 (0.8)	102 (0.8)
CHOLELITHIASIS	40 (0.3)	38 (0.3)
CHOLECYSTITIS	22 (0.2)	29 (0.2)
CHOLELITHIASIS	40 (0.3)	38 (0.3)
HEPATIC FAILURE	0	3 (<0.1)
HEPATITIS	1 (<0.1)	1 (<0.1)
HEPATITIS ACUTE	1 (<0.1)	1 (<0.1)
HEPATITIS TOXIC	1 (<0.1)	0
HEPATOTOXICITY	1 (<0.1)	0
ISCHAEMIC HEPATITIS	1 (<0.1)	1 (<0.1)
LIVER DISORDER	1 (<0.1)	0
IMMUNE SYSTEM DISORDERS *	19 (0.1)	7 (0.1)
INFECTIONS AND INFESTATIONS	612 (4.6)	600 (4.6)
APPENDICITIS	21 (0.2)	20 (0.2)
BRONCHITIS	26 (0.2)	26 (0.2)

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=13166) n (%)	Vorapaxar (N=13186) n (%)
CELLULITIS	36 (0.3)	38 (0.3)
GASTROENTERITIS	33 (0.3)	36 (0.3)
LOBAR PNEUMONIA	18 (0.1)	20 (0.2)
PNEUMONIA	152 (1.2)	150 (1.1)
SEPSIS	26 (0.2)	18 (0.1)
URINARY TRACT INFECTION	42 (0.3	55 (0.4)
UROSEPSIS	6 (<0.1)	20 (0.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	243 (1.8)	262 (2.0)
FALL	7 (0.1)	10 (0.1)
FEMUR FRACTURE	21 (0.2)	12 (0.1)
INVESTIGATIONS *	21 (0.2)	19 (0.1)
ALANINE AMINOTRANSFERASE INCREASED	2 (<0.1)	1 (<0.1)
ASPARTATE AMINOTRANSFERASE INCREASED	2 (<0.1)	2 (<0.1)
BLOOD CREATINE PHOSPHOKINASE INCREASED	1 (<0.1)	3 (<0.1)
HEPATIC ENZYME ABNORMAL	0	1 (<0.1)
HEPATIC ENZYME INCREASED	0	1 (<0.1)
METABOLISM AND NUTRITION DISORDERS	125 (0.9)	143 (1.1)
DEHYDRATION	27 (0.2)	24 (0.2)
HYPOGLYCAEMIA	14 (0.1)	20 (0.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	310 (2.4)	267 (2.0)
INTERVERTEBRAL DISC PROTRUSION	31 (0.2)	19 (0.1)
MUSCULOSKELETAL CHEST PAIN	25 (0.2)	36 (0.3)
OSTEOARTHRITIS	78 (0.6)	66 (0.5)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	424 (3.2)	407 (3.1)
BLADDER CANCER	18 (0.1)	23 (0.2)
COLON CANCER)	24 (0.2)	25 (0.2
LUNG CANCER METASTATIC	23 (0.2)	12 (0.1)
LUNG NEOPLASM MALIGNANT	24 (0.2)	25 (0.2)
PROSTATE CANCER	50 (0.4)	34 (0.3)
NERVOUS SYSTEM DISORDERS	195 (1.5)	246 (1.9)
AMYOTROPHIC LATERAL SCLEROSIS	1 (<0.1)	3 (<0.1)
PRESYNCOPE	19 (0.1)	20 (0.2)
SYNCOPE	50 (0.4)	73 (0.6)
SYRINGOMYELIA	0	1 (<0.1)
UPPER MOTOR NEURONE LESION	0	1 (<0.1)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (<0.1)	0
PSYCHIATRIC DISORDERS	67 (0.5)	78 (0.6)
RENAL AND URINARY DISORDERS	164 (1.2)	142 (1.1)
NEPHROLITHIASIS	26 (0.2)	21 (0.2)
RENAL FAILURE	28 (0.2)	30 (0.2)

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=13166) n (%)	Vorapaxar (N=13186) n (%)
RENAL FAILURE ACUTE	47 (0.4)	37 (0.3)
RENAL FAILURE CHRONIC	15 (0.1)	7 (0.1)
RENAL IMPAIRMENT	4 (<0.1)	2 (<0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	51 (0.4)	56 (0.4)
BENIGN PROSTATIC HYPERPLASIA	25 (0.2)	35 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	227 (1.7)	180 (1.4)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	65 (0.5)	71 (0.5)
PULMONARY EMBOLISM	38 (0.3)	12 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	23 (0.2)	24 (0.2)
ANGIOEDEMA	5 (<0.1)	7 (0.1)
DERMATITIS EXFOLIATIVE	1 (<0.1)	0
SKIN NECROSIS	3 (<0.1)	0
URTICARIA	0	1 (<0.1)
SOCIAL CIRCUMSTANCES	0	1 (<0.1)
SURGICAL AND MEDICAL PROCEDURES	3 (<0.1)	2 (<0.1)
VASCULAR DISORDERS	156 (1.2)	138 (1.0)
DEEP VEIN THROMBOSIS	18 (0.1)	16 (0.1)

Of note, vorapaxar is associated with increased rates of the following SAEs: atrial fibrillation, atrial flutter, ALS and “upper motor neuron disorder”. Vorapaxar was associated with a notably reduced rate of pulmonary embolism, but there was no similar reduction in the rate of DVT.

Information from the Investigations SOC for liver function testing does not suggest that vorapaxar is associated with transaminitis, strongly suggesting that there is not an increased risk of serious hepatocellular toxicity.

7.6.2 TRA•CER

Table 77 Is a display of non-bleeding SAEs in treated patients during treatment, defined as up to the last dose of study drug + 1 day). Only SAEs reported by 10 subjects or more in either arm are listed.

Table 77 TRA•CER – SAEs in Treated Patients During Treatment
Randomization to last dose + 1 day

(Starts on next page)

System Organ Class and Adverse Events	Placebo (n = 6441)	SCH 530348 (n = 6446)
SUBJECTS REPORTING ANY ADVERSE EVENT	**1372 (21.3)**	**1398 (21.7)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
ANAEMIA	18 (0.3)	28 (0.4)
THROMBOCYTOPENIA	19 (0.3)	19 (0.3)
CARDIAC DISORDERS		
ATRIAL FIBRILLATION	79 (1.2)	80 (1.2)
ATRIAL FLUTTER	15 (0.2)	14 (0.2)
BRADYCARDIA	20 (0.3)	12 (0.2)
CARDIAC FAILURE	128 (2.0)	119 (1.8)
CARDIAC FAILURE CONGESTIVE	24 (0.4)	33 (0.5)
CARDIOGENIC SHOCK	29 (0.5)	19 (0.3)
SUPRAVENTRICULAR TACHYCARDIA	14 (0.2)	7 (0.1)
VENTRICULAR FIBRILLATION	24 (0.4)	25 (0.4)
VENTRICULAR TACHYCARDIA	30 (0.5)	19 (0.3)
GASTROINTESTINAL DISORDERS		
ABDOMINAL PAIN	10 (0.2)	10 (0.2)
GASTRITIS	4 (0.1)	11 (0.2)
INGUINAL HERNIA	6 (0.1)	15 (0.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
CHEST PAIN	32 (0.5)	25 (0.4)
NON-CARDIAC CHEST PAIN	99 (1.5)	119 (1.8)
HEPATOBILIARY DISORDERS		
CHOLECYSTITIS	16 (0.2)	7 (0.1)
CHOLELITHIASIS	13 (0.2)	12 (0.2)
INFECTIONS AND INFESTATIONS		
BRONCHITIS	9 (0.1)	15 (0.2)
CELLULITIS	14 (0.2)	19 (0.3)
PNEUMONIA	59 (0.9)	79 (1.2)
SEPSIS	13 (0.2)	13 (0.2)
URINARY TRACT INFECTION	21 (0.3)	19 (0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
FALL	11 (0.2)	14 (0.2)
METABOLISM AND NUTRITION DISORDERS		
DIABETES MELLITUS	11 (0.2)	6 (0.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
MUSCULOSKELETAL CHEST PAIN	19 (0.3)	13 (0.2)
MUSCULOSKELETAL PAIN	5 (0.1)	10 (0.2)
OSTEOARTHRITIS	17 (0.3)	11 (0.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
COLON CANCER	6 (0.1)	17 (0.3)
NERVOUS SYSTEM DISORDERS		
CAROTID ARTERY STENOSIS	9 (0.1)	16 (0.2)
HEADACHE	10 (0.2)	1 (<0.1)
SYNCOPE	41 (0.6)	34 (0.5)

System Organ Class and Adverse Events	Placebo (n = 6441)	SCH 530348 (n = 6446)
RENAL AND URINARY DISORDERS		
RENAL FAILURE	39 (0.6)	47 (0.7)
RENAL FAILURE ACUTE	21 (0.3)	28 (0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
ACUTE PULMONARY OEDEMA	7 (0.1)	10 (0.2)
ACUTE RESPIRATORY FAILURE	9 (0.1)	14 (0.2)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	37 (0.6)	31 (0.5)
DYSPNOEA	16 (0.2)	16 (0.2)
PLEURAL EFFUSION	23 (0.4)	21 (0.3)
PULMONARY EMBOLISM	21 (0.3)	16 (0.2)
PULMONARY OEDEMA	10 (0.2)	13 (0.2)
RESPIRATORY FAILURE	15 (0.2)	17 (0.3)
VASCULAR DISORDERS		
DEEP VEIN THROMBOSIS	2 (<0.1)	10 (0.2)
HYPERTENSION	19 (0.3)	19 (0.3)
HYPERTENSIVE CRISIS	11 (0.2)	17 (0.3)
HYPOTENSION	23 (0.4)	26 (0.4)
INTERMITTENT CLAUDICATION	14 (0.2)	7 (0.1)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	10 (0.2)	11 (0.2)

In TRA•CER, unlike TRA 2°P, there was no suggestion of an increased rate of atrial fibrillation or flutter, or syncope with vorapaxar. As in TRA 2°P, the data for pulmonary embolism favored vorapaxar.

7.7 Submission Specific Safety Concerns

7.7.1 Ocular Safety Data

As noted in Sec. **4.3**, vacuoles in the inner nuclear layer (INL) of the retina of rats without evidence of or degenerative changes were observed in studies of 1 to 6 months in duration. These findings prompted the performance of ocular safety studies in humans.

7.7.1.1 Phase 1 Ocular Safety Study (P05185)

This was multicenter, double-blind, parallel placebo-controlled RCT in 118 normal volunteers and 19 patients with documented atherosclerotic disease. Vorapaxar (or matching placebo) was given as a loading dose of 40 mg followed by 2.5 mg daily starting the next day. Randomization was 3:1 (vorapaxar: placebo). Duration of dosing was 1 month, 2 months or 3 months in Groups 1 through 3, respectively; the groups were run serially. Subjects were seen monthly during treatment and then 1 and 2 months after the end of treatment. After each group was completed, the blinded results were reviewed by a Safety Review Committee before the next group began treatment. Spectral domain optical coherence tomography (SD-OCT, used to detect vacuoles), best corrected

visual acuity following standardized refraction, and fundus photography were performed at each visit.

The primary endpoint was the incidence of vacuolation of the retinal INL. Vacuolation was defined as at least one new vacuole (a clear round structure at least 30 µm in diameter.

All 3 groups completed the study. There was 1 subject (1%) in the vorapaxar arm compared to 0 in the placebo arm with vacuolation during treatment. This subject, a 25 year old healthy man with a pre-study quadranopsia (visual field loss in one quarter of the visual field of the eye) and a 1-year history of intermittent visual floaters, who had no vacuoles at baseline, developed multiple vacuoles in both eyes over 3 months of treatment. Vacuoles were apparent after 1 month. The maximal number of vacuoles during treatment was 6 in the right eye at month 1 and 10 in the left eye at month 3. The patient was followed for another 5 months after treatment. At the first monthly post treatment follow-up, there were 0 vacuoles in each eye. Over the next four months of follow-up there were 0 to 4 vacuoles in the right eye and 1 to 26 vacuoles in the left eye. Dr. William Boyd of DAIOP (who consulted on this NDA) noted that this subject did not have changes in visual acuity and suggested that the subject should not have been entered into the study because of his baseline ocular pathology. He also noted that a 7 letter change in acuity is not clinically relevant; the proper metric is a 15 letter change.

The sponsor interpreted this study as showing no ocular safety signal. The FDA ocular consult, Dr. William Boyd of basically agreed, writing: "There does not appear to be an increased ocular risk associated with the use of SCH 530348 based on the evaluations performed."

7.7.1.2 **Ocular Sub-Study in TRA 2ºP (P05183)**

This was multicenter, parallel, placebo controlled study (with randomization and dosing identical to TRA 2ºP). A total of 102 subjects who received treatment were studied. Again, vacuolation was the primary endpoint. Subjects had SD-OCT, best corrected visual acuity following standardized refraction, and fundus photography performed at enrollment and at 4, 8, and 12 months of treatment.

Results are shown below in Table 11 copied from Dr. Boyd's consult. There 2 subjects in the vorapaxar arm (2%) who developed vacuoles; one subject who completed the 12 months of treatment in the ocular study who had vacuolation at month 4 but not month 8 or 12. One other subject developed vacuolation at the 8 month visit, which was 5 months after discontinuation of study drug. There were no vacuoles at month 4 and the subject had no month 12 visit. Neither subject had "functional impairment" associated with these lesions per Dr. Boyd.

Dr. Boyd concluded that "There does not appear to be an increased ocular risk associated with the use of SCH 530348 based on the evaluations performed." He also reviewed the retinal disorder SMQ and ocular bleeding events in TRA 2ºP (the entire study, not just the ocular substudy) and noted that "The ocular bleeding events seen with the drug product in P04737 appear consistent with an anti-platelet product."
It should be noted that Dr. Boyd asked for CRFs for patients with vacuolation. Review of these documents is pending, as well as his review of the diplopia findings discussed below.

Table 11 **Number (%) of Subjects Who Developed Vacuolation Compared to Baseline in Either the Left or Right Eye (All Treated Population)**

(Protocol No. P05183)

	Placebo	Vorapaxar	Vorapaxar − Placebo	
Visit	n/N (%)	n/N (%)	Point Estimate	(95% CI[a])
4 Months	0/86	1[b]/91 (1.1)	1.1	(-13.7, 15.8)
8 Months	0/80	1[c]/86 (1.2)	1.2	(-14.1, 16.4)
12 Months	0/78	0/77	0	—
End of Study	0/87	1[c]/92 (1.1)	1.1	(-13.6, 15.8)

NOTE: Vacuolation is defined as the presence of two or more vacuoles (defined as a clear, round structure in the INL of the retina of at least 30 µm in diameter) compared to baseline in either the left or right eye.

Abbreviations: CI = confidence interval; INL = inner nuclear layer.

[a] Exact CI for the proportion difference.

[b] Subject 11/060025.

[c] Subject 35/060018; 8-month visit was end of study for this subject.

. **Source Data:** Section 14.2.1; Section 16.2.6.1.

7.7.1.3 Ocular Safety in the Phase I TQT Study

The thorough QT study was a typical placebo and moxifloxacin controlled, parallel arm RCT of single dose treatment with vorapaxar 120 mg. The vorapaxar vs. placebo comparison was double-blind. Subjects had eye exams at baseline and the end of the study (day 30), consisting of best corrected visual acuity with refraction, dilated examination of the lens, and dilated fundoscopic examination with 3-7 field retinal photography. Per the Sponsor, there were no notable changes in findings from baseline to after dosing. Dr. Boyd had no comment on this study. Review of the line listings by a DCRP reviewer (MR) revealed no retinal changes in any subject in the vorapaxar, placebo, or moxifloxacin arms (n=42,42, and 39, respectively with baseline and end of study data.

7.7.1.4 Diplopia AEs in the Phase 3 Studies

Diplopia was one of the very few non-bleeding related AEs that was notably more frequent with vorapaxar than placebo.

Cases of diplopia were ascertained by the sponsor's AE analyses in TRA 2ºP and TRA•CER (where an imbalance between the treatment arms was first noted) and also through the comments database in TRA 2ºP. Each of the two Phase 3 studies had an excess of diplopia cases in the vorapaxar arm.

Table 78 Diplopia Cases in Phase 3 Studies

	Diplopia Cases							
	Placebo			Vorapaxar				
Study	*x*	*n*	%	*x*	*n*	%	*% Δ*	*p-value*
TRACER	2	6471	0.03	13	6473	0.20	0.17	0.010
TRA2P	8	13224	0.06	18	13225	0.14	0.08	0.077
TRA2P*	10	13224	0.08	25	13225	0.19	0.11	0.018
TRACER+TRA2P*	12	19695	0.06	38	19698	0.19	0.13	0.018

*Sponsor identified cases plus cases identified by FDA medical officers

Source: Dr. Levine's analysis (see **Attachment 1 Diplopia Review**)

All of the tests of the risk differences were statistically significant (p<0.02) except for the analysis of TRA2P using only sponsor-defined cases.

Further review revealed that the rate of diplopia was highest in the first 180 days of therapy with vorapaxar, but that new reports of diplopia occurred as late as between 720 days to 900 days of therapy. None of the diplopia AEs led to discontinuation of study drug. One case was considered a serious AE. The patient (402-529522 in TRA•CER) was a 65 year old woman who enrolled on the basis of NSTEMI ACS, and had a history of prior MI, PCI, CABG, diabetes, hyperlipidemia, and PAD with a peripheral revascularization procedure. She was hospitalized on study treatment day 215 with acute diplopia. She had a work-up for cerebral ischemia, including a head CT that was negative. The diplopia resolved after one day. It was attributed to possible tiredness and "latent strabismus".

7.7.2 Amyotrophic Lateral Sclerosis

The AE database for TRA 2ºP contains 3 cases coded as ALS in the vorapaxar arm vs. one in the placebo arm. In addition, there was case of "upper motor neurone lesion" that was likely a case of primary lateral sclerosis (PLS) , a condition closely related to ALS. In TRA•CER, there was one case of ALS in the placebo arm. Other cases of spinal cord disease (coded as syringomyelia or spinal cord compression) were reviewed and seemed unlikely to be ALS, but the ALS/PLS cases all seemed possible/probable cases of the coded condition. Thus the final count in the pooled Phase 3 studies was 4 vs. 2 new possible/probable cases of ALS-related conditions in the placebo and vorapaxar arms respectively.

ALS occurs in the West at a rate of about 1-4 cases/100,000 person-years in the overall population.(6) ALS is rare before age 20. In a large Swedish survey, ALS onset occurred at a yearly rate of 1-2 cases/100,000 persons age 20-45 annually. The incidence climbed sharply after that, attaining a level of about 8 to 13 cases/100,000 in those 55 to 74 years, with the highest incidence occurring in those 65-74. Incidence fell after age 75. Incidence in men was slightly higher than in women.(7) In a recently published series of 728 cases from a single US academic center, the mean age of onset was 61years and about 2/3 of cases had onset between age 50 and 74.(8)

The years of high rates of ALS onset overlap with ages of the TRA 2°P and TRA•CER populations (mean (SD) of about 61 (11) and 64 (10) years, respectively). It thus seems reasonable to expect a rate of about 8 new cases of ALS in the pooled Phase 3 population/100,000 pt-years of follow-up. Each pooled treatment arm has about 35,000 patient-years of exposure to study drug, yielding about 2.8 expected cases in each treatment arm during treatment. The observed data from the pooled studies, with 2 vs. 4 possible or probable ALS cases in the placebo and vorapaxar arms, respectively, seem consistent with these expectations.

Reviewer comment: This reviewer (MR) believes there is no actionable signal here.

7.8 Supportive Safety Results

7.8.1 Common Adverse Events

The Sponsor's proposed list of common adverse events for inclusion in labeling is based on treatment-emergent AEs occurring in the vorapaxar arm in proposed label population in TRA 2°P at a rate of at least 2% and at a rate greater than placebo. It is acceptable if the NDA is approved, but should be supplemented by text below it relating to less common AEs (such as diplopia) that may be drug-related.

Table 79 TRA 2ºP - Applicant's Proposed List of Common AEs for Labeling
Clinical Adverse Reactions Occurring in ≥2% of Post-MI Patients with No History of Stroke or TIA Treated with TRADEMARK and at an Incidence Greater than Placebo, Regardless of Causality

System Organ Class **Adverse Reaction**	**PLACEBO N=8,412 %**	**TRADEMARK 2.5 mg N=8,444 %**
Infections and infestations		
Bronchitis	2.5	3.0
Urinary tract infection	4.1	4.3
Blood and lymphatic system disorders		
Anemia	1.9	2.5
Psychiatric disorders		
Depression	2.0	2.3
Cardiac disorders		
Palpitations	1.9	2.1
Respiratory, thoracic, and mediastinal disorders		
Cough	3.8	3.9
Musculoskeletal and connective tissue disorders		
Arthralgia	3.1	3.3
Myalgia	3.4	3.6
General disorders and administration site conditions		
Fatigue	4.7	4.8
Investigations		
Alanine aminotransferase increased	1.9	2.1
Injury, poisoning, and procedural complications		
Fall	2.6	2.7

Source: Vorapaxar proposed labeling

7.8.2 Laboratory Findings

With a few exceptions noted below, the laboratory findings of post-baseline abnormalities in the pooled Phase 3 studies (N=19607 and N=19632 in the placebo and vorapaxar arms respectively), were similar in treatment arms for blood studies (hematology, electrolytes, and other clinical chemistry), and urinalysis (source: ISS tables 4.2.1 to 4.2.14).

For the following laboratory studies, abnormal values were more common in the pooled vorapaxar group:

Table 80 Post-Baseline Laboratory Abnormalities with Notable Differences in Rates between Treatment Arms in the Pooled Phase 3 Studies

Laboratory test and abnormality	**PLACEBO N=19607 n (%)**	**VORAPAXAR N=19,632 n (%)**
GGT (Baseline <2x ULN)	*17142*	*17283*
>=3xULN	565 (3.3)	654 (3.8)
Hemoglobin (subjects with significant bleeds)* F: <8 g/dL M: <9 g/dL	327/1529 (21.4)	503/2153 (23.4)
Hemoglobin (no significant bleeds)* F, M: <10 g/dL	1406/19285 (7.3)	1703/19292 (8.8)
Urinary RBC (cells per HPF)	*2661*	*3238*
6-15	570 (21.4)	768 (23.7)
16-29	162 (6.1)	213 (6.6)
30-49	77 (2.9)	159 (4.9)
50-75	56 (2.1)	84 (2.6)
>75	126 (4.7)	175 (5.4)
Blood by dipstick	*16834*	*16811*
TRACE	1095 (6.5)	1285 (7.6)
SMALL	640 (3.8)	747 (4.4)
MODERATE	371 (2.2)	536 (3.2)
LARGE	264 (1.6)	389 (2.3)

*Significant bleeds defined as bleeding adjudicated by the CEC to be CABG or nonCABG TIMI Major bleeding, nonCABG TIMI Minor bleeding, and other nonCABG bleeding requiring medical attention with 2 weeks prior to blood draw.

GGT was the only liver function test with a difference in the rates of abnormality between the treatment arms. Thus, there was no signal of hepatocellular damage.

The difference in hemoglobin abnormalities is consistent with the increased risk of bleeding with vorapaxar. There was also an increased rate of abnormalities of hematocrit (data not shown).

The increased rates of urinary RBC on microscopy and positive urine dipstick values for blood with vorapaxar with vorapaxar are not expected. However, there was no increased rate of renal failure AEs or changes in creatinine or BUN. Of note, there was an increase rate of “cystitis” with vorapaxar – 118 (0.6%) vs. 156 (0.8%) subjects. Rates of “urinary tract infection” were similar while the rates of “pyelonephritis” favored vorapaxar (26 vs. 18 subjects, 0.1% in each arm).

7.8.3 Vital Signs

Based on specified and reasonable change and absolute value criteria for heart rate, diastolic blood pressure and systolic blood pressure, there were no notable differences of the effects of vorapaxar vs. placebo in the pooled Phase population (ISS Display 4.1). .

7.8.4 Electrocardiograms (ECGs)

No clinically relevant differences between treatment groups were observed in ECG changes over time in the pooled Phase 3 studies (ISS display 4.3)

7.8.5 Special Safety Studies/Clinical Trials (TQT)

The Applicant's TQT study, P03462 (blinded, placebo-controlled, positive control) was reviewed by the IRT(review dated 27 Sept 2010). Subjects received single doses of vorapaxar (120 mg), placebo or moxifloxacin control. The upper bound of the 90% CI for ΔΔ QTc Fridericia was 4.3 ms for vorapaxar, with mean (90% CI) value for moxifloxacin of 11.4 msec (8.8, 14.0). The study was interpreted as showing assay sensitivity and finding "no significant QT prolongation effect" of vorapaxar. With the 120 mg dose, vorapaxar Cmax was 733 ng/mL (CV 26%) and AUC 0-24 was 6768 (CV 23%) ng hr/mL.

7.8.6 Immunogenicity

Not applicable

7.9 Other Safety Explorations

7.9.1 Dose Dependency for Adverse Events

Only the 5 mg dose was used as a maintenance dose in Phase 3, so it is difficult to assess dose dependency of adverse events in those trials.

Summaries provided with the NDA included a summary of one Phase 2 study (P05005) in neurologically stable Japanese adults with a prior history of stroke 14 days – 1 year prior to entry. Subjects were randomized to either placebo, vorapaxar 1 mg daily, or vorapaxar 2.5 mg daily for 60 days to be added to standard care (n=28-33 per arm). The summary includes no information on standard care. The study was intended primarily evaluate safety. The primary efficacy endpoint was MACE, defined as CV death or nonfatal MI, nonfatal stroke, acute hospitalization due to cardiac ischemia not meeting the protocol definition of MI, emergency cardiac revascularization, or any revascularization, including coronary and carotid arteries, extra- or intracranial bypass surgery, and amputation for ischemic limb. Subjects were followed for 120 days. Bleeding data were captured using the TIMI classification system.

Rates of bleeding (any type) were 21%, 15% and 34% in the placebo, 1 mg and 2.5 mg arms. Nearly all bleeding was non-TIMI. One subject in the 2.5 mg arm had a cerebral bleed in the follow-up period and survived; this was the only TIMI bleed in the vorapaxar arms. One placebo patient had a TIMI minor bleed. Strokes occurred during treatment in one patient in the placebo arm and one in the 1 mg arm. In the followup period, strokes occurred in 2 placebo arm patients and 1 patient in each of the vorapaxar arms (the patient in the 1 mg arm with a follow-up period stroke also had a stroke during treatment. There were no deaths or MIs or other MACE events.

Clinical results of this study suggest that 1 mg may be a useful maintenance dose. Other than this one summary, this reviewer was unable to find any summary data comparing maintenance doses of vorapaxar.

7.9.2 Time Dependency for Adverse Events

Bleeding is the major toxicity of vorapaxar. Because of the use of a loading dose in TRA•CER, as well as frequent use of IV anticoagulants and antiplatelet agents in the hospital, only the TRA•CER bleeding data will be summarized for time dependency.

Table 81 is display of the incidence of bleeding events over time, and includes data on the first bleeding event for a patient (of any severity) as well as any bleeding event. Each period is 180 days long; the table covers first dose to day 1080 (about 3 years). In each period, bleeding with vorapaxar is more common than with placebo. In the first 180 days, first bleeds occur in about 14% of vorapaxar patients. After that, the rate of first bleeds falls dramatically and steadily to about 2% of remaining subjects in the period covering days 901 to 1080. However, the rate of any bleeding falls considerably less steeply and is never less than about 6.5% of vorapaxar arm patients.

Table 81 TRA 2ºP - Incidence of Bleeding Events during Treatment Over Time
Any First Bleeding Event and Any Bleeding Event

	First Bleeding Event		Any Bleeding Event	
Time Period (days)	Placebo n (%)*	Vorapaxar n (%)*	Placebo n (%)*	Vorapaxar n (%)*
≤180	1110 (8.4)	1782 (13.5)	1110 (8.4)	1782 (13.5)
181-360	561 (4.6)	745 (6.2)	865 (7.2)	1226 (10.2
361- 540	324 (2.8)	451 (3.9)	627 (5.4)	922 (8.0)
541-720	254 (2.3)	360 (3.3)	522 (4.8)	751 (6.9)
721-900	175 (2.1)	225 (2.8)	380 (4.6)	534 (6.5)
901-1080	91 (1.7)	126 (2.4)	248 (4.7)	334 (6.4)

*Percentages are based on N of subjects who received treatment in the relevant period. For vorapaxar, N ranges from 13186 for first period shown to N=5206 in the latest period shown. Placebo Ns are similar.

7.9.3 Drug-Demographic Interactions and Drug-Disease Interactions

See Sec. **7.4.1.4** for information regarding bleeding risk in various subgroups.

7.10 Additional Safety Evaluations

7.10.1 Human Reproduction and Pregnancy Data

Vorapaxar has not been studied in pregnant or lactating women. Studies in animals suggest that vorapaxar may affect fetal development; in addition vorapaxar was excreted in breast milk. TRADEMARK should be used during pregnancy or lactation only if the potential benefit to the mother justifies the potential risk to the fetus or the infant.

7.10.2 Pediatrics and Assessment of Effects on Growth

Not done.

7.10.3 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In TRA 2ºP and TRA•CER there were 39 cases of overdose reported (29 in TRA 2ºP and 10 in TRA•CER). In 5 cases, a clinical AE was associated with the overdose; all of these were in TRA 2ºP. The Applicant describes these cases as follows:

- "Subject 0112/003672 developed diarrhea. The diarrhea resolved after study drug was interrupted. The diarrhea was assessed as possibly related to study drug. There were no reports of diarrhea after study dug was restarted.
- Subject 3525/050009 experienced increased creatinine and worsening of renal insufficiency. Study drug was interrupted due to the increased creatinine and discontinued due to the worsening renal insufficiency. Both adverse events resolved. The investigator believed that the overdose possibly influenced the subject's increased creatinine/worsening kidney function.
- Subject 3661/020522 experienced mild bleeding of a pre-existing vascular angioma of the lip which required cauterization. Study drug was not interrupted. The subject recovered.
- Subject 1714/050207 had miscellaneous skin bleeding (multiple skin hematomas), headache, fatigue and dyssomnia. Laboratory results showed a platelet count of 130 (low range 150). Study drug was discontinued. The subject's condition improved.
- Subject 2410/000209 experienced spontaneous ecchymosis of the right arm one day after an intentional overdose. Study drug was interrupted. The bleeding event resolved and did not recur when study drug was resumed.

"Of the five reports of overdose with associated events, four were associated with intake of 5 mg of vorapaxar per day for ≥ 28 consecutive days of and one involved intake of a single dose greater than 120 mg [2410/000209, suicide attempt (TRA 2ºP-TIMI 50)]."

"Of the 34 overdoses without associated adverse events, 32 included ≥28 consecutive days of 5 mg per day and 2 overdoses included single doses greater than 120 mg (two cases of suicide attempt from TRA 2ºP-TIMI 50P: 1010/012607 and 1258/031499). Study drug was discontinued in one case from TRA 2ºP-TIMI 50 (1010/012607, suicide attempt). Study drug was interrupted in five cases in TRA 2ºP-TIMI 50 (0112/003672, 1010/012607, 2406/002009, 2410/000209, and 0204/051884).

"Although described as having no associated adverse event, the narratives for one of the 34 cases suggested that there may have been an event associated with the reported overdose. Subject 3676/040110 (TRA 2ºP-TIMI 50) was noted to have scleral hemorrhages."

Four additional cases involved family members or others who ingested study drug, but only two of these involved active drug.

- A 2 year old boy ingested 30 tablets. The child was asymptomatic but was taken to a hospital and treated with gastric lavage and a laxative. There were no relevant findings on blood tests (hemogram, biochemistry, and coagulation). The subject was discharged.

- A 14 year old female "accidently" ingested 15 tablets of study medication. The subject was hospitalized. Blood tests (unspecified) were normal. The subject recovered. 34 cases, there was not an AE, while subjects on vorapaxar ; overdose was either from study drug or concomitant nonstudy medications. Four of these subjects had overdoses during the 30 day post-treatment period. Overdose was reported as an SAE in 28 cases. Only 2 events led to treatment discontinuation. In TRA•CER, there were 5 cases of overdose reported in 4 subjects in the vorapaxar group. Four of these cases were SAEs and one led to treatment discontinuation. All events resolved. [Source: Applicant's Summary of Clinical Safety, p.216-17.

Rebound phenomena seem unlikely due to the very long elimination phase. The Applicant indicates that PAR-1 receptors are not upregulated as a result of blockade, but no data are cited to support this claim. The Applicant also notes that in TRA 2ºP, the ITT analysis is more favorable for vorapaxar than the on-treatment analysis, suggesting a lack of rebound effects.

There is no known pharmacological treatment to reverse the effects of vorapaxar. Use of platelet transfusion might help to reverse the antiplatelet effect of vorapaxar, but there has been no clinical experience with this technique. The sponsor suggests treatment of "signs and symptoms" in the event of overdose.

There was no evidence suggesting drug abuse/dependence on vorapaxar.

7.11 Additional Submissions / Safety Issues

There was no new safety information in the update report.

7.12 Data regarding adjudication of efficacy endpoints

The ENDPTS analysis file contains a variable("SOURCE") which indicates whether an endpoint was "called" by the investigator and the CEC (SOURCE=1) or only the CEC (SOURCE=2). By definition, unless the endpoint is called by the CEC, it is not endpoint.

All Key Secondary Endpoints (CV death, MI or stroke) were selected in the ENDPTS dataset. Table xx shows the distribution of SOURCE values in the two treatment arms.

Table 82 Key Secondary Endpoints by Treatment and Adjudication "Source"
ITT Population, Randomization to Last Visit

Source Variable	Placebo N=1173 n (%)	Vorapaxar N=1028 n (%)
1 (event called by investigator and CEC)	863 (73)	783 (76)
2 (event called by CEC only)	313 (27)	245 (24)

Overall, about ¼ of adjudicated events were not called by the investigator. Review of case records of a small sample of these events in the placebo arm (where the CEC's discordant adjudication would increase the placebo event rate) revealed that the investigator appropriately filled in forms that would trigger adjudication, but diagnosed the case as a non-endpoint event (i.e., TIA instead of stroke or unstable angina instead of MI, or one case, failed to appreciate a case of hemorrhagic conversion of a diagnosed stroke). . In all such cases, the CEC's adjudication of the event was supported by the case record.

After further discussions with the Applicant, I hope to find identify and review cases where the CEC reversed the investigator's call of an event.

8 Postmarketing Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

See p. **165** for reference list.

9.2 Labeling Recommendations

See **Proposed Labeling** starting on page **179.**

9.3 Advisory Committee Meeting

An advisory committee meeting to consider this NDA is scheduled for January 15, 2014.

Clinical questions that are unique to this application being considered for the committee include:

1. The Applicant proposes a contraindication for use in patients subjects with a prior history stroke or TIA due primarily to an increased risk of stroke on treatment. However, the Applicant's data suggests that patients whose stroke was earlier than 6 months prior to the start of therapy have good outcomes. Should the limit on use in those with prior stroke reflect these data?
2. Should the target population for vorapaxar use include those with PAD and prior MI or just those with prior MI?

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Post Text Tables and Figures

Table 83 TRA•CER – Medical History and Risk Factors

Variable	Placebo (n = 6471)	SCH 530348 (n = 6473)	Total (n = 12944)
Hypertension			
No	1878 (29.0)	1933 (29.9)	3811 (29.4)
Yes	4591 (70.9)	4537 (70.1)	9128 (70.5)
Missing	2 (<0.1)	3 (<0.1)	5 (<0.1)
History of Cigarette Smoking			
No	2598 (40.1)	2617 (40.4)	5215 (40.3)
Yes (current smoker?)	3870 (59.8)	3852 (59.5)	7722 (59.7)
No	2083 (32.2)	2103 (32.5)	4186 (32.3)
Yes	1787 (27.6)	1749 (27.0)	3536 (27.3)
Missing	3 (<0.1)	4 (0.1)	7 (0.1)
Hyperlipidemia			
No	2443 (37.8)	2431 (37.6)	4874 (37.7)
Yes	4024 (62.2)	4038 (62.4)	8062 (62.3)
Controlled by Medication	3096 (47.8)	3059 (47.3)	6155 (47.6)
Lifestyle Only	928 (14.3)	977 (15.1)	1905 (14.7)
Missing	0	2 (<0.1)	2 (<0.1)
Missing	4 (0.1)	4 (0.1)	8 (0.1)
Diabetes Mellitus			
No	4439 (68.6)	4429 (68.4)	8868 (68.5)
Yes	2030 (31.4)	2040 (31.5)	4070 (31.4)
Treated with Oral Hypoglycemic	1119 (17.3)	1144 (17.7)	2263 (17.5)
Treated with Insulin	593 (9.2)	578 (8.9)	1171 (9.0)
Lifestyle Only	318 (4.9)	318 (4.9)	636 (4.9)
Missing	2 (<0.1)	4 (0.1)	6 (<0.1)
Family History of Premature CAD			
No	3875 (59.9)	3812 (58.9)	7687 (59.4)
Yes	1747 (27.0)	1812 (28.0)	3559 (27.5)
Unknown	847 (13.1)	846 (13.1)	1693 (13.1)
Missing	2 (<0.1)	3 (<0.1)	5 (<0.1)

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Variable	Placebo (n = 6471)	SCH 530348 (n = 6473)	Total (n = 12944)
Prior Myocardial Infarction			
No	4579 (70.8)	4568 (70.6)	9147 (70.7)
Yes	1890 (29.2)	1901 (29.4)	3791 (29.3)
Type Most Recent			
STEMI	491 (7.6)	514 (7.9)	1005 (7.8)
NSTEMI	652 (10.1)	639 (9.9)	1291 (10.0)
Unknown	747 (11.5)	748 (11.6)	1495 (11.5)
Missing	2 (<0.1)	4 (0.1)	6 (<0.1)
Prior Angina			
No	3142 (48.6)	3096 (47.8)	6238 (48.2)
Yes	3325 (51.4)	3373 (52.1)	6698 (51.7)
Missing	4 (0.1)	4 (0.1)	8 (0.1)
Prior Stroke			
No	6207 (95.9)	6179 (95.5)	12386 (95.7)
Yes	262 (4.0)	291 (4.5)	553 (4.3)
When Most Recent			
≤3 Months	8 (0.1)	8 (0.1)	16 (0.1)
>3 Months to ≤6 Months	9 (0.1)	10 (0.2)	19 (0.1)
>6 Months to ≤12 Months	11 (0.2)	17 (0.3)	28 (0.2)
>12 Months	218 (3.4)	235 (3.6)	453 (3.5)
Missing/ Unknown	16 (0.2)	21 (0.3)	37 (0.3)
Modified Rankin Scale Score			
0 (no symptom)	131 (2.0)	142 (2.2)	273 (2.1)
1 (no disability)	68 (1.1)	81 (1.3)	149 (1.2)
2 (slight)	30 (0.5)	32 (0.5)	62 (0.5)
3 (moderate)	21 (0.3)	18 (0.3)	39 (0.3)
4 (moderately severe)	6 (0.1)	8 (0.1)	14 (0.1)
5 (severe)	0	0	0
Missing	6 (0.1)	10 (0.2)	16 (0.1)
Missing	2 (<0.1)	3 (<0.1)	5 (<0.1)

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Variable	Placebo (n = 6471)	SCH 530348 (n = 6473)	Total (n = 12944)
Prior Transient Ischemic Attack			
No	6309 (97.5)	6302 (97.4)	12611 (97.4)
Yes	157 (2.4)	168 (2.6)	325 (2.5)
When Most Recent			
≤12 Months	30 (0.5)	32 (0.5)	62 (0.5)
>12 Months	119 (1.8)	123 (1.9)	242 (1.9)
Missing/ Unknown	8 (0.1)	13 (0.2)	21 (0.2)
Missing	5 (0.1)	3 (<0.1)	8 (0.1)
Prior Peripheral Arterial Disease			
No	6000 (92.7)	6001 (92.7)	12001 (92.7)
Yes	468 (7.2)	468 (7.2)	936 (7.2)
Missing	3 (<0.1)	4 (0.1)	7 (0.1)
Claudication			
No	6246 (96.5)	6258 (96.7)	12504 (96.6)
Yes	209 (3.2)	196 (3.0)	405 (3.1)
Missing	16 (0.2)	19 (0.3)	35 (0.3)
Heart Failure			
No	5832 (90.1)	5895 (91.1)	11727 (90.6)
Yes	635 (9.8)	574 (8.9)	1209 (9.3)
Missing	4 (0.1)	4 (0.1)	8 (0.1)
History of Atrial Fibrillation/Flutter			
No	6177 (95.5)	6193 (95.7)	12370 (95.6)
Yes	291 (4.5)	277 (4.3)	568 (4.4)
Missing	3 (<0.1)	3 (<0.1)	6 (<0.1)
Prior PCI			
No	4936 (76.3)	4908 (75.8)	9844 (76.1)
Yes[a]	1531 (23.7)	1559 (24.1)	3090 (23.9)
Drug Eluting Stent	658 (10.2)	644 (9.9)	1302 (10.1)
Bare Metal Stent	714 (11.0)	754 (11.6)	1468 (11.3)
When Most Recent			
≤12 Months	376 (5.8)	389 (6.0)	765 (5.9)
>12 Months	1142 (17.6)	1160 (17.9)	2302 (17.8)
Missing/ Unknown	13 (0.2)	10 (0.2)	23 (0.2)
Missing	4 (0.1)	6 (0.1)	10 (0.1)

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Variable	Placebo (n = 6471)	SCH 530348 (n = 6473)	Total (n = 12944)
Prior CABG			
No	5703 (88.1)	5693 (87.9)	11396 (88.0)
Yes	766 (11.8)	777 (12.0)	1543 (11.9)
When Most Recent			
≤12 Months	65 (1.0)	69 (1.1)	134 (1.0)
>12 Months	697 (10.8)	707 (10.9)	1404 (10.8)
Missing/ Unknown	4 (0.1)	1 (<0.1)	5 (<0.1)
Missing	2 (<0.1)	3 (<0.1)	5 (<0.1)
Prior Percutaneous Carotid Intervention			
No	6427 (99.3)	6436 (99.4)	12863 (99.4)
Yes	41 (0.6)	33 (0.5)	74 (0.6)
Location			
Unilateral	33 (0.5)	28 (0.4)	61 (0.5)
Bilateral	6 (0.1)	5 (0.1)	11 (0.1)
Missing	2 (<0.1)	0	2 (<0.1)
When Most Recent			
≤12 Months	6 (0.1)	2 (<0.1)	8 (0.1)
>12 Months	34 (0.5)	30 (0.5)	64 (0.5)
Missing/ Unknown	1 (<0.1)	1 (<0.1)	2 (<0.1)
Missing	3 (<0.1)	4 (0.1)	7 (0.1)
Prior Carotid Endarterectomy			
No	6388 (98.7)	6379 (98.5)	12767 (98.6)
Yes	80 (1.2)	89 (1.4)	169 (1.3)
Location			
Unilateral	64 (1.0)	74 (1.1)	138 (1.1)
Bilateral	15 (0.2)	15 (0.2)	30 (0.2)
Missing	1 (<0.1)	0	1 (<0.1)
When Most Recent			
≤12 Months	10 (0.2)	10 (0.2)	20 (0.2)
>12 Months	69 (1.1)	77 (1.2)	146 (1.1)
Missing/ Unknown	1 (<0.1)	2 (<0.1)	3 (<0.1)
Missing	3 (<0.1)	5 (0.1)	8 (0.1)

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Variable	Placebo (n = 6471)	SCH 530348 (n = 6473)	Total (n = 12944)
Prior Peripheral Arterial Revascularization			
No	6266 (96.8)	6297 (97.3)	12563 (97.1)
Yes	203 (3.1)	172 (2.7)	375 (2.9)
Missing	2 (<0.1)	4 (0.1)	6 (<0.1)
Prior Amputation Related to Limb Ischemia			
No	6437 (99.5)	6436 (99.4)	12873 (99.5)
Yes	32 (0.5)	34 (0.5)	66 (0.5)
Missing	2 (<0.1)	3 (<0.1)	5 (<0.1)
Prior History of Hepatic Disease			
No	6352 (98.2)	6352 (98.1)	12704 (98.1)
Yes	116 (1.8)	117 (1.8)	233 (1.8)
Missing	3 (<0.1)	4 (0.1)	7 (0.1)
Hepatic Function at Baseline			
ALT ≥2xULN	240/6101 (3.9)	203/6117 (3.3)	443/12218 (3.6)
AST ≥2xULN	1172/6047 (19.4)	1062/6044 (17.6)	2234/12091 (18.5)
Alkaline phosphatase ≥2xULN	11/6136 (0.2)	15/6155 (0.2)	26/12291 (0.2)
GGT ≥2xULN	472/6127 (7.7)	408/6149 (6.6)	880/12276 (7.2)
Total Bilirubin ≥1.5xULN	100/6126 (1.6)	95/6147 (1.5)	195/12273 (1.6)
LDL Cholesterol at Baseline (mmol/L)			
Number of Subjects	5886	5930	11816
Mean (SD)	2.85 (1.05)	2.86 (1.05)	2.85 (1.05)
Median	2.75	2.77	2.75
25th to 75th Percentile	2.07 – 3.50	2.10 – 3.52	2.07 – 3.52
Min-Max[b]	0.03 – 8.42	0.00 – 8.57	0.00 – 8.57
Missing	585	543	1128

Variable	Placebo (n = 6471)	SCH 530348 (n = 6473)	Total (n = 12944)
Calculated Creatinine Clearance at Baseline[c]			
<60 mL/min	831 (12.8)	836 (12.9)	1667 (12.9)
≥60 mL/min	5289 (81.7)	5305 (82.0)	10594 (81.8)
Not Able to Calculate	351 (5.4)	332 (5.1)	683 (5.3)
Estimated Glomerular Filtration Rate (eGFR) at Baseline[d]			
<60 mL/min•1.73m^2	859 (13.3)	916 (14.2)	1775 (13.7)
≥60 mL/min•1.73m^2	5283 (81.6)	5249 (81.1)	10532 (81.4)
Not Able to Calculate	329 (5.1)	308 (4.8)	637 (4.9)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CABG = coronary artery bypass grafting; CAD = coronary artery disease; GGT = gamma-glutamyl transferase; HDL = high density lipoprotein; LDL = low density lipoprotein; MI = myocardial infarction; NSTEMI = non-ST-segment-elevation myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; SD = standard deviation; STEMI = ST-segment-elevation myocardial infarction; TIA = transient ischemic attack; UA = unstable angina; ULN = upper limit of normal (upper limit of the reference range).

[a] 'Drug Eluting Stent' and 'Bare Metal Stent' rows are not mutually exclusive and cannot be summed to yield the overall 'Yes' row.

[b] There was a data error as one subject was identified in the data base to have an LDL-C = 0 at baseline (subject number = 524441, site = 2802).

[c] Cockcroft-Gault equation.

[d] Modification of Diet in Renal Disease (MDRD) equation.

Table 84 TRA•CER – Enrollment by Geographic Region and Country

Region/Country	Placebo (n = 6471)	SCH 530348 (n = 6473)	Total (n = 12944)
North America	**1694 (26.2)**	**1710 (26.4)**	**3404 (26.3)**
Canada	304 (4.7)	287 (4.4)	591 (4.6)
USA	1390 (21.5)	1423 (22.0)	2813 (21.7)
Europe 1	**2930 (45.3)**	**2909 (44.9)**	**5839 (45.1)**
Austria	161 (2.5)	158 (2.4)	319 (2.5)
Belgium	77 (1.2)	76 (1.2)	153 (1.2)
Denmark	103 (1.6)	102 (1.6)	205 (1.6)
Finland	56 (0.9)	63 (1.0)	119 (0.9)
France	220 (3.4)	221 (3.4)	441 (3.4)
Germany	455 (7.0)	456 (7.0)	911 (7.0)
Israel[a]	207 (3.2)	203 (3.1)	410 (3.2)
Italy	394 (6.1)	370 (5.7)	764 (5.9)
Netherlands, The	235 (3.6)	236 (3.6)	471 (3.6)
Norway	127 (2.0)	124 (1.9)	251 (1.9)
Portugal	94 (1.5)	95 (1.5)	189 (1.5)
South Africa	103 (1.6)	104 (1.6)	207 (1.6)
Spain	188 (2.9)	191 (3.0)	379 (2.9)
Sweden	171 (2.6)	175 (2.7)	346 (2.7)
Switzerland	105 (1.6)	106 (1.6)	211 (1.6)
United Kingdom	234 (3.6)	229 (3.5)	463 (3.6)
Europe 2	**742 (11.5)**	**745 (11.5)**	**1487 (11.5)**
Czech Republic	246 (3.8)	250 (3.9)	496 (3.8)
Hungary	133 (2.1)	133 (2.1)	266 (2.1)
Poland	280 (4.3)	281 (4.3)	561 (4.3)
Turkey	83 (1.3)	81 (1.3)	164 (1.3)
Latin America	**420 (6.5)**	**428 (6.6)**	**848 (6.6)**
Argentina	61 (0.9)	69 (1.1)	130 (1.0)
Brazil	143 (2.2)	141 (2.2)	284 (2.2)
Chile	75 (1.2)	73 (1.1)	148 (1.1)
Colombia	136 (2.1)	139 (2.1)	275 (2.1)
Peru	5 (0.1)	6 (0.1)	11 (0.1)
Asia/Pacific	**474 (7.3)**	**462 (7.1)**	**936 (7.2)**
Hong Kong	8 (0.1)	9 (0.1)	17 (0.1)
Japan	143 (2.2)	133 (2.1)	276 (2.1)
Malaysia	25 (0.4)	27 (0.4)	52 (0.4)
Peoples Republic of China	109 (1.7)	110 (1.7)	219 (1.7)
Singapore	14 (0.2)	12 (0.2)	26 (0.2)
South Korea	64 (1.0)	63 (1.0)	127 (1.0)
Taiwan	111 (1.7)	108 (1.7)	219 (1.7)
Australia/New Zealand	**211 (3.3)**	**219 (3.4)**	**430 (3.3)**
Australia	115 (1.8)	120 (1.9)	235 (1.8)
New Zealand	96 (1.5)	99 (1.5)	195 (1.5)

Table 85 TRA 2ºP – Enrollment by Region and Country

	Placebo n=13224	SCH 530348 n=13225	TOTAL n=26449
North America	3920(29.6)	3916(29.6)	7836(29.6)
Canada	949 (7.2)	943 (7.1)	1892 (7.2)
Puerto Rico	19 (0.1)	17 (0.1)	36 (0.1)
United States	2952(22.3)	2956(22.4)	5908(22.3)
Europe 1	5604(42.4)	5612(42.4)	11216(42.4)
Austria	141 (1.1)	146 (1.1)	287 (1.1)
Belgium	426 (3.2)	428 (3.2)	854 (3.2)
Denmark	283 (2.1)	282 (2.1)	565 (2.1)
Finland	92 (0.7)	89 (0.7)	181 (0.7)
France	179 (1.4)	182 (1.4)	361 (1.4)
Germany	500 (3.8)	505 (3.8)	1005 (3.8)
Israel	372 (2.8)	377 (2.9)	749 (2.8)
Italy	377 (2.9)	374 (2.8)	751 (2.8)
Netherlands	954 (7.2)	952 (7.2)	1906 (7.2)
Norway	236 (1.8)	237 (1.8)	473 (1.8)
Portugal	89 (0.7)	86 (0.7)	175 (0.7)
South Africa	628 (4.7)	629 (4.8)	1257 (4.8)
Spain	234 (1.8)	232 (1.8)	466 (1.8)
Sweden	348 (2.6)	347 (2.6)	695 (2.6)
Switzerland	220 (1.7)	219 (1.7)	439 (1.7)
United Kingdom	525 (4.0)	527 (4.0)	1052 (4.0)
Europe 2	1319(10.0)	1317(10.0)	2636(10.0)
Czech Republic	680 (5.1)	676 (5.1)	1356 (5.1)
Hungary	102 (0.8)	105 (0.8)	207 (0.8)
Poland	537 (4.1)	536 (4.1)	1073 (4.1)
Latin America	1646(12.4)	1648(12.5)	3294(12.5)
Argentina	475 (3.6)	477 (3.6)	952 (3.6)
Brazil	568 (4.3)	566 (4.3)	1134 (4.3)
Chile	198 (1.5)	198 (1.5)	396 (1.5)
Colombia	405 (3.1)	407 (3.1)	812 (3.1)
Asia/Pacific	389 (2.9)	388 (2.9)	777 (2.9)
Hong Kong	45 (0.3)	44 (0.3)	89 (0.3)
Japan	291 (2.2)	289 (2.2)	580 (2.2)
Malaysia	40 (0.3)	41 (0.3)	81 (0.3)
Singapore	13 (0.1)	14 (0.1)	27 (0.1)
Australia/New Zealand	346 (2.6)	344 (2.6)	690 (2.6)
Australia	206 (1.6)	205 (1.6)	411 (1.6)
New Zealand	140 (1.1)	139 (1.1)	279 (1.1)

Israel and South Africa were included in "Europe 1" for administrative reasons.

Table 86 TRA 2°P Study Visits and Assessments

Assessment, Collection, Evaluation, or Procedure	Enrollment/ Randomization	Visits During First Year[a]				Visits After First Year (every 6 months)		Completion or Early Discontinuation of Treatment[a]	Early Discontinuation Telephone Follow-up[b]
		30 Days (±7 days)	4 Months (±10 days)	8 Months (±10 days)	12 Months (±10 days)	Semi-Annual (±10 days)	Annual (±10 days)		
Explain Study / Written Informed Consent(s)[c]	X	-	-	-	-	-	-	-	-
Review Inclusion/Exclusion Criteria	X	-	-	-	-	-	-	-	-
Medical History	X[d]	-	-	-	-	-	-	-	-
Physical Examination	X[d]							X	-
Determine Resting Ankle/Brachial Index (ABI)	X[d]							X[e]	-
Perform Claudication Grading	X				X			X	-
Determine Killip Classification	X	X			X			X	-
Determine New York Heart Association (NYHA) and Canadian Cardiovascular Society (CCS) Classifications	X	X	X	X	X	X	X	X	-
Determine Modified Rankin Scale Score ***(NOTE: If subject has a history of stroke, or initial stroke occurs during study, instructions in Section 5.3 supersede these instructions)***	If history of stroke	If suspected stoke occurs, determine at time of suspected event, at hospital discharge, 90-120 days after event, and every visit thereafter							-
Pregnancy Test (all women of child-bearing potential)[f]	X	-	X	X	X	X	X	X	-
Record Concomitant Medications/Therapies as specified in Section 7.4.2.1, and Concomitant Illness	X (outpatient therapies only)	X	X	X	X	X	X	X	-
Clinic Assessment (blood pressure and pulse at every assessment; waist circumference, body weight, and height at enrollment only)	X	X	X	X	X	X	X	X	-

Assessment, Collection, Evaluation, or Procedure	Enrollment/ Randomization	Visits During First Year[a]				Visits After First Year (every 6 months)		Completion or Early Discontinuation of Treatment[b]	Early Discontinuation Telephone Follow-up[b]
		30 Days (±7 days)	4 Months (±10 days)	8 Months (±10 days)	12 Months (±10 days)	Semi-Annual (±10 days)	Annual (±10 days)		
Electrocardiogram	X[d]	J[j]	J[j]	J[j]	X	J[j]	X	X	-
Sample Collections: all protocol-required samples collected on an outpatient basis are to be sent to the central laboratory									-
Standard Laboratory Tests									-
CBC[f]/Platelet Count	X	X	X	X	X	X	X	X	-
PT/aPTT/INR	X	-	-	-	X	-	X	X	-
Abbreviated Safety Panel[f]	-	X	X	X	-	X	-	-	-
Extended Safety Panel[f]	X	-	-	-	X	-	X	X	-
Special Tests and Collections									-
sCD40 Ligand	X	X	X	-	X	-	-	X	-
hs-CRP	X	X	-	-	X	-	-	X	-
Plasma/Serum for Vascular Biomarkers[h]	X	X	-	-	X	-	-	X	-
Sample for DNA Extraction[c]	X[c]	-	-	-	-	-	-	-	-
Record Suspected Efficacy Endpoint Events, Bleeding Events, and Adverse Events	X	X	X	X	X	X	X	X	X
Randomized Treatment Assignment	X[j]	-	-	-	-	-	-	-	-
Dispense New Study Medication	X[j]	-	X	X	X	X	X	-	-
Collect/Keep Unused Study Medication From Previous Visit and Assess Compliance	-	-	X	X	X	X	X	X	-

a Timing of visits is relative to the day of randomized assignment of study treatment.
b A subject is considered to have completed study treatment when he/she, while still taking study treatment, returns for a final study visit as a result of the Executive Committee recommendation to close the trial. Subjects who discontinue study treatment early will continue to participate in the study with follow-up monitoring via telephone contact by the investigator/qualified designee on the same schedule above to collect information on any suspected efficacy endpoint/bleeding event. During these telephone contacts, the investigator/qualified designee will also collect information about any serious adverse event that occurred up to 60 days after the last dose of study treatment.
c Written informed consent for DNA sampling may be contained in the same instrument as written informed consent for the rest of the study, or may be a separate document, at the discretion of the institutional review board/independent ethics committee. Regardless, a separate signature of informed consent is required to collect the DNA sample. Consent and the sample for

DNA extraction should be collected at Enrollment/Randomization, but may be obtained at any subsequent visit if not done at enrollment. See also **Section 7.3.3** and **Appendix 2**.

d Accept information collected within the previous 3 weeks for subjects who are clinically stable.

e Not required if treatment is discontinued <12 months after enrollment.

f The investigator will affirm (method left to discretion of investigator) that the subject is not pregnant, as well as send a sample to the central laboratory to allow processing of a serum pregnancy test. The investigator does not have to affirm at Completion or Early Discontinuation of Treatment. If more frequent pregnancy testing is required by local law, perform the testing as required and report pregnancy as specified in **Section 7.7.2.2.7**.

g If the subject had symptoms of cardiac ischemia since the previous visit and an ECG recorded in response to those symptoms is not available, record an ECG at the current visit.

h RBC count, total and differential WBC count, hemoglobin concentration, and hematocrit. Note that only hemoglobin concentration and hematocrit are required for blood samples collected in association with the intercurrent events coronary revascularization (PCI/CABG), focal neurological deficit (stroke), and bleeding.

i Abbreviated Safety Panel: albumin, serum creatinine, CPK, alkaline phosphatase, ALT, AST, GGT, total bilirubin. Every attempt should be made to collect samples at the specified times/visits.

j Extended Safety Panel: abbreviated safety panel plus total protein, calcium, inorganic phosphorus, glucose, BUN, uric acid, Na, K, Cl, lipid panel (total cholesterol, HDL-C, calculated LDL-C, nonHDL-C, triglycerides), and urinalysis. Every attempt should be made to collect samples at the specified times/visits.

k This is plasma/serum for testing for biomarkers of cardiovascular disease and response.

l Randomized treatment assignment and dispensing of initial study drug supply may be delayed up to 10 days after eligibility criteria are confirmed and the subject completes informed consent (enrollment), as dictated by good clinical practice and the subject's individual circumstances. The first dose should be taken immediately, or as soon as possible, after randomized treatment assignment.

Clinical Reviewer: Martin Rose
Application type: Standard, NDA 204886
ZONTIVITY (vorapaxar)

Attachment 1 Diplopia Review

12/2/2013

Jonathan G. Levine, PhD

Quantitative Analysis of Diplopia Cases in Vorapaxar NDA 204886

Summary

Adverse events in both TRACER and TRA2P were analyzed. Based on the sponsor's coding of the adverse events, three adverse event terms were found to have statistically significant between treatment differences at the p<0.10 (two-tailed) level in both studies. Two of these events, "anemia" and "iron deficiency anemia" were expected. One, of them 'diplopia' (p <0.01 in TRACER, p<0.08 in TRA2P, two-tailed), was not expected, but seemed plausible because vorapaxar animal studies indicate vorapaxar is associated with retinal vacuolization, and is distributed in the brain and brain stem. Dr. Marciniak subsequently identified via patient narratives nine additional cases of diplopia in TRA2P. Inclusion of these cases in the analysis resulted in the between treatment difference in TRA2P being statistically significant at the p<0.02 level. While statistically significant, the absolute number of cases was small. (12/19695 for placebo, 35/19698 for vorapaxar, risk difference= 0.0012) . All the diplopia patients recovered, and none had to stop treatment. It is concluded that vorapaxar can in rare cases result in patients developing transient diplopia.

Background

In any clinical trial a variety of adverse events are observed that may or not be caused by the drug or drugs being studied. The large size and long duration of the TRACER and TRA2P studies resulted in both a large number different event terms, and a relatively large number of events per term.

In order to identify adverse events that were more frequent in vorapaxar treated patients than in placebo patients, risk differences for adverse events were tested using the R software package's prop.test procedure. Summary results are given in Table 1.

Table 87

Number of MedDRA Preferred Terms

Study	Unique Terms	Between Treatment Differences Significant at p < 0.10*	p<0.10* and Vorapaxar Rate > Placebo Rate	p<0.10* and Vorapaxar Rate > Placebo Rate In Both Studies
TRACER, N=12944	2380	58	35	3
TRA2P, N=26449	3393	77	34	

* Two-tailed test from R prop.test

Table 1 indicates that only a small number of adverse event terms had statistically significant risk differences at the p=0.10 level in each study, and only three terms had had statistically significant risk differences in both studies. The three MedDRA terms with p values less than 0.10 in both studies are "ANAEMIA", "IRON DEFICIENCY ANAEMIA" and "DIPLOPIA" . Since "ANAEMIA" and "IRON DEFICIENCY ANAEMIA" would be expected in a drug such as vorapaxar that is associated with bleeding, only diplopia was analyzed further.

Analysis

Table 2 shows the results for the analysis of diplopia in TRACER and TRA2P. Additional review by FDA medical officers identified nine additional cases of diplopia, two in the placebo and seven in the vorapaxar group. Eight of these cases explicitly mentioned diplopia or double-vision in the investigator comments for an adverse event, and one had 6th nerve ophthalmoplegia.

Table 88

Diplopia Cases								
	Placebo			Vorapaxar				
Study	*x*	*n*	*x/n*	*x*	*n*	*x/n*	*Difference*	*p-value*
TRACER	2	6471	0.0003	13	6473	0.0020	0.0017	0.010
TRA2P	8	13224	0.0006	18	13225	0.0014	0.0008	0.077
TRA2P*	10	13224	0.0008	25	13225	0.0019	0.0011	0.018
TRACER+TRA2P*	12	19695	0.0006	38	19698	0.0019	0.0013	0.018

*Sponsor indentified cases plus cases identified by FDA medical officers

All of the tests of the risk differences were statistically significant (p<0.02) except for the analysis of TRA2P using only sponsor-defined cases.

Conclusions

Vorapaxar appears to be associated with an increased risk of developing transient diplopia. The risk appears to be small (approximately 1 extra case of diplopia per 1000 treated subjects). While it is possible that this finding is due to chance, animal studies indicating that vorapaxar is associated with retinal vacuolization, and has distribution in the brain and brain stem, gives credibility to the idea that vorapaxar causes transient diplopia. It is recommended that transient diplopia be mentioned in the adverse reactions section of the label as an adverse event that occurs more frequently with vorapaxar than with placebo.

Attachment 2 Proposed Labeling

(With reviewer edits -begins on next page)

PROPOSED LABELING WITHHELD IN FULL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN ROSE
12/16/2013

THOMAS A MARCINIAK
12/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	204886 (S0000)
Drug Name:	MK-5348/SCH 530348 (Vorapaxar Sulfate)
Indication:	Secondary Prevention of Ischemic Events
Applicant:	Merck
Dates:	Date of Document: (b) (4)
	PDUFA Due Date: (b) (4)
Review Priority:	Standard
Biometrics Division:	Biometrics I
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardiovascular and Renal Drug Products
Clinical Team:	Martin Rose, M.D.
	Thomas Marciniak, M.D.
Project Manager:	Alison Blaus, RAC

Table of Contents

1. EXECUTIVE SUMMARY

The vorapaxar's efficacy in addition to the standard of care for preventing patients' atherothrombotic ischemic events appears to be demonstrated in TRA 2°P-TIMI 50 trial for the overall study population and also for the proposed label population, i.e., post MI patients without history of stroke or TIA. We are concerned about several unplanned interim analyses, sample size increase and change of patient population, even though these analyses are performed by an independent statistician through the Data Safety Monitoring Board (DSMB). Whether these analyses might have impacted the trial integrity is uncertain.

2. INTRODUCTION

2.1 OVERVIEW

The sponsor's vorapaxar Phase III clinical program included two placebo-controlled clinical outcome studies, TRACER and TRA 2°P-TIMI 50 Trials (hereafter referred to as TRA-2P in this review) that were designed to test the hypothesis that vorapaxar added to standard of care would reduce the incidence of atherothrombotic events compared to placebo with standard of care in two distinct patient populations. They were two independent, long-term, large outcome studies intended to support different indications of acute coronary syndromes (ACS) and secondary prevention of post myocardial infaction (MI), post stroke or PAD separately.

According to the sponsor, TRACER enrolled subjects in the midst of an acute episode during hospitalization that invariably resulted in parenteral use of anti-coagulants and loading dose regimens of both anti-coagulants and anti-platelet agents. However, TRA-2P, on the other hand, enrolled subjects that were clinically stable as they were 2 weeks to 1 year post the index event (median 77 days). Due to the remote qualifying events for TRA-2P inclusion, subjects with good tolerance to anti-platelet agents could have been selected.

The primary endpoint of TRACER study was the composite of cardiovascular (CV) death, MI, stroke, recurrent ischemia with rehospitalization (RIR) and recurrent ischemia leading to urgent coronary revascularization (UCR) and the key secondary endpoint was the composite of CV death, MI and stroke. In TRACER study, 12,944 subjects (6,471 receiving placebo and 6,473 receiving vorapaxar) were randomized and the final results showed a non-significant hazard reduction of 8% with p-value equal to 0.072, even though vorapaxar reduced the hazard of the key secondary composite of CV death, MI or stroke by 11%.

The primary endpoint of TRA-2P was the composite of CV death, MI, stroke and UCR and the key secondary endpoint was the composite of cardiovascular death, MI and stroke. In TRA-2P study, 26,449 subjects (13,224 subjects receiving placebo and 13,225 receiving vorapaxar) were randomized and the sponsor's final results demonstrated hazard reduction of 12 % with p-value of 0.001 for the primary endpoint and a hazard reduction of 13% with p-value less than 0.001 for the key secondary endpoint.

Although two studies showed different efficacy conclusions, the two studies had some similar design elements; both studies had one official interim analysis planned and they shared the same Clinical Endpoint Committee (CEC) charter and the Data Safety Monitoring Board (DSMB). As a result, the principal investigators of the two trials were to engage in routinely scheduled communication to assess the conduct and consistency of adjudication process within the two trials and the DSMB members knew both trials' interim analysis findings. Due to the large size of the TRA-2P study, it was also noted that although TRA-2P was conducted about three months earlier than TRACER study but completed about six months later than the TRACER study.

Now that TRACER was a non-positive study, our evaluation was mainly on TRA-2P. Although based on the sponsor's results, which clearly demonstrated that TRA-2P had positive findings in the overall ITT patient population, during an interim analysis, the DSMB observed an increased incidence and relative risk of ICH in subjects with prior history of stroke and thus recommended discontinuing the study drug in all subjects with a prior history of stroke or a stroke occurring during the course of the study. The sponsor decided to update and pre-define in the data analysis plan the following supplementary secondary objectives including the evaluation of the first occurrence of the primary and key secondary endpoints in populations including the following:

NSH population-subjects with no stroke history, regardless of the qualifying condition, who received randomized treatment assignment

Post MI or CAD with no history stroke – subjects whose qualifying condition was Coronary Artery Disease (CAD), and did not have a documented history of stroke prior to randomization

Following data-base lock and unblinding, the sponsor and trial's Executive Committee determined that, for the purpose of clinical clarity and patient safety, subjects with a history of TIA be granted the same consideration as subjects with a history of stroke given that the clinical diagnosis of stroke vs. TIA can be difficult, especially when based on patient medical history alone. This TIA subgroup was then removed from the pre-specified post MI with no history of stroke population, yielding this definition for the proposed label population:

Proposed Label Population (post MI with no history of stroke or TIA) – subjects whose qualifying condition was CAD and did not have a documented history of stroke or TIA prior to randomization

The following Table 1 shows the sponsor's analysis results for different types of patient population. Based on their findings, they concluded that efficacy in both the primary and key secondary endpoint was evident in the pre-specified NSH population, as well as in the pre-specified, post MI (CAD) subjects without a history of stroke and in the Proposed Label Population.

Table 1 Sponsor's Efficacy Findings for Different Patient Population for TRA-2P Study

Population	Placebo		Vorapaxar		Hazard Ratio (95% CI) , P-value
	Events (%)	KM %	Events (%)	KM %	
Overall	n = 13224		n = 13225		
Primary Endpoint	1417 (10.7%)	12.4%	1259 (9.5%)	11.2%	0.88 (0.82-0.95) 0.001
Key Secondary Endpoint	1176 (8.9%)	10.5%	1028 (7.8%)	9.3%	0.87 (0.80-0.94) <0.001
No Stroke History (NSH)	n = 10344		n = 10355		
Primary Endpoint	1104 (10.7%)	11.8%	959 (9.3%)	10.6%	0.86 (0.79-0.94) <0.001
Key Secondary Endpoint	878 (8.5%)	9.6%	742 (7.2%)	8.3%	0.84 (0.76-0.93) <0.001
Post MI NSH	n = 8583		n = 8608		
Primary Endpoint	887 (10.3%)	11.5%	757 (8.8%)	10.1%	0.84 (0.76-0.93) <0.001
Key Secondary Endpoint	687 (8.0%)	9.1%	564 (6.6%)	7.7%	0.81 (0.73-0.91) <0.001
Proposed Label	n = 8439		n = 8458		
Primary Endpoint	867 (10.3%)	11.4%	719 (8.5%)	9.8%	0.82 (0.74-0.90) <0.001
Key Secondary Endpoint	671 (8.0%)	9.0%	532 (6.3%)	7.4%	0.78 (0.70- 0.88) <0.001

Source: Sponsor's Table 4 of clinical overview.pdf

2.2 DATA SOURCES

The sponsor's original submission including data files and clinical study reports is stored in the following link: \\Cdsesub1\evsprod\NDA204886\0000.

During the NDA review cycle, we requested the sponsor to respond to the questions listed in the 74 Days' letter. The statistical questions include the unplanned interim analysis and also the needed alpha adjustment, the clarification of sample size increase as well as the interim analysis results. The relevant submissions are stored in the following links:

\\CDSESUB1\evsprod\NDA204886\0032 (for unplanned IAs and alpha adjustment)
\\CDSESUB1\evsprod\NDA204886\0034 (for unplanned sample size re-estimation)
\\CDSESUB1\evsprod\NDA204886\0039 (for interim analysis results)

3. STATISTICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

The submitted data and the quality of the analyses performed by the sponsor appear to be acceptable. However, during the review cycle, the statistical reviewer noted that the sponsor did not include their interim analysis (IA) results and also the interim data in the submission, thus requested the sponsor to submit them. It is interesting to note that the interim analyses were conducted by an independent statistician through the company appointed Data Monitoring Committee and the sponsor indicated that they did not further verify the IA results as the study had been completed, thus no need to perform the verification. Another issue is that during the review cycle, the medical reviewer Dr. Rose found that some patients discontinued study early but were censored on an earlier date without information available on any component of the primary endpoint. Per our request, the sponsor later conducted a sensitivity analysis in which the identified 110 subjects were censored on the last date when ascertainment of subjects' cardiovascular efficacy and safety status was made. They confirmed that the primary and key secondary efficacy results are not impacted. Finally, during the review cycle, the statistical reviewer found that one variable for capturing events'

adjudication status in TRACER study was problematic. The sponsor confirmed that it was due to a mistake in their SAS program, but ensured us the primary efficacy analysis results were not affected by this mistake in any way.

3.2 EVALUATION OF EFFICACY

3.2.1 Study Design and Endpoints

Description of Study TRA 2^{o}P – TIMI 50

Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 (Vorapaxar) in Addition to Standard of Care in Subjects with a History of Atherosclerotic Disease: Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events

The following study description was mostly extracted from the sponsor's clinical study report.

3.2.1.1 Study Objectives

Primary Objective

To evaluate the hypothesis that vorapaxar added to standard of care will reduce the incidence of atherothrombotic ischemic events relative to standard of care alone, as measured by the composite of cardiovascular (CV) death, myocardial infarction (MI), stroke, and urgent coronary revascularization.

Secondary Objectives

The key secondary objective was to evaluate clinical benefit with respect to the composite of CV death, MI, and stroke. Other secondary efficacy objectives included evaluation of the incidence of and time to the following composites or individual components as indicated:

1. all-cause death, MI, stroke, and urgent coronary revascularization
2. CV death and MI
3. CV death, MI, stroke, urgent coronary revascularization, or urgent hospitalization for vascular cause of ischemic nature
4. all-cause death, MI, stroke, any revascularization (including amputation for ischemic limb)
5. CV death, MI, stroke, any revascularization (including amputation for ischemic limb), or urgent hospitalization for vascular cause of ischemic nature
6. the following individual components of the primary endpoint
   a. cardiovascular death
   b. MI
   c. stroke
   d. urgent coronary revascularization
7. all-cause death

3.2.1.2 Study Design

TRA 2^{o}P – TIMI 50 (Protocol P04737) was a multicenter, international, randomized, double-blind, placebo-controlled, balanced-parallel-groups, events-driven investigation of orally administered vorapaxar in the secondary prevention of ischemic events conducted in conformance with GCP.

Men and women at least 18 years old who had evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems were eligible to participate. Following completion of informed consent, subjects were considered enrolled, and were to receive randomized assignment of daily treatment with either vorapaxar at 2.5 mg or placebo, with assignment stratified for

- underlying presentation history at the time of enrollment, in the following hierarchical order of priority
  1. CAS as manifested by MI
  2. Ischemic (presumed thrombotic) CVD
  3. PAD

- planned treatment with a thienopyridine (being taken or added at enrollment versus not taken and not added)

Subjects were to receive randomized treatment assignment no later than 10 days after enrollment (giving informed consent), and were to begin taking daily treatment immediately, or as soon as possible, after randomized treatment assignment.

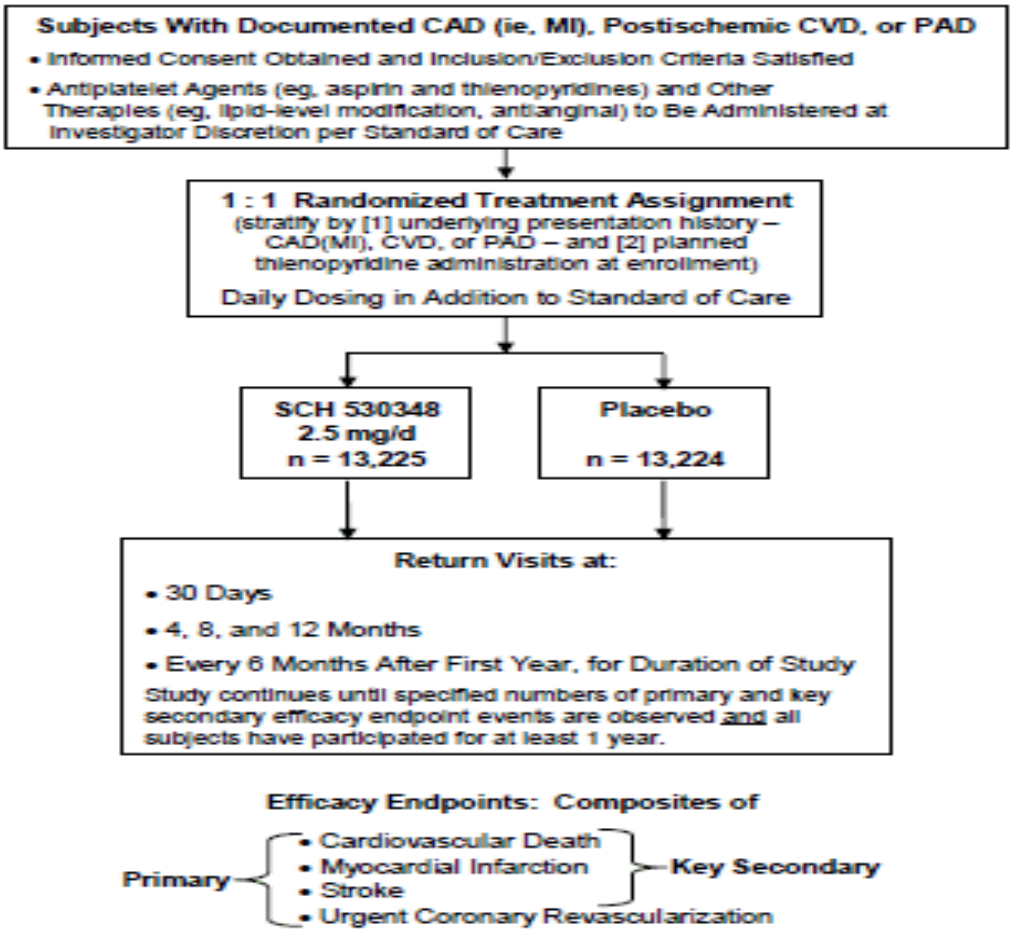
Treatment was to continue until study completion; that is, when a statistically defined number of efficacy endpoint events had been observed and every subject had the opportunity to participate in the study for at least 1 year.

Up to 25,000 subjects were anticipated to participate at approximately 1000 centers. This sample size was required to provide adequate power to test the hypothesis of a 15% relative risk reduction with vorapaxar relative to placebo, each added to the existing standard of care, for occurrence of the primary and key secondary composite efficacy endpoints, plus adjust for potential dropouts during the study.

One interim efficacy analysis was planned for when approximately 50% of the primary and 50% of the key secondary efficacy endpoints (best available data: total of adjudicated and unadjudicated) required for completion of the TRA-2P-TIMI 50 trial were available and was conducted on 24 FEB 2010. The purpose of the interim analysis was to confirm initial estimates of event rates and to allow the DSMB to make recommendations to the Executive Committee; these recommendations could have included continuing under the current protocol, amending the current protocol, or stopping the study.

The following Figure 1 shows a schematic representation of the study design.

Figure 1 Schematic Representation of the Study Design for TRA-2P Study



Source: Sponsor's Figure 1 from CSR

3.2.1.3 Efficacy Endpoints

The primary efficacy endpoint was the first occurrence of any component of the composite of CV death, MI, stroke, and urgent coronary revascularization.

The key secondary efficacy endpoint was the first occurrence of any component of the composite of CV death, MI, or stroke.

Other secondary endpoints included the first occurrence of the following composites or individual components, as shown:

- all-cause death, MI, stroke, and urgent coronary revascularization
- CV death and MI
- CV death, MI, stroke, urgent coronary revascularization, or urgent hospitalization for vascular cause of ischemic nature
- all-cause death, MI, stroke, and any revascularization

- CV death, MI, stroke, any revascularization, or urgent hospitalization for vascular cause of ischemic nature
- The following individual components of the primary endpoint
  1. CV death
  2. MI
  3. urgent coronary revascularization
  4. stroke
- all-cause death

3.2.2 Statistical Methodologies

Efficacy analyses will be carried out on an intent-to-treat basis, and all evaluations will include all subjects who receive treatment, or who receive randomization assignment without receiving treatment. Safety evaluations will include all subjects who receive at least one dose of study treatment. The statistical methods described here are intended for the analyses of the primary and key secondary efficacy endpoints. The primary efficacy analysis will be based on the time from randomized treatment assignment until the first occurrence of one of the following: cardiovascular death, MI, stroke, or urgent coronary revascularization. A Cox proportional-hazard model with covariates of treatment and stratification factors will be used to perform this analysis. Estimates of the hazard ratios and associated 95% confidence intervals comparing placebo with vorapaxar will be provided with the use of this model. The key secondary efficacy endpoint, first occurrence of cardiovascular death, MI, or stroke, will be evaluated using similar methodology. Kaplan-Meier estimates for the time to the primary and key secondary efficacy endpoints will be plotted. The potential influence of baseline risk factors and concomitant therapies such as statins, thienopyridines, and aspirin dosing on the occurrences of the primary and key secondary efficacy endpoints will be explored using the Cox proportional-hazard model.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

A total of 26,449 subjects were enrolled in the study and received randomized treatment assignment at 1029 study sites in 32 different countries. Of the total subjects enrolled, 13,224 subjects were assigned to receive placebo and 13,225 were assigned to receive vorapaxar at 2.5 mg daily. These subjects comprised the “Intent to Treat” population.

Following the DSMB recommendation of 08 Jan 2011 to stop treatment in all subjects with a medical history of stroke or who had a stroke during the study, a series of communications that included new risk information to subjects were sent to the study sites on 13 Jan 2011 to guide them on treatment discontinuation and follow-up.

Of the total 26,449 subjects who were assigned to receive randomized treatment assignment (ITT population), 97 subjects did not receive treatment (58 were assigned to receive placebo and 39 who were assigned to receive vorapaxar). The remaining 26,352 subjects (13,166 placebo and 13,186 vorapaxar) comprised the “As Treated” population. Of note, a low percent

of subjects withdrew consent for telephone follow-up (255 subjects on placebo; 277 subjects on vorapaxar). A total of 32 subjects were lost to follow-up.

Of these 26,449 subjects, the DSMB recommendation involved 4,510 subjects who had either a prior history of stroke or had experienced a stroke endpoint during the study. Therefore, subjects randomized and stratified to the CVD stratum who had a history of stroke had their study drug and participation in the trial discontinued. The remaining subjects with a history of stroke or stroke endpoint who were randomized and stratified to the CAD and PAD strata and 25 subjects in the stroke stratum who did not have a history of stroke (and thus were incorrectly stratified) had their study drug discontinued but continued participation in the trial.

A detailed description of the disposition of subjects through the study is shown in the following Table 2.

Table 2 Subject Disposition for TRA-2P Study

Number (%) of Subjects	Placebo	SCH 530348	Total
Randomized	13,224 (100)	13,225 (100)	26,449 (100)
Never Received Study Drug	58 (0.4)	39 (0.3)	97 (0.4)
Discontinued Study Drug Prematurely	2,948 (22.3)	3,145 (23.8)	6,093 (23.0)
Adverse/Bleeding/Clinical Experience	1,299 (9.8)	1,381 (10.4)	2,680 (10.1)
Withdrew Consent to Study Treatment	1,211 (9.2)	1,257 (9.5)	2,468 (9.3)
Did not Meet Protocol Eligibility	48 (0.4)	42 (0.3)	90 (0.3)
Non-compliance with Protocol	297 (2.2)	355 (2.7)	652 (2.5)
Required Prohibited Medication	57 (0.4)	67 (0.5)	124 (0.5)
Other/Missing	36 (0.3)	43 (0.3)	79 (0.3)
Subjects with History of Stroke or New Stroke Discontinued Study Drug at Recommendation of DSMB	2,248 (17.0)	2,262 (17.1)	4,510 (17.1)
Completed Treatment	7,970 (60.3)	7,779 (58.8)	15,749 (59.5)
Died	589 (4.5)	556 (4.2)	1,145 (4.3)
Lost to Follow-up	15 (0.1)	17 (0.1)	32 (0.1)
Withdrew Consent for Follow-up	277 (2.1)	255 (1.9)	532 (2.0)

Source: Sponsor's Display A-1.4 on Page 769 of CSR.

Demographic and Baseline Characteristics

The following Tables 3 to 5 summarize patients' demographic and baseline characteristics for the overall subjects, subjects without a history of stroke prior randomization, and the Proposed Label Population (i.e., post MI subjects without history of stroke or TIA). According to the sponsor, at study entry, the qualifying and stratifying conditions were well balanced between the treatment groups, and the two treatment groups overall were well balanced in terms of demographic characteristics at baseline. Subjects were predominately white (87%), male (76%), and a median of 61 years. Additionally, 11% of subjects were over 75 years old. Median body weight for subjects was 81 kg with 93% of subjects having a weight ≥ 60 kg. Median body mass index was 27.6 kg/m^2, in the midrange of 'overweight' (25-<30 kg/m^2), and approximately one quarter of the subjects were obese (≥30 kg/m^2).

Table 3 Demographic and Other Baseline Characteristics for All Randomized Patients in TRA-2P Study

Number (%) of Subjects	Placebo N=13,244	Voparaxar N=13,225	Total N=26,449
Age (years), Mean (SD)	60.9 (10.84)	61.0 (10.90)	60.9 (10.87)
Sex, n (%)			
Female	3,172 (24.0)	3,154 (23.8)	6,326 (23.9)
Male	10,052 (76.0)	10,071 (76.2)	20,123 (76.1)
Race, n (%)			
White	11,524 (87.1)	11,562 (87.4)	23,086 (87.3)
Non-White	1,695 (12.8)	1,656 (12.5)	3,351 (12.7)
American Indian or Alaskan Native	30 (0.2)	19 (0.1)	49 (0.2)
Asian	606 (4.6)	588 (4.4)	1,194 (4.5)
Black or African American	350 (2.6)	339 (2.6)	689 (2.6)
Multiracial	694 (5.2)	696 (5.3)	1,390 (5.3)
Native Hawaiian or Other Pacific Islander	15 (0.1)	14 (0.1)	29 (0.1)
Missing	5 (<0.1)	7 (0.1)	12 (<0.1)
Ethnicity, n (%)			
Arab	27 (0.2)	37 (0.3)	64 (0.2)
Asian Indian	163 (1.2)	158 (1.2)	321 (1.2)
Bangladeshi	1 (<0.1)	2 (<0.1)	3 (<0.1)
Cambodian	1 (<0.1)	0	1 (<0.1)
Chinese	62 (0.5)	63 (0.5)	125 (0.5)
Filipino	11 (0.1)	11 (0.1)	22 (0.1)
Hispanic or Latino	1,836 (13.9)	1,857 (14.0)	3,693 (14.0)
Indonesian	8 (0.1)	10 (0.1)	18 (0.1)
Japanese	299 (2.3)	297 (2.2)	596 (2.3)
Korean	2 (<0.1)	2 (<0.1)	4 (<0.1)
Malaysian	31 (0.2)	27 (0.2)	58 (0.2)
Middle Easterner / North African	98 (0.7)	96 (0.7)	194 (0.7)
Pakistani	9 (0.1)	10 (0.1)	19 (0.1)
Thai	1 (<0.1)	0	1 (<0.1)
Vietnamese	2 (<0.1)	4 (<0.1)	6 (<0.1)
Other	10,629 (80.4)	10,604 (80.2)	21,233 (80.3)
Missing	44 (0.3)	47 (0.4)	91 (0.3)
Weight (kg), Mean (SD)	82.8 (17.3)	82.3 (16.9)	82.5 (17.1)
Height (cm), Mean (SD)	170.6 (9.6)	170.6 (9.6)	170.6 (9.6)
Calculated Body Mass Index (kg/m^2), Mean (SD)	28.3 (5)	28.2 (4.9)	28.3 (4.9)
Heart Rate (beats/minute), Mean (SD)	66.5 (11.5)	66.5 (11.6)	66.5 (11.5)
Systolic Blood Pressure (mm Hg), Mean (SD)	133.4 (19.4)	133.5 (19.5)	133.5 (19.5)
Diastolic Blood Pressure (mm Hg), Mean (SD)	78.1 (10.8)	78.0 (10.9)	78.0 (10.8)
Waist Circumference (cm), Mean (SD)	99.5 (12.8)	99.2 (13.0)	99.3 (12.9)
Ankle/Brachial Index, Mean (SD)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)

Source: Sponsor's Display A-10.1 from Pages 578 to 581 of CSR.

Table 4 Demographic and Other Baseline Characteristics for Patients With No History of Stroke Prior to Randomization in TRA-2P Study

Number (%) of Subjects	Placebo N=10,344	Vorapaxar N=10,355	Total N=20,699
Age (years), Mean (SD)	59.9 (10.84)	60.0 (10.80)	60 (10.7)
Sex, n (%)			
Female	2,228 (21.5)	2,274 (22.0)	4,502 (21.7)
Male	8,116 (78.5)	8,081 (78.0)	16,197 (78.3)
Race, n (%)			
White	9,160 (88.6)	9,197 (88.8)	18,357 (88.7)
Non-White	1,181 (11.4)	1,151 (11.1)	2,332 (11.3)
American Indian or Alaskan Native	24 (0.2)	16 (0.2)	40 (0.2)
Asian	357 (3.5)	333 (3.2)	690 (3.3)
Black or African American	245 (2.4)	239 (2.3)	484 (2.3)
Multiracial	542 (5.2)	553 (5.3)	1,095 (5.3)
Native Hawaiian or Other Pacific Islander	13 (0.1)	10 (0.1)	23 (0.1)
Missing	3 (<0.1)	7 (0.1)	10 (<0.1)
Ethnicity, n (%)			
Arab	19 (0.2)	20 (0.2)	39 (0.2)
Asian Indian	155 (1.5)	149 (1.4)	304 (1.5)
Bangladeshi	1 (<0.1)	2 (<0.1)	3 (<0.1)
Cambodian	1 (<0.1)	0	1 (<0.1)
Chinese	42 (0.4)	42 (0.4)	84 (0.4)
Filipino	8 (0.1)	9 (0.1)	17 (0.1)
Hispanic or Latino	1,393 (13.5)	1,419 (13.7)	2,812 (13.6)
Indonesian	8 (0.1)	10 (0.1)	18 (0.1)
Japanese	85 (0.8)	77 (0.7)	162 (0.8)
Korean	2 (<0.1)	1 (<0.1)	3 (<0.1)
Malaysian	31 (0.3)	25 (0.2)	56 (0.3)
Middle Easterner / North African	73 (0.7)	71 (0.7)	144 (0.7)
Pakistani	7 (0.1)	10 (0.1)	17 (0.1)
Thai	1 (<0.1)	0	1 (<0.1)
Vietnamese	2 (<0.1)	4 (<0.1)	6 (<0.1)
Other	8,479 (82.0)	8,476 (81.9)	16,955 (81.9)
Missing	37 (0.4)	40 (0.4)	77 (0.4)
Weight (kg), Mean (SD)	83.89 (17.30)	83.35 (16.85)	83.62 (17.08)
Height (cm), Mean (SD)	171.31 (9.4)	171.18 (9.4)	171.3 (9.4)
Calculated Body Mass Index (kg/m^2), Mean (SD)	28.5 (5.03)	28.4 (4.9)	28.4 (4.9)
Heart Rate (beats/minute), Mean (SD)	65.4 (11.2)	65.4 (11.3)	65.4 (11.2)
Systolic Blood Pressure (mm Hg), Mean (SD)	131.9 (19.1)	132.1 (19.4)	132.0 (19.3)
Diastolic Blood Pressure (mm Hg), Mean (SD)	77.5 (10.7)	77.4 (10.8)	77.5 (10.7)
Waist Circumference (cm), Mean (SD)	99.8 (12.7)	99.5 (12.9)	99.6 (12.8)
Ankle/Brachial Index, Mean (SD)	1.03 (0.23)	1.03 (0.22)	1.03 (0.23)

Source: Sponsor's Display A-10.2 from Pages 582 to 585 of CSR.

Table 5 Demographic and Other Baseline Characteristics for Proposed Label Population in TRA-2P Study

Number (%) of Subjects	Placebo N=8,439	Vorapaxar N=8,458	Total N=16,897
Age (years), Mean (SD)	58.5 (10.46)	58.7 (10.58)	58.6(10.52)
Sex, n (%)			
Female	1,676 (19.9)	1,723 (20.4)	3,399 (20.1)
Male	6,763 (80.1)	6,735 (79.6)	13,498 (79.9)
Race, n (%)			
White	7,415 (87.9)	7,481 (88.4)	14,896 (88.2)
Non-White	1,021 (12.1)	971 (11.5)	1,992 (11.8)
American Indian or Alaskan Native	18 (0.2)	11 (0.1)	29 (0.2)
Asian	340 (4.0)	321 (3.8)	661 (3.9)
Black or African American	177 (2.1)	172 (2.0)	349 (2.1)
Multiracial	474 (5.6)	457 (5.4)	931 (5.5)
Native Hawaiian or Other Pacific Islander	12 (0.1)	10 (0.1)	22 (0.1)
Missing	3 (<0.1)	6 (0.1)	9 (0.1)
Ethnicity, n (%)			
Arab	18 (0.2)	16 (0.2)	34 (0.2)
Asian Indian	150 (1.8)	146 (1.7)	296 (1.8)
Bangladeshi	1 (<0.1)	2 (<0.1)	3 (<0.1)
Cambodian	1 (<0.1)	0	1 (<0.1)
Chinese	42 (0.5)	42 (0.5)	84 (0.5)
Filipino	8 (0.1)	9 (0.1)	17 (0.1)
Hispanic or Latino	1,154 (13.7)	1,170 (13.8)	2,324 (13.8)
Indonesian	7 (0.1)	9 (0.1)	16 (0.1)
Japanese	75 (0.9)	70 (0.8)	145 (0.9)
Korean	2 (<0.1)	1 (<0.1)	3 (<0.1)
Malaysian	31 (0.4)	25 (0.3)	56 (0.3)
Middle Easterner / North African	55 (0.7)	60 (0.7)	115 (0.7)
Pakistani	7 (0.1)	9 (0.1)	16 (0.1)
Thai	1 (<0.1)	0	1 (<0.1)
Vietnamese	0	4 (<0.1)	4 (<0.1)
Other	6,872 (81.4)	6,880 (81.3)	13,752 (81.4)
Missing	15 (0.2)	15 (0.2)	30 (0.2)
Weight (kg), Mean (SD)	84.7 (17.3)	84.0 (16.8)	84.3 (17.1)
Height (cm), Mean (SD)	171.72 (9.4)	171.51 (9.4)	171.62 (9.4)
Calculated Body Mass Index (kg/m^2), Mean (SD)	28.6 (5.0)	28.5 (4.8)	28.6 (4.9)
Heart Rate (beats/minute), Mean (SD)	64.6 (10.8)	64.5 (11)	64.5 (10.9)
Systolic Blood Pressure (mm Hg), Mean (SD)	130.2 (18.6)	130.3 (18.8)	130.2 (18.7)
Diastolic Blood Pressure (mm Hg), Mean (SD)	77.8 (10.7)	77.6 (10.7)	77.7 (10.7)
Waist Circumference (cm), Mean (SD)	99.9 (12.6)	99.6 (12.87)	99.8 (12.7)
Ankle/Brachial Index, Mean (SD)	1.08 (0.19)	1.08 (0.18)	1.07 (0.18)

Source: Sponsor's Display A-10.2 from Pages 606 to 609 of CSR.

3.2.4 Results and Conclusions

3.2.4.1 Sponsor's Efficacy Results-Primary Endpoint and Key Secondary Endpoint

Due to an increased number of ICH events, the DSMB provided the recommendation to discontinue study drug in all subjects with a prior history of stroke or stroke that occurred during the course of the study. The DSMB members also decided unanimously to recommend that the TRP-2P study continue in subjects without history of stroke until the requisite number

of clinical events had been met. In light of the DSMB recommendation, in an effort to determine the subject population with the optimal benefit/risk profile for vorapaxar, the sponsor predefined populations of interest:

- Overall Population- subjects, regardless of the qualifying condition, who received randomized treatment assignment; this was the efficacy population originally defined in the protocol and the data analysis plan
- NSH population- subjects with no stroke history, regardless of the qualifying condition, who received randomized treatment assignment
- Post MI (CAD) and no history of stroke – subjects whose qualifying condition was CAD and did not have a documented history of stroke prior to randomization

In assessing benefit/risk, an additional population was defined following database lock:

- Proposed Label Population (Post MI with no history of stroke or TIA) – subjects whose qualifying condition was CAD and did not have a documented history of stroke or TIA prior to randomization. This population was defined post-hoc to account for the difficulty in diagnosis of stroke versus TIA based on subject history alone.

The sponsor's analysis results for the primary endpoint and key secondary endpoint for the overall patient population, the NSH patient population, the CAD subjects with no prior history of stroke and the proposed label population are shown in Table 6 to Table 9 respectively. Their Kaplan Meier survival curves for the overall and proposed label population are shown in Figure 2 and 3, respectively.

Table 6 Sponsor's Results for Primary and Key Secondary Endpoints for the Overall ITT Population for TRA-2P Study

Endpoint and Contributing Component	Placebo (n=13,224)		Vorapaxar (n=13,225)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Primary Efficacy Endpoint	1,417 (10.7%)	12.4%	1,259 (9.5%)	11.2%	0.88 (0.82-0.95)	0.001
CV Death	199 (1.5%)		172 (1.3%)			
MI	629 (4.8%)		536 (4.1%)			
Stroke	297 (2.2%)		297 (2.2%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	256 (1.9%)		210 (1.6%)			
Hemorrhagic Stroke	27 (0.2%)		67 (0.5%)			
Uncertain	14 (0.1%)		20 (0.2%)			
UCR	292 (2.2%)		254 (1.9%)			
Key Secondary Efficacy Endpoint	1,176 (8.9%)	10.5%	1,028 (7.8%)	9.3%	0.87 (0.80-0.94)	<0.001
CV Death	207 (1.6%)		175 (1.3%)			
MI	665 (5.0%)		554 (4.2%)			
Stroke	304 (2.3%)		299 (2.3%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	260 (2.0%)		212 (1.6%)			
Hemorrhagic Stroke	28 (0.2%)		67 (0.5%)			
Uncertain	16 (0.1%)		20 (0.2%)			

Source: Sponsor's Table 30 of CSR.

Table 7 Sponsor's Results for Primary and Key Secondary Endpoints for NSH Population for TRA-2P Study

Endpoint and Contributing Component	Placebo (n=10,344)		Vorapaxar (n=10,355)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Primary Efficacy Endpoint	1,104 (10.7%)	11.8%	959 (9.3%)	10.6%	0.86 (0.79-0.94)	<0.001
CV Death	161 (1.6%)		137 (1.3%)			
MI	546 (5.3%)		473 (4.6%)			
Stroke	127 (1.2%)		113 (1.1%)			
UCR	270 (2.6%)		236 (2.3%)			
Key Secondary Efficacy Endpoint	878 (8.5%)	9.6%	742 (7.2%)	8.3%	0.84 (0.76-0.93)	<0.001
CV Death	167 (1.6%)		140 (1.3%)			
MI	578 (5.6%)		488 (4.7%)			
Stroke	133 (1.3%)		114 (1.1%)			

Source: Sponsor's Table 31 of CSR.

Table 8 Sponsor's Results for Primary and Key Secondary Endpoints for CAD Subjects With No Prior History of Stroke for TRA-2P Study

Endpoint and Contributing Component	Placebo (n=8,583)		Vorapaxar (n=8,608)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Primary Efficacy Endpoint	887 (10.3%)	11.5%	757 (8.8%)	10.1%	0.84 (0.76-0.93)	<0.001
CV Death	98 (1.1%)		86 (1.0%)			
MI	462 (5.4%)		388 (4.5%)			
Stroke	86 (1.0%)		73 (0.85%)			
UCR	241 (2.8%)		210 (2.4%)			
Key Secondary Efficacy Endpoint	687 (8%)	9.1%	564 (6.5%)	7.7%	0.81 (0.73-0.91)	<0.001
CV Death	103 (1.2%)		88 (1.0%)			
MI	493 (5.7%)		402 (4.7%)			
Stroke	91 (1.1%)		74 (0.86%)			

Source: Sponsor's Table 32 of CSR.

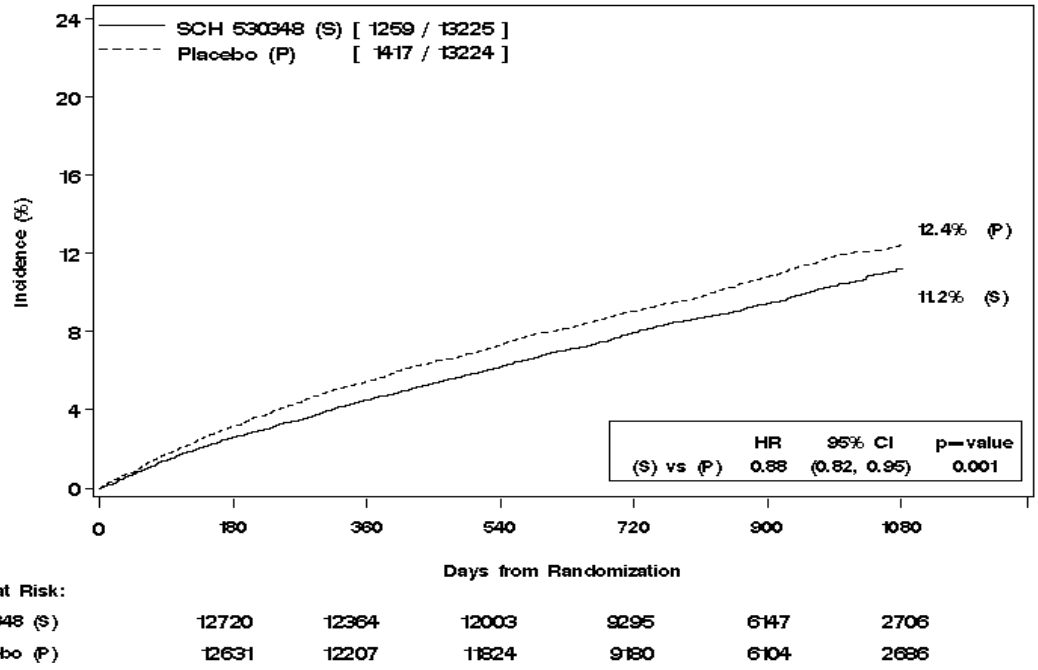
Table 9 Sponsor's Results for Primary and Key Secondary Endpoints for the Proposed Label Population for TRA-2P Study

Endpoint and Contributing Component	Placebo (n=8,439)		Vorapaxar (n=8,458)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Primary Efficacy Endpoint	867 (10.3%)	11.4%	719 (8.5%)	9.8%	0.82 (0.74-0.90)	<0.001
CV Death	96 (1.1%)		82 (1.0%)			
MI	451 (5.3%)		374 (4.4%)			
Stroke	84 (1.0%)		60 (0.7%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	69 (0.8%)		38 (0.4%)			
Hemorrhagic Stroke	11 (0.1%)		16 (0.2%)			
Uncertain	4 (0.0%)		6 (0.1%)			
UCR	236 (2.8%)		203 (2.4%)			
Key Secondary Efficacy Endpoint	671 (8.0%)	9.0%	532 (6.3%)	7.4%	0.78 (0.70-0.88)	<0.001
CV Death	101 (1.2%)		84 (1.0%)			
MI	481 (5.7%)		387 (4.6%)			
Stroke	89 (1.1%)		61 (0.7%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	72 (0.9%)		39 (0.5%)			
Hemorrhagic Stroke	12 (0.1%)		16 (0.2%)			
Uncertain	5 (0.1%)		6 (0.1%)			

Source: Sponsor's Table 33 of CSR.

Figure 2 Sponsor's Kaplan-Meier Survival Curves for Overall Patient Population for TRA-2P Study

2A: <u>For Primary Endpoint</u>

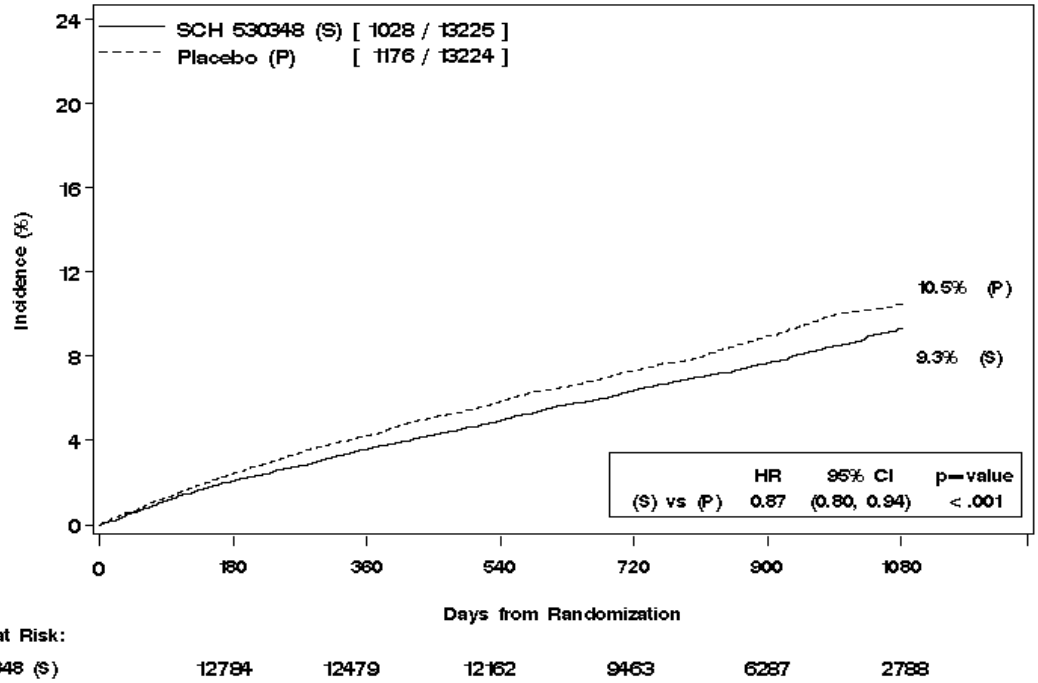


No. at Risk:

SCH 530348 (S)	12720	12364	12003	9295	6147	2706
Placebo (P)	12631	12207	11824	9180	6104	2686

Source: Sponsor's Figure 3 of CSR

2B: <u>For Secondary Endpoint</u>

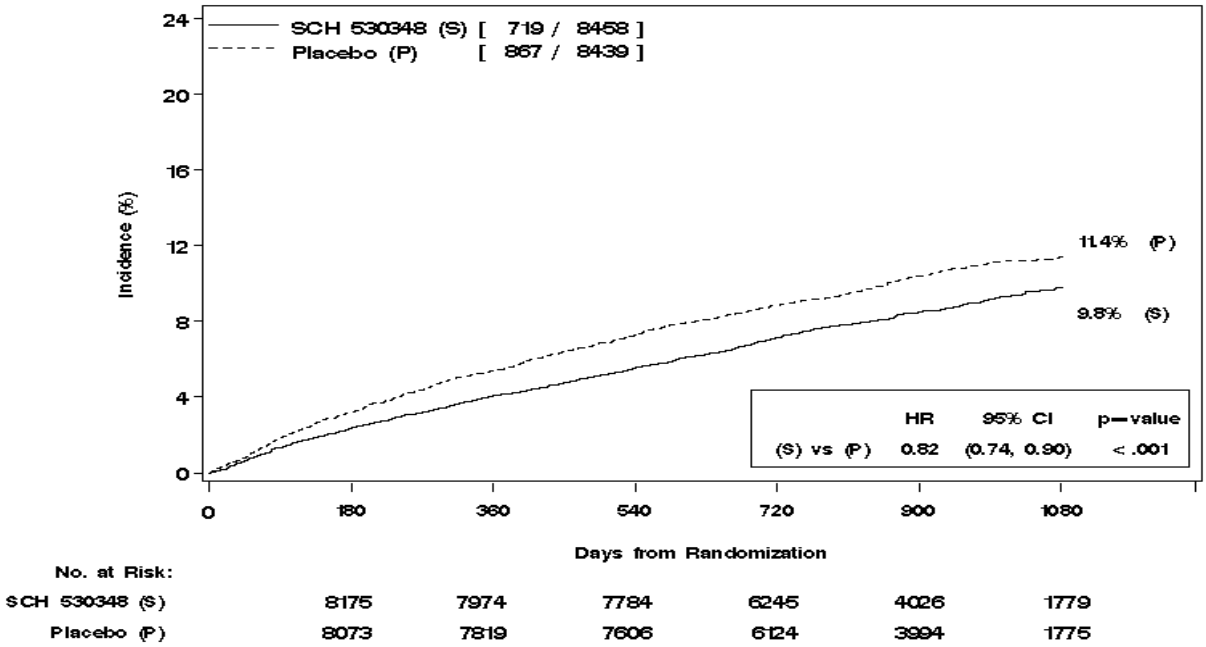


No. at Risk:

SCH 530348 (S)	12784	12479	12162	9463	6287	2788
Placebo (P)	12727	12364	12013	9366	6239	2751

Source: Sponsor's Figure 4 of CSR

Figure 3 Sponsor's Kaplan-Meier Survival Curves for the Primary Endpoint Based on the Proposed Label Population for TRA-2P Study



Source: Sponsor's Figure 4 of CSR

3.2.4.2 Sponsor's Efficacy Results-Other Secondary Endpoints

The sponsor's analysis results for other secondary endpoints including the time to each component of the primary endpoint for the overall patient population, the CAD patients without stroke history and the proposed label population are shown from Table 10 to Table 12, respectively.

Table 10 Sponsor's Analysis Results for Other Secondary Endpoints for the Overall Patient Population for TRA-2P Study

Endpoints	Placebo (n=13,224)		Vorapaxar (n=13,225)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
All-Cause Death/MI/Stroke/UCR	1,614 (12.2%)	14.2%	1,481 (11.2%)	13.2%	0.91 (0.85-0.98)	0.009
CV Death/MI	913 (6.9%)	8.2%	789 (6.0%)	7.3%	0.86 (0.78-0.94)	0.002
CV Death/MI/Stroke/UCR/UH-VCIN	1,681 (12.7%)	14.7%	1,481 (11.2%)	13.1%	0.87 (0.81-0.93)	<0.001
All-Cause death/MI/Stroke/Any Revascularization	2,594 (19.6%)	22.6%	2,395 (18.1%)	20.7%	0.91 (0.86-0.96)	0.001
CV Death/MI/Stroke/Any Revascularization/UH-VCIN	2,542 (19.2%)	22.1%	2,314 (17.5%)	19.9%	0.90 (0.85-0.95)	<0.001
CV Death	319 (2.4%)	3.0%	285 (2.2%)	2.7%	0.89 (0.76-1.04)	0.151
MI	673 (5.1%)	6.1%	564 (4.3%)	5.2%	0.83 (0.74-0.93)	0.001
UCR	316 (2.4%)	2.6%	279 (2.1%)	2.5%	0.88 (0.75-1.03)	0.108
All-Cause Death	565 (4.3%)	5.3%	540 (4.1%)	5.0%	0.95 (0.85-1.07)	0.411
Stroke	324 (2.5%)	2.8%	315 (2.4%)	2.8%	0.97 (0.83-1.14)	0.733
UH-VCIN	646 (4.9%)	5.5%	539 (4.1%)	4.7%	0.83 (0.74-0.93)	0.001
Any Revascularization	1,768 (13.5%)	15.5%	1,583 (12.0%)	13.6%	0.89 (0.83-0.95)	<0.001

Source: Sponsor's Table 55 of CSR.

Table 11 Sponsor's Analysis Results for Other Secondary Endpoints for the CAD patients with No History of Stroke for TRA-2P Study

Endpoints	Placebo (n=8,583)		Vorapaxar (n=8,608)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
All-Cause Death/MI/Stroke/UCR	972 (11.3%)	12.7%	854 (9.9%)	11.4%	0.87 (0.79-0.95)	0.002
CV Death/MI	616 (7.2%)	8.2%	510 (5.9%)	7.0%	0.82 (0.73-0.92)	<0.001
CV Death/MI/Stroke/UCR/UH-VCIN	996 (11.6%)	12.9%	877 (10.2%)	11.6%	0.87 (0.79-0.95)	0.002
All-Cause death/MI/Stroke/Any Revascularization	1,456 (17.0%)	18.7%	1,342 (15.6%)	17.5%	0.91 (0.85-0.98)	0.013
CV Death/MI/Stroke/Any Revascularization/UH-VCIN	1,433 (16.7%)	18.4%	1,318 (15.3%)	17.2%	0.91 (0.84-0.98)	0.012
CV Death	163 (1.9%)	2.2%	138 (1.6%)	1.9%	0.84 (0.67-1.05)	0.131
MI	499 (5.8%)	6.6%	408 (4.7%)	5.6%	0.81(0.71-0.92)	0.002
UCR	259 (3.0%)	3.2%	230 (2.7%)	3.1%	0.88 (0.74-1.05)	0.165
All-Cause Death	266 (3.1%)	3.7%	247 (2.9%)	3.4%	0.92 (0.77-1.10)	0.353
Stroke	103 (1.2%)	1.4%	78 (0.9%)	1.1%	0.75 (0.56-1.01)	0.056
UH-VCIN	399 (4.6%)	5.0%	370 (4.3%)	4.9%	0.92 (0.80-1.06)	0.254
Any Revascularization	1,052 (12.3%)	13.6%	963 (11.2%)	12.6%	0.91 (0.83-0.99)	0.029

Source: Sponsor's Table 56 of CSR.

Table 12 Sponsor's Analysis Results for Other Secondary Endpoints for the Proposed Label Population for TRA-2P Study

Endpoints	Placebo (n=8,583)		Vorapaxar (n=8,608)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
All-Cause Death/MI/Stroke/UCR	951 (11.3%)	12.6%	815 (9.6%)	11.1%	0.84 (0.77-0.93)	<0.001
CV Death/MI	601 (7.1%)	8.1%	490 (5.8%)	6.8%	0.81 (0.72-0.91)	<0.001
CV Death/MI/Stroke/UCR/UH-VCIN	972 (11.5%)	12.8%	834 (9.9%)	11.3%	0.85 (0.77-0.93)	<0.001
All-Cause death/MI/Stroke/Any Revascularization	1,424 (16.9%)	18.7%	1,294 (15.3%)	17.2%	0.90 (0.83-0.97)	0.005
CV Death/MI/Stroke/Any Revascularization/UH-VCIN	1,398 (16.6%)	18.2%	1,269 (15.0%)	16.8%	0.90 (0.83-0.97)	0.005
CV Death	159 (1.9%)	2.2%	131 (1.5%)	1.9%	0.82 (0.65-1.03)	0.088
MI	486 (5.8%)	6.6%	393 (4.6%)	5.4%	0.80 (0.70-0.92)	0.001
UCR	253 (3.0%)	3.2%	223 (2.6%)	3.1%	0.88 (0.73-1.05)	0.148
All-Cause Death	259 (3.1%)	3.7%	238 (2.8%)	3.4%	0.91 (0.77-1.09)	0.308
Stroke	101 (1.2%)	1.4%	63 (0.7%)	0.9%	0.62 (0.45-0.85)	0.003
UH-VCIN	387 (4.6%)	4.9%	357 (4.2%)	4.8%	0.92 (0.79-1.06)	0.234
Any Revascularization	1,027 (12.2%)	13.5%	939 (11.1%)	12.5%	0.91 (0.83-0.99)	0.029

Source: Sponsor's Table 56 of CSR.

3.2.4.3 Sponsor's Conclusion

- In the overall population, vorapaxar when added to standard therapy significantly reduced the primary (CV Death/MI/Stroke/UCR) and key secondary efficacy composite endpoints (CV Death/MI/Stroke).

- In the context of reducing all components of the composite endpoints, the rate of reduction of MI was the major component that contributed to this reduction besides stroke. Importantly, of these MI's most were spontaneous in nature (Type 1), thus defined by associated chest pain, and necessitating emergency hospitalizations.
- Regardless of time from the qualifying MI to randomization, vorapaxar reduced the rate of endpoint MI compared to placebo.
- In the overall population, a statistically significant reduction in the key secondary endpoints including the composite of CV death and MI was observed.
- Based on the composite endpoints, there was little evidence of efficacy observed in subjects with a history of stroke.
- Efficacy in both the primary and key secondary endpoints was evident in the NSH, post MI (CAD) subjects with no history of stroke and in the Proposed Label Population.
- There was a consistency of effect of vorapaxar among subgroups examined that included age, sex, hypertension, use of anti-platelet agents, and diabetes mellitus.
- In both overall and Proposed Label populations, vorapaxar was associated with a reduction in the incidence of recurrent events in the multiple occurrences of adjudicated endpoints in the vorapaxar group was associated with a reduction in the incidence of recurrent events.
- In both overall and Proposed Label populations, a reduction in definite stent thrombosis was observed.

3.2.4.4 Statistical Reviewer's Findings for Efficacy

1. (Unplanned Interim Analyses) Study TRA-2P was initiated on September 26, 2007 and completed on December 23, 2011. Based on the original study protocol dated May 31, 2007, only one formal unblinded interim analysis (IA) for efficacy was planned. It was to be performed by an independent Data and Safety Monitoring Board (DSMB) when approximately 50% of the primary and 50% of the key secondary efficacy endpoint events (either adjudicated or un-adjudicated [i.e., called best available events]) occurred. It was clearly stated in the protocol that the analysis would be based on the CEC-adjudicated events and the O'Brien-Fleming methodology would be implemented to protect the overall Type I error of 0.05. In particular, a nominal alpha level of 0.003 was planned for the interim analysis and 0.049 for the final analysis for both the primary and key secondary efficacy endpoints.

Although only one IA for efficacy was officially planned for Study TRA-2P, due to potential safety concerns, there were 11 DSMB meetings conducted throughout the trial, where the first meeting was held on 2/11/2008 and the last meeting on 1/8/2011. For all 11 meetings, some languages about findings for safety events, either for bleeding or ICH, were recorded in the meeting minutes. In addition to the DSMB meeting of 2/24/2010, when the results for the officially planned IA for TRA-2P study was discussed, the results of efficacy analysis including the p-value of the primary endpoint were also recorded in the minutes of the two other meetings dated 10/20/2010 and 1/8/2011. The exact dates for the sponsor's 11 DSMB meetings are shown on Table 13.

Table 13 Dates for all DSMB Meetings for both Study TRACER and TRA-2P

Meeting No.	Date
1	2/11/2008
2	5/9/2008
3	9/11/2008
4	2/12/2009
5	5/25/2009
6	9/30/2009
7	2/24/2010 (IA for TRA-2P)
8	6/25/2010 (IA for TRACER)
9	10/20/2010
10	12/15/2010
11	1/8/2011

The reviewers asked the sponsor to explain why those efficacy analyses were conducted and exactly what analyses had been performed in each interim analysis and how these unblinded efficacy analyses would affect the study type I error rate.

The sponsor's response noted: "*The DSMB received periodic aggregated safety reports that were partially blinded – results separated by treatment, but treatment was not identified. At the third meeting on September 11, 2008, the committee requested that the treatment assignment be identified. From that point on, the DSMB received Hazard Ratios for a total of 9 safety evaluations.*"

The sponsor also emphasized that "*Based on the minutes from the open session of the February 12, 2009 meeting [P04737, Section 16.1.9.5.2, volume o] total efficacy event rates were being monitored in accordance with the DSMB charter for an interim analysis at 50% of accrued events, but there is no indication that efficacy endpoint event rates were being monitored by treatment assignment. Importantly, there is no mention of any Hazard Ratios (HR) by treatment assignment or confidence intervals around those HRs for the PEP (Primary Efficacy Endpoint) in the DSMB minutes until February 24, 2010.*"

Regarding how many times that the efficacy results were revealed, they stated: "*Consequently, the DSMB had knowledge of treatment assignment for efficacy data for that meeting, the June 25th meeting, the October 20th meeting of 2010 and the January 8th meeting of 2011. No efficacy results were reported in the minutes of the December 2010 DSMB meeting*."

Regarding the question about alpha adjustment for these interim looks of the study data, the sponsor acknowledged: "*To our knowledge, after review of the DSMB minutes and a discussion on August 12, 2013 with the DCRI Statisticians who worked with the unblinded DSMB, there were 3 examinations of the efficacy data in an unblinded fashion, in addition to the planned interim analysis. While the charter stated there was no intention of stopping the trial early for efficacy, the DSMB did have safety concerns and therefore requested to see the efficacy and safety information to balance the risk and protect the subjects of the trial. Given these 4 separate examinations of the unblinded efficacy data, a more conservative approach, ignoring the intent in the charter, would be to adjust the alpha for the 4 interim analyses.*" The sponsor further stated that "*However, as stated in the charter, there was no intent of stopping the trial other than at the 50% of accrued events interim analysis, and therefore there*

was no pre-specified alpha spending function necessary, leading to lack of such a function to provide a basis for a post-hoc adjustment. In lieu of a pre-specified alpha-spending function, a conservative methodology, such as a Bonferonni adjustment, could be utilized. If such an adjustment for 4 interim analyses is applied to the TRA°2P primary and key secondary endpoints, these endpoints would still reach statistical significance. This statement also holds in the most extreme circumstance where FDA believes that an adjustment for 11 interim analyses is appropriate. Utilizing a Bonferonni adjustment by multiplying the final p-values by 11, yields a p-value for the primary endpoint of ≈ 0.01164, and a p-value for the key secondary endpoint of ≈0.01079, both of which are still less than 0.05."

In this reviewer's opinion, it can be argued that the single trial TRAP-2P may need to achieve a p-value of 0.01 or less for vorapaxar's efficacy on atherothrombotic ischemic events, especially that Study TRACER is non-positive. The Bonferroni adjustment for interim analyses, however, is very conservative; thus, by this adjustment, the maximum p-value is about 0.01. Therefore, TRAP-2P seems to have achieved statistical significance at 0.01 level for both the primary and the secondary endpoints.

2. (Sample Size Re-Estimation) According to the sponsor's original protocol for Study TRA-2P, 19,500 subjects (9,750 subjects per treatment group) were to be randomized to observe 2,279 primary efficacy endpoint events and 1,322 Key secondary efficacy endpoint events. This sample size was to provide for detection of a 15% relative risk reduction in the incidence of the key secondary efficacy endpoint with SCH 530348 relative to placebo with approximately 85% power at a two-sided significance level of 0.05. The original protocol was initiated on May 31, 2007 and the study was initiated on Sep. 26, 2007.

About one and half year after Study TRA-2P was initiated, the sponsor amended the protocol, dated Jan. 21, 2009 (i.e., Amendment #1), to perform sample size reassessment for both the primary and key secondary efficacy endpoints using the aggregated, blinded accumulation of events prior to completion of enrollment. On the basis of the estimated event rates for the primary and key secondary efficacy endpoints at one year, as well as adjusting for potential numbers of dropouts for this sample size reassessment, the sponsor decided to increase the sample size to approximately 25,000 subjects (12,500 subjects per treatment group) and an increase in the minimum number of key secondary efficacy endpoint events to approximately 1,400 events. They then amended the protocol the second time to reflect this change (i.e., Amendment #2, dated March 23, 09). In addition to the required number of events for the primary and key secondary efficacy endpoint, each patient must participate for a minimum of one year. The sponsor also left a room for an additional reassessment of sample size up to 27,000 subjects if required to maintain the planned power and overall duration of the trial.

While reviewing Study TRA-2P's results, the reviewer noted that the sponsor's final analysis for Study TRA-2P was based on 2,676 primary endpoint events and 2,204 key secondary observed, which were much larger than what was planned. It is unclear why the sponsor made a decision to amend the protocol for performing the sample size reassessment after one and half year after the study was initiated. Thus, we asked the sponsor to provide us with explanation for why the sample size was increased, information about the exact time(s) of the sample size re-estimation, the overall event rate and dropout rate at the time(s) of the sample

size re-estimation as well as any observed results that triggered the SSI decision, and who performed the re-estimation.

The sponsor responded: "*The original protocol did not pre-specify for an analysis for sample size adjustment. As part of **routine operational procedure** the TIMI group monitored the progress of TRA 2ºP - TIMI 50 using TIMI generated operational reports."* They further stated that*" These reports were shared with the Sponsor. Among the parameters captured in these reports were patient enrollment and total events triggered and adjudicated. As all data were blinded as to treatment assignment and all data were reported as total, aggregate values."*

The sponsor noted that there was a communication between TIMI Group and the Sponsor: *"On October 22, 2008, the TIMI Group Study Chair (Eugene Braunwald) issued a letter to the Sponsor noting that **the aggregate event rates** were lower than the anticipated 8% and that this finding was driven principally by the 3% aggregate event rate in the PAD stratum. The TIMI Group also recommended (although no action was taken) that in the then upcoming amendment (01) , enrollment into the PAD stratus be limited to 3,000 subjects and that sample size be increased by 4,000 subjects to maintain current study timelines."*

After the sponsor received the TIMI Group's Oct. 2008's letter, the sponsor also performed some independent calculations to confirm the TIMI Group's finding. In the sponsor's response, it states that "*Independent calculations by the Sponsor in response to the October 22, 2008 TIMI request confirmed that in the context of lower than anticipated event rates and a more vigorous subject enrollment, there was a need to incorporate into the first amendment to the protocol, a formal re-assessment of sample size and target events."*

It should be noted that TIMI Group's Oct. 2008's letter was sent out a month or so after the 3rd DSMB meeting (September 11, 2008). Recall that the treatment groups had been unblinded since that 3rd DSMB meeting even though the sponsor emphasized that this sample size reassessment was performed as a part of routine operational procedure. Due to the fact of the exact treatment groups had been identified, it is really unclear whether this sample size reassessment could have been influenced by the findings based on the unblinded treatment groups.

3. (Sponsor's Interim Analysis Results) For Study TRA-2P, the only interim efficacy analysis was planned/conducted when 50%/49% of the number of primary endpoint events (from total of adjudicated and un-adjudicated) and 50%/61% of the key secondary endpoint events were observed although the primary analysis would be based on the CEC-adjudicated events and the analyses based upon the best available events would be supportive.

The sponsor's results for IA are shown on Table 14. Note that the interim analysis results based on the best available events suggest stronger efficacy findings than those based on the CEC adjudicated events, which account for only 34% and 43% of the required number of events for the primary and key secondary endpoints, respectively.

Table 14 Sponsor's Interim Efficacy Analysis for the Primary Endpoint for TRA-2P Study

For Overall Patient Population	Placebo (N=13224)	Vorapaxar (N=13225)	HR	P-Value
Based on the CEC adjudicated events				
Primary Endpoint	405 (3.1%)	363 (2.7%)	0.90	0.133
Key Secondary Endpoint	313 (2.4%)	283 (2.1%)	0.91	0.231
Based on the best available events				
Primary Endpoint	609 (4.6%)	518 (3.9%)	0.85	0.007
Key Secondary Endpoint	464 (3.5%)	395 (3.0%)	0.85	0.022

4. (Modification of Study Population) Due to the safety concern, the DSMB made a recommendation of discontinuing patients who had prior history of stroke while the study was ongoing and the sponsor followed the recommendation. Although the study population was changed, the sponsor performed analyses for the overall patient population and the NSH population (i.e., excluding patients with prior history of stroke) and also the proposed label population. All the analyses in different populations showed that the p-values are less than 0.001; the sponsor concluded that the vorapaxar is effective in reducing patient's events composited in the primary endpoint based on not only the overall population but also the different subsets.

It is worth noting that the mixture of the overall patient population in terms of patients who had prior history of stroke or in CVD stratum was changed. It is unclear whether such a change has any ramification on how to best interpret the positive trial findings.

This reviewer performed an analysis using only data before the final DSMB meeting (i.e., data closed by 1/8/2011); see Table 15. The p-values for both the primary and the secondary endpoints are less than 0.01, suggesting that had the study been closed early before the study population was changed, the study would have shown positive findings.

Table 15 Statistical Reviewer's Analysis Results Using Data Closed by Final IA

Data Closed by 1/8/2011	Placebo (N=13224)	Vorapaxar (N=13225)	HR	P-Value
Primary Endpoint	1186 (9%)	1047 (8%)	0.88	0.002
Key Secondary Endpoint	965 (7.3%)	851 (6.4%)	0.88	0.005

5. (Statistical Reviewer's Sensitivity Analyses) Based on this reviewer's analysis, there seems to be little difference between the treatment arms in terms of discontinued patients' follow-up time (Figure 4) and the time of treatment end (Figure 5).

Figure 6 shows the hazard ratio over time for the overall population, patients with no prior history of stroke (i.e., NSH population) and patients with prior history of stroke, where plots based on calendar date and patients' days after randomization are presented for each population. For the overall patient population and the NSH population, the hazard ratio appears to be stable quickly, way before 200 days and was a bit smaller earlier than later. On the contrary, vorapaxar did not seem to have an effect in the patients with prior history of stroke. Figure 7 is to examine the fluctuation of the p-values over time along with the total number of events. It shows that the p-value was well below 0.05 after 100 days and below 0.01 after 200 days based on patients' day after randomization, but the p-value did not stop

fluctuating until 2010 based on calendar date. In summary, the vorapaxar appears effective in reducing the risk of ischemic events in atherosclerotic patients although the effect seems small (14-16% hazard reduction).

Figure 4 Censored Patients' Follow-up for TRA-2P Study

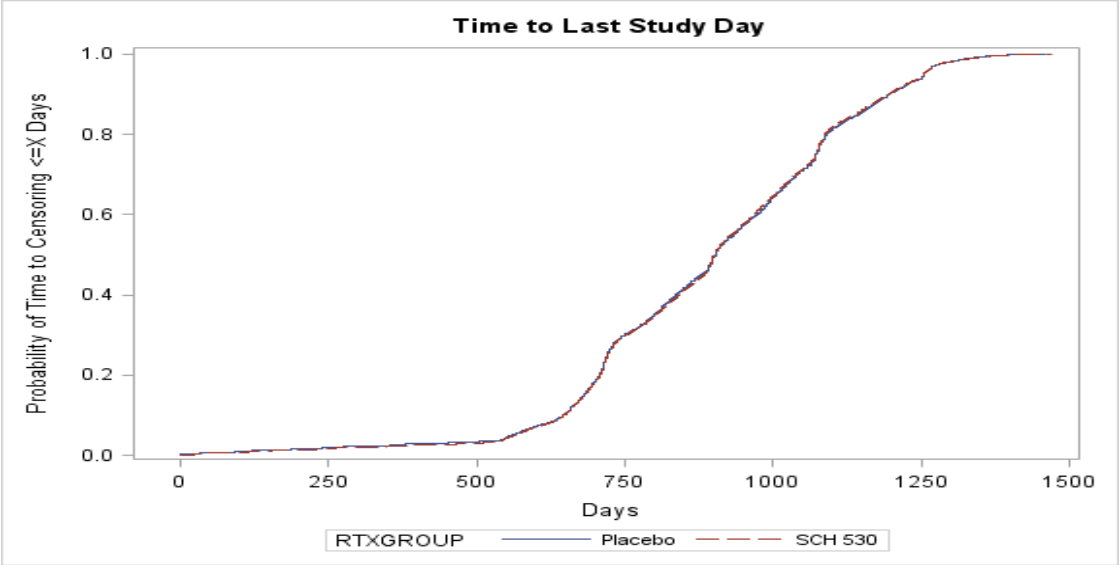


Figure 5 Time to Treatment Discontinuation Over Time for TRA-2P Study

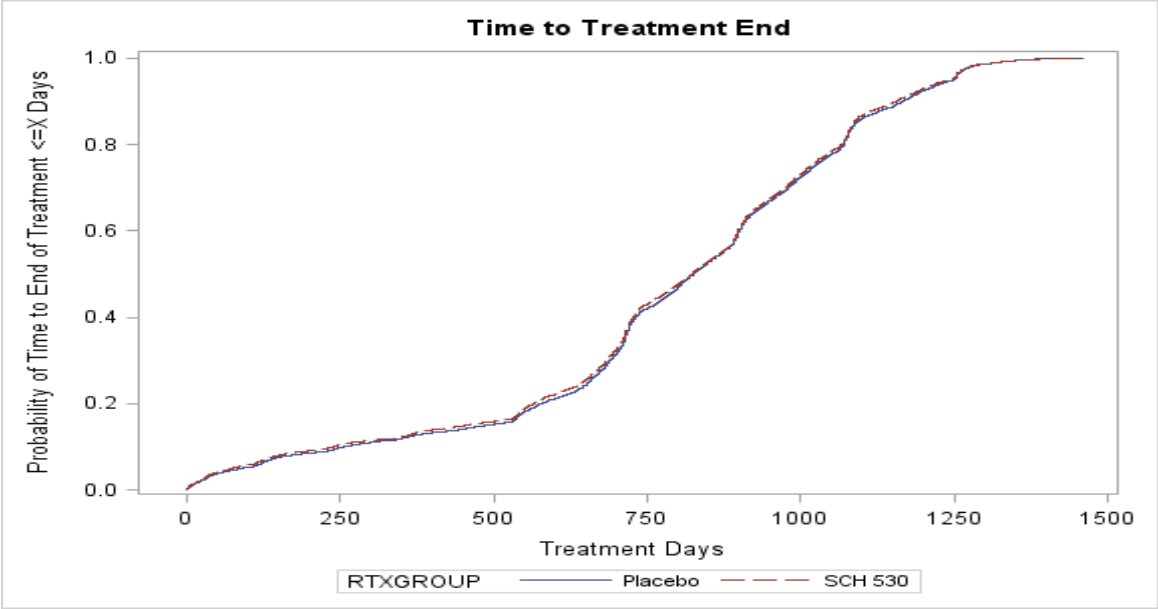
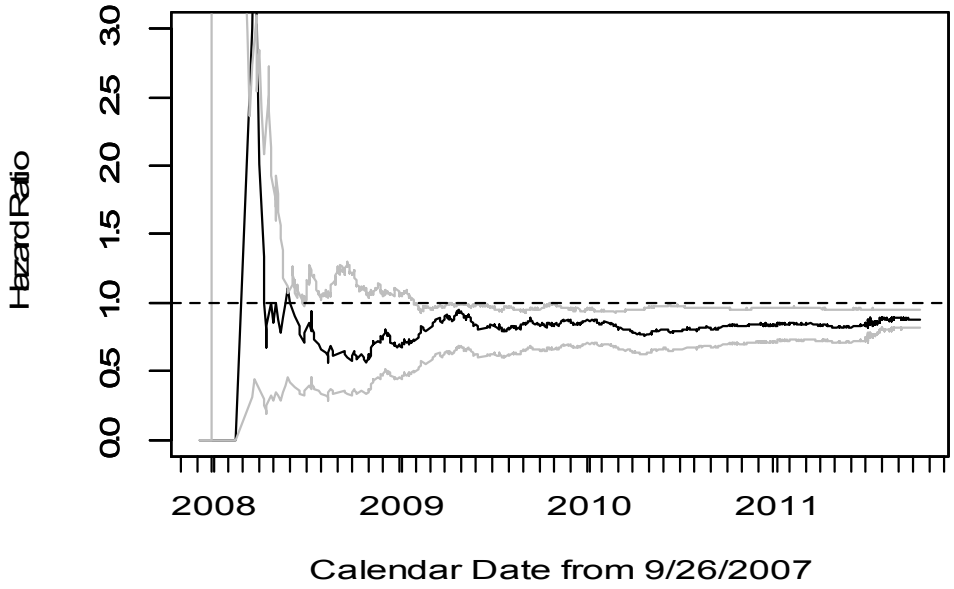
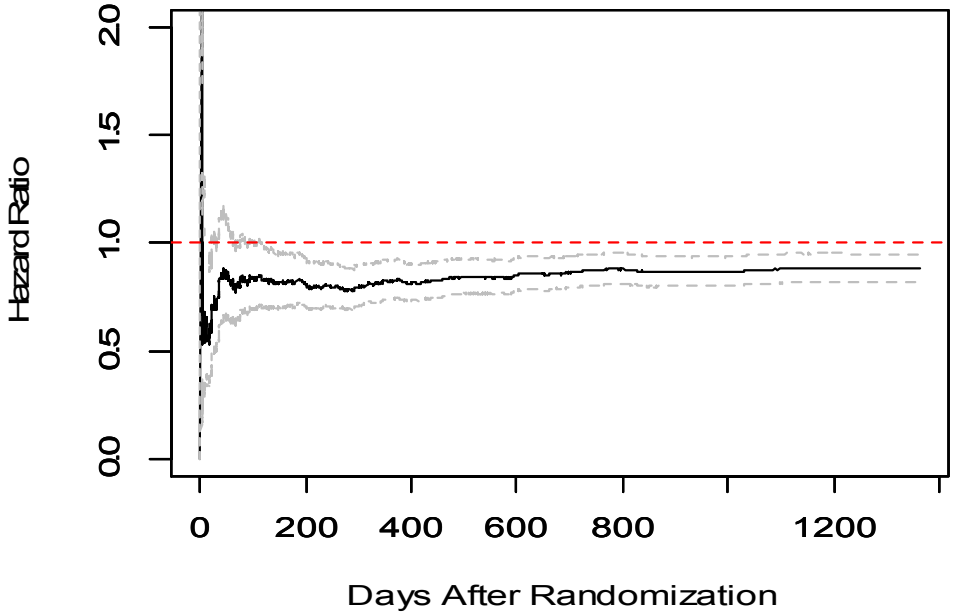


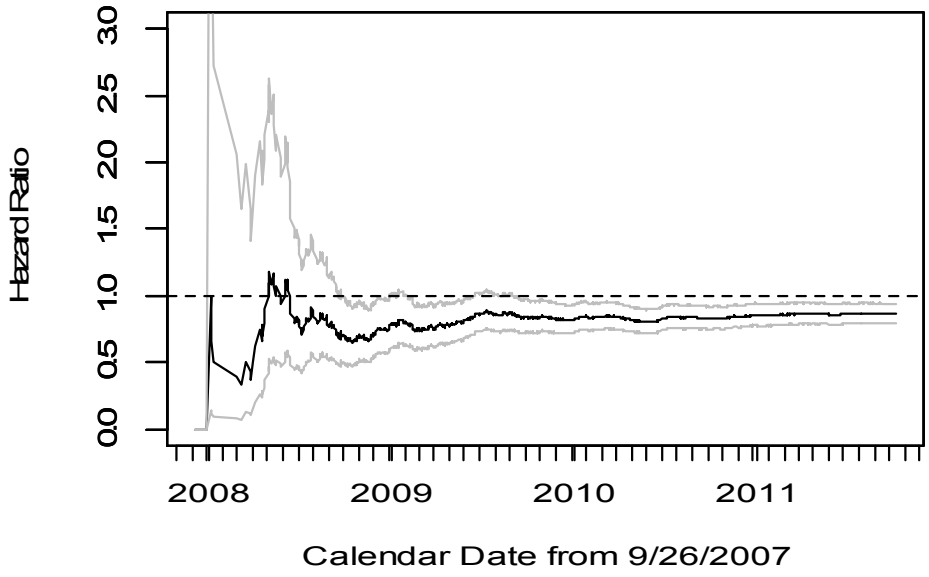
Figure 6 Hazard Ratio Over Time For TRA-2P Study (Based on Calendar Dates and Patients' Days After Randomization)

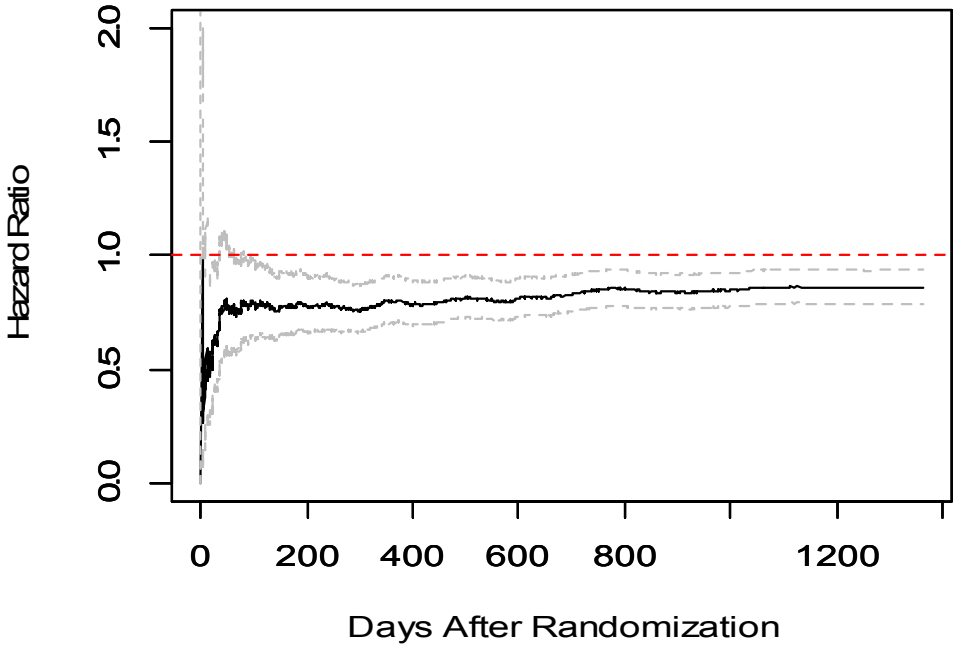
A. For Overall Population



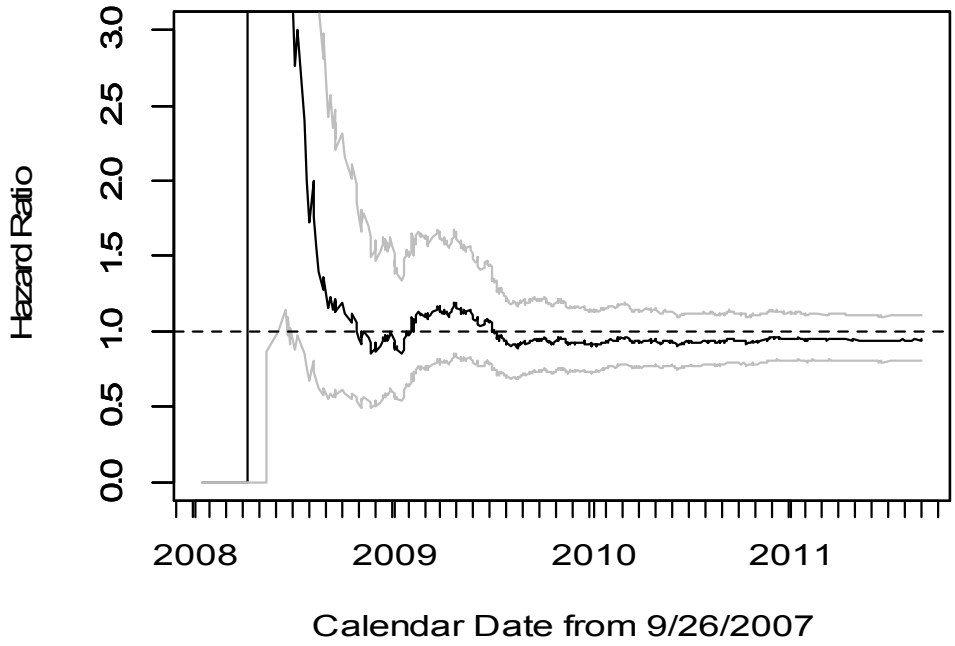


B. For NSH Population





C. For Non-NSH Population



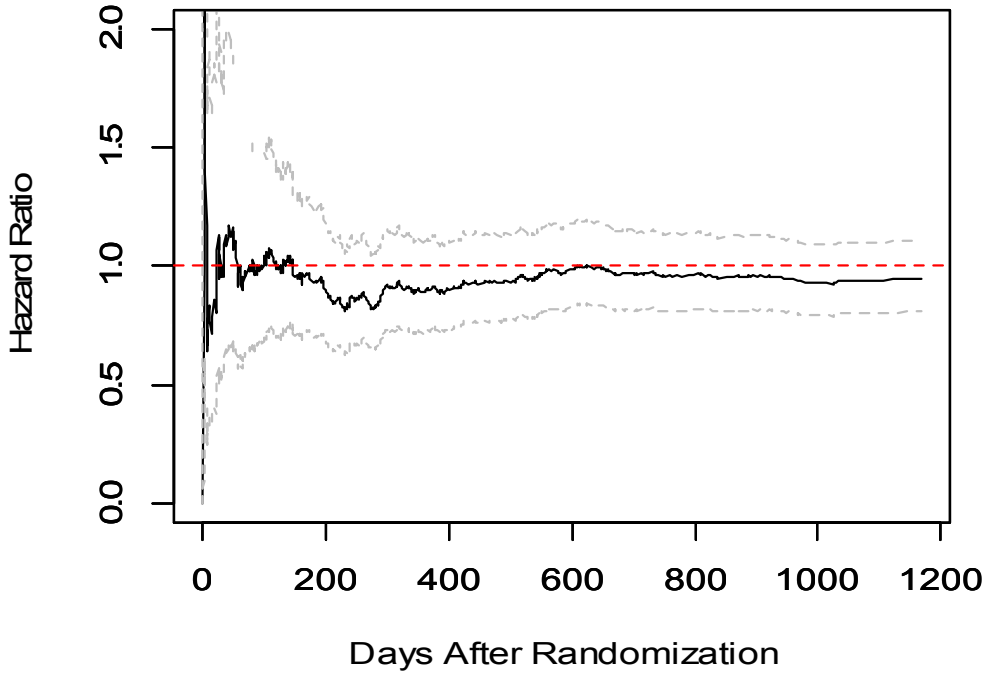
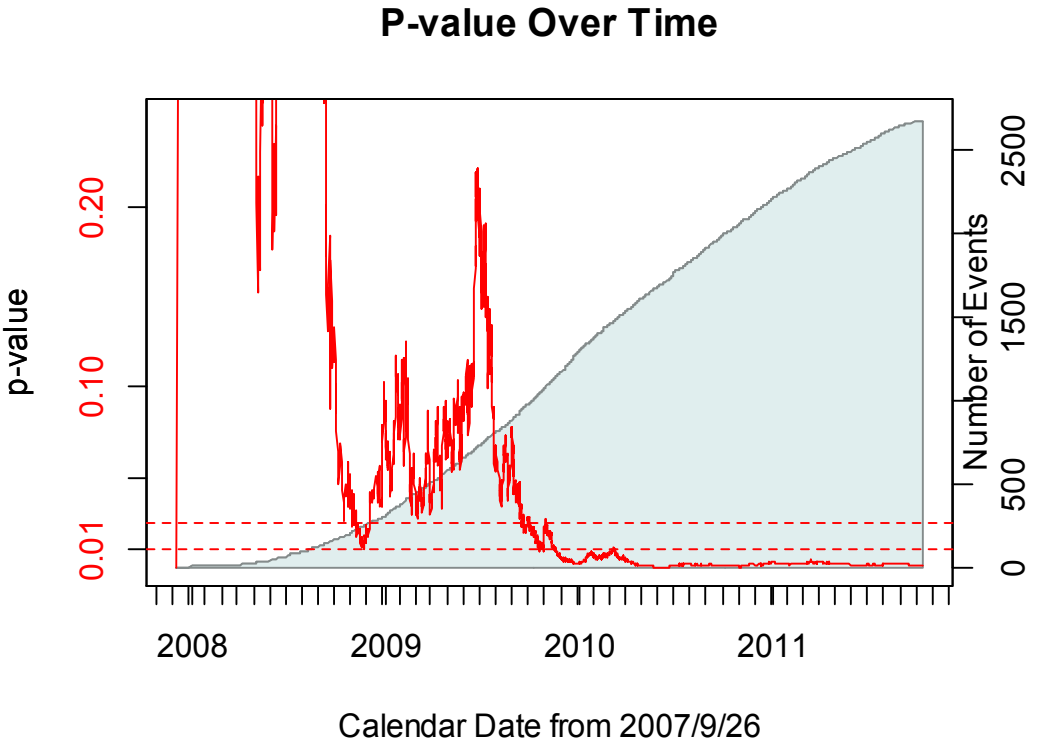
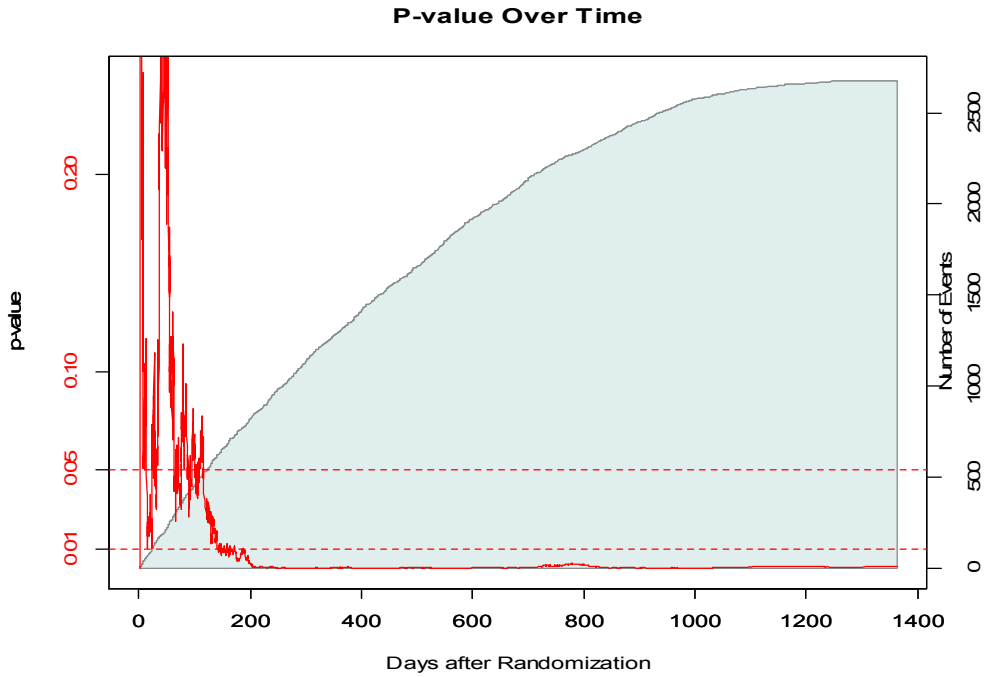


Figure 7 P-Value Over Time for TRA-2P Study (Based on Calendar Dates and Patients' Days After Randomization)





3.3 EVALUATION OF SAFETY

The evaluation of safety is not performed in this review.

3.4 BENEFIT-RISK ASSESSMENT (OPTIONAL)

The benefit-risk assessment is not performed in this review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

The sponsor's subgroup analysis results for gender, race and age are shown in Table 16. According to the results, vorapaxar seemed to have similar performance in male and female patients, but appeared more effective in younger patients than older patients and non-white patients than white patients.

Table 16 Sponsor's Subgroup Analysis for Gender, Race and Age for TRA-2P Study

Subgroup	Placebo n = 13224		Vorapaxar n = 13225		HR (95% CI)
	Subject with Events m/n (%)	KM %	Subject with Events m/n (%)	KM%	
Sex					
Male	1061/10052 (10.6%)	12.1%	939/10071 (9.3%)	10.9%	0.88 (0.88-0.96)
Female	356/3172 (11.2%)	13.3%	320/3154 (10.1%)	12.4%	0.89 (0.77-1.04)
Age					
<65 years	779/8273 (9.4%)	10.6%	648/8188 (7.9%)	9.3%	0.83 (0.75-0.93)
≥65 years	638/4951 (12.9%)	15.3%	611/5037 (12.1%)	14.3%	0.93 (0.84-1.04)
Age					
<75 years	1181/11718 (10.1%)	11.7%	1042/11711 (8.9%)	10.5%	0.87 (0.81-0.95)
≥75 years	236/1506 (15.7%)	18.0%	217/1514 (14.3%)	17.2%	0.90 (0.75-1.09)
Race					
White	1224/11524 (10.6%)	12.3%	1083/11562 (9.4%)	10.9%	0.96 (0.86-1.08)
Non-white	193/1695 (11.4%)	13.5%	176/1656 (10.6%)	13.5%	0.81 (0.73-0.90)

Source: Sponsor's Display E-2, Page 800 of CSR

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

The sponsor's subgroup analysis results for weight, enrollment stratum and region are shown in Table 17. The patients weighted less than 60 kg or the patients from Asia/Pacific islands seemed to have a large hazard ratio. But their sample sizes are small and thus the opposite trends are difficult to interpret. Interestingly, vorapaxar seemed to have little effect in CVD or PAD stratum. .

To further assess if this reverse findings of vorapaxar comparing with placebo in the light weighted group of patients (<60 kg) needs to be concerned, per the medical reviewer's request, the statistical reviewer performed a more detailed subgroup analysis using more categories for both TRACER and TRA-2P studies and results are shown on Table 18. The vorapaxar's effect

seems larger as the body weight is larger (Table 18) and seems little or negative in patients with weigh ≤ 60 kg.

Table 17 Sponsor's Other Subgroup Analysis Result for TRA-2P Study

Subgroup	Placebo n = 13224		Vorapaxar n = 13225		HR (95% CI)
	Subject with Events m/n (%)	KM %	Subject with Events m/n (%)	KM%	
Body Weight					
< median	650/6489 (10.0%)	12.0%	634/6574 (9.6%)	11.8%	0.96 (0.86-1.08)
≥ median	765/6703 (11.4%)	12.9%	622/6632 (9.4%)	10.7%	0.81 (0.73-0.90)
Body Weight					
< 60 kg	75/921 (8.1%)	9.6%	96/931 (10.3%)	13.6%	1.28 (0.95-1.73)
≥ 60 kg	1340/12271 (10.9%)	12.6%	1160/12275 (9.5%)	11.1%	0.86 (0.79-0.93)
Stratum					
CAD	956/8881 (10.8%)	12.1%	809/8898 (9.1%)	10.5%	0.83 (0.76-0.92)
CVD	216/2448 (8.8%)	12.1%	217/2435 (8.9%)	12.9%	1.02 (0.84-1.23)
PAD	245/1895 (12.9%)	13.4%	233/1892 (12.3%)	12.7%	0.95 (0.79-1.14)
Region					
North America	535/3920 (13.6%)	15.4%	501/3916 (12.8%)	14.2%	0.93 (0.82-1.05)
Latin America	188/1646 (11.4%)	13.3%	161/1648 (9.8%)	12.4%	0.85 (0.69-1.05)
Europe 1	543/5604 (9.7%)	11.0%	459/5612 (8.2%)	9.7%	0.84 (0.74-0.95)
Europe 2	105/1319 (8.0%)	9.0%	92/1317 (7.0%)	8.3%	0.87 (0.66-1.16)
Asia/Pacific	24/389 (6.2%)	8.7%	26/388 (6.7%)	8.8%	1.10 (0.63-1.92)
Austratia/New Zeland	22/346 (6.4%)	8.5%	20/344 (5.8%)	6.7%	0.90 (0.49-1.66)

Source: Sponsor's Display E-2, Page 800-803 of CSR

Table 18 Statistical Reviewer's Subgroup Analysis Results for Body Weight for both TRACER and TRA-2P Studies (Reported are HR and 95% C.I.)

Primary Endpoint	TRACER	TRA-2P Overall Population	TRA-2P Proposed Label
Baseline Weight<60	1.06 (0.80, 1.42)	1.29 (0.96, 1.74)	1.1 (0.71, 1.70)
60<= Baseline Weight <70	0.99 (0.80, 1.24)	0.90 (0.74, 1.09)	0.91 (0.69, 1.19)
70<= Baseline Weight <80	0.88 (0.73, 1.06)	0.94 (0.81, 1.10)	0.85 (0.69, 1.05)
80<= Baseline Weight <100	0.94 (0.82, 1.08)	0.82 (0.72, 0.92)	0.78 (0.67, 0.91)
100<= Baseline Weight <200	0.80 (0.65, 0.99)	0.81 (0.67, 0.98)	0.75 (0.60, 0.95)
Key2nd Endpoint	TRACER	TRA-2P Overall Population	TRA-2P Proposed Label
Baseline Weight<60	1.01 (0.75, 1.37)	1.24 (0.90, 1.71)	1.1 (0.66, 1.81)
60<= Baseline Weight <70	1.02 (0.8, 1.29)	0.91 (0.74, 1.13)	0.99 (0.72, 1.36)
70<= Baseline Weight <80	0.84 (0.68, 1.03)	0.93 (0.78, 1.10)	0.81 (0.64, 1.03)
80<= Baseline Weight <100	0.91 (0.78, 1.07)	0.81 (0.71, 0.93)	0.74 (0.62, 0.88)
100<= Baseline Weight <200	0.74 (0.58, 0.93)	0.76 (0.61, 0.94)	0.68 (0.51, 0.89)

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The statistical reviewer confirmed the sponsor's analysis results for the primary, key secondary and other important secondary endpoints in both TRACER and TRA-2P studies. The efficacy results for vorapaxar demonstrated from TRA-2P appear positive in all different patient populations and the findings appear robust throughout the trial.

This reviewer is concerned with the unplanned interim efficacy analyses conducted, though the trial seems still to achieve significance level of 0.01 for both the primary and the key secondary endpoints (see Section 3.2.4.4). It is unclear whether such unplanned unblinded interim efficacy analyses, sample size re-estimation and change of patient population might have some impact on trial integrity.

Finally, to further examine the reverse finding of the vorapaxar observed for patients' in the light weighted subgroup (i.e., body weight <60 kg) in comparing with placebo, this reviewer performed the more detailed subgroup analyses by different body weight groups for both TRACER and TRA-2P studies. The vorapaxar's effect seems larger as the body weight is larger (Table 18) and seems little or negative in patients with weigh ≤ 60 kg.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The vorapaxar's efficacy in addition to the standard of care for preventing patients' atherothrombotic ischemic events appears to be demonstrated based on TRA 2°P-TIMI 50 trial for the overall study population and also the proposed label population, i.e., post MI patients without history of stroke or TIA. However, we are concerned about several unplanned interim analyses, sample size increase and change of patient population, even though these analyses are performed by an independent statistician through the Data Safety Monitoring Board (DSMB). Whether these analyses might have impacted the trial integrity is uncertain.

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Yeh-Fong Chen, Ph.D.
Mathematical Statistician

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HFD-110/Dr. Marciniak
HFD-110/Dr. Rose
HFD-110/Ms. Alison
HFD-700/Ms. Patrician
HFD-710/Dr. Hung

6. APPENDIX

6.1 Brief Description of TRACER Study

Study Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard of Care in Subjects With Acute Coronary Syndrome: Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome

Study Objectives and Efficacy Endpoints

The primary objective was to evaluate the hypothesis that vorapaxar added to standard of care will reduce the incidence of atherothrombotic ischemic events relative to standard of care alone, as measured by the composite of cardiovascular death, myocardial infarction (MI), stroke, recurrent ischemia with rehospitalization, and urgent coronary revascularization.
The key secondary objective was to evaluate clinical benefit with respect to the composite of CV death, MI, and stroke.

Primary Analysis

Analyses of the primary efficacy endpoint and key secondary endpoint were accomplished via the Cox proportional hazards model with covariates of treatment and stratification factors. Treatment differences were tested at 0.049 to account for one interim analysis. P-values and estimates of the hazard ratios and 95% confidence intervals were provided. Similar analyses were performed for other secondary and exploratory efficacy endpoints at α=0.05.

Patient Disposition and Demographics and Baseline Characteristics

Table 19 Subject Disposition for TRACER Study

Number (%) of Subjects	Placebo	SCH 530348	Total
Randomized	n = 6471	n = 6473	n = 12944
Received treatment	6441 (99.5)	6,446 (99.6)	12,887 (99.6)
Never Received Study Drug	30 (0.5)	27 (0.4)	57 (0.4)
Discontinued Study Drug Prematurely	1,726 (26.8)	1,818 (28.2)	3,544 (27.5)
Adverse/Bleeding/Clinical Experience	489 (7.6)	649 (10.1)	1,138 (8.8)
Did not wish to continue	865 (13.4)	858 (13.3)	1,723 (13.4)
Non-compliance	287 (4.5)	232(3.6)	519 (4.0)
Did not have disease of interest	65 (1.0)	56 (0.9)	121 (0.9)
Unknown	20 (0.3)	23 (0.4)	43 (0.3)
Completed Study on Treatment	4,715 (73.2)	4,628 (71.8)	9,343 (72.5)
Died on treatment	156 (2.4)	153 (2.4)	309 (2.4)
Completed treatment	4,559 (70.8)	4,475 (69.4)	9,034 (70.1)

Source: Sponsor's Display A-1.4 on Page 544 of CSR.

Table 20 Demographic and Other Baseline Characteristics for All Randomized Patients in TRACER Study

Number (%) of Subjects	Placebo N=6,471	Vorapaxar N=6473	Total N=12,944
Age (years), Mean (SD)	64.4 (9.98)	64.4 (9.95)	64.4 (9.96)
Sex, n (%)			
Female	1,822 (28.2)	1,810 (28.0)	3,632 (28.1)
Male	4,649 (71.8)	4,663 (72.0)	9,312 (71.9)
Race, n (%)			
White	5,510 (85.1)	5,529 (85.4)	11,039 (85.3)
Non-White	943 (14.6)	927 (14.3)	1,870 (14.4)
American Indian or Alaskan Native	16 (0.2)	19 (0.3)	35 (0.3)
Asian	533 (8.2)	523(8.1)	1,056 (8.2)
Black or African American	161 (2.5)	151 (2.3)	312 (2.4)
Multiracial	213 (3.3)	222 (3.4)	435 (3.4)
Native Hawaiian or Other Pacific Islander	20 (0.3)	12 (0.2)	32 (0.2)
Missing	18 (0.3)	17 (0.3)	35 (0.3)
Ethnicity, n (%)			
Chinese	136 (2.1)	137 (2.1)	273 (2.1)
Hispanic/Latino	532 (8.2)	557 (8.6)	1,089 (8.4)
Japanese	145 (2.2)	136 (2.1)	281 (2.2)
Korean	65 (1.0)	64 (1.0)	129 (1.0)
Taiwanese	111 (1.7)	107 (1.7)	218 (1.7)
Other	5,336 (82.5)	5,311 (82.0)	10,647 (82.3)
Missing	17 (0.3)	30 (0.5)	47 (0.4)
Weight (kg), Mean (SD)	82.25 (17.66)	82.66 (18.12)	82.45 (17.89)
Height (cm), Mean (SD)	169.74 (9.6)	169.78 (9.64)	169.76 (9.62)
Calculated Body Mass Index (kg/m^2), Mean (SD)	28.44 (5.16)	28.57 (5.34)	28.51(5.25)
Heart Rate (beats/minute), Mean (SD)	70.9 (13.24)	70.8 (13.07)	70.9 (13.15)
Systolic Blood Pressure (mm Hg), Mean (SD)	131.8 (20.83)	132.0 (20.67)	131.9 (20.75)
Diastolic Blood Pressure (mm Hg), Mean (SD)	75.0 (12.48)	74.8 (12.42)	74.9 (12.45)
Waist Circumference (cm), Mean (SD)	100.36 (14.09)	100.61 (14.18)	100.49 (14.13)

Source: Sponsor's Table 16 from Pages 126 to 128 of CSR.

Efficacy Results

Table 21 Sponsor's Results for Primary and Key Secondary Endpoints for the Overall ITT Population for TRACER Study

Endpoint and Contributing Component	Placebo (n=6,471)		Vorapaxar (n=6,473)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Primary Efficacy Endpoint	1,102 (17.0%)	19.9%	1,031 (15.9%)	18.5%	0.92 (0.85-1.01)	0.072
CV Death	122 (1.9%)		115 (1.8%)			
MI	668 (10.3%)		596 (9.2%)			
Stroke	89 (1.4%)		83 (1.3%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	82 (1.3%)		63 (1.0%)			
Hemorrhagic Stroke	6 (0.1%)		19 (0.3%)			
Uncertain	1 (0%)		1 (0.0%)			
RIR	53 (0.8%)		60 (0.9%)			
UCR	170 (2.6%)		177 (2.7%)			

Endpoint and Contributing Component	Placebo (n=6,471)		Vorapaxar (n=6,473)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Key Secondary Efficacy Endpoint	910 (14.1%)	16.4%	822 (12.7%)	14.7%	0.89 (0.81-0.98)	0.018
CV Death	127 (2.0%)		122 (1.9%)			
MI	692 (10.7%)		614 (9.5%)			
Stroke	91 (1.4%)		86 (1.3%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	84 (1.3%)		66 (1.0%)			
Hemorrhagic Stroke	6 (0.1%)		19 (0.3%)			
Uncertain	1 (0%)		1 (0.0%)			

Source: Sponsor's Table 31 of CSR.

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/s/

YEH FONG CHEN
12/13/2013

HSIEN MING J HUNG
12/13/2013

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	204886
Submission Date	(b) (4)
Submission Type	Original, NME – Standard Review
Brand Name	ZONTIVITY®
Generic Name	Vorapaxar Sulfate
Sponsor	Merck, Sharp and Dohme Corp.
Therapeutic Class	Protease Activated Receptor-1 [PAR-1] antagonist [anti-platelet]
Formulation	Oral immediate release tablet
[Strengths]	[2.5 mg]
Dosing Regimen	2.5 mg once-daily
Proposed Indication	Reduction of atherothrombotic events in patients with a history of myocardial infarction [MI] and no prior history of stroke or transient ischemic attack [TIA]
OCP Division	Division of Clinical Pharmacology I
OND Division	Division of Cardiovascular and Renal Products
Primary Reviewers	Sudharshan Hariharan, Ph.D. AbuAsal Bilal, Ph.D. Fang Li, Ph.D.
Team Leaders	Rajanikanth Madabushi, Ph.D. Yaning Wang, Ph.D.

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1. EXECUTIVE SUMMARY

Merck Sharp and Dohme Corp. is seeking approval of vorapaxar sulfate [NDA 204886] for use in reduction of atherothrombotic events in patients with a history of MI and no history of stroke or TIA. Vorapaxar is a first-in-class, selective, competitive and reversible antagonist of protease activated receptor-1 [PAR-1], the receptor that mediates the downstream effects of thrombin on human platelets. Aspirin and clopidogrel are the other two approved drugs for the secondary prevention of thrombotic events in patients with MI.

The efficacy and safety of vorapaxar was evaluated in two independent, large, multi-center, outcome studies - TRACER[1] and TRA2°P - TIMI 50[2], designed to support acute coronary syndrome [ACS] and secondary prevention post MI indications, respectively. The applicant identified a subgroup of patients post MI with no prior history of stroke or TIA, which does not have an excess of intracranial hemorrhage [ICH] risk in TRA2°P - TIMI 50 and is seeking approval for this population. The applicant does not seek approval of vorapaxar for treatment of ACS.

The clinical pharmacology program consists of 19 *in vivo* studies designed to characterize mass balance, relative bioavailability/bioequivalence, pharmacokinetics [PK], pharmacodynamics [PD], and impact of intrinsic factors and extrinsic factors on vorapaxar PK and/or PD. In addition, 15 *in vitro* studies were conducted to characterize protein binding, and identify the role of metabolizing enzymes/transporters in the disposition of vorapaxar and its monohydroxy metabolite, M20.

1.1. Recommendations

The Office of Clinical Pharmacology [OCP] has reviewed the clinical pharmacology and biopharmaceutics information submitted to this NDA and recommends approval pending agreement with the applicant on labeling.

Based on the review, OCP has the following labeling recommendation: Avoid use of vorapaxar in patients with body weight < 60 kg due to unfavorable benefit-risk.

1.2. Phase 4 Commitments

No specific post-marketing commitments or requirements are proposed at this point of time.

[1] Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome
[2] Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The key findings are listed below.

Pharmacokinetics:

- Following oral administration, median T_{max} for vorapaxar is 1 to 2 h. The disposition is biphasic, characterized by a relatively faster distribution and slow terminal elimination [$t_{1/2}$ = 7 to 11 days]. The absolute bioavailability as estimated by a microdosing study is ~ 100%.

- The steady state is attained by day 21 [earliest available PK] following repeat once-daily dosing regimen. The accumulation at steady state for vorapaxar is 5- to 6-fold. The effective half-life based on accumulation at steady state is 3 to 4 days.

- The monohydroxy metabolite M20, is active as shown by inhibition of calcium efflux in human coronary artery smooth muscle cells with similar potency to that of vorapaxar. Exposure of M20 was in the range of 8% to 29% of vorapaxar across Phase 1 studies. The concentration-time course of M20 generally mirrors that of vorapaxar, suggesting M20 is formation rate-limited.

- Vorapaxar is extensively metabolized followed by excretion in urine and feces. Based on a mass balance study, <2% of vorapaxar is excreted unchanged in feces and none in urine.

Pharmacodynamics:

- Vorapaxar inhibits platelet aggregation induced by thrombin receptor activating peptide [TRAP]. Following repeat oral doses of 2.5 mg once-daily, the onset of platelet inhibition [i.e., <10% aggregation relative to baseline] is projected to be achieved by day 2. Time to offset platelet inhibition is relatively slow with ~50% of platelet function recovered by 4 weeks post-last dose.

PK/PD:

- Vorapaxar demonstrates a steep exposure-platelet inhibition relationship. Over a narrow range of vorapaxar concentration [~1 to 5 ng/mL], the TRAP-induced platelet aggregation changes from non-effect to maximal inhibition.

- Based on population PK and PK//PD data from Phase 1, 2 and 3 studies, 2.5 mg vorapaxar sulfate administered once-daily is predicted to achieve the target engagement i.e., ≥ 80% platelet inhibition in almost all patients by day 7.

Impact of intrinsic factors:

- Based on an increased risk of bleeding [hazard ratio (HR) = 1.87; GUSTO severe or moderate bleeding events] and potential lack of benefit [HR = 1.28; primary efficacy MACE endpoint] for vorapaxar in patients with body weight < 60 kg, the use of vorapaxar should be avoided in this subgroup.

- Though vorapaxar is extensively metabolized, the results of a dedicated hepatic impairment study showed that the pharmacokinetics of vorapaxar was not significantly impacted. It should be noted that one subject from the severe hepatic impairment group in the dedicated study experienced severe gastrointestinal hemorrhage secondary to esophageal varices. As severe hepatic impaired subjects are predisposed to a higher risk of bleeding due to compromised coagulatory state, the use of vorapaxar should be avoided in this subgroup.

- Renal impairment does not affect the pharmacokinetics of vorapaxar. No dose-adjustment is proposed in patients with renal impairment.

Impact of extrinsic factors:

- Vorapaxar is metabolized by CYP3A4 and CYP2J2. Inhibition or induction of these enzymes may affect the systemic exposures to vorapaxar.

- Upon repeat co-administration, ketoconazole, a strong CYP3A inhibitor, increases the systemic exposures to vorapaxar by 2-fold, while rifampin, a strong CYP3A inducer, decreases the systemic exposure to vorapaxar by 55%. The efficacy or bleeding risk for a change in exposure of this magnitude is not known due to the absence of concentration-outcome relationship. Further, concomitant administration of these drugs with vorapaxar was excluded in the phase 3 studies. Therefore, avoid use of vorapaxar with strong inhibitors or inducers of CYP3A.

- The phase 3 trial allowed the use of mild and moderate CYP3A inhibitors. The bleeding risk of vorapaxar in the patients concomitantly receiving these drugs was similar to the control group. No dose adjustments are required when used with mild or moderate CYP3A inhibitors.

- The role of vorapaxar as a perpetrator is low. There is no PK or PD interaction between vorapaxar and digoxin, warfarin, and rosiglitazone.

- Co-administration with a high fat meal, or an antacid, or a proton pump inhibitor [PPI], has a modest impact on the rate of absorption of vorapaxar, but does not significantly alter the extent of absorption. No dose-adjustments are required.

Biopharmaceutics:

- Vorapaxar sulfate converts partially to the amorphous free base upon manufacturing and storage. A pivotal bioequivalence study was performed to evaluate the impact of the base content in the batches used in Phase 3 trial on PK. The low base product [23%] and high base product [46%] were bioequivalent in the presence of a PPI [worst case scenario].

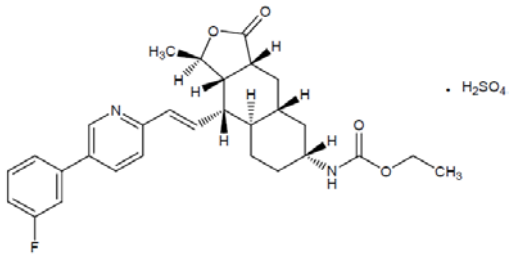
2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Drug substance: The physicochemical characteristics of vorapaxar sulfate are summarized in Table 1.

Table 1: Physicochemical properties of vorapaxar sulfate

Appearance	White to off-white crystalline powder
Chemical name	Ethyl[(1R,3aR,4aR,6R,8aR,9S,9aS)-9-{(1E)-2-[5-(3-fluorophenyl) pyridin-2-yl]ethen-1-yl}-1-methyl-3-oxododecahydronaphtho[2,3-c] furan-6-yl]carbamate sulfate
Molecular formula	$C_{29}H_{33}FN_2O_4 \bullet H_2SO_4$
Molecular weight	590.7
Structural formula	
Solubility	pH dependent • fasted conditions, stomach [pH 1.4] = 0.65 mg/mL • fasted conditions, small intestine [pH 6.7] = 0.065 mg/mL • pH 7.5 = 0.001 mg/mL
pKa	4.7
Partition coefficient	Log P = 5.1
Stability	Vorapaxar sulfate salt converts partially to the amorphous free base upon manufacturing and storage
Hygroscopicity	Slightly hygroscopic, adsorbs 1% wt at 85% RH

Drug product: Vorapaxar sulfate is formulated as an immediate release, yellow, oval, film-coated tablet. The formulation does not contain any excipients that impact the release of the drug substance.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Vorapaxar is a selective, competitive and reversible antagonist of PAR-1, the receptor that mediates the downstream effects of thrombin on human platelets. The EC_{50} of vorapaxar is 15 nM, as shown *in vitro* by the effects on human platelet aggregation induced by thrombin receptor activating peptide [TRAP]. The monohydroxy metabolite of vorapaxar M20, is also reported to be active in an activity assay involving inhibition of calcium efflux induced by a specific PAR-1 agonist in human coronary artery smooth muscle cells. Based on this assay, M20 [EC_{50} = 3.4 nM] and vorapaxar are equipotent [EC_{50} = 4.5 nM].

The proposed indication for vorapaxar in the current submission is for the reduction of atherothrombotic events in patients with a history of MI and no prior history of stroke or TIA.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed dosage form is an immediate release tablet for oral use to be administered once-daily without regards to food. The dosage form is available at a single strength of 2.5 mg.

2.1.4. What are the current treatments available for the proposed indications?

Aspirin [80-325 mg once daily] and clopidogrel [75 mg once daily] are the other approved treatment options available to reduce the rate of thrombotic cardiovascular events in patients with a prior history of MI.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical pharmacology program for vorapaxar comprised of 19 *in vivo* studies which are listed in Table 2. The submission also included 15 *in vitro* studies which characterized plasma protein binding and the enzymes/transporters responsible for metabolism/transport of vorapaxar and M20.

Table 2: List of *in vivo* clinical pharmacology studies

Relative bioavailability/Bioequivalence studies	
P03445	Pilot effect of food on vorapaxar PK administered as a 1 mg tablet Relative BA of tablet *vs* capsule
P03447	Effect of food and antacid on PK Relative BA of different dose strengths of vorapaxar
P06452	Relative BA of vorapaxar sulfate salt *vs* free base
P06558	BE study of vorapaxar sulfate 2.5 mg tablets containing high and low percentage of drug as the free base within the range used in Phase 3 trials
P07045	Absolute BA and mass balance of vorapaxar using a microdosing technique
P07969	Effect of food on vorapaxar PK administered as a 2.5 mg tablet
Healthy volunteer PK and PD studies	
P03449	Rising single dose safety, tolerability, PK and PD
P03450	Rising multiple dose safety, tolerability, PK and PD
P03454	^{14}C-vorapaxar absorption, metabolism, excretion
P06559	PK of vorapaxar and M20 in healthy volunteers (Caucasians)
Intrinsic factor studies	
P03448	Effect of race and food on vorapaxar PK, PD and safety (Japanese *vs* Caucasians)
P03464	Effect of renal impairment on vorapaxar PK and PD
P03465	Effect of hepatic impairment on vorapaxar PK
P06453	PK of vorapaxar and M20 in healthy volunteers (Chinese)
Extrinsic factor studies	
P03458	Effect of vorapaxar on digoxin PK and PD
P03629	Effect of ketoconazole and rifampin on vorapaxar PK
P04132	Effect of vorapaxar on warfarin PK and PD
P05361	Effect of vorapaxar on rosiglitazone PK and PD
P06560	Evaluation of PK drug interaction between vorapaxar and prasugrel

The clinical development program comprised of a Phase 2 study [P03573, N = 1030] aimed to establish proof-of-concept, evaluating a range of loading and maintenance doses in patients eligible for non-emergent percutaneous coronary intervention [PCI]. Two other Phase 2 studies with smaller sample size were conducted in Japanese patients.

In Phase 3, the efficacy and/or safety of vorapaxar to reduce the rate of atherothrombotic cardiovascular events in two different at-risk populations was explored in two independent multi-center trials. TRACER and TRA2°P - TIMI 50 were long-term, large-scale, outcome studies designed to support different indications of ACS and secondary prevention post MI, post stroke or peripheral artery disease [PAD], respectively. TRACER enrolled subjects in the midst of an acute episode during hospitalization while TRA2°P - TIMI 50 enrolled clinically stable subjects, 2 weeks- to 1 year-post the index event. The results of TRACER showed an excess of ICH in the vorapaxar group. Hence, the applicant is not pursuing approval of vorapaxar in ACS patients.

A similar finding was also observed in the TRA2°P - TIMI 50 trial. The applicant identified a subgroup of patients with a prior history of stroke, to have a higher risk of ICH on vorapaxar.

The protocol was amended to discontinue vorapaxar in patients with a prior history of stroke for the remainder of the trial. Upon trial completion and data analysis, the applicant has further identified specific patient population in whom the benefit may outweigh the risk and is seeking approval only in patients post MI with no history of stroke or TIA.

2.2.2. What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Inhibition of platelet aggregation induced by TRAP was used as a target engagement biomarker for dose-selection. The primary efficacy endpoint in TRA2°P - TIMI 50 was a composite of cardiovascular death, MI, stroke and urgent coronary revascularization [UCR]. Safety assessments included primarily pre-specified bleeding endpoints defined by GUSTO and TIMI categories and reported individual bleeding events.

2.2.3. Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Vorapaxar and M20 are the active moieties in plasma. These were appropriately identified and measured to permit adequate assessment of the pharmacokinetics in Phase 1 studies. Systemic exposures of vorapaxar and M20 was not measured in TRA2°P - TIMI 50 and available only from a small subset of patients [N=95] in TRACER, thus limiting a direct evaluation of concentration-outcome relationship.

2.3. Exposure-Response

2.3.1. What was the basis of dose selection for Phase 3 trial and is the rationale acceptable?

Exposure-TRAP induced platelet aggregation relationship from Phase 1 and 2 studies was utilized for selection of dose in TRA2°P - TIMI 50. The selected dose was 2.5 mg vorapaxar sulfate administered once-daily.

TRAP induced platelet aggregation was measured in 4 Phase 1 [P03449, P03448, P03450, P03464], 3 PK sub studies from Phase 2 [P3573, P04772, P05005] and a PK/PD sub study of TRACER [P04736] trial. Based on preclinical and clinical experience, achievement of ≥80% inhibition of TRAP-induced platelet aggregation by high proportion of patients on day 7 was considered as the target engagement for vorapaxar to show clinical efficacy. It should be noted that the type and nature of the relationship between platelet inhibition and prevention of atherothrombotic ischemic events is not known.

Vorapaxar demonstrated a steep exposure-platelet inhibition relationship [Fig. 1]. In a narrow range of vorapaxar concentration, the TRAP-induced platelet aggregation can switch from a low to a high inhibition; however, there existed large variations in EC_{50} value among studies. While most Phase 1 to 3 studies demonstrated comparable EC_{50}, two Phase 1 studies [P03448 and P03464] showed exceptionally high EC_{50}, as demonstrated in Figure 1. There is no

pharmacogenomic basis to account for the differences in EC_{50} values in studies P03448 and P03464. Further, there were no identifiable methodological differences between these studies and the rest which could explain a shift in EC_{50} value.

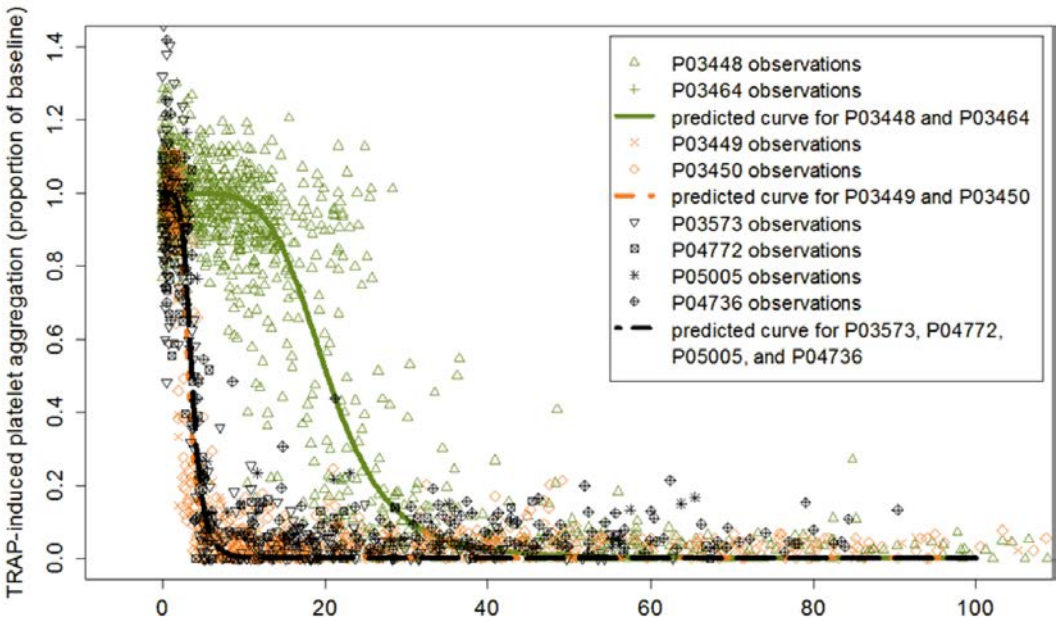


Figure 1: TRAP-induced platelet aggregation data versus effective concentration

[Source: Figure 9 on page 47 of applicant's Summary of Clinical Pharmacology Studies]

The applicant used the combined population PK and PK/PD models to simulate the percentage of patients achieving ≥ 80% inhibition of TRAP-induced platelet aggregation on day 7 and 28 [Fig. 2]. In patients representative of low EC_{50} value, 2.5 mg dose once-daily would achieve maximum platelet inhibition in almost all patients by day 7. In patients representative of high EC_{50} value, 80% of patients are projected to achieve ≥ 80% inhibition by day 28 following 2.5 mg dose once-daily.

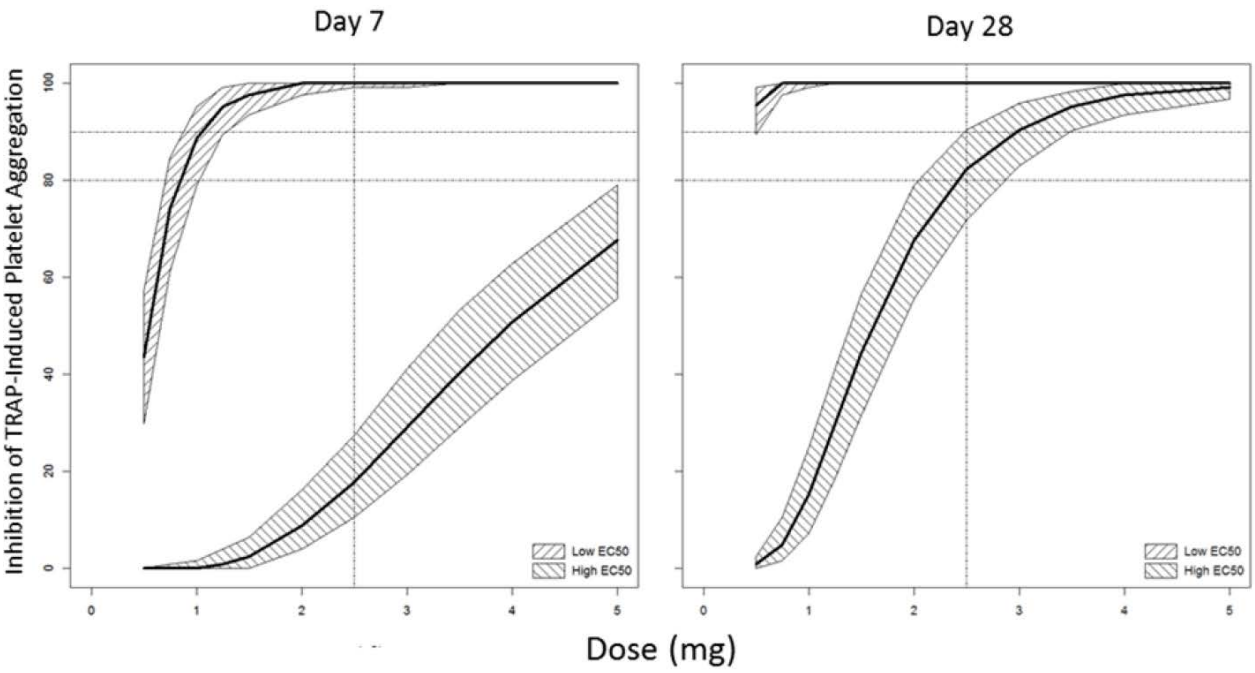


Figure 2: Proportion of subjects achieving at least 80% inhibition of TRAP-induced platelet aggregation after 7 days (left) and 28 days (right) of treatment

[Source: Figure 19 on page 62 of applicant's Population PK and PK/PD report]

In the absence of a plausible explanation for the differences in EC_{50}, discussion on the choice of 2.5 mg once-daily as the selected Phase 3 dose can be made in light of low and high EC_{50} values. If the high EC_{50} subgroup is a spurious finding [given the lack of plausible explanation], then a lower dose of 1 mg once daily can also achieve the desired target engagement. On the other hand, if there truly exists a subgroup with the high EC_{50} and that this subgroup cannot be identified prior to treatment, the selected dose of 2.5 mg once day is not optimal. As the target engagement is not achieved until 4 weeks post-dosing, a regimen with loading dose would be more appropriate in this scenario.

Hence, based on the applicant's choice of defined target engagement for vorapaxar, a 2.5 mg once-daily dose may not be optimal. As stated earlier, the relationship between TRAP-induced platelet aggregation and clinical outcomes is not known. Also, based on the results of the phase 2 study, there was no dose response for bleeding risk at 0.5 mg, 1 mg or 2.5 mg doses, when administered concomitantly with aspirin and clopidogrel.

2.3.2. What are the characteristics of the exposure-response relationship for efficacy?

No PK sampling was included in the pivotal study. Therefore, it was not possible to estimate individual patient-level vorapaxar exposure to allow for a direct evaluation of exposure-response relationships for the primary efficacy endpoint [composite of cardiovascular death, MI, stroke, and UCR]. The applicant conducted an exploratory exposure-efficacy analysis based on population PK model-predicted average exposure data for subgroups of patients. No obvious exposure-efficacy relationship was identified. The reviewer agrees with the limitations of this

analysis outlined by the applicant, i.e., the lack of individual exposure and the assumption of balanced distribution of other risk factors among the subgroups. This highlights the fact that the population PK model from Phase 1 and 2 studies cannot entirely alleviate the need for sparse PK sample collection in Phase 3, for the evaluation of exposure-response relationship.

2.3.3. What are the characteristics of the exposure-response relationship for safety?

The applicant conducted an exploratory exposure-bleeding analysis based on a similar approach described under [Q. 2.3.2]. An upward trend was observed in the overall population, suggesting higher bleeding risk was associated with higher drug exposure. Despite the limitations of this analysis as outlined by the applicant [the lack of individual exposure and the assumption of balanced distribution of other risk factors among the subgroups], such a relationship is considered reasonable and is consistent with other drugs with similar mechanism of action. This relationship may be partially responsible for the observed higher risk of bleeding in the subgroup of patients with body weight < 60 kg [HR = 1.87 in patients with body weight < 60 kg versus 1.48 in patients with body weight ≥ 60kg, ITT population] because higher drug exposure was observed in patients with lower body weight.

2.3.4. Does this drug prolong the QT or QTc interval?

No, vorapaxar does not appear to prolong QTc interval. Please refer to the QT-IRT review [DARRTS date: 11/29/2010].

2.4. Pharmacokinetics

2.4.1. What are the single- and multiple-dose PK parameters?

The pharmacokinetics of vorapaxar was evaluated following a single dose range of 0.25 to 120 mg as well as following once daily repeat administration of 1 to 5 mg up to 28 days in healthy volunteers. Upon oral administration, the median T_{max} of vorapaxar was 1 to 2 h. This was followed by a relatively faster distribution and a slow terminal elimination phase. The mean apparent clearance [CL/F] and volume of distribution [V_d/F] of vorapaxar is 2.2 L/h [CV%=32] and 634 L [CV%=43], respectively. The mean terminal elimination half-life of vorapaxar is about 7 to 11 days across Phase 1 studies. However, based on the accumulation ratios at steady state which ranged from 4.7 to 6.4, the effective half-life can be estimated to be about 3 to 4 days. Upon once-daily dosing, steady state exposures of vorapaxar are achieved by day 21 [earliest available PK].

Pharmacokinetics of M20 was evaluated following a single dose of 120 mg and repeat doses of 2.5 mg vorapaxar sulfate [once-daily, 42 days]. The median time to reach peak concentration was 4 h post-dose with the elimination phase of the concentration-time course mirroring that of the parent drug, vorapaxar [Fig. 3]. This suggests that M20 is a formation rate-limited metabolite, where the rate of elimination of the metabolite is faster than the rate at which it is formed. Across Phase 1 studies where M20 was quantified, the exposure to M20 was in the range of 8% to 29% to that of vorapaxar.

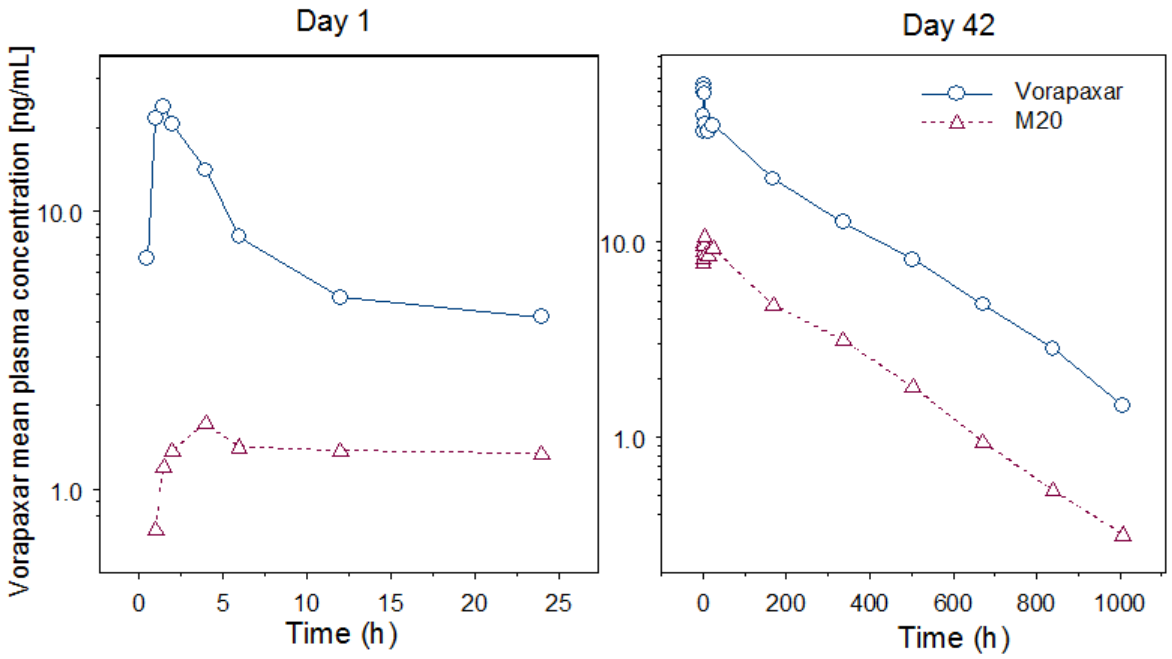


Figure 3: Plot of vorapaxar and M20 plasma concentration-time profile following repeat doses of 2.5 mg vorapaxar sulfate on day 1 and day 42

2.4.2. How does the PK in healthy volunteers compare to that in patients?

A population PK analyses was conducted to evaluate the influence of disease on the PK of vorapaxar. The results show that there is a 9% reduction in bioavailability and 82% increase in Vc/F in patients relative to healthy subjects. This translated to a 14% decrease in steady state exposures to vorapaxar [$AUC_{0-\tau}$], which may not be clinically meaningful [Fig. 4].

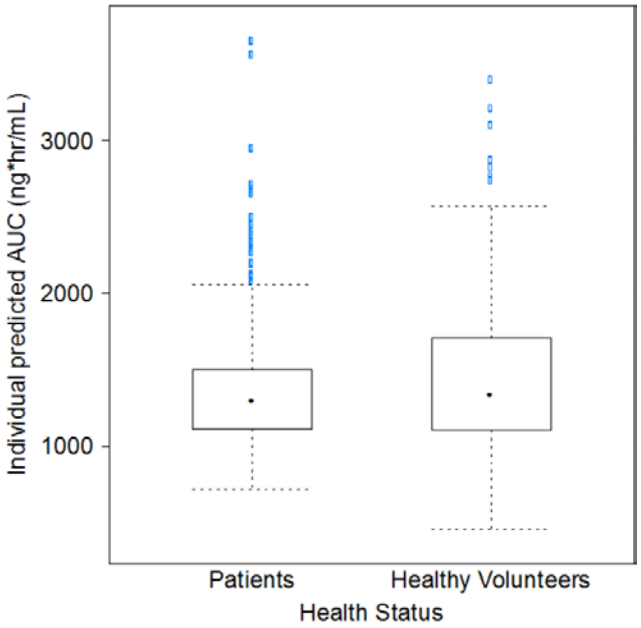


Figure 4: Box-plot of individual vorapaxar exposure [$AUC_{0-\tau}$] determined using population PK model in healthy volunteers versus patients

[Source: Figure 16 on page 59 of applicant's Summary of Clinical Pharmacology Studies]

2.4.3. What are the characteristics of drug absorption?

The absolute oral bioavailability of vorapaxar evaluated using a microdosing technique is ~ 100%. Co-administration with a high fat meal, or an antacid, or a proton pump inhibitor, has a modest impact on the rate of absorption of vorapaxar, but does not significantly alter the extent of absorption [Table 3].

Table 3: Impact of a high fat meal, an antacid and proton pump inhibitor on the PK measures of vorapaxar

	C_{max}	$AUC_{0\text{-}72\ h}$	T_{max}
Standardized high fat meal	↓21%	↓3%	delayed by 45 min
20 mL Gaviscon®	↓38%	↓11%[a]	delayed by 60 min
40 mg Pantoprazole[b]	↓15%	↓10%	No change

[a] $AUC_{0\text{-}t}$

[b] 7 day pretreatment with pantoprazole before vorapaxar administration

2.4.4. What are the characteristics of drug distribution?

Vorapaxar is widely distributed with a volume of distribution of 379 L. The protein binding [predominantly to serum albumin] of vorapaxar and M20 as determined using equilibrium dialysis is high [≥ 99%]. The binding of vorapaxar to plasma proteins is not concentration dependent in the range 40 to 10,000 ng/mL. The mean blood-to-plasma ratio of vorapaxar is 0.60, indicating limited partitioning into red blood cells.

2.4.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

Vorapaxar is eliminated mainly by metabolism followed by excretion in urine and feces. Following oral administration of ^{14}C-vorapaxar sulfate solution, only 39.2% [35% in feces, 4.2% in urine] of the administered dose was recovered in 7 days. Metabolite profiling showed that vorapaxar and M20 are the primary circulating moieties in plasma. Vorapaxar was not detected unchanged in urine in the 7 day collection period, suggesting that renal clearance of vorapaxar is low. Vorapaxar appears to be extensively metabolized followed by excretion of vorapaxar [minor, < 2%] and the metabolites [major] predominantly in feces [Table 4]. When the radioactivity recovery period was extended to 6 weeks, 83.5% [58.4% in feces, 25.1% in urine] of administered dose was recovered, however, metabolite profiling was not performed in this study [P07045].

Table 4: LC-MS/FSA[3] characterized drug derived material in 0-168 h post-dose pooled urine and 0-168 h, days 13-14 and 20-21 post-dose pooled feces following a single dose of 9.3 mg (100 µCi) ^{14}C-vorapaxar sulfate administered as oral solution

Metabolite label	Metabolite name	m/z	% dose in urine	% dose in feces
NA	Unknown	--	0.11	--
M8	Monohydroxy-vorapaxar-gluc	685[a]	0.42	ND
M10	Monohydroxy-vorapaxar-gluc	685[a]	0.31	ND
M13	Monohydroxy-vorapaxar-sulfate	589[b]	0.11	ND
M14	Monohydroxy-vorapaxar-sulfate	589[b]	0.05	ND
M15	Monohydroxy-vorapaxar	509	0.21	ND
M16	Carboxylic acid metabolite	523	0.41	2.30
M17	M+34	527	1.40	0.87
M17a	Dihydroxy-vorapaxar	525[c]	ND	0.88
M17b/c	Dihydroxy-vorapaxar	525[c]	ND	2.30
NA	Unknown	--	--	1.08
NA	Unknown	--	--	1.15
M19	Amine metabolite	421	1.21	18.4
M19a	Monohydroxy-vorapaxar	509[d]	ND	3.51
M20	Monohydroxy-vorapaxar	509[d]	ND	0.68
M20b	Monohydroxy-vorapaxar	509[d]	ND	2.44
M21	Monohydroxy-vorapaxar	509[d]	ND	6.96
Parent	Vorapaxar	493	ND	1.59
Cumulative recovery (% of dose)			**4.23**	**42.2**

ND Not detected
[a] Retention times for M8 and M10 are 18.4 and 18.9 min, respectively
[b] Retention times for M13 and M14 are 21.6 and 22.7, respectively
[c] Retention times for M17a and M17b/c are 24.0 and 26.2 min, respectively
[d] Retention times for M19a, M20, M20b and M21 are 30.0, 30.7, 31.5 and 31.9 min, respectively

2.4.6. What are the characteristics of drug metabolism?

Vorapaxar is extensively metabolized by the liver. The major route of metabolism is carbamate hydrolysis leading to the amine metabolite [M19], the predominant metabolite [44%] in excreta. In addition, vorapaxar undergoes oxidation at one or more sites resulting in numerous monohydroxy [M15, M19a, M20, M20b, M21] and dihydroxy [M17a/b/c] metabolites as shown

[3] Flow Scintillation Analysis

in Figure 5. Monohydroxy metabolites are also excreted as glucuronide [M8, M10] or sulfate [M13, M14] conjugates. All characterized human metabolites were also observed in the preclinical species used in toxicity and carcinogenicity studies.

The role of various cytochrome [CYP] P450 enzymes in the biotransformation of vorapaxar was studied *in vitro*. CYP3A4 and CYP2J2 are the predominant enzymes involved in the formation of M19 and M20.

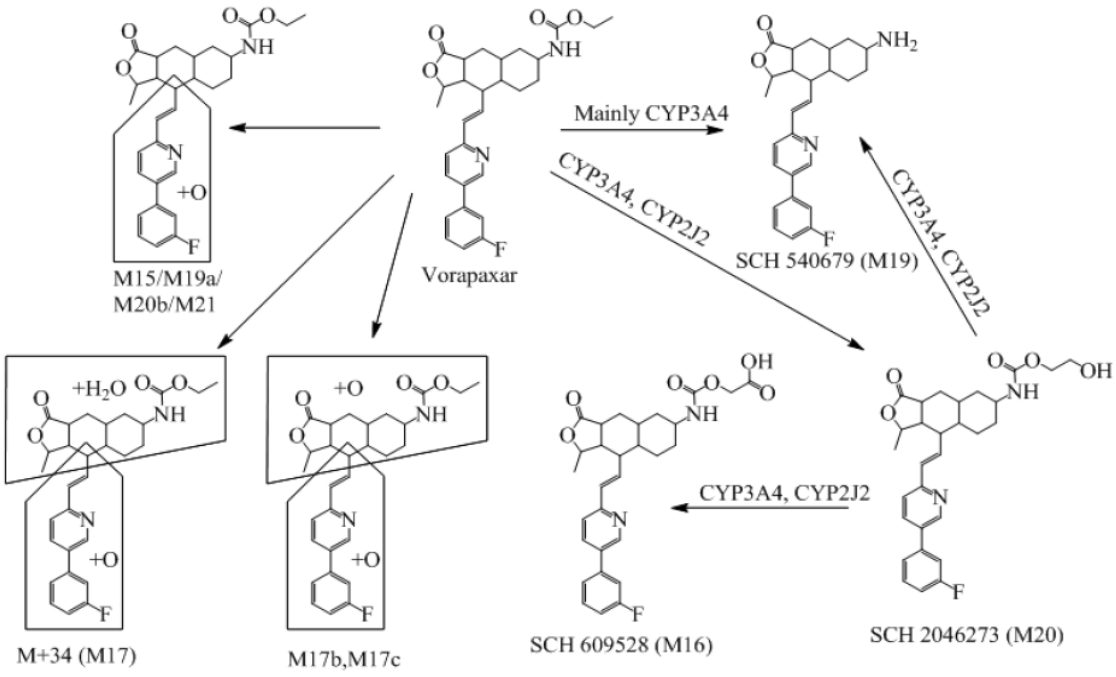


Figure 5: Proposed in vitro and in vivo biotransformation pathway for vorapaxar. Boxed region represent probable region of metabolism.

[Source: Figure 1 on page 19 of applicant's Summary of Clinical Pharmacology Studies]

2.4.7. What are the characteristics of drug elimination?

Vorapaxar is eliminated mainly by metabolism followed by excretion in urine and feces. Based on the mass balance study [P03454], a small fraction [< 2%] of vorapaxar as unchanged drug is excreted in feces [Table 4].

2.4.8. Based on PK parameters, what is the degree of linearity in dose-concentration relationship?

The PK measures of vorapaxar in the dose range 2.5 mg to 40 mg are dose-related with a slight less than-proportional increase in exposure.

2.4.9. What is the inter- and intra-subject variability of PK parameters in healthy volunteers and patients, and what are the major causes of variability?

The between subject variability in the PK measures i.e., C_{max} and $AUC_{0-\tau}$ as observed across individual Phase 1 healthy volunteer studies is in the range of 15% to 40% for vorapaxar and 30% to 50% for M20, expressed as percent coefficient of variation. The between subject variability in the PK parameters of vorapaxar i.e., CL/F, Vc/F and Vp/F based on the final population PK model is 30%, 45% and 42%, respectively. Based on the results of a bioequivalence study [P06558] which employed a crossover design, the within subject variability of vorapaxar is estimated to be 6% and 14% for AUC_{0-72h} and C_{max}, respectively.

2.5. Pharmacodynamics

2.5.1. What are the PD characteristics of the drug?

Inhibition of platelet aggregation induced by 15 µM TRAP was the primary pharmacodynamic measure in the vorapaxar development program. Vorapaxar was shown not to inhibit platelet aggregation in response to adenosine diphosphate [ADP]. The PD characteristics of vorapaxar were evaluated in a dedicated study following repeat doses of 1, 3 and 5 mg once-daily for 28 days. A dose dependent inhibition in platelet aggregation was observed at 24 hours following the first dose. The 3 mg dose group showed 70 to 80% platelet inhibition by 24 h post-dose [Fig. 6]. On the next available sampling time point i.e., day 7, all the dose groups including 1 mg showed <10% platelet aggregation relative to baseline and continued at maximal inhibition through vorapaxar dosing period. Based on this data, following 2.5 mg once-daily, >90% inhibition of platelet aggregation can be expected 48 hours after the start of the treatment.

Relative to the onset of pharmacodynamic effect, complete recovery of the platelet function upon drug discontinuation takes a long time. In the same study [P03450], after 28 days of stopping treatment, complete recovery of platelet function was not achieved in any of the dose groups by week 4. The mean % platelet aggregation relative to baseline was 84%, 43% and 4% for the dose groups 1, 3 and 5 mg, respectively at week 4 post-drug discontinuation [Fig. 6]. It took about 6 weeks for 90% of the subjects to recover to at least 50% platelet function at baseline for the 3 mg dose group and ~9 weeks for the 5 mg dose group.

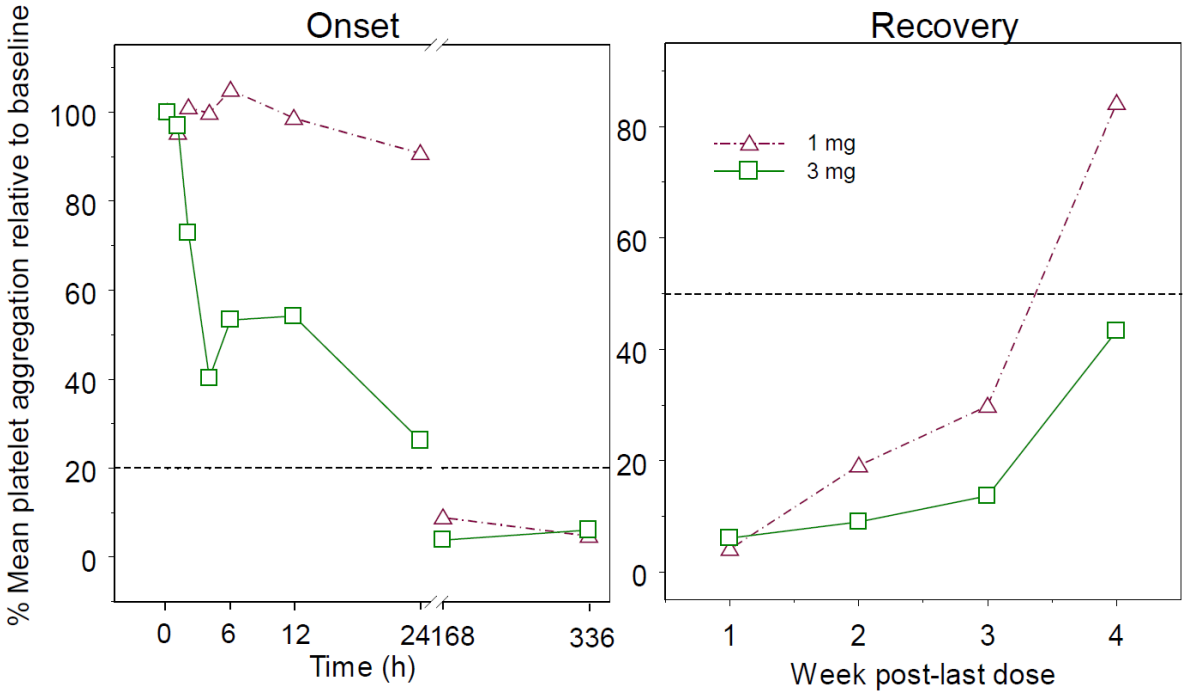


Figure 6: Onset and offset of pharmacodynamic effect following repeat doses of 1 and 3 mg vorapaxar sulfate [once-daily, 28 days] in healthy volunteers

2.6. Intrinsic Factors

2.6.1. What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Vorapaxar is extensively metabolized, thus suggesting that impairment in hepatic function might impact the pharmacokinetics of vorapaxar.

Hepatic impairment: The effect of hepatic impairment on the PK of vorapaxar was assessed following administration of a single dose of 40 mg vorapaxar sulfate in subjects with mild [Child-Pugh A], moderate [Child-Pugh B] and severe [Child-Pugh C] hepatic impairment versus matched healthy volunteers. The results appeared to show a trend towards lower systemic exposures with increasing severity of hepatic impairment [Fig. 7]. The modest decrease in extent of absorption is driven by decrease in peak concentration, while the elimination half-life was similar [data not shown]. The pharmacokinetics of M20 was not affected by impairment in hepatic function. The metabolite-to-parent ratio across all groups of hepatic impairment and the matched healthy volunteers was similar [19 to 26%]. Pharmacodynamics or protein binding was not measured in this study.

One subject from the severe hepatic impairment group experienced severe gastrointestinal hemorrhage secondary to esophageal varices, which was considered a serious adverse event with possible relationship to vorapaxar administration. Patients with severe hepatic impairment are

predisposed at a higher risk for bleeding events due to reduced synthesis of coagulation proteins. In the phase 3 program, patients with clinically significant hepatobiliary disease or an ALT/AST > 3 times ULN were excluded. Hence, use of vorapaxar should be avoided in patients with severe impairment of hepatic function.

Renal impairment: As the expectation for renal impairment to have a significant impact on the pharmacokinetics of vorapaxar was negligible, the applicant conducted a reduced design study in subjects with end stage renal disease [ESRD] requiring hemodialysis versus matched normal renal function subjects. The results show that the pharmacokinetics of vorapaxar is similar between ESRD and matched normal renal function subjects [Fig. 7]. The PK/PD relationship in ESRD subjects relative to matched normal renal function group could not be characterized as the data were limited.

Population PK analyses showed that creatinine clearance [CrCl] was a significant predictor of vorapaxar CL/F. The estimated increase in systemic exposure to vorapaxar is 17% and 34% for mild and moderate renal impairment groups, respectively. However, the mass balance study indicates minimal excretion via renal route. Hence, this finding may be confounded with body weight, as subjects with impaired renal function usually have lower body weights. A subgroup analysis from TRA2°P - TIMI 50 for GUSTO severe or moderate bleeding events in subjects with CrCl < 60 mL/min [N=1510] when compared to CrCl ≥ 60 mL/min [N=15131] did not show any increase in bleeding risk. Integrating all these results, a dose-adjustment in patients with impairment of renal function is not required.

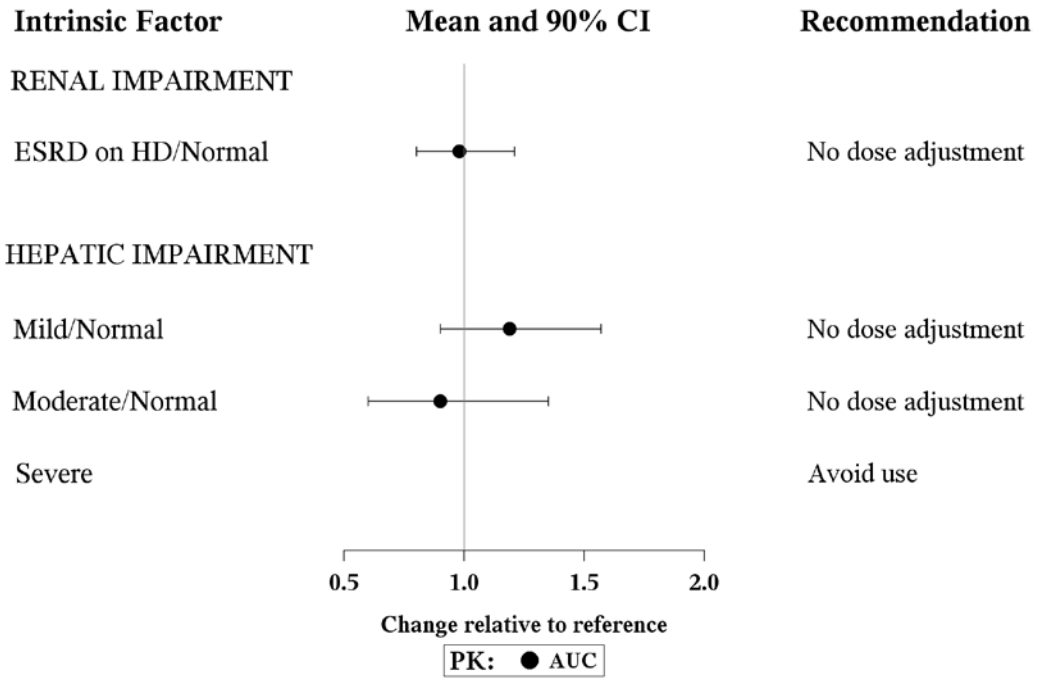


Figure 7: Impact of renal and hepatic impairment on the PK measures of vorapaxar

Age, Gender, Race:

The applicant conducted a population PK study that characterized the PK profile of vorapaxar in healthy volunteers and patients. Effect of covariates such as health status [healthy versus patients], body weight, age, sex, race, and creatinine clearance on key PK parameters was also explored [Fig. 8].

Results demonstrated that health status [healthy versus patients], gender, race and renal function had modest effects on vorapaxar exposure. But due to the high correlation among these demographic covariates, body weight may be the underlying driver for other covariates. Low body weight [< 60 kg] and high body weight [> 100 kg] patients have 33% [90% CI: 28% - 38%] higher and 19% [90% CI: 16% - 22%] lower steady state AUC, respectively, than typical patients weighing 60 to 100 kg. Since females and Asians tend to have lower body weight compared to male and White patients, exposures in females were estimated to be 32% [90% CI: 26% - 40%] higher than those in male patients and exposures were estimated to be 22% [90% CI: 16% - 30%] higher in Asian patients and 19% [90% CI: 13% - 24%] lower in Black patients relative to exposures in White patients. Patients were estimated to have 14% [90% CI: 10% - 17%] lower steady state AUC compared to healthy volunteers. Except body weight [which is discussed further] no other covariates require dose-adjustments.

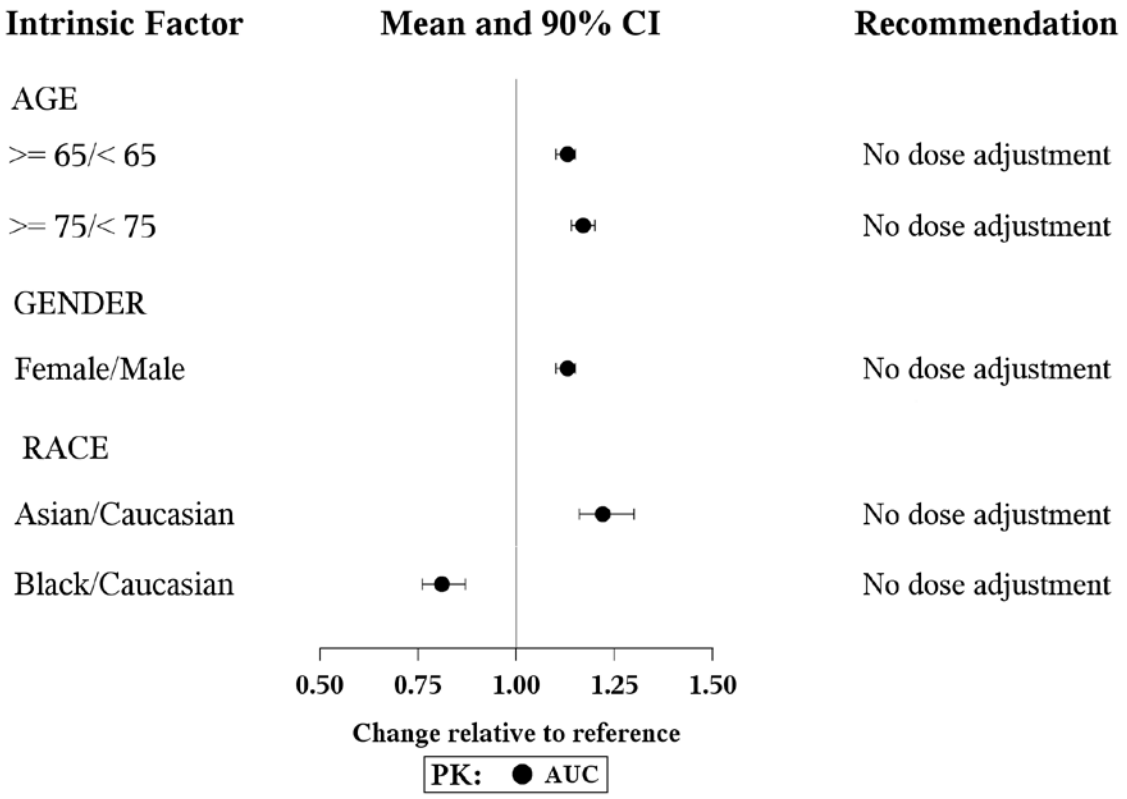


Figure 8: Impact of intrinsic factors on the PK measures of vorapaxar estimated using population PK model

Body weight:

The increased drug exposure in lighter patients and the exposure-bleeding relationship provided a clear pharmacological justification to look into the safety subgroup analysis based on body weight. A subgroup analysis of the overall population from TRA2°P - TIMI 50 for GUSTO severe or moderate bleeding events showed that the hazard ratio between vorapaxar and placebo was 1.87 [95% CI: 1.19-2.94] in patients with body weight < 60 kg while it was estimated to be 1.48 [95% CI: 1.28-1.73] in patients with body weight ≥ 60 kg patients. The larger point estimate of HR for the lighter patients suggested that the increased bleeding risk of vorapaxar relative to placebo was even higher [87%] in lighter patients when the hazard of bleeding was already 48% higher for vorapaxar relative to placebo in heavier patients.

Individual steady state AUC was calculated based on the population PK model for vorapaxar. The median steady state AUC of vorapaxar in patients with body weight < 60 kg was 48% higher than that in patients with body weight ≥ 60 kg. In addition, the lighter patients included more elderly and female patients [Table 5]. Therefore, higher vorapaxar exposure, older age, and higher percentage of female patients all contributed to the higher bleeding risk of vorapaxar relative to placebo in patients with body weight < 60 kg. Exclusion of patients with prior history of stroke/TIA reduced the percentage of patients with body weight < 60 kg [Table 5]. However, the higher bleeding risk in patients with body weight < 60 kg was still evident as indicated by the HR of 1.78 [95% CI: 0.85-3.74] for GUSTO severe or moderate bleeding events even within the proposed label population. The wide confidence interval was due to the small sample size in this subgroup [N=857]. The median steady state AUC of vorapaxar in patients with body weight < 60 kg was 49% higher than that in patients with body weight ≥ 60 kg in the proposed label population.

Table 5: The distribution of elderly and female patients in weight based subgroups: overall and proposed label population

Weight Group [kg]	**Age > 65**		**Age > 75**		**Female**		**Overall**	
	Plc	Vor	Plc	Vor	Plc	Vor	Plc	Vor
	Overall population							
<60	53%	56%	23%	24%	68%	68%	7%	7%
≥60	36%	37%	11%	10%	21%	21%	93%	93%
	Proposed label population							
<60	40%	46%	15%	16%	68%	66%	5%	5%
≥60	28%	29%	7%	7%	17%	18%	95%	95%

Plc = Placebo; Vor = Vorapaxar

Given the increased risk of bleeding in patients with body weight < 60 kg, a reasonable benefit on the efficacy endpoint should be demonstrated to justify the increased bleeding risk from a risk/benefit perspective. However, the weight based subgroup analysis for the efficacy endpoint showed that vorapaxar was almost statistically worse than placebo with a HR of 1.28 [95% CI: 0.95-1.73] in the overall population.

To explore whether the results for the weight based subgroup analyses were due to chance, a resampling procedure was used to randomly select 1852 patients from the overall population of

26449 [ITT population] with a randomization allocation of 1:1 between placebo and vorapaxar arms [926 per arm]. The hazard ratio of the randomly selected subgroups [vorapaxar relative to placebo] was calculated. Such a procedure was repeated 100,000 times to evaluate the chance of estimating a hazard ratio of 1.28 or larger when the hazard ratio was 0.88 between the two arms in the overall population. The random chance of generating a subgroup [N=1852] with a hazard ratio of 1.28 or larger was estimated to be 0.0057, suggesting the results for the weight based subgroup analyses were unlikely due to random chance.

The applicant's supplementary secondary analysis for efficacy [Table 6] showed that the numerically worse efficacy result for vorapaxar was mainly driven by hemorrhagic stroke with 10 events [1.1%] in vorapaxar arm and 1 event [0.1%] in placebo arm. This observation is consistent with the increased bleeding risk in this subgroup. Exclusion of patients with prior history of stroke/TIA mitigated the body weight effect to a certain degree as demonstrated by a HR of 1.07 [95% CI: 0.69-1.66] for patients with body weight < 60 kg in the proposed label population [Table 7]. However, the point estimate still suggested a numerically worse efficacy for vorapaxar compared to placebo.

Table 6: Applicant's supplementary secondary analysis: Primary and key secondary composite efficacy endpoints in subjects with body weight < 60 kg: ITT Population [Event Accrual Period: Randomization to Last Visit]

	Placebo (n =921)		Vorapaxar (n =931)		
Endpoint & Contributing Component	Subjects With Events (%)	KM%[c]	Subjects With Events (%)	KM%[c]	Hazard Ratio[a,b] (95% CI)
Primary Efficacy Endpoint	75 (8.1%)	9.6%	96 (10.3%)	13.6%	1.28 (0.95 – 1.73)
CV Death	16 (1.7%)		16 (1.7%)		
MI	24 (2.6%)		35 (3.8%)		
Stroke	25 (2.7%)		29 (3.1%)		
Ischemic (Non-hemorrhagic CI)	23 (2.5%)		16 (1.7%)		
Hemorrhagic Stroke	1 (0.11%)		10 (1.1%)		
UCR	10 (1.1%)		16 (1.7%)		
Key Secondary Efficacy Endpoint	65 (7.1%)	8.4%	80 (8.6%)	11.5%	1.22 (0.88 – 1.69)
CV Death	16 (1.7%)		16 (1.7%)		
MI	24 (2.6%)		35 (3.8%)		
Stroke	25 (2.7%)		29 (3.1%)		
Ischemic (Non-hemorrhagic CI)	23 (2.5%)		16 (1.7%)		
Hemorrhagic Stroke	1 (0.1%)		10 (1.1%)		
Uncertain	1 (0.1%)		3 (0.3%)		

a: Kaplan-Meier estimate at 1080 days.
b: Hazard Ratio (HR) is vorapaxar group versus placebo group.
c: HR was calculated based on Cox PH model with covariates treatment and stratification factors (planned thienopyridine use).
d: Each subject was counted only once (first event) in the summary that contributed to primary or key secondary efficacy endpoint.
e: Hemorrhagic stroke includes primary intracerebral hemorrhage, non-hemorrhagic infarction with hemorrhagic conversion and subarachnoid hemorrhage.

Table 7: Applicant's supplementary secondary analysis: Primary and key secondary composite efficacy endpoints in subjects with no history of stroke or TIA whose qualifying condition was CAD with body weight < 60 kg: ITT Population [Event Accrual Period: Randomization to Last Visit]

Endpoint and Contributing Component	Placebo (n =429)		Vorapaxar (n =432)		Hazard Ratio[b,c] (95% CI)
	Subjects With Events (%)	KM%[a]	Subjects With Events (%)	KM%[a]	
Primary Efficacy Endpoint[d]	38 (8.9%)	10.0%	41 (9.5%)	11.5%	1.07 (0.69 – 1.66)
CV Death	4 (0.9%)		7 (1.6%)		
MI	20 (4.7%)		20 (4.6%)		
Stroke	5 (1.2%)		4 (0.9%)		
Ischemic (Non-hemorrhagic Cerebral Infarction)	5 (1.2%)		2 (0.5%)		
Hemorrhagic Stroke	0		2 (0.5%)		
UCR	9 (2.1%)		10 (2.3%)		
Key Secondary Efficacy Endpoint	29 (6.8%)	7.9%	31 (7.2%)	8.9%	1.06 (0.64 – 1.76)
CV Death	4 (0.9%)		7 (1.6%)		
MI	20 (4.7%)		20 (4.6%)		
Stroke	5 (1.2%)		4 (0.9%)		
Ischemic (Non-hemorrhagic Cerebral Infarction)	5 (1.2%)		2 (0.5%)		
Hemorrhagic Stroke[e]	0		2 (0.5%)		

a: Kaplan-Meier estimate at 1080 days.
b: Hazard Ratio is vorapaxar group versus placebo group.
c: HR was calculated based on Cox PH model with covariates treatment and stratification factors (planned thienopyridine use).
d: Each subject was counted only once (first component event) in the summary that contributed to the primary or key secondary efficacy endpoint.
e: Hemorrhagic stroke includes primary intracerebral hemorrhage, non-hemorrhagic infarction with hemorrhagic conversion and subarachnoid hemorrhage.

Similar resampling analysis was repeated for the proposed label population [N=16897]. The random chance of generating a subgroup [N=861] with a hazard ratio of 1.07 or larger was estimated to be 0.114. Given the increased bleeding risk in this subgroup, the efficacy result for this subgroup cannot justify the risk/benefit balance. The lack of clear efficacy in the non-bleeding related components of the efficacy endpoint [Table 7] in this subgroup also precludes the dose reduction strategy.

The applicant's rationale to use 60 kg as the cutoff was based on precedent set by product labeling for other anti-platelet agents. Further analyses were conducted to explore different cutoff values. Figure 9 shows that 60 kg is a reasonable choice to identify a subgroup with no clear benefit on the efficacy endpoint.

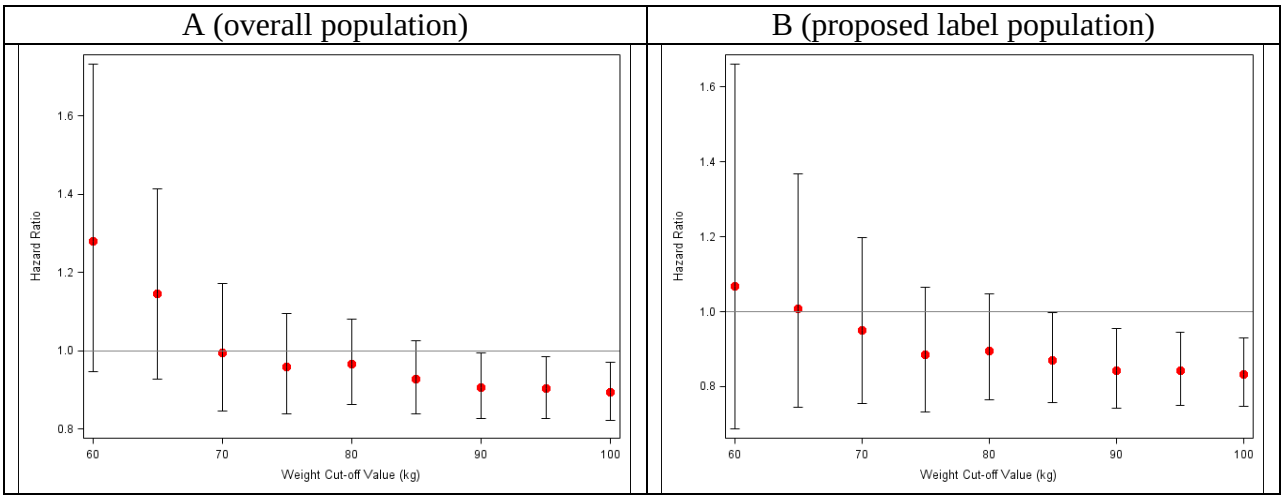


Figure 9: Hazard ratio of efficacy endpoint between vorapaxar and placebo for a subgroup based on different body weight cutoff values. Each dot represents the hazard ratio for subgroup of patients with body weight < cut-off value [error bars represent the 95% CI]

Prior stroke was considered the most important risk factor for intracranial hemorrhage by the data safety monitoring board [DSMB] and was the first exclusion criterion applied by the applicant to limit the patient population to achieve a favorable risk/benefit balance. However, the body weight based subgroup analyses suggested that the similar risk/benefit could be achieved by excluding patients with body weight < 60 kg [Table 8].

Table 8: Comparison of efficacy and safety results based on two different subgroups

Endpoint	**Subgroup**	**Hazard Ratio [95% CI]**	**Total sample size**
Efficacy	Post MI and ≥60 kg	0.82 [0.74-0.90]	16836
	Post MI and no prior stroke/TIA	0.82 [0.74-0.90]	16897
GUSTO severe or moderate bleeding	Post MI and ≥60 kg	1.45 [1.18-1.77]	16795
	Post MI and no prior stroke/TIA	1.48 [1.21-1.82]	16856

Further, within the post MI patient population with body weight ≥ 60 kg, patients with prior stroke showed numerically better efficacy between vorapaxar and placebo compared to patients without prior stroke [Table 9]. Despite the small sample size [N=543] in patients with prior stroke, the 95% CI of HR excluded 1, suggesting that vorapaxar showed statistically better efficacy than placebo in this subgroup. On the contrary, the prior TIA subgroup tends to numerically favor the control arm.

Table 9: The impact of prior stroke, prior TIA on efficacy within patients with post MI and body weight ≥ 60 kg

Population	Hazard Ratio [95% CI]	Total sample size
With prior stroke*	0.66 [0.46-0.96]	543
With prior TIA*	1.56 [0.97-2.5]	357
Without prior stroke or prior TIA	0.80 [0.73-0.89]	16012

* 77 patients had both prior stroke and TIA

The relative risk for GUSTO severe or moderate bleeding events in the prior stroke subgroup was 0.96 [95% CI: 0.42-2.17], indicating that the benefit-risk of vorapaxar in this subgroup is maintained [Table 10].

Table 10: The impact of prior stroke, prior TIA on GUSTO severe or moderate bleeding events within patients with post MI and body weight >=60 kg

Population	Hazard Ratio [95% CI]	Total sample size
With prior stroke*	0.96 [0.42-2.17]	540
With prior TIA*	1.79 [0.66-4.83]	354
Without prior stroke or prior TIA	1.46 [1.18-1.81]	15977

* 77 patients had both prior stroke and TIA

Similar body weight effect can also be observed in the TRACER trial [Table 11].

Table 11: The impact of body weight on efficacy and safety in TRACER trial

Endpoint	Subgroup	Hazard Ratio [95% CI]	Total sample size
Efficacy	<60 kg	1.07 [0.80-1.42]	987
	≥60 kg	0.91 [0.83-1.00]	11898
GUSTO severe or moderate bleeding	<60 kg	1.64 [1.06-2.54]	982
	≥60 kg	1.34 [1.16-1.56]	11856

Based on these analyses, vorapaxar should be avoided in patients with body weight < 60 kg.

2.7. Extrinsic Factors

2.7.1. Is there an in vitro basis to suspect in vivo drug-drug interactions?

CYP3A4 is involved in the metabolism of vorapaxar to M19 and M20. Hence, *in vivo* studies with ketoconazole [strong CYP3A inhibitor] and rifampin [potent CYP3A inducer] were conducted.

In vivo drug interaction studies with warfarin and rosiglitazone were performed as vorapaxar showed a very modest potential to inhibit CYP2C8 [IC_{50}=1.5 µM] and 2C9 [IC_{50}=~30 µM] *in vitro*. The inhibition potential towards other CYP enzymes [2A6, 2C19, 2D6] is minimal as shown by IC_{50} values ≥ 30 µM. Vorapaxar and M20 did not demonstrate time-dependent inhibition of CYP enzymes nor CYP-induction potential at clinically relevant concentrations.

Vorapaxar is not a substrate of P-glycoprotein [P-gp], but inhibited the transport of digoxin with an IC_{50} of 1.2 µM. The steady-state peak plasma concentration following a one daily administration of 2.5 mg vorapaxar sulfate is 0.11 µM. This suggests that vorapaxar can possibly act as a P-gp inhibitor at the intestinal level, but not systemically. An *in vivo* drug interaction study with digoxin was conducted to validate the *in vitro* findings.

The potential for vorapaxar being a substrate for OATP1B1, OATP1B3, BCRP, OAT1, OAT3 and OCT2 has not been evaluated. However, given the absence or very minimal renal and biliary component in the clearance of vorapaxar, the potential for vorapaxar being a substrate is low. Vorapaxar and M20 were also not potent inhibitors of these transporters and the interaction liability is minimal.

2.7.2. What are the drug-drug interactions?

The applicant conducted 5 *in vivo* drug interaction studies to evaluate the impact of CYP3A modulators [ketoconazole, rifampin] on the pharmacokinetics of vorapaxar and the effect of vorapaxar on other concomitantly administered drugs [digoxin, warfarin, rosiglitazone, prasugrel].

Impact of CYP3A modulators on vorapaxar PK

The effect of 400 mg once-daily ketoconazole [strong CYP3A, weak CYP2J2, P-gp inhibitor] on vorapaxar following first dose [20 mg, day 7] and at steady state [2.5 mg once-daily, day 28] was evaluated. Following the first dose of co-administration of vorapaxar with ketoconazole, there was no change in C_{max}, but, a modest 20% increase in $AUC_{0-\tau}$ of vorapaxar. However, upon repeat administration of both vorapaxar and ketoconazole, there was a 2-fold increase in C_{max} and $AUC_{0-\tau}$ as observed on day 28 [Fig. 10]. The effect of ketoconazole is consistent for a victim drug with long half-life as observed by a marginal increase in exposure following the first dose and significant increase in exposure at steady state. The plasma concentrations of M20 were not measured in this study.

Upon concomitant administration of 600 mg once-daily rifampin [strong CYP3A inducer], there was no change in exposures following the first dose of vorapaxar. However, a 39% and 55% decrease in C_{max} and $AUC_{0-\tau}$, respectively at steady state were observed [Fig. 10]. The efficacy or bleeding risk for a change in exposure of this magnitude [2-fold increase or 55% decrease] is not known due to the absence of concentration-outcome relationship. Therefore, avoid use of vorapaxar with strong inhibitors or inducers of CYP3A.

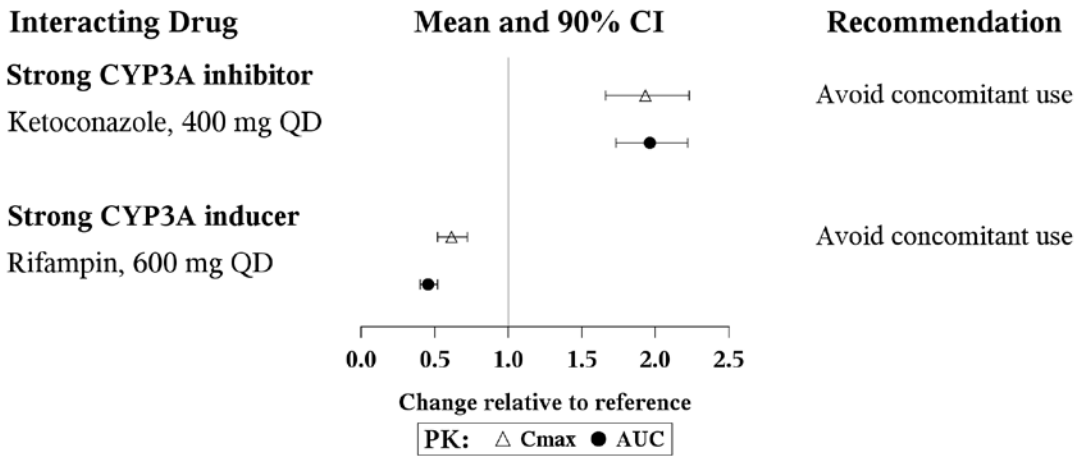


Figure 10: Impact of ketoconazole and rifampin on the PK measures of vorapaxar at steady state [day 21]

There was no dedicated drug interaction study performed to evaluate the impact of mild or moderate CYP3A inhibitors on the pharmacokinetics of vorapaxar. However, in TRA2°P - TIMI 50, 57% of the patients were on mild or moderate CYP3A inhibitors for a period of at least 7 days. An analysis of bleeding endpoints stratified by use of CYP3A inhibitors shows no increase in bleeding events [data not shown]. Hence, co-administration of vorapaxar with mild or moderate CYP3A inhibitors does not require dose-adjustments.

Impact of vorapaxar on other co-administered drugs

Digoxin: Upon administration of 2.5 mg vorapaxar sulfate on days 1 to 6 and co-administration of digoxin 0.5 mg with vorapaxar sulfate 40 mg on day 7, showed that the C_{max} of digoxin increased by 50% with no change in AUC_{0-t}. Hence, the potential for vorapaxar at clinically relevant dose of 2.5 mg to interact with digoxin or other P-gp substrates is expected to be lower.

Warfarin, Rosiglitazone and Prasugrel: Dedicated *in vivo* interaction studies show that vorapaxar does not alter the pharmacokinetics or pharmacodynamics of warfarin and rosiglitazone. There was no pharmacokinetic interaction between prasugrel and vorapaxar. The pharmacodynamic interaction potential was not assessed in this study. Though we know that vorapaxar does not affect platelet aggregation induced by ADP, this study would have informed if prasugrel affected platelet aggregation induced by TRAP.

2.7.3. What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Other extrinsic factors that may affect the systemic exposures to vorapaxar are (i) a high fat meal, (ii) co-administration with an antacid, and (iii) co-administration with a proton pump inhibitor. The impact of these factors has been addressed in response to Q. 2.4.3 and Q. 2.8.3.

2.8. General Biopharmaceutics

2.8.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Vorapaxar is a BCS class II drug [low solubility, high permeability]. Refer to Table 1 for solubility values across a range of pH medium. Permeability of vorapaxar is high, as exhibited by an apparent permeability [P_{app}] of 3 x 10^{-5} cm/s across Caco-2 cell monolayers.

2.8.2. What is the relative bioavailability of the to-be-marketed formulation with Phase 3 trial formulation?

Vorapaxar sulfate salt converts partially to the amorphous free base upon manufacturing and storage. The phase 3 trial had batches with varying salt content ranging from 23% to 46% free base. A pivotal bioequivalence study was performed by the applicant to compare the bioavailability of low base lot [23%] and high base lot [46%]. This study was performed by co-administering vorapaxar with a proton pump inhibitor [7 day pretreatment with 40 mg pantoprazole], so as to maximize the ability to detect differences in bioavailability between the two products. The results show that the rate and extent of absorption of vorapaxar was bioequivalent between the products with 23% and 46% free base [Fig. 11].

The to-be-marketed formulation of vorapaxar sulfate is compositionally identical [base content range] to the formulation used in Phase 3 trial with changes only to colorants [blue or white to yellow] and shape [round to oval]. These changes were bridged using dissolution data and did not require an in vivo evaluation of product performance.

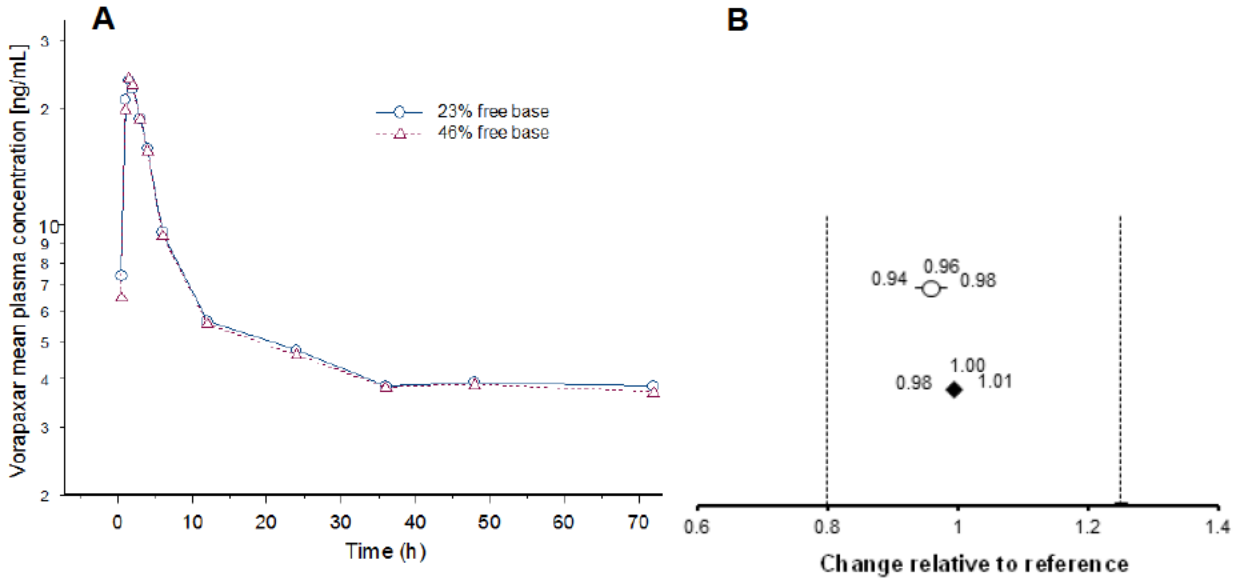


Figure 11: [A] Mean vorapaxar plasma concentration-time profile following single dose of 2.5 mg vorapaxar sulfate containing 23% and 46% free base content. [B] Impact of 46% free base vorapaxar sulfate on PK measures when compared with 23% free base product.

2.8.3. What is the effect of food on the bioavailability of the drug from the dosage form?

The effect of food on the pharmacokinetics of vorapaxar was evaluated in four studies – P03445, P03448 [pilot] and P03447, P07969 [definitive]. To directly support the present application, the effect of a standardized high fat breakfast on the pharmacokinetics of vorapaxar following 2.5 mg registration dose was evaluated. The results show that a high fat meal decreased mean peak concentration by 21%, delayed time to peak concentration by 45 min, but, did not affect the extent of absorption [AUC_{0-t}] to vorapaxar [Fig. 12]. The phase 3 registration trial [TRA°2P TIMI], which demonstrated efficacy and safety of vorapaxar was performed by administering vorapaxar sulfate without regards to meals.

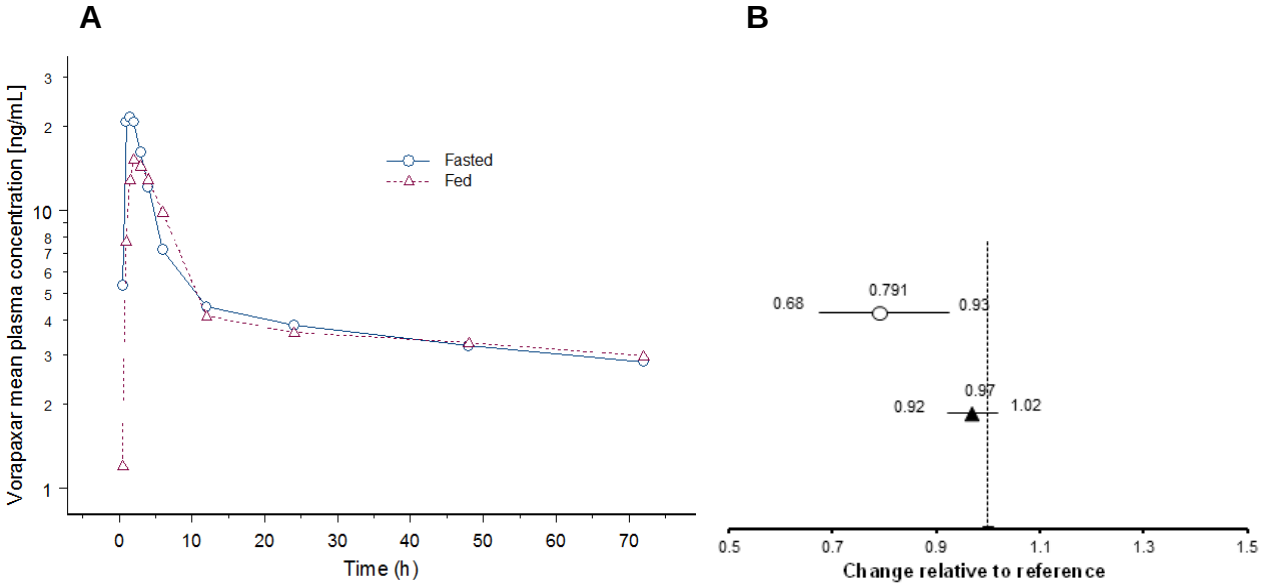


Figure 12: [A] Mean vorapaxar plasma concentration-time profile following single dose of 2.5 mg vorapaxar sulfate in fed and fasted states. [B] Impact of a high fat meal on PK measures of vorapaxar compared to fasted state.

2.9. Bioanalytical Method

Plasma concentrations of vorapaxar and M20 were quantified using validated UPLC-MS/MS methods. Standard curves were constructed in the range of 0.1 to 50 ng/mL or 1 to 1000 ng/mL [vorapaxar] and 0.5 to 500 ng/mL [M20]. The accuracy and precision values of at least two-thirds of the overall quality control [QC] samples from all supporting bio-analytical reports were equal to or better than 15% [20% at the LLOQ]. All the supporting bio-analytical methods [inclusive of HPLC-accelerator mass spectrometry (AMS) method for quantification of radiolabeled vorapaxar concentration in plasma and that of co-administered drugs used in DDI studies] satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development', and is acceptable [Table 12].

Table 12: Summary of bioanalytical methods

Report	**Range [ng/mL]**	**Accuracy**	**Precision**
LC-MS/MS - Vorapaxar			
SN03176	0.1 to 50	1.1 to 6.0	0.9 to 10.8
DM27304	1 to 1000	-14.8 to 3.6	5.7 to 12.7
DM27721	0.834 to 1000	-2.3 to 0.4	3.0 to 10.5
DM11003	1 to 1000	-1.8 to 1.8	3.1 to 7.9
LC-MS/MS – M20			
DM27721	0.5 to 500	-4.5 to -0.8	5.0 to 11.9
AMS - Vorapaxar			
P1180	0.011 to 3.92	-7.3 to 3.1	3.1 to 4.6

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