Meeting Background
Package

1.6.2 Meeting Background Materials

Vorapaxar Advisory
Committee Briefing
Document

Vorapaxar Advisory Committee Briefing Document

Vorapaxar Sulfate
Secondary Prevention of Atherothrombosis in Patients with a History of Myocardial Infarction
NDA 204886

Cardiovascular and Renal Drugs Advisory Committee Meeting

January 15, 2014

Merck, Sharpe & Dohme Corporation
Whitehouse Station, New Jersey, USA

ADVISORY COMMITTEE BRIEFING DOCUMENT
AVAILABLE FOR PUBLIC RELEASE
WITHOUT REDACTION

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1 List of Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
ABI	ankle/brachial index
ACE	angiotensin converting enzyme
ACS	acute coronary syndromes
ACT	activated clotting time
ADP	adenosine diphosphate
AE	adverse event
AMI	acute myocardial infarction
ARB	angiotensin II receptor blocker
ASA	Aspirin
AUC	area under the curve
BB	beta blockers
BMI	body mass index
B/R	Benefit-risk
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAPRIE	acronym for a clinical study in secondary prevention of ischemic events: Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CEC	Clinical Events Committee
CHARISMA	acronym for a clinical study in primary and secondary prevention of ischemic events: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CI	Confidence interval
CrCl	Creatinine clearance
CSR	Clinical study report
CV	Cardiovascular
CVD	Cerebrovascular disease
CYP	refers to cytochrome P450 isoenzymes
DAP	data analysis plan
DDI	drug-drug Interactions
DSMB	data and safety monitoring board
ECG	Electrocardiogram
eCRF	electronic case report form
ECT	ecarin clotting time
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
F	Female
FFP	Fresh Frozen Plasma
GCP	good clinical practice
GMR	geometric mean ratio

Abbreviation/Term	Definition
GUSTO	**G**lobal **U**tilization of **S**treptokinase and **T**issue Plasminogen Activator for **O**ccluded Arteries cooperative group; a classification system for degree of bleeding
HR	Hazard Ratio
ICH	Intracranial Hemorrhage
INR	international normalized ratio
KM, K-M	Kaplan-Meier
LDL-C	low-density-lipoprotein cholesterol
MACE	Major Adverse Coronary Event
M	Male
MI	myocardial infarction
N/A	not applicable
NSTEACS	non-ST segment elevation acute coronary syndrome
NSTEMI	non ST segment elevation myocardial infarction
NNH	number needed to harm
NNT	number needed to treat
NSH	no stroke history - subjects with no stroke history, regardless of the qualifying condition, who received randomized treatment assignment
Overall Population	Entire study population (CAD, PAD, CVD strata)
PAD	peripheral artery(arterial) disease
PAR-1	protease-activated receptor 1
PCI	percutaneous coronary intervention
PD	Pharmacodynamics
PH	proportional hazard
PK	Pharmacokinetics
PT	prothrombin time
PY	Patient-years
RAAS	renin-angiotensin aldosterone system
Revasc	Revascularization
RD	Risk Difference
RR	risk reduction
RIR	recurrent ischemia with rehospitalization
RRR	relative risk reduction
SAE	serious adverse event
SCH 530348	Vorapaxar
STEMI	ST segment elevation myocardial infarction
$t_{1/2}$	half life
TIA	transient ischemic attack
TIPA	Thrombin-induced platelet activation
TIMI	Thrombolysis in Myocardial Infarction Study Group
TRA	thrombin-receptor antagonist
TRAP	thrombin receptor agonist peptide

Abbreviation/Term	Definition
TRA2°P– TIMI50	Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events
TRACER	Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome)
TT	thrombin time
TQT	thorough QT
UA	unstable angina
UCR	urgent coronary revascularization
US	United States

1 INTRODUCTION TO THE BRIEFING DOCUMENT

1 INTRODUCTION TO THE BRIEFING DOCUMENT

The Sponsor has submitted a New Drug Application for the use of vorapaxar at an oral dose of 2.5 mg daily for the reduction of atherothrombotic events in patients with a history of Myocardial Infarction (MI). The application is based on the highly significant results of the pivotal Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Events (TRA 2°P – TIMI 50) trial and the population found to benefit the most, patients with a history of MI with no history of stroke or transient ischemic attack (TIA).

This briefing document provides an overall Executive Summary, describes the preclinical, mechanistic, pharmacokinetic (PK)/pharmacodynamic (PD), clinical efficacy and safety/tolerability analyses in the cumulative clinical database and quantitatively analyzes the benefit-risk of vorapaxar.

The vorapaxar clinical development program included two Phase 3 trials that were designed to evaluate the hypothesis that vorapaxar added to standard of care would reduce the incidence of atherothrombotic events relative to standard of care alone in two distinct populations and in two distinct clinical situations:

The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial was designed to evaluate the use of vorapaxar 40mg loading dose in the acute setting followed by 2.5 mg/day maintenance dose added to standard of care in moderate-to-high risk subjects with non-ST-segment elevation Acute Coronary Syndrome (NSTEACS). The trial was conducted in 12,944 subjects who began study treatment during hospitalization for the index event. Subjects were followed for a median of approximately 1.4 years.

The TRA 2°P – TIMI 50 trial was designed to evaluate the use of vorapaxar 2.5mg/day added to standard of care (including aspirin or other antiplatelet agents, e.g., thienopyridine) in stable subjects with established vascular disease. The trial was conducted in 26,449 subjects assigned to one of three strata based on qualifying condition. Subjects were followed for a median of approximately 2.5 years.

A single, independent Data and Safety Monitoring Board (DSMB) oversaw both the TRA 2°P – TIMI 50 and TRACER trials. On January 8, 2011, the DSMB held an ad hoc meeting, triggered by an increase in the number of intracranial hemorrhage (ICH) events reported across the two Phase 3 studies.

The DSMB recommended the discontinuation of study drug in all subjects and close out of the TRACER trial. The DSMB recommended the discontinuation of study drug in TRA 2°P – TIMI 50 subjects with stroke occurring pre- and post-randomization and also recommended continuing the TRA 2°P – TIMI 50 trial in subjects who did not have a history of stroke.

Section 7 of the briefing document describes the TRACER trial in brief. Following the presentation of the results of the overall TRA 2°P–TIMI 50 trial, the Sponsor discusses the sample that benefited the most from vorapaxar treatment, the Proposed Label Population which consisted of patients with a history of MI with no history of stroke or TIA. The

relevance of the TRACER study is discussed further in **Section 11**. The document closes with a description of benefit-risk in the Proposed Label Population.

Based on the data provided in this document, the Sponsor is seeking the following indication:

Patients with History of Myocardial Infarction (MI)

Vorapaxar, an antagonist of the protease-activated receptor-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

Vorapaxar use will be contraindicated in patients with a history of stroke, TIA, intracranial hemorrhage, or active pathological bleeding.

2 EXECUTIVE SUMMARY

BACKGROUND

Vorapaxar is a selective antagonist of the protease-activated receptor-1 (PAR-1), the primary thrombin receptor on human platelets, which mediates the downstream effects of thrombin, a critical coagulation factor in hemostasis and thrombosis. Thrombin-induced platelet activation (TIPA) has been implicated in a variety of cardiovascular disorders including thrombosis, atherosclerosis, and restenosis following percutaneous coronary intervention (PCI). As an antagonist of PAR-1, vorapaxar blocks thrombin-mediated platelet activation and thereby has the potential to reduce the risk of atherothrombotic complications of coronary disease.

The use of vorapaxar for the prevention of thrombosis and the reduction of cardiovascular events was evaluated in two major clinical outcomes studies in two distinct populations: TRACER (P04736) and TRA 2°P - TIMI 50 (P04737). TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) was a study in moderate-to-high risk subjects with Non-ST Elevation acute coronary syndromes (NSTEACS) and TRA 2°P - TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of atherothrombotic ischemic events) was a secondary prevention study in subjects who had evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems. The proposed indication is based on the pivotal TRA 2°P - TIMI 50 study.

Vorapaxar at an oral dose of 2.5 mg once daily has been shown to reduce the rate of a combined endpoint of cardiovascular (CV) death, myocardial infarction (MI), stroke, and urgent coronary revascularization (UCR) in stable patients with a history of atherosclerosis. The Sponsor is requesting approval of an indication based on the results of TRA 2°P - TIMI 50 in secondary prevention.

The Sponsor is proposing the following indication:

> *Patients with History of Myocardial Infarction (MI)*
>
> *Vorapaxar, an antagonist of the protease-activated receptor-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*
>
> *Vorapaxar use will be contraindicated in patients with a history of stroke, TIA, intracranial hemorrhage, or active pathological bleeding.*

UNMET MEDICAL NEED

Secondary prevention of CV events post MI remains a significant medical and societal problem despite available therapies and patient needs are under-served by existing medicines. Patients with a history of MI are at substantial risk of recurrent atherothrombotic events. Each year, approximately 525,000 Americans will have a new MI, and approximately 190,000 will have a recurrent event [1]. Most of these patients will require secondary prevention measures in an attempt to prevent recurrent cardiovascular events.

Current secondary prevention guidelines, which include antiplatelet therapy for established coronary and other atherosclerotic vascular disease, prescribe aspirin for long-term therapy [2]. Definitive benefit has not been established for any treatment other than aspirin. Clopidogrel monotherapy is recommended as an alternative for aspirin for patients who are intolerant of or allergic to aspirin. Dual antiplatelet therapy is recommended by guidelines in patients where an intracoronary stent has been placed and is limited to one year duration [2]. However, the effectiveness of additional antiplatelet therapy for secondary prevention of atherothrombotic events is not established in stable patients with a history of MI. Therefore, there is a need for further risk reduction in long-term treatment of stable patients with established atherothrombotic risk. The Sponsor has investigated whether a new class of antiplatelet agents, PAR-1 antagonists, can further decrease the risk of cardiovascular events with an acceptable balance of efficacy and bleeding risk in a population of established atherothrombosis when added to standard of care by studying vorapaxar, a PAR-1 receptor antagonist, in secondary prevention of atherothrombotic diseases.

Vorapaxar is a first-in-class reversible, high affinity, highly selective PAR - 1 antagonist that inhibits thrombin related platelet aggregation and thereby has the potential to reduce the risk of atherothrombotic complications of coronary disease. Vorapaxar prevents platelet aggregation by a mechanism distinct from aspirin and $P2Y_{12}$ receptor inhibitors. Vorapaxar does not inhibit anticoagulant mechanisms, including other modes of thrombin activity (e.g., PAR-4, fibrin formation), has a clean off-target profile and has achieved consistent inhibition of TRAP-induced ex-vivo platelet aggregation in non-human primate models and in the Phase 1-3 clinical programs. Vorapaxar is the first antiplatelet therapy to demonstrate benefit on top of standard of care and has the potential to meet the unmet medical need in a population that is at risk of recurrent thrombotic events.

VORAPAXAR DEVELOPMENT PROGRAM

Phase 1 Studies

An evaluation of vorapaxar's, safety, tolerability, PK and PD profile has been performed. Twenty-one (21) Phase 1 studies have been conducted to evaluate the initial safety and tolerability, PK and PD (TRAP-induced platelet aggregation (TIPA) used as target engagement biomarker) of vorapaxar in healthy subjects and special populations.

Phase 2 Studies

Three Phase 2, randomized, double-blind, placebo-controlled studies of safety and efficacy were conducted. Two of the Phase 2 studies included subjects with coronary artery disease

who were either eligible for non-emergent PCI (P03573) or who had symptoms of acute coronary syndrome (ACS) and were possible candidates for PCI (P04772), while the third study included subjects who were stable following a thrombotic stroke from 2 weeks to 1 year previously (P05005). The results of these Phase 2 studies confirmed the tolerability and potential therapeutic utility of vorapaxar in the regimens evaluated in Phase 3.

Phase 3 Dose Selection

Vorapaxar[1], at an oral dose of 2.5 mg once-daily, was the lowest dose to consistently achieve successful target engagement as assessed by TIPA in a high proportion (≥80%) of the subjects exposed across all studies. There was no evidence of dose-response for bleeding risk with vorapaxar compared to placebo at 0.5 mg, 1 mg or 2.5 mg doses in the Phase 1 and 2 studies, even when administered concomitantly with aspirin and clopidogrel, indicating that there was no rationale to reduce the dose below 2.5 mg once-daily. Based on this information, an oral dose of vorapaxar 2.5 mg daily was selected for chronic administration in the Phase 3 TRA 2ºP –TIMI 50 study.

Phase 3 Studies

The Phase 3 program evaluated the safety and efficacy of vorapaxar in two large, international, double-blind, placebo-controlled studies. Each Phase 3 study was designed to independently support two different indications in two clinically distinct at-risk populations, ACS and Secondary Prevention.

TRACER STUDY DESIGN AND RESULTS

The first Phase 3 trial to be initiated was A Multicenter, Randomized, Double-Blind, Placebo-controlled Trial to Evaluate the Safety and Efficacy of Vorapaxar in Addition to Standard of Care in Subjects With Acute Coronary Syndrome, referred to as the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) trial. TRACER evaluated the hypothesis that vorapaxar, added to standard of care in an acute in-hospital setting, would reduce the incidence of atherothrombotic events compared to standard of care alone among 12,944 (6471 receiving placebo and 6473 receiving vorapaxar) moderate-to-high risk subjects with non-ST segment elevation acute coronary syndrome (NSTEACS) followed for a median of 1.4 years. A 40 mg loading dose of vorapaxar, started acutely in the hospital and followed by a 2.5 mg daily maintenance dose, was studied. The median treatment duration was approximately 1.4 years. The primary endpoint was a composite of CV death, MI, stroke, recurrent ischemia with rehospitalization (RIR) and UCR. The key secondary endpoint was a composite of CV death, MI and stroke. The primary efficacy analysis was based on the first occurrence of any component of the composite endpoint.

[1] Vorapaxar sulfate 2.5 mg is equivalent to 2.08 mg of vorapaxar free base. Vorapaxar sulfate 2.5 mg will be referred to as vorapaxar throughout this document.

On January 8, 2011, the combined Data Safety Monitoring Board (DSMB) for TRACER and TRA 2°P - TIMI 50 recommended discontinuation of study drug in all subjects in TRACER and close-out of the trial. The Executive Committee and the Sponsor accepted the recommendation of the DSMB. A communication dated January 13, 2011 was sent to all study sites in TRACER directing them to stop treatment in all subjects still receiving treatment and to close out the study in a timely manner due to an excess of bleeding, including intracranial hemorrhage (ICH) and that there were sufficient events to make a determination of efficacy.

In the TRACER trial, vorapaxar, initiated in the setting of NSTEACS in addition to standard of care, resulted in a non-significant hazard reduction of 8% (Hazard ratio [HR], 0.92; 95% Confidence Interval [CI] 0.85-1.01; p=0.072) in the primary efficacy composite end point of CV death, MI, stroke, RIR, and UCR **(Figure 9**). Vorapaxar reduced the hazard of the key secondary composite end point of CV death, MI, or stroke by 11%, (HR 0.89; 95% CI 0.81-0.98; p=0.018) however superiority could not be declared as the primary endpoint was not met. However, TRACER also demonstrated that vorapaxar was associated with an increased risk of ICH. The 2-year KM event rates were 1.0% for vorapaxar and 0.4% for placebo (HR 2.52; 95% CI 1.48 to 4.29; p< 0.001) **(Table 7)**. Upon full analysis, it is apparent that the use of vorapaxar, administered with a loading dose of 40 mg and then maintained at 2.5 mg/day, in subjects with NSTEACS was associated with unacceptably high risk for ICH that was not balanced by sufficient efficacy in this acute coronary syndrome population.

As a result of the outcome of the TRACER trial, the indication for the initiation of vorapaxar in NSTEACS is not being pursued. The currently proposed indication for vorapaxar is based on the results of the TRA 2°P-TIMI 50 trial at a dose of vorapaxar 2.5 mg daily.

Therefore, the efficacy and safety results of TRACER are presented and treated separately from those of the TRA 2°P – TIMI 50 secondary prevention study. A discussion of the relevance of TRACER with regard to the use of vorapaxar in a chronic stable population of patients following an MI is provided in **Section 11** and in **Appendix 1**.

THROMBIN-RECEPTOR ANTAGONIST IN SECONDARY PREVENTION OF ATHEROTHROMBOTIC ISCHEMIC EVENTS (TRA 2°P - TIMI 50) TRIAL

TRA 2°P - TIMI 50: Study Overview

The second Phase 3 trial, the TRA 2°P - TIMI 50 trial was designed to evaluate the use of vorapaxar added in an outpatient setting to standard of care (including aspirin and/or thienopyridine) in secondary prevention of CV events. The TRA 2°P - TIMI 50 trial was conducted in 26,449 subjects stratified to three hierarchical groups with a ratio of 70:15:15 with known atherosclerotic disease:

Subjects with:

- CAD comprised of history of MI (post MI refers to the CAD stratum and is used interchangeably) defined by a history of MI from 2 weeks up to 12 months prior to randomization,

- CVD defined by a history of ischemic (presumed thrombotic) stroke from 2 weeks up to 12 months prior to randomization, or
- PAD defined as history of intermittent claudication and either an ankle brachial index (ABI) of >0.85, or amputation or revascularization of the extremities secondary to ischemia.

The second stratification was based on the planned use of a $P2Y_{12}$ inhibitor.

Subjects were randomly assigned in a 1:1 ratio to treatment with vorapaxar 2.5 mg (13,225 subjects) or placebo (13,224 subjects) in the context of two different stratifications. The study drug was administered once daily in addition to antiplatelet standard of care and other therapies (e.g. statins, renin-angiotensin aldosterone system [RAAS] agents and beta blockers [BB]). The median treatment duration was 2.4 years (followed for up to 4 years) sufficient to characterize the efficacy and safety profile of vorapaxar when used chronically at a 2.5 mg daily dose.

The primary endpoint was a composite of CV death, MI, stroke, and UCR. The key secondary endpoint was a composite of CV death, MI and stroke[2]. The primary efficacy analysis was based on the first occurrence of any component of the composite endpoint in the intent-to-treat (ITT) population. HRs for the TRA 2°P – TIMI 50 trial are based on 3 year KM estimates as a convention throughout this document unless stated otherwise.

A 2.5 mg daily dose of vorapaxar was studied. Following the start of dosing, subjects returned for scheduled efficacy/safety evaluations at 30 days, 4, 8, and 12 months, and every 6 months thereafter until the end of the trial, i.e., when a statistically defined number of efficacy endpoint events had been observed and every subject had participated in the trial for at least 1 year.

TRA 2°P - TIMI 50: Operational Events that Affected Study Conduct

Data Safety Monitoring Board Recommendation

As mentioned above, on January 8, 2011, the combined DSMB for TRACER and TRA 2°P - TIMI 50 recommended that subjects with any stroke prior to or post randomization discontinue study treatment due to increased risk of ICH.

Executive Committee (EC) Action in response to DSMB Action

Upon receiving the DSMB recommendation, the EC took the following actions in the TRA 2°P - TIMI 50 trial:

- As per the DSMB recommendation, subjects randomized to the CAD and PAD strata who had a stroke history or a stroke endpoint were instructed to discontinue study drug but continue to be followed in the trial until the trial is completed.

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[2] TIMI publication reverses the primary and secondary endpoints after knowledge of TRACER trial, however the SPONSOR maintains the originally specified order.

- For subjects in the CVD stratum, all subjects were instructed to discontinue study drug. In addition, the EC decided that subject in the CVD stratum should come in for a final visit and complete their participation in the trial unless they had experienced a stroke endpoint in the study. Subjects who had a stroke endpoint in the study were instructed to continue to be followed in the trial until the trial is completed.

Protocol Amendment and associated Data Analysis Plan (DAP)

In addition to the pre-specified Overall Population in the original protocol and the DAP, the DAP and the protocol was amended after the DSMB findings to examine additional subpopulations without a history of stroke. The protocol amendment did not alter the original pre-specified primary and key secondary endpoints, nor the approach that all randomized subjects would be included in the analysis of these endpoints. The DAP was amended prior to database lock by the Sponsor and EC who remained blinded to study data until after database lock.

TRA 2°P - TIMI 50: Overall Study Results

Efficacy - Overall Population

The results were significant both on the primary and key secondary endpoints in the pre-specified (CAD, PAD, CVD) Overall Population. For the 26,449 subjects that comprised the Overall Population (MI, ischemic stroke, or PAD) vorapaxar reduced the hazard of the composite primary endpoint of CV death, MI, stroke, or UCR by 12% (HR 0.88; 95% CI 0.82 - 0.95; p=0.001). These results were driven by fewer CV death and MI events in the vorapaxar group, with a reduction of spontaneous MI being the primary efficacy driver. Vorapaxar reduced all of the components of the composite primary endpoint except stroke where the rate of ischemic strokes was reduced by vorapaxar but the rate of hemorrhagic strokes was increased resulting in a net lack of effect on total strokes. A 13% reduction in events was observed in the key secondary efficacy composite endpoint of CV death, MI, or stroke (HR, 0.87; 95% CI, 0.80 - 0.94; p<0.001). **(Table 10)**

Safety - Overall Population

Bleeding

Bleeding risk was considered the major potential safety concern for vorapaxar. The bleeding endpoints defined in the TRA 2°P - TIMI 50 protocol included (1) a composite of moderate or severe GUSTO bleeding and (2) "clinically significant bleeding". GUSTO severe bleeding was defined as fatal, intracranial, or bleeding with hemodynamic compromise requiring intervention. GUSTO moderate bleeding was defined as bleeding requiring transfusion of whole blood or packed red blood cells without hemodynamic compromise. Clinically significant bleeding was defined as Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding or bleeding requiring medical attention (defined as bleeding that required treatment or laboratory evaluation). TIMI major bleeding was defined as any intracranial hemorrhage or clinically significant overt signs of bleeding associated with a

drop in hemoglobin (Hgb) of ≥ 5 g/dL. TIMI minor bleeding was defined as any clinically significant overt sign of hemorrhage that is associated with a fall in Hemoglobin of 2 to < 5 g/dL.

Bleeding risk was greater in vorapaxar group vs. placebo group for all pre-specified bleeding endpoints (GUSTO moderate or severe, clinically significant bleeding) except CABG-related bleeding. The 3-year KM estimates for GUSTO severe or moderate bleeding were 4.2% in the vorapaxar group (severe 1.7% and moderate 2.6%) and 2.9% in the placebo group (severe 1.4% and moderate 1.6%) (HR 1.51; 95% CI 1.31 - 1.74; p<0.001). Fatal bleeding event rates were 0.4% for vorapaxar vs. 0.3% for placebo (HR: 1.40; 95% CI 0.86-2.30; p=0.179). ICH rates were 1.0% for vorapaxar vs. 0.6% for placebo (HR: 1.70; 1.25 - 2.32, p<0.001) (Table 15). Importantly, subjects with a history of stroke had a 3-year KM rate for ICH of 2.7% in the vorapaxar group and 0.9% in the placebo group (HR 2.55; 95% CI 1.56 - 4.18; p<0.001). The observed difference between the treatment groups was predominantly due to an increase in spontaneous ICH. In contrast, subjects with no prior stroke history presented a lower overall 3-year KM estimate of 0.6% for vorapaxar vs. 0.5% for placebo (HR 1.25; 95% CI 0.84-1.88; p=0.273) **(Table 18).**

The most frequently reported individual bleeding event was epistaxis, with 6.2% of subjects in the vorapaxar group reporting this event, compared with 3.1% in the placebo group. Epistaxis was also the most frequently reported bleeding event resulting in treatment discontinuation in both treatment groups: 57 (0.4%) in subjects in the vorapaxar group and 23 (0.2%) in the placebo group.

Non-bleeding Adverse Events

In the Overall Population in TRA 2°P - TIMI 50, most of the reported other (non-bleeding) AEs occurred at comparable rates between the two treatment groups. Most events leading to treatment discontinuation occurred at a frequency of 0.1% or less for either treatment group. Of the events reported, anemia was the most frequently reported event that that had a higher incidence between vorapaxar (0.3%) and placebo (0.1%). In approximately one half of the subjects in the vorapaxar group, the report of anemia was associated with a bleeding event. This was true of approximately one third of the subjects on placebo.

The overall incidence of non-bleeding serious adverse events (SAEs) in TRA 2°P - TIMI 50 was similar in the vorapaxar group compared to the placebo group in the Overall Population **(Table 19)**.

Conclusions - Overall Population

The efficacy results for the Overall Population were significant both on the primary and key secondary endpoints. Although the treatment effect of vorapaxar was associated with robust efficacy, it was also associated with the risk of severe bleeding and ICH which was primarily driven by subjects with a history of stroke. Consistent with prasugrel [3], patients with a history of prior TIA or stroke should not be given vorapaxar. As a result, additional

subpopulations of interest were identified prior to unblinding and database lock as described below.

TRA 2°P - TIMI 50: Proposed Label Population Results

The Proposed Label Population is defined as the Post MI (CAD stratum) with no history of stroke or TIA (n=16,897, 64% of the Overall Population).

Rationale for the Proposed Label Population

In the context of robust efficacy results in the Overall Population, benefit-risk assessment resulted in refinement of the Overall Population to the Proposed Label Population. Subjects with a history of stroke demonstrated a safety concern that was recognized by the DSMB and confirmed by analysis of the final results. Subjects with a stroke history are not candidates for vorapaxar given that the risk of ICH **(Table 18)** outweighs the benefits **(Table 14)**.

Given that it is difficult in some clinical situations to distinguish stroke and TIA, subjects with a history of TIA were also excluded from the Proposed Label Population. Removing subjects with a history of stroke and TIA reduced the risk of ICH with vorapaxar. In the Proposed Label Population, the Sponsor recommends that vorapaxar be contraindicated in patients with a history of stroke or TIA.

The subjects enrolled in the PAD stratum, which excluded patients with recent MI (<1 year), did not demonstrate an adequate benefit-risk profile. The demonstrable risks in this stratum without more definitive evidence of benefit argues for excluding such patients from the Proposed Label Population.

As a result of these findings, the benefit-risk was best substantiated in the Post MI (CAD stratum) with no history of stroke or TIA (Proposed Label Population). The pre-specified Overall Population (CAD, CVD, PAD) remained the primary population for analysis. Efficacy results for the Proposed Label Population (n=16,897) are consistent with those of the primary Overall Population (N=26,449).

Efficacy - Proposed Label Population

The Proposed Label Population substantiated an already robust treatment effect observed in the overall population. There was an 18% reduction in the primary efficacy endpoint (HR 0.82; 95% CI 0.74-0.90) and a 22% reduction in the composite key secondary endpoint (HR 0.78; 95% CI 0.70 - 0.88) **(Table 24)**. The reduction in the hazard for all components of the composite was consistent. As with the Overall Population, the individual component of the composite endpoints that most contributed to the difference between vorapaxar and placebo was the reduction in the rate of MI; 4.4% vs. 5.3% in the primary endpoint and 4.6% vs. 5.7% in the key secondary endpoint. Importantly, in subjects without a history of stroke or TIA (the Proposed Label Population), vorapaxar was associated with a 38% reduction in the risk of first strokes (0.7% in the vorapaxar group vs. 1.2% in the placebo group) **(Table 25)**.

Safety - Proposed Label Population

By refining the population to be treated with vorapaxar to the population to derive benefit with the least amount of risk, i.e., the post MI with no history of stroke or TIA, the safety profile of the drug was improved as described below.

Bleeding

Excluding subjects with history of stroke or TIA in the Proposed Label Population, reduced the occurrence of ICH and associated GUSTO severe endpoints associated with vorapaxar. The 3 year KM estimates for GUSTO severe or moderate bleeding endpoints were 3.1% in the vorapaxar group (severe 1.2% and moderate 2.1%) and 2.2% in the placebo group (severe 1.0% and moderate 1.2%) (HR 1.48; 95% CI, 1.21 to 1.82; p<0.001). Annualized event rates for GUSTO severe or moderate bleeding were 1.1 events per 100 subject-years of exposure in the vorapaxar group and 0.8 events per 100 subject-years of exposure in the placebo group.

ICH event rates were 0.5% for vorapaxar and 0.4% for placebo (HR, 1.26; 95% CI 0.78 to 2.03; p=0.348) and the annualized rates for ICH were 0.2% for vorapaxar and 0.1% for placebo.

Fatal bleeding event rates were 0.2 % for the vorapaxar and placebo groups (HR, 0.99; 95% CI, 0.47 to 2.09; p=0.989) **(Table 30)**.

For clinically significant bleeding (i.e., TIMI major or minor bleeding, or bleeding that required unplanned treatment or evaluation) the 3 year KM estimate was 14.6% for vorapaxar vs. 10.2% for placebo (HR 1.46; 95% CI, 1.34 to 1.60; p<0.001).

Despite the recommendation to continue study drug during CABG, CABG-related TIMI major bleeding occurred at the same event rate (0.1%) in both treatment groups (HR; 1.00: 95% CI 0.37-2.66; p=0.996).

Non-bleeding Adverse Events and Non-bleeding Serious Adverse Events

In the Proposed Label Population in TRA 2°P-TIMI 50, most of the reported other (non-bleeding) AEs occurred at comparable rates in the two treatment groups. Anemia was the most frequently reported event leading to treatment discontinuation with a higher incidence observed with vorapaxar than with placebo (0.3% for vorapaxar and 0.1% for placebo).

The overall incidence of non-bleeding serious adverse events (SAEs) in TRA 2°P - TIMI 50 was similar in the vorapaxar group compared to the placebo group in the Proposed Label Population **(Table 33)**.

Conclusions – Proposed Label Population

In the Proposed Label Population (post MI subjects with no history of stroke or TIA), a daily dose of 2.5 mg vorapaxar reduced the primary and key secondary efficacy endpoints

compared to placebo. The risk of GUSTO moderate or severe bleeding was greater in the vorapaxar group compared to placebo, driven principally by GUSTO moderate bleeding. The critical components of GUSTO severe bleeding, namely the risks of ICH and fatal bleeds associated with vorapaxar relative to placebo, were reduced in the Proposed Label Population compared to the Overall Population. Fatal bleeding rates were the same in both treatment groups. The diminished GUSTO severe bleeding risk (that includes fatal bleeding and ICH) provides support for a favorable benefit-risk profile of vorapaxar in the Proposed Label Population, a clinically well-defined population with significant unmet medical need.

BENEFIT-RISK ANALYSIS

Given the size of this trial and the robust findings, the Sponsor believes the TRA 2°P TIMI-50 results provide a favorable benefit - risk balance to support an indication for the reduction of atherothrombotic events in patients with a history of myocardial infarction. Because of an increased risk of ICH in subjects with a prior history of stroke, the proposed labeling contraindicates vorapaxar in patients with a history of stroke or TIA.

In the Proposed Label Population, the use of vorapaxar resulted in early and durable benefit-risk effects compared to placebo. Vorapaxar reduced the rate of the composite endpoint of CV death excluding fatal bleed/MI excluding CV death/ischemic stroke excluding CV death by 71 patients per 10,000 patient-years (PY) compared to placebo. An excess of 6 GUSTO severe bleed events, including 2 non-fatal ICH events but zero fatal bleeding events, per 10,000 PY occurred compared to placebo. The ratio of benefit to risk is 71:6 (CV death excluding fatal bleed/MI excluding CV death/ischemic stroke excluding CV death vs. GUSTO severe bleeding), suggesting that vorapaxar is 12 times more likely to result in a benefit event compared to risk event.

With 2.5 years median follow-up, vorapaxar is the first antiplatelet therapy to show benefit in addition to standard of care and has the potential to meet the unmet medical need in a population that is at risk of recurrent events.

A detailed discussion of benefit-risk can be found in **Section 12**.

3 BACKGROUND

3 BACKGROUND

3.1 Epidemiology of atherothrombosis and athero-ischemic disease

Atherosclerosis is a diffuse process that starts early in childhood and progresses asymptomatically through adult life and manifests later in life as coronary artery disease, stroke, transient ischemic attack, and peripheral arterial disease. Thrombosis caused by a rupture or erosion of an atherosclerotic plaque may result in partial or complete occlusion of a coronary, cerebral, or other small arteries, and patients with an established history of disease are at particular risk of future vascular events and death [1]. Despite significant medical advances over the past several decades, atherothrombotic disease still remains the leading cause of death worldwide, with an estimated 17.3 million deaths in 2008 [4][5]. Of these deaths, an estimated 7.3 million were due to coronary heart disease and 6.2 million were due to stroke.

In the United Sates, there are approximately 525,000 Americans each year with a new MI, and approximately 190,000 with a recurrent MI. [1]. Common comorbidities in acute MI patients include hypertension, diabetes, and hypercholesterolemia. The average age at first MI is 64.7 years for men and 72.2 years for women. In-hospital mortality rates are approximately 5-10% with higher rates reported for STEMI vs. NSTEMI patients. [6][7] Those discharged from the hospital continue to experience significant morbidity and mortality with 30 day and 1-year cardiovascular mortality rates of 2.4% and 6.4%, respectively. [8] Of those with a first MI, the percentage with a recurrent MI or fatal Coronary Heart Disease (CHD) events within five years is approximately 15% of men and 22% of women for those 45-64 years of age and 22% for those ≥65 years of age [1]. For those age 45-64 with a first MI, the proportion who experience a stroke within five years is 2% of men and 6% of women [1]. For those ≥65 years of age, this increases to 5% of men and 8% of women.

3.2 Current Treatment/Medical Need

Current secondary prevention guidelines for established coronary and other atherosclerotic vascular disease prescribe aspirin for long-term therapy [2]. Meta-analyses estimate that the relative risk reductions resulting from the institution of aspirin monotherapy are in the range of 25-30% [9]. However, a real and substantial residual risk of 3.5% to 5.8% annually (for CV death, MI, or stroke) persists in the secondary prevention population [10]. Definitive benefit has not been established for any treatment other than aspirin. Clopidogrel monotherapy is recommended as an alternative for aspirin for patients who are intolerant of or allergic to aspirin [11]. Dual antiplatelet therapy is recommended by guidelines in patients where an intracoronary stent has been placed and is limited to one year duration [2]. The effectiveness of additional antiplatelet therapy to aspirin for secondary prevention of atherothrombotic events is not established in stable patients with a history of MI.

Clinical studies to date have evaluated the efficacy of three antiplatelet medications in outpatient–based secondary prevention of atherothrombotic complications: 1) ASA which inhibits the cyclooxygenase pathway; 2) the thienopyridine based $P2Y_{12}$ inhibitor clopidogrel: 3) Oral GPIIb-IIIa inhibitors were also tested for long term therapy and are not

suitable due to the inherent agonist activity after long term use. Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) and Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) were the only studies designed to directly address the unmet medical need and further our knowledge in the secondary prevention of atherothrombotic cardiovascular diseases. CAPRIE, completed in 1996, tested whether clopidogrel as monotherapy was superior to aspirin in secondary prevention treatment of atherothrombotic cardiovascular events. The results of CAPRIE demonstrated an overall 8.7% (95% CI 0.3-16.5; p=0.043) benefit when clopidogrel was used in place of aspirin in vascular death, MI, or ischemic stroke which focused on the reduction of CV events in the peripheral artery disease (PAD) stratum [12].

It was not until a decade later with the completion of CHARISMA that the incremental benefits of combination therapy with aspirin and clopidogrel were assessed in both secondary prevention and high-risk primary prevention populations. CHARISMA demonstrated that the addition of clopidogrel to aspirin resulted in a non-significant 7% RRR in the overall primary endpoint of MI, stroke or CV death. A secondary analysis demonstrated a 17% risk reduction in secondary prevention subpopulation with established atherothrombotic disease. Because the results from CHARISMA did not achieve statistical significance for the primary endpoint, the CHARISMA trial did not permit a definitive conclusion for the use of clopidogrel on top of ASA in primary or chronic secondary prevention [10][13].

The potential benefits of antiplatelet therapy need to be weighed against the potential risks. All antiplatelet therapies carry a risk for bleeding. For example, in a recent meta-analysis of randomized controlled trials of low-dose aspirin (75 to 325 mg/day), aspirin treatment versus placebo was associated with an increased relative risk (RR) of any major bleeding (RR 1.71; 95% CI 1.41 - 2.08; multiple definitions of major bleeding), major gastrointestinal bleeding (RR 2.07; 95% CI 1.61 - 2.66), and intracranial bleeding (RR 1.65; 95% CI 1.06 - 5.99) [14]. The addition of clopidogrel to baseline aspirin therapy resulted in an incremental GUSTO severe bleeding relative risk of 1.25 (95% CI 0.97 - 1.61; p = 0.09) (aspirin plus clopidogrel 1.7% and aspirin plus placebo 1.3%;) and an increased risk for GUSTO moderate bleeding (aspirin plus clopidogrel 2.1% and aspirin plus placebo 1.3%; RR 1.62; 95% CI 1.27 - 2.10; p <0.001) [10].

The lack of data evaluating the use of antiplatelet therapy in a secondary prevention setting is troubling. There is a need for further preventative long-term treatment of stable patients with established atherothrombotic risk. The Sponsor has investigated whether vorapaxar, belonging to a new class of antiplatelet agents, PAR-1 antagonists, can further decrease the risk of cardiovascular events, with an appropriate balance of efficacy and bleeding risk, in a population of established atherothrombosis when added to standard of care by studying vorapaxar in the secondary prevention of atherothrombotic diseases.

3.3 Thrombosis and PAR1 Receptor Biology

Platelets play a key role in thrombosis following plaque rupture. Platelet activation leading to aggregation and thrombosis is mediated by multiple agonists that each signal through distinct and independent pathways. Among the many agonists, thrombin, adenosine diphosphate and thromboxane are considered as the primary agonists. Despite the use of dual

antiplatelet therapy with aspirin and $P2Y_{12}$ inhibitors atherothrombotic events continue to occur.

Thrombin is a serine protease that plays a critical role in hemostasis and thrombosis. Thrombin enzymatically cleaves fibrinogen to form fibrin that subsequently polymerizes and creates a mesh network essential for thrombus formation. Moreover, acting through a special subgroup of G-protein coupled receptors (GPCRs) also referred to as protease activated receptors (PARs), thrombin induces cellular signaling in platelets and other cells. To date three thrombin-responsive PARs (PAR-1, PAR-3 and PAR-4) have been identified. Human platelets express PAR-1 and PAR-4 of which PAR-1 is the high affinity receptor that is activated at low thrombin concentrations. The PAR expression profile is different comparing human, primate, and rodent platelets. Rodent platelets do not express PAR-1, but use PAR-3 and PAR-4 as the thrombin receptor system. However, PAR-1 is expressed by other rodent cell types. Only the non-human primates express PAR-1 and PAR-4 on platelets, which is similar to the expression profile in human platelets. Thus, the pharmacologic effects of PAR-1 inhibition on platelets can only be recapitulated in primate disease models.

Thrombin binds to the extracellular domain of the PAR-1 receptor and enzymatically cleaves the N-terminus of the receptor between the Arg41-Ser42 peptide bond. Cleavage exposes a new amino terminal sequence SFLLRN that functions as a tethered ligand, binding via an intra-molecular interaction to sites on the second extracellular loop of the receptor, leading to its activation. In order to inhibit tethered ligand-mediated receptor activation, antagonists, such as vorapaxar, that display a slow off-rate from the receptor may be desirable. This would effectively compete with an intra-molecular mode of receptor activation (as opposed to an inter-molecular mode of receptor activation for the traditional GPCR's). Synthetic peptides that mimic the new N-terminal sequences (also referred to as TRAP's) can directly activate PAR-1 independent of thrombin activation and have been used to demonstrate the antiplatelet effects of vorapaxar. PAR-1 is widely expressed by cells outside of the megakaryocytic lineage, including endothelial cells and smooth muscle cells. PAR-1 gene expression is upregulated at sites of vascular injury and in human atherosclerotic tissues.

4 OVERVIEW OF PRECLINICAL DATA

4 OVERVIEW OF PRECLINICAL DATA

4.1 Vorapaxar Mechanism of Action and Preclinical Pharmacology

Vorapaxar is a potent, selective, reversible and orally active antagonist of PAR-1. The binding and dissociation of vorapaxar to the PAR-1 receptor is relatively slow. When added to human platelet rich plasma in vitro, vorapaxar inhibited platelet aggregation mediated by thrombin or TRAP. However, vorapaxar did not inhibit platelet aggregation mediated by other platelet agonists such as adenosine diphosphate, collagen or a PAR-4 agonist peptide, demonstrating exquisite selectivity for the PAR-1 receptor. When dosed orally to cynomolgus monkeys, vorapaxar (0.1 mg/kg) achieved a rapid and complete inhibition of TRAP-induced platelet aggregation ex-vivo for up to 24 hours after a single dose. Given the poor solubility of vorapaxar in formulations for parenteral administrations, we demonstrated anti-thrombotic efficacy of a close structural, more soluble analog of vorapaxar (SCH 602539) in a Folts model of thrombosis in cynomolgus monkeys [15]. Vorapaxar (1 mg/kg, po) did not increase the forearm bleeding triggered by skin incisions using a Surgicutt bleeding devise.

Vorapaxar inhibited PAR-1 mediated cellular signaling in human coronary artery smooth muscle cells and human embryonic kidney cells. Thus, vorapaxar is expected to inhibit PAR-1 activation in non-platelet cells in vivo. Vorapaxar demonstrated >100-fold selectivity for PAR-1 over a panel of >100 receptors, ion channels and enzymes in counter screening assays. Vorapaxar is a pure antagonist and did not demonstrate any agonist activity. The overall nonclinical pharmacology profile supports the conclusion that vorapaxar is a highly potent, selective and reversible antagonist of the PAR-1 receptor with strong antiplatelet activity.

4.2 Preclinical Safety

Vorapaxar has been extensively evaluated in nonclinical safety pharmacology studies, genetic toxicology studies, repeat-dose toxicity studies up to 6 months in duration in rats and 12 months in duration in monkeys, carcinogenicity studies in CD-1 mice and Sprague Dawley rats, fertility studies in female and male rats, embryo-fetal developmental toxicity studies in rats and rabbits, two pre- and post-natal developmental (PPND) toxicity studies in rats, including a repeat PPND with cross-fostering, a three day oral photo-toxicity evaluation in pigmented rats, a photo-Ames assay and several investigative studies in rats.

Vorapaxar was not genotoxic or carcinogenic. There were no effects on fertility or embryo-fetal development. Repeat dose-findings in rats, mice, and monkeys were noted at generally high exposure margins and, with the exception of phospholipidosis, have been species specific. Phospholipidosis was observed in all species, however, rats are typically particularly sensitive and it was only observed in mice and monkeys at very high exposures. In addition, it was fully reversible. Retinal vacuolation was reversible, of minimal severity and observed only in rats.

In nonclinical toxicology studies with vorapaxar, there were no bleeding-related findings noted. Ocular findings in Sprague Dawley rats were further evaluated in nonclinical studies in order to inform and support clinical investigation of vorapaxar.

4.2.1 Retinal Findings in Rat Model

A low incidence of vacuoles in the inner nuclear layer of the retina of the eye (bilateral) was noted in rats administered 10 mg/kg/day and greater. The cells within the inner nuclear layer appeared healthy with no evidence of degeneration. All other layers of the retina and all other parts of the eye were unremarkable. The vacuolation was minimal in severity and was considered unrelated to phospholipidosis based on evaluation by electron microscopy. The no-effect level for the vacuoles in the retina is 3 mg/kg, representing an exposure of 1.3-times (males) and 1.8-times (females) the human steady-state exposure at a dose of 2.5 mg/day.

The vacuolation was found to be species specific, with no indication of similar findings in any other species tested (monkeys and mice) at very high vorapaxar exposures (up to 398-times in mice and 214-times in monkeys the human steady-state exposure at 2.5 mg/day). The vacuolation was not associated with any detectable functional changes (assessed by electroretinography), was not associated with any evidence of degenerative changes, was fully reversible following a 1-month recovery period and did not progress in incidence or severity with chronic administration. In addition, the vacuolation was not noted upon fixation of the eyes with a non-aldehyde based fixative (Carnoy's) and it was not observed in Wistar rats administered a compound similar to vorapaxar that did show the vacuolation in Sprague-Dawley rats, suggesting it is rat strain specific. As such, the finding was considered unlikely to be predictive of a significant risk to patients. (See **Section 10.3 Ocular Safety)**

Vorapaxar has been extensively evaluated in nonclinical toxicology studies and was well tolerated. Overall, the nonclinical profile supports the safety of vorapaxar as a chronic treatment in adult patients.

5 CLINICAL PHARMACOLOGY

5 CLINICAL PHARMACOLOGY

5.1 Overview

The vorapaxar program involved 21 clinical pharmacology studies that were conducted in a total of 1,215 subjects of which 1,060 received vorapaxar. Across these single- and multiple-dose studies, vorapaxar was found to be generally safe and well tolerated. Vorapaxar plasma concentration data were collected in Phase 1 studies and also in a subset of subjects with atherosclerotic disease from three Phase 2 studies, and from a small subgroup in the Phase 3 TRACER trial. As available exposure-response data do not suggest a strong association with exposure for efficacy or bleeding within the PK variation seen at 2.5 mg daily, direct assessments of efficacy and safety in the large Phase 3 dataset inform the clinical relevance of PK differences and appropriate recommendations for intrinsic and extrinsic factors. Vorapaxar has low potential for affecting the pharmacokinetics of co-administered drugs. Consistent with its metabolic pathways, co-administration of strong CYP3A inducers cause a significant decrease and strong CYP3A inhibitors cause a significant increase in vorapaxar exposure. Based on an integrated assessment of the magnitude of exposure changes as well as clinical assessments of efficacy and safety in subgroups from the Phase 3 studies (**Sections 8.5-8.6**), dose adjustments are not required for age, gender, race, renal function, or mild or moderate hepatic impairment. However, vorapaxar is not recommended in patients with severe hepatic impairment due to an increased risk of bleeding, and caution is recommended when used in patients with bodyweights below 60 kg as is recommended with other antiplatelet agents, such as prasugrel. The clinical pharmacology data support 2.5 mg once-daily as the proposed clinical dose. Vorapaxar does not prolong the QTc interval. Vorapaxar does not have a clinical ocular safety signal **(Section 10.3)**.

5.2 Pharmacokinetics

The PK of vorapaxar following single doses up to 120 mg and multiple doses up to 7.5 mg/day for 6 days (with loading doses up to 40 mg), 5 mg/day for 28 days, or 2.5 mg/day for 3 months (after a 40 mg loading dose) were evaluated.

Absorption: Vorapaxar is rapidly absorbed following oral administration with a median T_{max} of 1 hour (range: 1 to 2 hours) after dosing of 2.5 mg vorapaxar sulfate. The estimated absolute bioavailability (F) for 2.5 mg is approximately 100%. Ingestion of vorapaxar with a high-fat meal resulted in no meaningful change in area under the curve (AUC) with a small (21%) decrease in C_{max} and delayed T_{max} (45 min); therefore, vorapaxar may be administered without regard to meals.

Distribution: Vorapaxar is widely distributed, with a volume of distribution of 424 L (95% CI: 351-512 L). Vorapaxar is extensively bound (≥99.8%) to serum albumin and does not preferentially distribute into red blood cells.

Metabolism: Vorapaxar is eliminated primarily via metabolism. CYP3A4 and CYP2J2 play important roles in the formation of M20, the major circulating metabolite of vorapaxar, and M19, the predominant metabolite in excreta. M20 is an active metabolite with similar *in vitro* pharmacological activity as vorapaxar. M20 is highly bound to plasma proteins (99%).

M20 exhibits formation-rate limited pharmacokinetics such that the terminal phase of plasma concentration-time profiles largely parallel those of vorapaxar **(Figure 1)**.

In addition, the M20:vorapaxar AUC ratio (~20%, **Figure 1**) is generally conserved across a broad range of vorapaxar exposures, doses and sub-populations. Therefore, vorapaxar concentrations are reasonably representative of total active exposures and can be used for clinical decisions. Given its clinical exposure, M20 is not expected to have a major contribution to overall activity. All of the identified metabolites observed in human plasma, urine, or feces have also been observed in the preclinical safety assessment species with similar protein binding.

Elimination: Vorapaxar metabolites are predominantly excreted in the feces with negligible renal clearance of unchanged parent. The apparent terminal half-life ($t_{1/2}$) of vorapaxar is 187 hours (95% CI: 131-265 hours).

Steady-state is achieved by 21 days of once-daily dosing with accumulation of ~6-fold from single- to multiple-dose. There is a modest, clinically unimportant deviation from dose-proportionality over vorapaxar doses of 2.5 mg to 40 mg, estimated as a 20% reduction in bioavailability over the dose range. Vorapaxar has low to moderate PK variability (inter-subject CV ~20-40%).

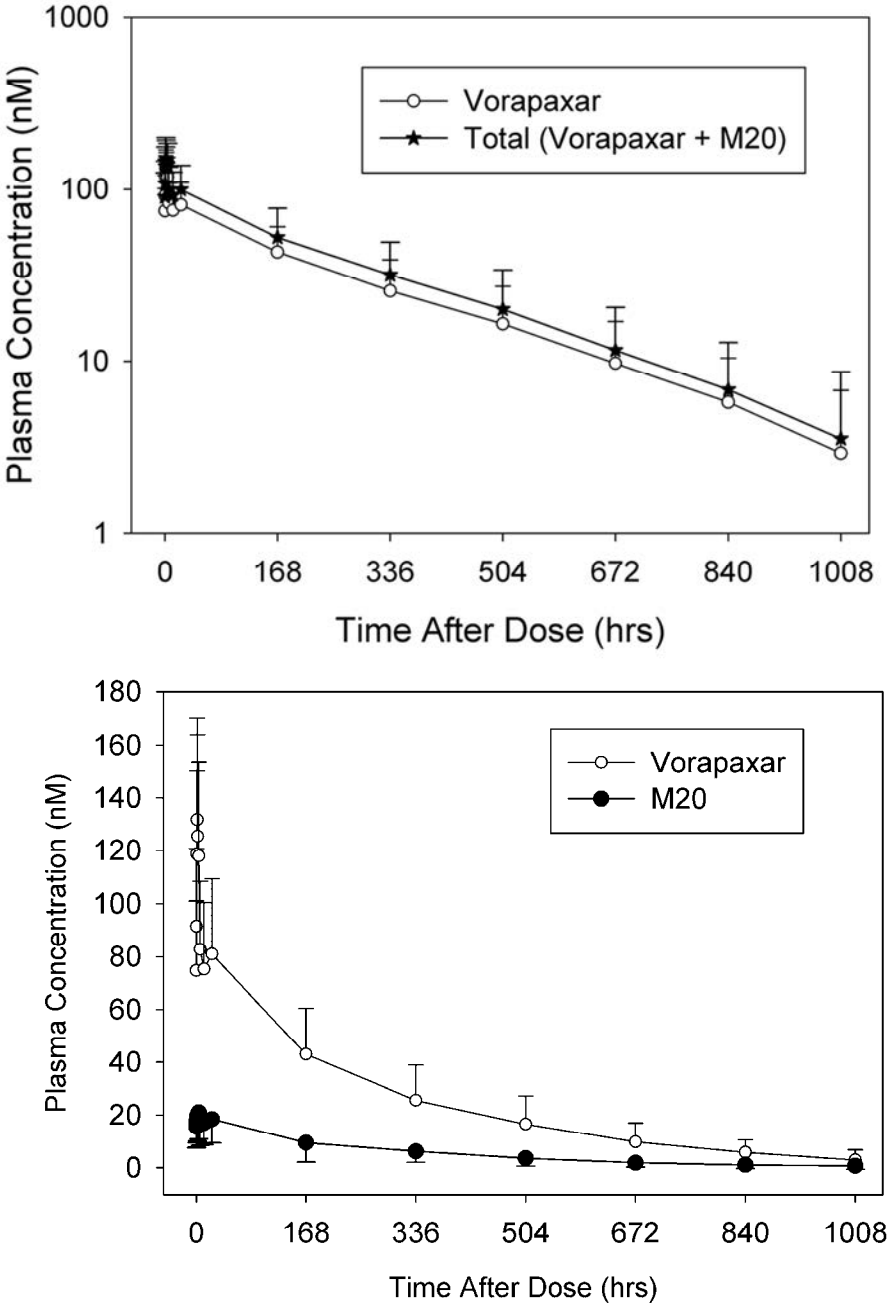


Figure 1 **The concentration-time profiles of vorapaxar and its major circulating metabolite (M20). Top: M20 parallels vorapaxar profile after steady-state dosing of 2.5 mg vorapaxar. Bottom: M20 has ~20% exposure compared to vorapaxar.**

5.3 Influence of Intrinsic Factors on Vorapaxar Pharmacokinetics

Impacts on exposure by intrinsic factors drawn from individual clinical studies, Phase 1 meta-analysis, and Phase 1/2/3 Population PK analysis are summarized in a forest plot **(Figure 2)**. Assessments of efficacy and safety across subpopulations in Phase 3 (TRA 2ºP-TIMI 50) informed dosing recommendations in subgroups and special populations below. A population PK model was developed using data from healthy volunteers (n=354) in Phase 1 and patients (n=806) in Phase 2 studies, along with the PK/PD subgroup in TRACER, to assess the effect of covariates on vorapaxar PK. The disposition of vorapaxar is comparable between healthy subjects and patients with atherosclerotic disease, thus properties observed in healthy subjects are applicable to the intended target patient population. No dose adjustment is deemed necessary for mild or moderate hepatic insufficiency based on results of a dedicated study.

The effects of chronic renal insufficiency on the pharmacokinetics of vorapaxar were evaluated in a Phase 1 study of patients with end stage renal disease (ESRD) and in a population PK analysis. The pharmacokinetics of vorapaxar were similar between subjects with ESRD (requiring dialysis) and matched healthy controls (CrCl ≥ 90 mL/min) in the Phase I study. In addition, an assessment of vorapaxar PK vs. renal function was performed using population PK modeling. This dataset included Phase 2/3 data from ~350 subjects with mild renal impairment (CrCl ≥ 60 to < 90 mL/min) and ~150 patients with moderate renal impairment (CrCl ≥ 30 to < 60 mL/min), as well as 4 subjects with severe renal impairment (CrCl < 30 mL/min). Creatinine clearance was estimated based on Cockcroft-Gault using body weight, gender and age, thus, the interpretation of results may be confounded. Exposures were predicted to be 17-34% higher in subjects with mild and moderate renal impairment compared to those with normal renal function. Subgroup analyses of subjects with renal insufficiency showed no increased risk for bleeding events or other adverse events (**Section 8.6**). Although exposure data in severe renal impairment is limited (n=4), renal impairment shows only a gradual continuous relationship with PK, such that the exposure and safety experience in moderate renal impairment supports no need for specific label guidance around severe impairment. Furthermore, Phase 1 data suggest no need for dosing guidance alteration in ESRD. Gender, age, bodyweight, race were assessed for influence in a population pharmacokinetic model. Effects on vorapaxar exposure by age (≥75 years), Asian race, bodyweight (<60 kg) and female gender were modest (20-40%; see **Figure 2**). However, as discussed below, prescribing to patients with low bodyweight (<60 kg) should be done with caution based on experience with other antiplatelet agents.

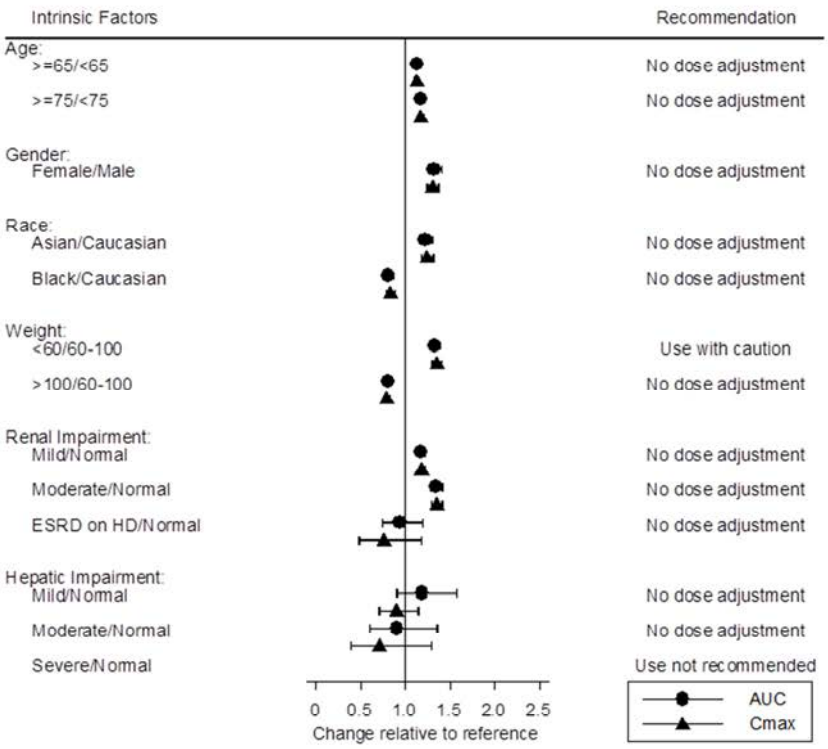


Figure 2 The effects of intrinsic factors on the pharmacokinetics of vorapaxar are presented as change (with 90%CI) relative to vorapaxar administered in a reference group. Modest differences in vorapaxar pharmacokinetics were observed across intrinsic factors

Based on an integrated assessment of these modest pharmacokinetic changes and clinical assessments of risk-benefit in subgroups from the Phase 3 studies **(Section 8.5 and 8.6)**, no specific recommendations are made for these intrinsic factors, except for bodyweight <60 kg for which caution is advised. The use of vorapaxar in severe hepatic impairment is not recommended. Neither of these recommendations is based on differences in vorapaxar exposure in these cohorts compared to other subgroups, but rather on the available safety experience.

5.4 Influence of Extrinsic Factors on Vorapaxar Pharmacokinetics (Potential for Drug-Drug Interactions)

5.4.1 Potential for Other Drugs to Affect Vorapaxar Pharmacokinetics

Figure 3 summarizes the change in vorapaxar pharmacokinetic parameters (AUC and C_{max}) after co-administration with various drugs. Consistent with the CYP3A/2J2 mediated

metabolism of vorapaxar, drug-drug interactions affecting vorapaxar pharmacokinetics were observed with ketoconazole (strong CYP3A and weak CYP2J2 inhibitor), and rifampin (strong CYP3A inducer). Consequently, concomitant use of strong inhibitors and inducers were excluded in the Phase 2/3 studies, thereby limiting the clinical experience. Thus, concomitant use of vorapaxar should be avoided in patients taking strong inhibitors or strong inducers of CYP3A.

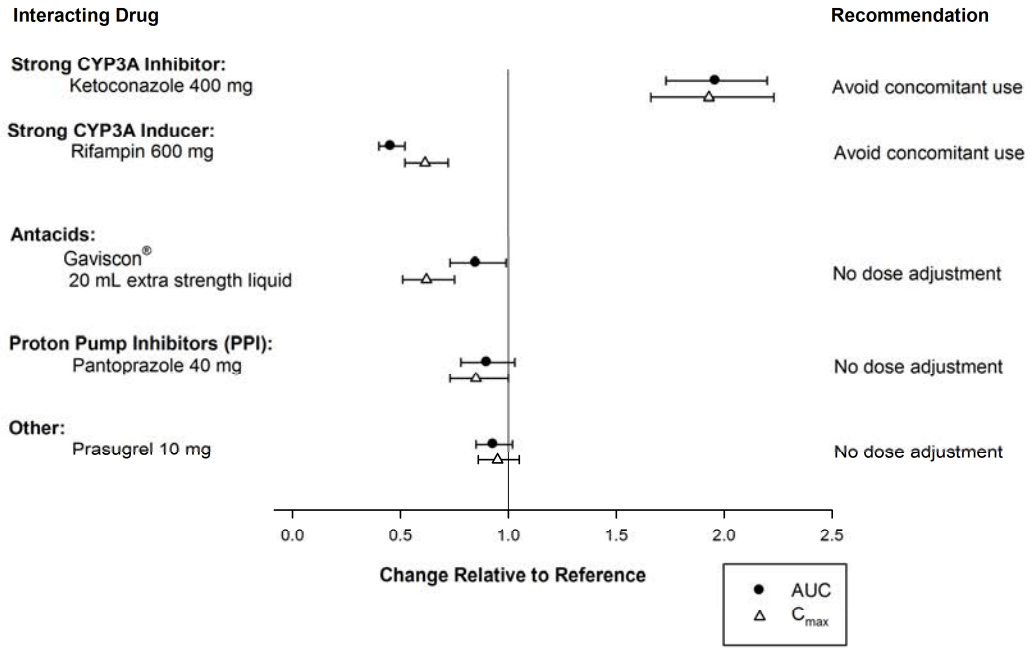


Figure 3 The effects of other drugs on the pharmacokinetics of vorapaxar are presented as change (with 90% CI) relative to vorapaxar administered alone (reference) and were modest except for strong inhibitors and inducers of CYP3A.

Although weak to moderate CYP3A inhibitors may increase vorapaxar exposures, the effect is anticipated to be less than that observed with ketoconazole. In Phase 3 approximately 60% of patients received a weak or moderate CYP3A inhibitor (amlodipine, amiodarone, amprenavir, aprepitant, atazanivir, atorvastatin, ciprofloxacin, cimetidine, cyclosporine, diltiazem, ethinyl estradiol, erythromycin, fluconazole, fluoxetine, fluvoxamine, fosamprenavir, gestodene, imatinib, isoniazid, mifepristone, norfloxacin, verapamil) for at least 7 days. The difference in bleeding events for vorapaxar compared to placebo was similar to those not receiving concomitant CYP3A inhibitors. Thus, co-administration of a weak or moderate CYP3A inhibitor with vorapaxar does not increase the hazard for bleeding. No dose adjustment is required when vorapaxar is co-administered with weak to moderate inhibitors of CYP3A. No clinically relevant pharmacokinetic interactions followed co-administration of antacids or proton pump inhibitors; restrictions on the co-administration of vorapaxar with these drugs are not necessary. No pharmacokinetic drug-drug interaction was observed between prasugrel and vorapaxar in a dedicated Phase 1 study. There is limited

clinical experience with prasugrel and no experience with ticagrelor in the vorapaxar Phase 3 studies (**Section 8.3**).

5.4.2 Potential for Vorapaxar to Affect Other Drugs

Figure 4 summarizes the change in pharmacokinetic parameters (AUC and C_{max}) of various drugs after co-administration with vorapaxar. Overall vorapaxar has a low potential to affect the exposure of co-administered drugs. Based on results from the in vitro studies, specific clinical pharmacokinetic studies have been conducted with digoxin (P-gp substrate) and rosiglitazone (CYP2C8 substrate). Furthermore, *in vitro* and *in vivo* data suggested that clinically meaningful effects on the pharmacokinetics of drugs that are substrates of other CYPs or transporters following co-administration with vorapaxar are not anticipated.

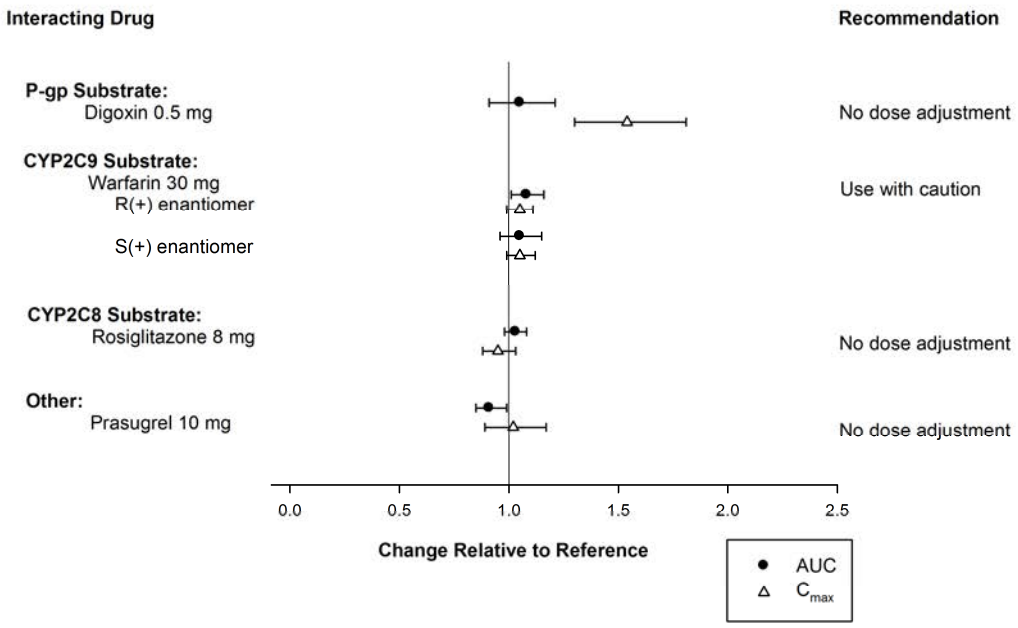


Figure 4 Vorapaxar has low potential for affecting the pharmacokinetics of co-administered drugs. Specific *in vivo* effects on the pharmacokinetics of digoxin, warfarin, rosiglitazone and prasugrel are presented as a change (with 90% CI) relative to the interacting drug administered alone (reference).

Vorapaxar causes a modest increase in the peak concentration (54%) of digoxin at a dose (40 mg) exceeding 2.5 mg once-daily. Although vorapaxar concentrations required to achieve P-gp inhibition are not expected following the recommended clinical dose of 2.5 mg, owing to the narrow therapeutic index of digoxin, when co-administering digoxin with vorapaxar, digoxin should be monitored as clinically indicated. No clinically significant pharmacokinetic interactions were observed following co-administration of rosiglitazone and vorapaxar. No significant pharmacokinetic drug-drug interactions were anticipated with warfarin or prasugrel, but owing to their potential use in the intended target population, clinical drug-drug interaction studies were conducted. Daily dosing of vorapaxar, co-

administered with warfarin, had no effect on the pharmacokinetics of warfarin as measured by both R(+) enantiomer and S(-) enantiomer. No clinically meaningful effects on the pharmacodynamics of warfarin, measured by international normalized ratio (INR) $AUC_{0\text{-}168h}$ and prothrombin time (PT), were observed. As noted above (**Section 5.4.1**), no drug interaction between prasugrel and vorapaxar was observed when the two agents were co-administered in a dedicated Phase 1 study. There is limited experience with prasugrel and no experience with ticagrelor in the vorapaxar Phase 3 studies **(Section 8.3**).

5.5 Pharmacodynamics

In the vorapaxar development program, TRAP-induced platelet aggregation (TIPA) was used as a target engagement biomarker in the Phase 1 and 2 programs. For the program, ≥80% inhibition has been used to define target engagement in the TIPA biomarker based on experience from other platelet aggregation inhibitors: 1) preclinical experiments with abciximab which demonstrated that ≥80% blockade of GPIIb/IIIa was required to prevent or reverse platelet-induced coronary occlusion in dog models; and 2) clinical data from studies involving eptifibitide which demonstrated that the efficacious dose of this GPIIb/IIIa inhibitor is associated with >80% inhibition of both ADP- and TRAP-induced platelet aggregation. Vorapaxar shows steep exposure response relationships indicating the appropriateness of ≥80% inhibition level.

5.5.1 Pharmacokinetic/Pharmacodynamic Relationships

Exposure-response: TRAP-induced platelet aggregation data were well characterized by a sigmoid Emax PK/PD relationship that reflects a steep exposure-response relationship with complete inhibition (100%) at Emax. Individuals rapidly transition from low to high inhibition following the initiation of treatment and experience a similar rapid transition from high to low inhibition during washout, but the timing of these transitions varies across individuals. Notably, in vivo potency parameter estimates (EC50) differed ~5-fold between one set of Phase 1 studies (P03448, P03464) compared to another set of Phase 2 and 3 patient studies (P03573, P04772, P05005, P04736) and Phase 1 studies (P03449, P03450) **(Table 2)**. Within-study variability in potency was considerably less variable. Investigation of demographic factors, study design/execution and assay methodology/performance did not yield an explanation for the differing exposure-response relationships between these clusters of studies. As such the two EC50 estimates are viewed as reflective of uncertainty in the vorapaxar exposure-response assessment between studies.

Table 2 List of Studies with Pharmacodynamic Data and Associated in Vivo Potency Parameter Estimate (EC50 High vs. EC50 Low)

Study	Phase	Sites	Number Subjects in Modeling Data Set[a]	Number Data Points in Modeling Data Set	EC50
Single and Multiple Ascending Dose Studies (P03449, P03450)	1	Zuidlaren, Netherlands	64	967	Low
Race/Ethnicity Study (P03448)	1	Long Beach, CA	99	1362	High
Renal Disease Study (P03464)	1	Philadelphia, PA	15	150	High
Three Phase II Studies (P03573, P04772, P05005)	2	Multiple Sites	81	451	Low
TRACER Substudy (P04736)	3	Multiple Sites	43	264	Low

a. Excludes Placebo Subjects

Dose justification: Predictions of target engagement (TIPA inhibition) accounted for the observed variability between studies by including both estimates of EC50 **(Figure 5)**. Using a low EC50 estimate (i.e., high potency), the simulations indicated that appropriate target engagement for >80% of patients was achieved with 2.5 mg once-daily dosing within 7 days. When the higher estimate of EC50 was used (i.e., low potency), once-daily dosing with 2.5 mg did achieve appropriate target engagement for >80% of patients within 28 days.

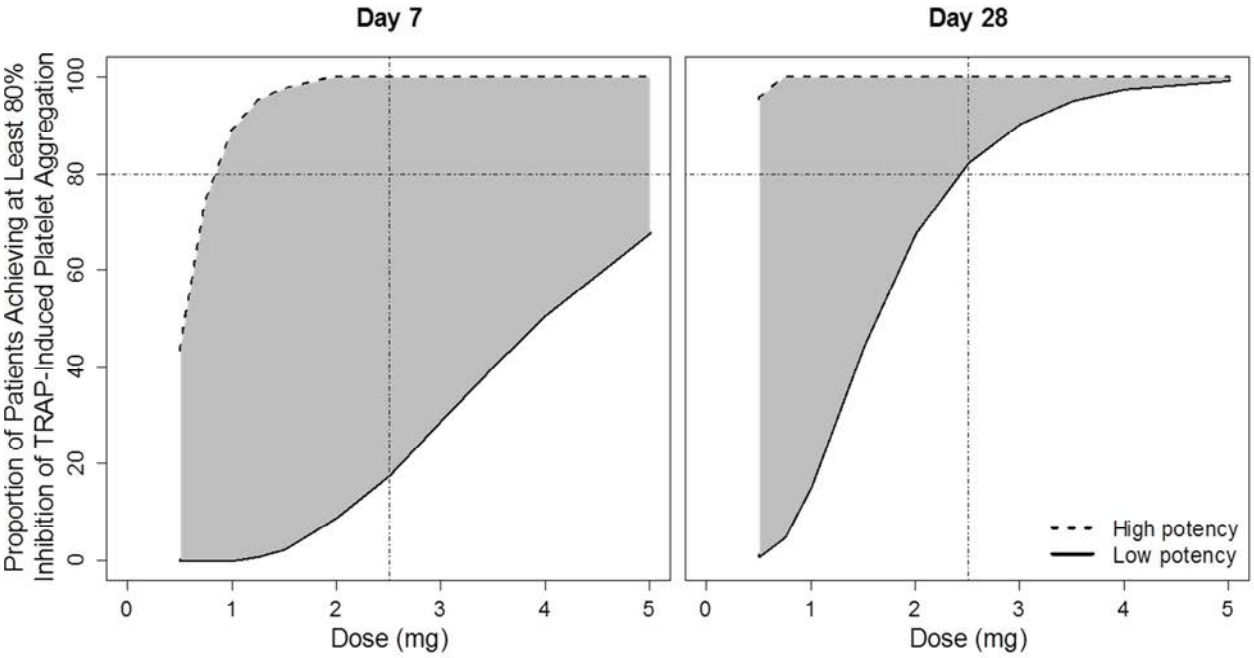


Figure 5 Proportion of patients achieving ≥80% inhibition of TRAP-induced platelet aggregation (TIPA).

Upper and lower lines represent median response (proportion of patients achieving at least 80% inhibition of TIPA) based on simulations using low EC50 (high potency) and high EC50 (low potency) estimates, respectively. Area between the two lines is shaded.

When once-daily dosing with 1 mg was evaluated in this simulation, assuming the high EC50 estimate (i.e., low potency), appropriate target engagement for >80% of patients would not be achieved at 7 or 28 days. Furthermore, simulations indicated that the 1 mg dose would not have achieved target engagement for >80% of patients even when dosing for an extended duration **(Figure 6)**. Specifically, assuming the high EC50 estimate (i.e., low potency), only 20-30% of patients would achieve appropriate target platelet inhibition. The totality of these data and simulations support the choice of the 2.5 mg daily dose for Phase III as the lowest dose that achieves target engagement in >80% of patients allowing for an EC50 estimate that is on the higher end of the range (i.e., the lower end of the range for potency).

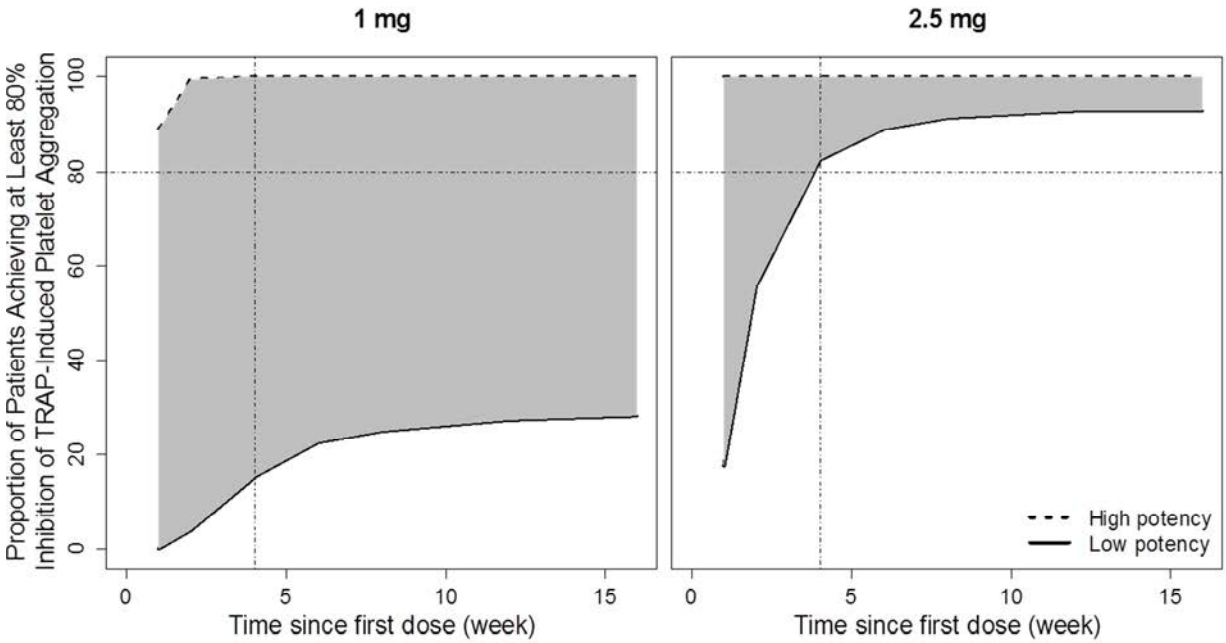


Figure 6 Proportion of patients achieving ≥80% inhibition of TRAP-induced platelet aggregation (TIPA) over time dosing 1 mg (left panel) and 2.5 mg (right panel).

Upper and lower lines represent median response (proportion of patients achieving at least 80% inhibition of TIPA) based on simulations using low EC50 (high potency) and high EC50 (low potency) estimates, respectively. Area between the two lines is shaded.

Washout: **Figure 7** describes the predicted plasma concentration curves (left panel) and change in % TRAP-induced platelet aggregation (TIPA) inhibition (with curves for both high [low EC50] and low [high EC50] estimates of potency; right panel) over time for 2.5 mg daily dosing over an 8 week treatment period and a 10 week post-dose follow-up period. Percent TIPA inhibition rises rapidly over the first week of dosing (right panel) despite a more gradual increase in trough concentration (left panel). Upon cessation of dosing (after steady-state has been achieved), plasma concentrations fall rapidly but inhibition of TIPA can persist at near maximal levels for up to 4 weeks (assuming the higher potency estimate; timing of normalization based on the lower potency estimate is more rapid).

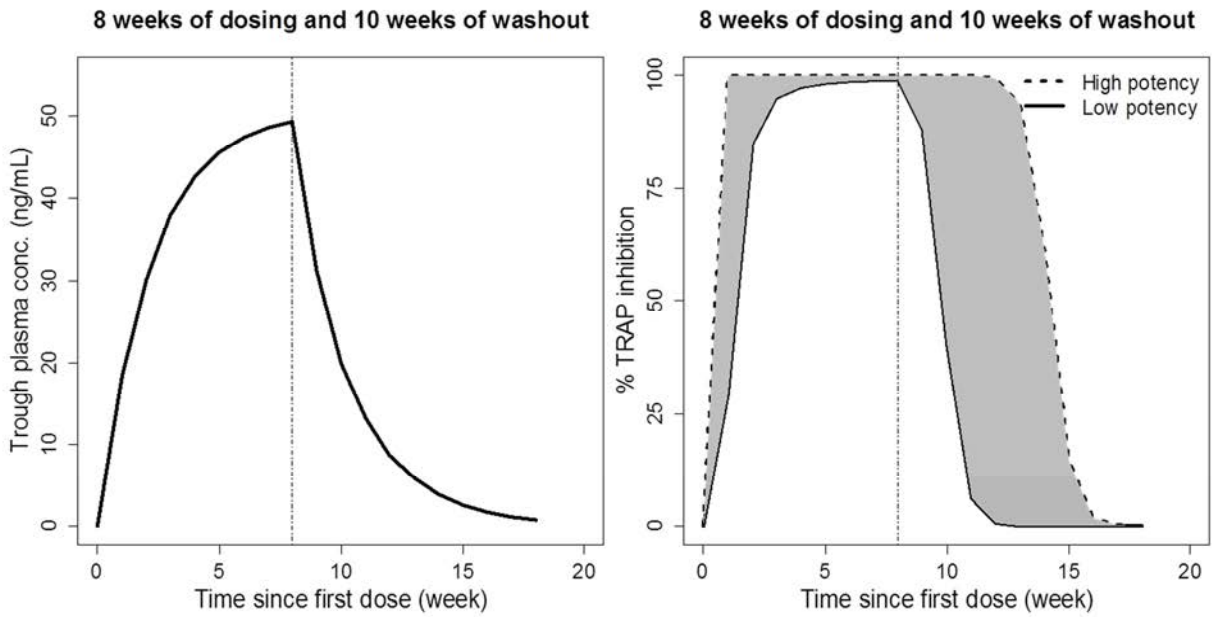


Figure 7 Vorapaxar pharmacokinetics (left panel, C_{trough}) and TRAP-induced platelet aggregation inhibition over time (right panel, TIPA) dosing 2.5 mg to steady-state and subsequent cessation (vertical line at 8 weeks).

Right panel: upper and lower lines represent median response (% TRAP inhibition) based on simulations using low EC50 (high potency) and high EC50 (low potency) estimates, respectively. Area between the two lines is shaded.

The reduction in vorapaxar plasma concentrations is gradual due to the long half-life of vorapaxar (187 hours) and is the basis for a relatively long period before there is rapid normalization in platelet function.

Exposure-bleeding risk: Platelet aggregation inhibition as assessed by TIPA is indicative for both efficacy and bleeding risk. A dose of 2.5 mg was selected to ensure a consistent antiplatelet response (**Section 5.5.1**): >80% of patients achieving at least 80% inhibition of TIPA. Since the exposure-response relationship is near the maximum effect after steady-state is achieved for a 2.5 mg dose of vorapaxar, no meaningful increase in bleeding risk is expected for the modest increases in plasma exposure from intrinsic and extrinsic factors (mostly 20-40%, **Sections 5.3 and 5.4.1**). This was further supported by the observation that patient subgroups defined by these intrinsic and extrinsic factors (e.g., based on age, gender and race) did not demonstrate an increased bleeding risk in Phase 3. Although weak to moderate CYP3A inhibitors may increase vorapaxar exposures, the effect is anticipated to be less than that observed with strong inhibition (i.e., with ketoconazole). Similar to other factors that increase vorapaxar exposure, co-administration of a weak or moderate CYP3A4 inhibitor with vorapaxar does not increase the hazard for bleeding in Phase 3. The most pronounced increase in exposure was observed with strong CYP3A inhibitors (1.93-fold), although this increase in exposure has little effect given that near maximal inhibition of TRAP induced platelet aggregation was achieved at steady state with a 2.5 mg dose of vorapaxar **(Figure 8)**. Nonetheless, as a precaution, the use of strong inhibitors of CYP3A is not recommended.

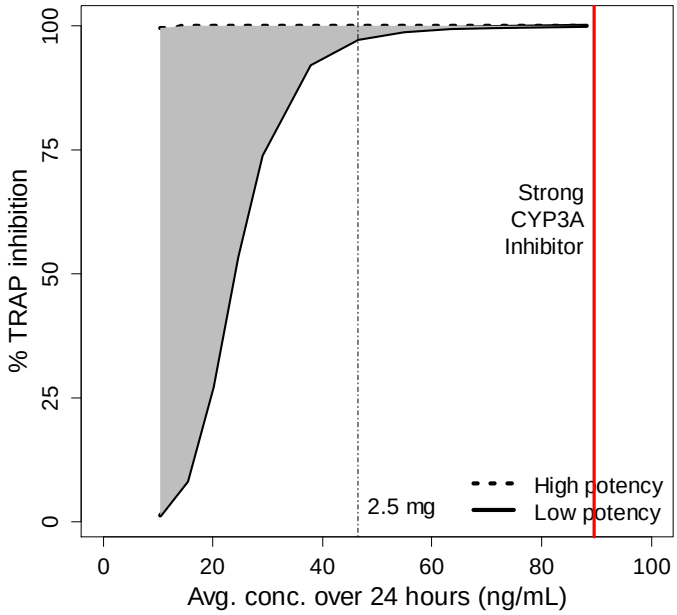


Figure 8 Predicted change in TRAP-induced platelet aggregation inhibition for ketoconazole using exposure-response (% TRAP inhibition vs. the average concentration over 24 hours at steady-state) at day 28.

Upper and lower lines represent median response (% TRAP inhibition) based on simulations using low EC50 (high potency) and high EC50 (low potency) estimates, respectively. Area between the two lines is shaded. For each dose (0.5 to 5 mg), median Cavg (0-24 hrs) values were calculated and plotted on x-axis. The dashed vertical black line indicates the typical exposure after steady-state dosing of 2.5 mg vorapaxar, whereas the red solid vertical line indicates the impact of a strong CYP3A inhibitor (1.93-fold by ketoconazole) on that exposure.

6 CLINICAL DEVELOPMENT

6 CLINICAL DEVELOPMENT

6.1 Overview of Vorapaxar Clinical Development Program

The Phase 2 program was designed to evaluate dose-dependent inhibition of platelet aggregation to guide the selection of dose regimens for Phase 3. Three, Phase 2 randomized, double blind, placebo-controlled studies of safety and efficacy were conducted.

The Phase 3 program included two large pivotal outcome studies (totaling 39,393 patients) to evaluate safety and efficacy in two distinctly different populations for two separate indications. In addition, two ocular safety studies were performed to address preclinical ocular findings, one Phase 1 study (P05185) and a substudy of TRA 2°P - TIMI 50 (P05183). **(Section 10.3)**

6.2 Phase 2 Development Program

The three Phase 2 studies (P03573, P04772, P05005) were designed primarily to investigate safety/tolerability, and in particular the bleeding potential of vorapaxar, in men and women with CAD who were undergoing non-emergent catheterization with intent to perform PCI, had symptoms of ACS, or were stable after ischemic stroke. All three studies were placebo-controlled, double-blinded studies that utilized an initial loading dose of vorapaxar followed by treatment with a lower maintenance dose daily for 59 days after PCI, or maintenance dosing for 60 days (no loading dose) in the stroke study. A 60 day post-treatment follow-up phase was included in all three studies.

6.2.1 Phase 2 TRA-PCI

This was a multicenter study in 1030 subjects eligible for non-emergent PCI (TRA-PCI) (P03573); 573 subjects received vorapaxar at an initial loading dose of 10, 20, or 40 mg followed by treatment with 0.5, 1, or 2.5 mg/day for 59 additional days (60 days total), then no-treatment follow-up for 60 days**.** TIMI bleeding was adjudicated by an independent, blinded Clinical Events Committee.

P03573: Summary of results and discussion

Overall, administration of vorapaxar was not associated with a demonstrable increase in TIMI or non-TIMI bleeding. Administration of vorapaxar was not associated with any specific identifiable risk among other indicators of safety. Although the study was not designed to be able to make inferences about clinical outcomes and adverse experiences, the data supported further study in an expanded Phase 3 program. TRAP (15 μM) induced platelet aggregation of plasma samples obtained during the first 2 hours after loading dose was administered demonstrated that the 40-mg dose was most effective in producing ≥80% inhibition in 1 to 2 hours after dosing.

6.2.2 Phase 2 Japan - ACS/Stroke

Two smaller phase 2 studies were conducted in Japan to gain experience in a Japanese subject population. One was a study involving 117 subjects with ACS with a design similar to TRA-PCI (P04772). The second was a study in 90 subjects with a history of ischemic stroke that included treatment with placebo or vorapaxar in doses of 1 or 2.5 mg for 60 days, then no-treatment follow-up for 60 days (P05005). In these two studies, blinded investigators made the final determination of TIMI category.

P04772: Summary of results and discussion

P04772 was similar in design to TRA-PCI (P03573). In P04772, the administration of vorapaxar was well tolerated and not associated with an increase in adverse events, or with any specific, identifiable risk among other indicators of safety when co-administered with aspirin and ticlopidine. Vorapaxar administered in combination with aspirin and ticlopidine did not increase the incidence of TIMI major/minor bleeding and non-TIMI bleeding. Clinically significant bleeding events were reported for approximately 7% of vorapaxar-treated subjects and no placebo-treated subjects.

Both 20 mg and 40 mg vorapaxar administered as a loading dose inhibit TRAP-induced platelet aggregation (≥ 80%) within 2 hours after administration. Daily maintenance dosing with 1.0 mg and 2.5 mg vorapaxar is sufficient to maintain inhibition of TRAP-induced platelet aggregation by greater than 80%. Although this study was not designed to be able to make inferences about clinical outcomes, an imbalance in favor of vorapaxar for the occurrence of myocardial infarctions among PCI subjects supported further investigation in an expanded Phase 3 program.

P05005: Summary of results and discussion

P05005 enrolled 89 subjects with a history of cerebral infarction (excluding cardiogenic cerebral embolism) and was a multicenter, randomized, double-blind, multiple-dose, placebo-controlled, parallel-group study. Subjects with cerebral infarction were randomized to receive vorapaxar 1 mg, 2.5 mg, or placebo daily for 60 days in a 1:1:1 ratio, in addition to aspirin in the range of 75 to 150 mg daily.

In P05005, administration of daily doses of 1 mg or 2.5 mg of vorapaxar, together with 75 to 150 mg of aspirin daily, was not associated with an increase in overall safety events in Japanese subjects with a history of cerebral infarction. Vorapaxar was not associated with a higher rate of TIMI major or minor bleeding, nor of clinically significant bleeding. There was a higher incidence of non-TIMI bleeding in the vorapaxar 2.5-mg group than in the placebo group, during both treatment and follow-up phases, but the difference was not statistically significant.

6.2.3 Safety Summary from Phase 2

The overall safety profile among the three studies during the protocol-specified treatment phase is summarized in **Table 3** below. In the Phase 2 program, there were 3 cases of ICH, all in subjects treated with vorapaxar. In the P03573 trial, one subject experienced a subdural hematoma resulting from a fall with head trauma and a fractured zygomatic arch 36 days following the single 40 mg loading dose of vorapaxar. One subject in the P04772 trial in the 40/2.5-mg treatment group had a traumatic subarachnoid hemorrhage beginning on Day 2 and ending on Day 16. This bleeding resulted from a fall on the day after the loading dose, during which the subject experienced head trauma. Additionally, an asymptomatic cerebral hemorrhage was observed for one subject in the P5005 trial during the end-of-study T2-STAR scan on Day 122 (59 days after the last dose of vorapaxar 2.5 mg).

TIMI Major and Minor bleeding and of non-TIMI bleeding were not meaningfully different between placebo and vorapaxar in all three trials. Similarly, the occurrences of serious adverse events and discontinuations because of adverse events were not different between placebo and vorapaxar across the three trials. The similarity of results is noteworthy, given the range of doses administered in the three trials. Thus, these results are consistent and mutually supportive.

Table 3 Number (%) of Subjects With Bleeding, a Serious Adverse Event, or Who Discontinued Because of an Adverse Event During the Protocol-Specified Treatment Phase in the Three Phase 2 Trials With Vorapaxar

Major Safety Indicators	Treatment	**P03573** Eligible for Non-Emergent PCI (PCI Subjects)	**P04772** Acute Coronary Syndrome (PCI Subjects)	**P05005** After Ischemic Stroke (All Subjects)
Any Bleeding[a]	All Placebo	53/151 (35)	11/21 (52)	6/28 (21)
	All Vorapaxar	173/422 (41)	43/71 (61)	15/62 (24)
TIMI Major/Minor Bleeding	All Placebo	5/151 (3)	2/21 (10)	1/28 (4)
	All Vorapaxar	12/422 (3)	10/71 (14)	0/62
Non-TIMI Bleeding	All Placebo	48/151 (32)	11/21 (52)	6/28 (21)
	All Vorapaxar	169/422 (40)	39/71 (55)	15/62 (24)
Serious Adverse Event	All Placebo	16/151 (11)	3/21 (14)	1/28 (4)
	All Vorapaxar	63/422 (15)	6/71 (8)	2/62 (3)
Discontinuation[b] for Adverse Event	All Placebo	9/151 (6)	8/21 (38)	1/28 (4)
	All Vorapaxar	33/422 (8)	14/71 (20)	7/62 (11)

Note: TIMI Major bleeding= intracranial hemorrhage or observable site (including imaging) of bleeding plus decrease in hemoglobin concentration by >5g/dL (or hematocrit >15%), corrected for any transfusion.
TIMI Minor bleeding= observable site (including imaging) of bleeding plus decrease in hemoglobin concentration by 3 to ≤5g/dL (or hematocrit 9% to ≤15%), corrected for any transfusion.

Note: Numbers in parenthesis are % (n/N)

a Includes all bleeding, regardless of how trivial and whether or not medical intervention was required. Does not include fecal occult blood, which was not assayed in P03573.

b Discontinuation of treatment while remaining in the trial, or discontinuation from the trial.

6.3 Vorapaxar Phase 3 Development Program

6.3.1 Dose Selection

A 2.5 mg once-daily oral dose of vorapaxar was selected for chronic administration in Phase 3 outcomes studies based on pharmacokinetic and pharmacodynamic data from Phase 1 and Phase 2 studies. This was the lowest dose to consistently achieve successful target engagement as assessed by *ex vivo* TRAP-induced platelet aggregation (TIPA) in a high proportion (≥80%) of the subjects exposed across all studies; a dose of 1 mg or less may achieve responses as low as 20-30% of maximal TIPA at steady state and independent of dosing duration. This target engagement level was supported by experiences with other drugs and preclinical experiments. There was no evidence of dose-response for bleeding risk with vorapaxar compared to placebo at 0.5 mg, 1 mg or 2.5 mg doses in the Phase 1 and 2 studies, even when administered concomitantly with aspirin and clopidogrel. Given that the 2.5 mg dose was the lowest dose to achieve sufficient platelet inhibition and there was no discernible increase in bleeding risk across the dose range of 0.5 – 2.5 mg, a 2.5 mg once daily dose was selected for chronic administration in the Phase 3 TRA 2ºP –TIMI 50 study.

6.3.2 Overview of the Phase 3 Program

Two large outcome trials of mutually exclusive populations were designed to assess the safety and efficacy of vorapaxar, for a total of 39,393 subjects, with two separate disease presentations:

(1) A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Vorapaxar in Addition to Standard of Care in Subjects with Acute Coronary Syndrome: Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) (P04736). This was designed to study the prevention of major cardiovascular events, recurrent ischemia with re-hospitalization and urgent coronary revascularizations in moderate to high-risk patients who were acutely hospitalized with NSTEACS (TRACER, N=12,944)

(2) A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of 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 2°P - TIMI 50) (Protocol No. P04737). This was designed to study the prevention of secondary major cardiovascular events and urgent coronary revascularizations in stable outpatients with a history of MI (CAD), PAD or stroke (CVD) (TRA 2°P - TIMI 50, N=26,449).

The two populations in the studies were distinctly different; fundamentally, a patient randomized to one study could not have been randomized to the other study based on both the major qualifying characteristics (primarily an acute [TRACER] versus chronic condition [TRA 2°P - TIMI 50] and the site of randomization (hospital [TRACER] versus outpatient [TRA 2°P - TIMI 50]) (Table 4).

The sample sizes for the two studies reflected the different event rate assumptions with projected annual event rates in the placebo groups of 18% (TRACER) and 8% (TRA 2°P - TIMI 50), further underscoring inherent differences between the two samples. As described below, TRACER patients had different entry criteria. Differences between the two samples for demographics, background therapy and procedures can be found in **Appendix 1**.

Table 4 Key Inclusion/Exclusion Criteria of TRACER and TRA 2°P-TIMI 50

	TRACER	TRA 2°P-TIMI 50
	Inclusion Criteria	
Age	> 18 years old	> 18 years old
Primary Diagnosis	Current clinical manifestations of moderate to high risk NSTEACS	Atherosclerosis involving the coronary, cerebral or peripheral vascular systems
Evidence of Primary Diagnosis	• Cardiac ischemic related symptoms at least 10 minutes duration ≤24 hours prior to initial presentation AND • Concurrent biomarker evidence and/or concurrent electrocardiographic evidence of cardiac ischemia AND • Any one of the following criteria o Age ≥55 years o Documented prior MI or coronary revascularization o Diabetes o Peripheral arterial disease	• CAD as evidenced by a history of presumed spontaneous MI ≥ 2 weeks but ≤ 12 months prior OR • Ischemic CVD as indicated by a history of ischemic stroke ≥ 2 weeks but ≤ 12 months prior OR • PAD as indicated by a history of claudication and a resting ankle/brachial index of <0.85 or amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia
	Exclusion Criteria Common to Both Trials	
Concomitant Medications	• Warfarin, oral factor Xa, oral direct thrombin inhibitor • Potent inducer or inhibitor of CYP3A4 isoenzymes	• Warfarin, oral factor Xa, oral direct thrombin inhibitor • Potent inducer or inhibitor of CYP3A4 isoenzymes
Medical History	• Bleeding diathesis or abnormal bleeding 30 days before enrollment • ICH, intracranial or spinal cord injury or central nervous system tumor or aneurysm • Documented sustained severe hypertension (SBP > 200 mm Hg or DBP > 110 mm Hg) at enrollment or within10 days prior to enrollment • Severe valvular heart disease • Major surgery 2 weeks prior to enrollment • Ischemic stroke 2weeks prior to enrollment • Thrombocytopenia • Active hepatobiliary disease • Serious medical comorbidity such that subject's life expectancy is < 24 months	• Bleeding diathesis or abnormal bleeding 30 days before enrollment • ICH, intracranial or spinal cord injury or central nervous system tumor or aneurysm • Documented sustained severe hypertension (SBP > 200 mm Hg or DBP > 110 mm Hg) at enrollment or within10 days prior to enrollment • Severe valvular heart disease • Major surgery 2 weeks prior to enrollment • Ischemic stroke 2weeks prior to enrollment • Thrombocytopenia • Active hepatobiliary disease • Serious medical comorbidity such that subject's life expectancy is < 24 months

	TRACER	TRA 2°P-TIMI 50
Exclusion Criteria that are Different in Each Study		
Additional Exclusion Criteria		• Clinically unstable at time of enrollment • Planned coronary revascularization or peripheral intervention

6.3.3 Statistical Methodology and Operational Issues in the Phase 3 Studies

Cox proportional hazard (PH) models with covariates of treatment and stratification factors were used to perform the analysis in both Phase 3 studies. Estimates of the hazard ratios and associated 95% confidence intervals comparing placebo with vorapaxar were evaluated for primary efficacy endpoints. The key secondary efficacy endpoint (i.e. the first occurrence of CV death, MI, or stroke) was evaluated using similar methodology. Three year KM estimates for the time to the primary and key secondary efficacy endpoints were plotted and are used throughout this document for TRA 2°P TIMI- 50 unless otherwise specified.

6.3.4 Safety Evaluations and Bleeding Definitions in the Phase 3 Studies

All safety analyses were performed in the As-Treated population (all subjects who received at least one dose of study medication). Safety assessments included pre-specified bleeding endpoints, reported individual bleeding events, adverse events by other categories (serious and treatment related), clinical laboratory evaluations, vital signs, and electrocardiograms.

Bleeding risk was considered the major potential safety concern for vorapaxar. All bleeding events reported throughout the trial were adjudicated by the CEC to determine if the event met the criteria for the pre-specified study bleeding endpoints as defined as: (1) a composite of moderate or severe GUSTO bleeding and (2)"clinically significant bleeding". GUSTO severe bleeding was defined as fatal, intracranial, or bleeding with hemodynamic compromise requiring intervention. GUSTO moderate bleeding was defined as bleeding requiring transfusion of whole blood or packed red blood cells without hemodynamic compromise. Clinically significant bleeding was defined as Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding or bleeding that required treatment or laboratory evaluation.

GUSTO severe is the bleeding category most likely to be associated with irreversible damage, whereas GUSTO moderate bleeding categorization required the presence of a transfusion without hemodynamic instability. Administration of transfusions was not defined by protocol and thus was subject to potentially varying standards. Recent literature supports greater emphasis on the incidence of GUSTO severe bleeding as it most accurately portrays the overall long-term risk of an antiplatelet agent [16].

It was recommended that subjects continue study treatment during the time of surgery (CABG or other). CABG-related bleeding has been long considered a key component for assessing surgical bleeding with antithrombotic agents. TIMI CABG major bleeding is the most specific and thus most reliable measurement of surgical bleeding risk associated with CABG. CABG related fatal bleeding is defined as death that occurred within 7 days among subjects with CABG related bleeding.

To facilitate objective evaluation of CABG-related bleeding, TIMI major CABG-related bleeding, a CABG-specific bleeding endpoint was pre-defined and adjudicated, in accordance with the CEC charter as follows:

TIMI Major CABG-related: Any hemorrhage that met any of the following criteria:

a. Fatal bleeding (i.e., bleeding that directly results in death), or
b. Peri-operative intracranial bleeding, or
c. Re-operation following closure of the sternotomy incision for the purpose of controlling bleeding, or
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.

As such, TIMI major CABG-related bleeding is the only appropriate categorization for assessment of bleeding events due to CABG. In addition, the number of subjects requiring transfusion and re-operation, as well as the extent of chest tube drainage was captured in the electronic case report forms (eCRF) to facilitate evaluation of the outcome of the bleeding events.

Bleeding events were captured by the study site investigator and adjudicated by an independent CEC.

Analysis of the pre-specified bleeding endpoints, individual bleeding events, and other (non-bleeding) adverse events are presented in **Sections 7.4, 8.6** (Overall Population) 9.4 (Proposed Label Population) and Appendix 1.

6.3.5 Trial Oversight Committees in the Phase 3 Studies

One independent (i.e., no affiliation with study Sponsor) Data Safety Monitoring Board to protect the rights, safety, and well-being of subjects, and one independent Clinical Events Committee (CEC) reviewed and adjudicated each suspected efficacy and bleeding endpoint event while blinded to treatment for both Phase 3 studies. The principal committees formed to oversee conduct of the Phase 3 studies included a Steering Committee and an Executive Committee for each study.

6.3.6 Trial Conduct

The TRACER study was coordinated by the Duke Clinical Research Institute (DCRI). DCRI is an academic research organization (ARO) and an Institute within the Duke University School of Medicine, Durham, North Carolina, United States of America (USA).

The TRA 2°P-TIMI 50 study was coordinated by TIMI, an ARO of Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA.

These AROs provided intellectual and support services with respect to the design and operation of the respective clinical studies, independent analysis of study data, and also shared responsibilities for the coordination of the common DSMB and CEC.

6.3.7 Vorapaxar Exposure in the Phase 3 program

Vorapaxar was evaluated for safety in 19,632 subjects in the Phase 3 program (13,186 subjects in TRA 2°P-TIMI 50 and 6446 in TRACER). Of the 13,186 subjects exposed in TRA 2°P-TIMI 50, 2187 received vorapaxar for more than 3 years.

7 ACUTE CORONARY SYNDROME TRIAL - TRACER

7 ACUTE CORONARY SYNDROME TRIAL - TRACER

7.1 TRACER Trial Overview

TRACER was a multicenter, global, randomized, double-blind, placebo-controlled, balanced-parallel-groups investigation of orally administered vorapaxar in men and women at least 18 years old with clinical manifestation and objective evidence of non-ST-segment-elevation acute coronary syndrome (NSTEACS), conducted in conformance with Good Clinical Practice. Randomized treatment assignment was stratified by use of or intent to use a GP IIb/IIIa inhibitor and type of antithrombin used or anticipated to be used (heparin vs. direct thrombin inhibitor).

Subjects were to be enrolled into the study after the index event (which was the ACS event that qualified the subject for inclusion into the study) and before discharge from acute care for the index event. The interval between continuous acute care for the index event, beginning with the initial presentation and ending with discharge from acute care was determined to be the index hospitalization period.

Upon enrollment, subjects were to receive randomized allocation of treatment. A loading dose of vorapaxar 40 mg or matching placebo was to be administered at the time of randomized treatment assignment, followed by daily maintenance dosing with 2.5 mg or matching placebo beginning the next calendar day after administration of the loading dose. Following randomized treatment assignment, subjects were to return after 30 days, 4, 8, and 12 months, and every 6 months thereafter for scheduled evaluations until the end of the study. Minimum duration of follow-up was intended to be one year.

On January 8, 2011, the combined Data Safety Monitoring Board (DSMB) for TRACER and TRA 2°P - TIMI 50 recommended discontinuation of study drug in all subjects in TRACER, and close-out of the trial (the DSMB recommendation for the TRA-2P TIMI 50 trial are discussed in **Section 8.2.1**). The Executive Committee and the Sponsor accepted the recommendation of the DSMB. A communication dated January 13, 2011 was sent to all study sites in TRACER directing them to stop treatment in all subjects still receiving treatment, and to close out the study in a timely manner due to an excess of bleeding, including intracranial hemorrhage (ICH) and that there was sufficient events to make a determination of efficacy.

7.2 TRACER Population

The study population was comprised of moderate-risk to high-risk subjects with a clinical manifestation of non-ST-segment-elevation acute coronary syndrome (NSTEACS) according to the criteria shown in Table 4.

Subjects were to be enrolled during the index hospitalization period as early as possible after the index event and before discharge from acute care for the index event.

Table 5 provides a brief description of demographics and medical history for the TRACER subjects. 12944 subjects received randomized treatment assignment: 6471 placebo and 6473 vorapaxar (Intent to Treat [As Randomized] population). Included were 9312 men and 3632

(28%) women aged 29 to 94 years with a median age of 64; 17% of patients were 75 or older. Over 70% of patients had no prior history of myocardial infarction. Just under one-third of patients were diabetic and few patients had prior history of stroke (4%). A history of heart failure was reported in under 10% and 12% had CKD stage 3 GFR levels or worse.

Table 5 TRACER Demographics and Medical History

(Protocol No. P04736)

	Placebo N=6741	Vorapaxar N=6473
Age (yr)		
Mean	64.4±9.98	64.4±9.95
Median	64.0	64.0
25th-75th Percentile	58-72	58-71
Age, n (%)		
<65	3369 (52.1)	3390 (52.4)
65-75	2006 (31.0)	1973 (30.5)
≥75	1096 (16.9)	1110 (17.1)
Gender, n (%)		
Female	1822 (28.2)	1810 (28.0)
Race, n (%)		
White	5510 (85.1)	5529 (85.4)
Asian	533 (8.2)	523 (8.1)
Black/African American	161 (2.5)	151 (2.3)
Other	249 (3.8)	253 (3.9)
Medical History, n (%)		
Myocardial Infarction	1890 (29.2)	1901 (29.4)
Stroke	262 (4.0)	291 (4.5)
Diabetes Mellitus	2030 (31.4)	2040 (31.5)
Heart Failure	635 (9.8)	574 (8.9)
CrCl <60 mL/min 1.73 m^2	831 (12.8)	836 (12.9)

Nearly 60% of subjects in the TRACER trial were naïve to antiplatelet therapy and only 10% had received both aspirin and thienopyridine prior to the index hospitalization **(Table 6)**. As will be noted later in this document, this circumstance was distinctly different in the TRA 2P-TIMI -50 population where nearly all (98%) subjects had received aspirin and more than 75% of patients had received and tolerated dual antiplatelet therapy (aspirin and a thienopyridine) and at the time of randomization to vorapaxar or placebo.

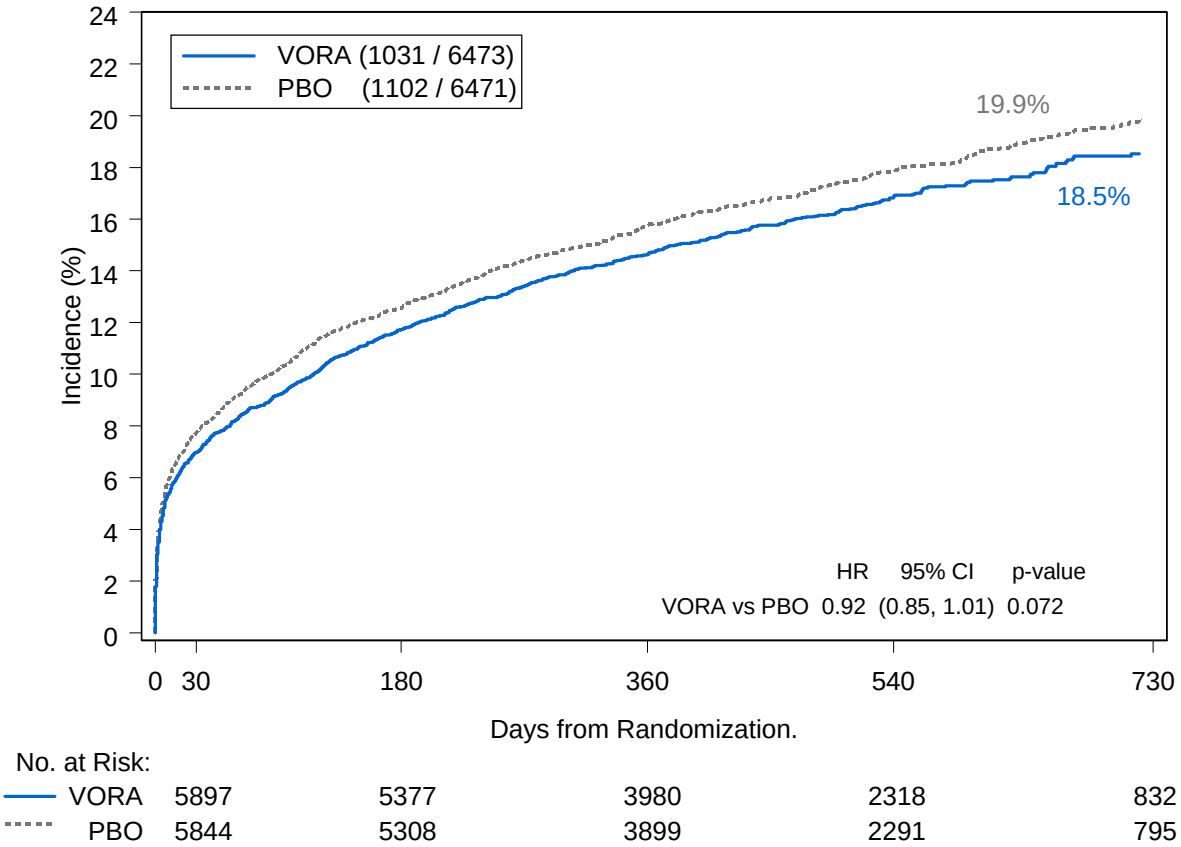
Table 6 Subject Use of Antiplatelet Therapy Prior to Index Hospitalization in the TRACER Trial (All Randomized Subjects)

	Placebo (N=6471)	Vorapaxar (N=6473)	Total (N=12994)
Dual Antiplatelet Therapy (Aspirin and Thienopyridine)	636 (9.8)	642 (9.9)	1278 (9.9)
Single Antiplatelet Therapy (Aspirin or Thienopyridine)	1970 (30.4)	1966 (30.4)	3936 (30.4)
Naïve to Antiplatelet Therapy (None)	3865 (59.7)	3865 (59.7)	7730 (59.7)

7.3 TRACER Results for Primary and Secondary Efficacy Endpoints

The findings for the primary efficacy composite endpoint (first occurrence of CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) show 2-year Kaplan-Meier event rates of 18.5% in the vorapaxar group compared with 19.9% in the placebo group. These results were not statistically significant (hazard ratio [HR], 0.92; 95% CI, 0.85 to 1.01; p = 0.072) **(Figure 9)**.

For the key secondary efficacy composite endpoint (first occurrence of CV death, MI, or stroke), 2-year Kaplan-Meier event rates of 14.7% in the vorapaxar group versus 16.4% in the placebo group were observed (HR, 0.89; 95% CI, 0.81 to 0.98; P = 0.018) **(Figure 10)**. While the observed nominal p-value was 0.018, these results are not statistically significant after adjustment under the pre-specified multiplicity strategy.



No. at Risk:

VORA	5897	5377	3980	2318	832
PBO	5844	5308	3899	2291	795

Figure 9 Kaplan-Meier Estimate of Time to the First Occurrence of Primary Efficacy Endpoint (CV Death/MI/Stroke/RIR/UCR)
All Subjects in the Intent to Treat Population
(Event Accrual Period: Randomization to Last Visit)
(Protocol No. P04736)

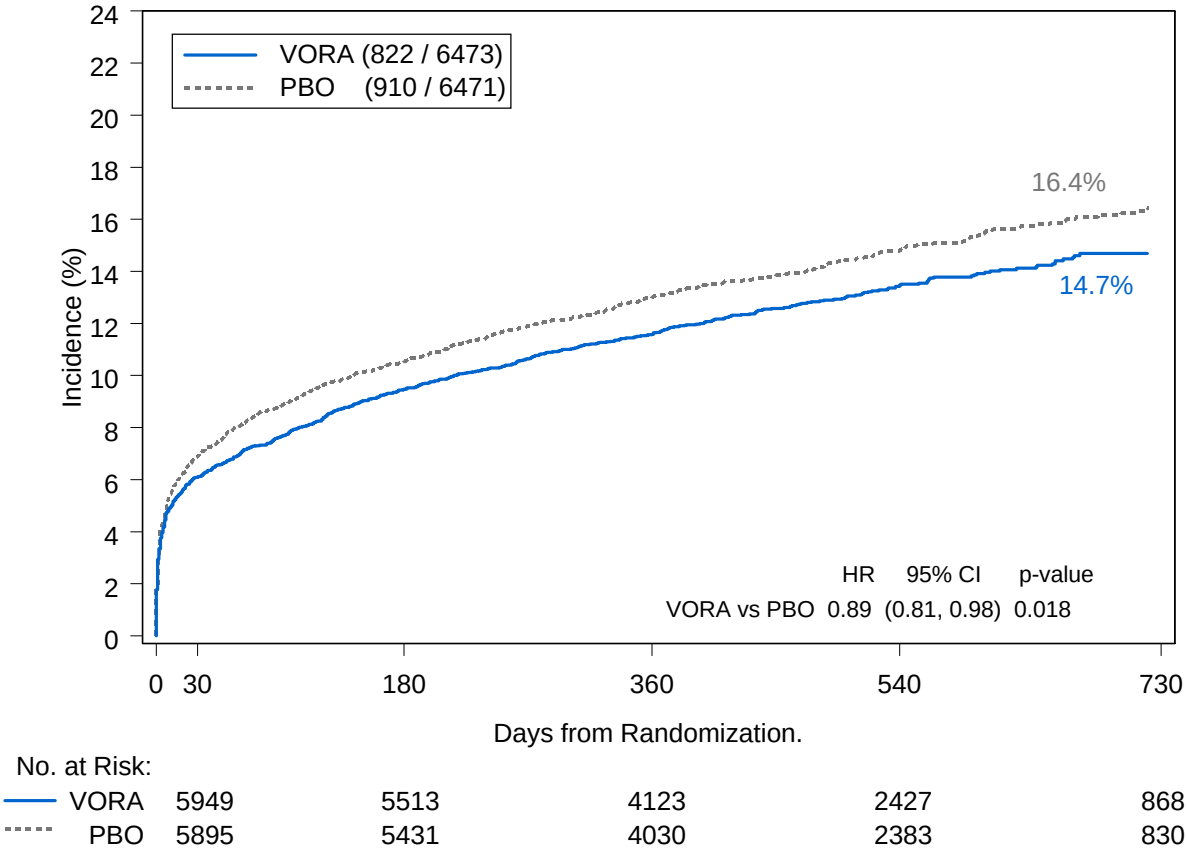


Figure 10 Kaplan-Meier Estimate of Time to the First Occurrence of Key Secondary Efficacy Endpoint (CV Death/MI/Stroke) All Subjects in the Intent to Treat Population (Event Accrual Period: Randomization to Last Visit) (Protocol No. P04736)

7.4 TRACER Safety Endpoints – Bleeding

Bleeding events in TRACER were more frequent during the initial 30 days following randomization compared to the period after the first 30 days of treatment. Results for the protocol-pre-specified secondary and exploratory bleeding endpoints related to safety were examined over the study and are described as follows. In the TRACER trial, there was a statistically significant increase in the risk of ICH (1.0% vorapaxar vs. 0.4% placebo, HR 2.52; 95% CI 1.48-4.29) and fatal bleeding (0.5% vorapaxar vs. 0.3% placebo, HR 1.81; 95% CI 0.98 - 3.34) in the vorapaxar group compared to placebo **(Table 7)**.

Spontaneous ICH occurred in 24 vorapaxar subjects vs. 9 placebo subjects and traumatic ICH occurred in 17 vorapaxar subjects and 6 placebo subjects.

For all other bleeding endpoints, the risk of bleeding was greater for subjects on vorapaxar than for subjects on placebo. The differences between the two treatment groups were statistically significant for most of the GUSTO and TIMI categories, including for the secondary endpoints of GUSTO moderate or severe bleeding and clinically significant bleeding, and for intracranial hemorrhage as described in **Table 7**.

Table 7 TRACER Bleeding Endpoints with Annualized Event Rates: Overall Population: Event Accrual Period: Randomization to Last Visit

	Placebo (n=6441)			Vorapaxar (n=6446)				
	Subjects with Events (%)	KM %[a]	Annualized Event Rate	Subjects with Events (%)	KM %[a]	Annualized Event Rate	Hazard Ratio [b,c] (95% CI)	p-value[c]
GUSTO Bleeding Categories								
Severe or Moderate	332 (5.2%)	5.8%	4.0%	449 (7.0%)	7.6%	5.5%	1.36 (1.18 - 1.57)	<0.001
Severe	106 (1.6%)	1.9%	1.2%	172 (2.7%)	3.0%	2.0%	1.62 (1.27 - 2.06)	<0.001
Moderate	236 (3.7%)	4.1%	2.8%	296 (4.6%)	5.0%	3.5%	1.26 (1.06 - 1.49)	0.009
TIMI Bleeding Categories								
Major or Minor	248 (3.9%)	4.4%	3.0%	375 (5.8%)	6.5%	4.5%	1.52 (1.29 - 1.78)	<0.001
Major	162 (2.5%)	2.9%	1.9%	242 (3.8%)	4.1%	2.9%	1.49 (1.22 - 1.82)	<0.001
Minor	92 (1.4%)	1.6%	1.1%	144 (2.2%)	2.6%	1.7%	1.56 (1.20 - 2.03)	<0.001
Clinically Significant[d]	813 (2.6%)	14.6%	10.5%	1128 (17.5%)	19.5%	15.2%	1.41 (1.29 - 1.54)	<0.001
Non CABG Related Major or Minor	182 (2.8%)	3.3%	2.2%	292 (4.5%)	5.2%	3.5%	1.61 (1.34 - 1.94)	<0.001
Major	95 (1.5%)	1.8%	1.1%	157 (2.4%)	2.8%	1.8%	1.65 (1.28 - 2.13)	<0.001
Minor	92 (1.4%)	1.6%	1.1%	144 (2.2%)	2.6%	1.7%	1.56 (1.20 - 2.03)	<0.001
TIMI Major CABG Related	68 (1.1%)	1.1%	0.8%	89 (1.4%)	1.4%	1.0%	1.31 (0.95 - 1.79)	0.098

Table 7 TRACER Bleeding Endpoints with Annualized Event Rates: Overall Population: Event Accrual Period: Randomization to Last Visit

	Placebo (n=6441)			Vorapaxar (n=6446)				
	Subjects with Events (%)	**KM %[a]**	**Annualized Event Rate**	**Subjects with Events (%)**	**KM %[a]**	**Annualized Event Rate**	**Hazard Ratio [b,c] (95% CI)**	**p-value[c]**
Other categories								
Intracranial Hemorrhage	19 (0.3%)	0.4%	0.2%	48 (0.7%)	1.0%	0.6%	2.52 (1.48 - 4.29)	<0.001
Fatal ICH	6 (0.1%)	0.2%	0.1%	13 (0.2%)	0.3%	0.2%	2.15 (0.82 - 5.66)	0.120
Fatal Bleeding[e]	16 (0.2%)	0.3%	0.2%	29 (0.4%)	0.5%	0.3%	1.81 (0.98 - 3.34)	0.056

a. Kaplan-Meier estimate at 730 days.

b. Hazard Ratio is vorapaxar group vs. placebo group.

c. Hazard Ratio and p-value were calculated based on Cox proportional hazards model with covariates treatment and stratification factors (use of GP IIb/IIIa inhibitors and type of antithrombin).

d. TIMI major or minor bleeding or bleeding that requires unplanned medical or surgical treatment, or unplanned evaluation through laboratory testing.

e. Patient 520303 in the vorapaxar group had a fatal bleed event. Since the fatal bleed event occurred after the last visit date for the patient, the event was not included in the analysis. When including this fatal bleed event, the HR is 1.87 (1.02 - 3.44) and p-value is 0.042)

7.5 TRACER Summary and Conclusions

It is apparent from the TRACER study results that the initiation of vorapaxar (administered with a loading dose of 40 mg and then maintained at 2.5 mg/day) in subjects with NSTEACS, was associated with unacceptably high risk for ICH that was not balanced by sufficient efficacy in this acute coronary syndrome population.

A discussion of the relevance of TRACER with regard to the use of vorapaxar in a chronic stable population of patients following an MI is provided in **Section 11**. Additional information is presented in **Appendix 1** including a side-by side comparison of patient characteristics and safety from TRACER and TRA 2°P – TIMI 50, a condensed integrated summary of safety, and a presentation of bleeding using pooled data from TRACER and TRA 2°P – TIMI 50 (as requested by the FDA).

8 SECONDARY
PREVENTION TRIAL - TRA
2ÁP - TIMI 50

8 SECONDARY PREVENTION TRIAL - TRA 2°P - TIMI 50

The pivotal Phase 3 study that supports the proposed indication is TRA 2°P - TIMI 50. As depicted in **Figure 11**, TRA 2°P - TIMI 50 was a multicenter, international, randomized, double-blind, placebo-controlled, fixed-dose, balanced parallel-groups comparison of placebo versus vorapaxar 2.5 mg taken orally each day in men and women at least 18 years old, in addition to standard of care, conducted in conformance with Good Clinical Practice. Randomized treatment assignment was stratified by qualifying condition at entry –CAD, CVD, or PAD – and planned use of a thienopyridine (none versus already being taken or to be added).

In the TRA 2°P-TIMI 50 trial, investigators were to follow contemporaneous applicable guidelines outlining appropriate medical therapy for subjects with established atherosclerosis, including antiplatelet therapy (e.g. aspirin, thienopyridine), lipid-modification therapy, anti-hypertensive therapy, cardiac remodeling therapy, and antianginal therapies.

The TRA 2°P-TIMI 50 clinical efficacy and safety results will be presented in **Section 8** for the Overall Population and Section 9 for the Proposed Label Population**.**

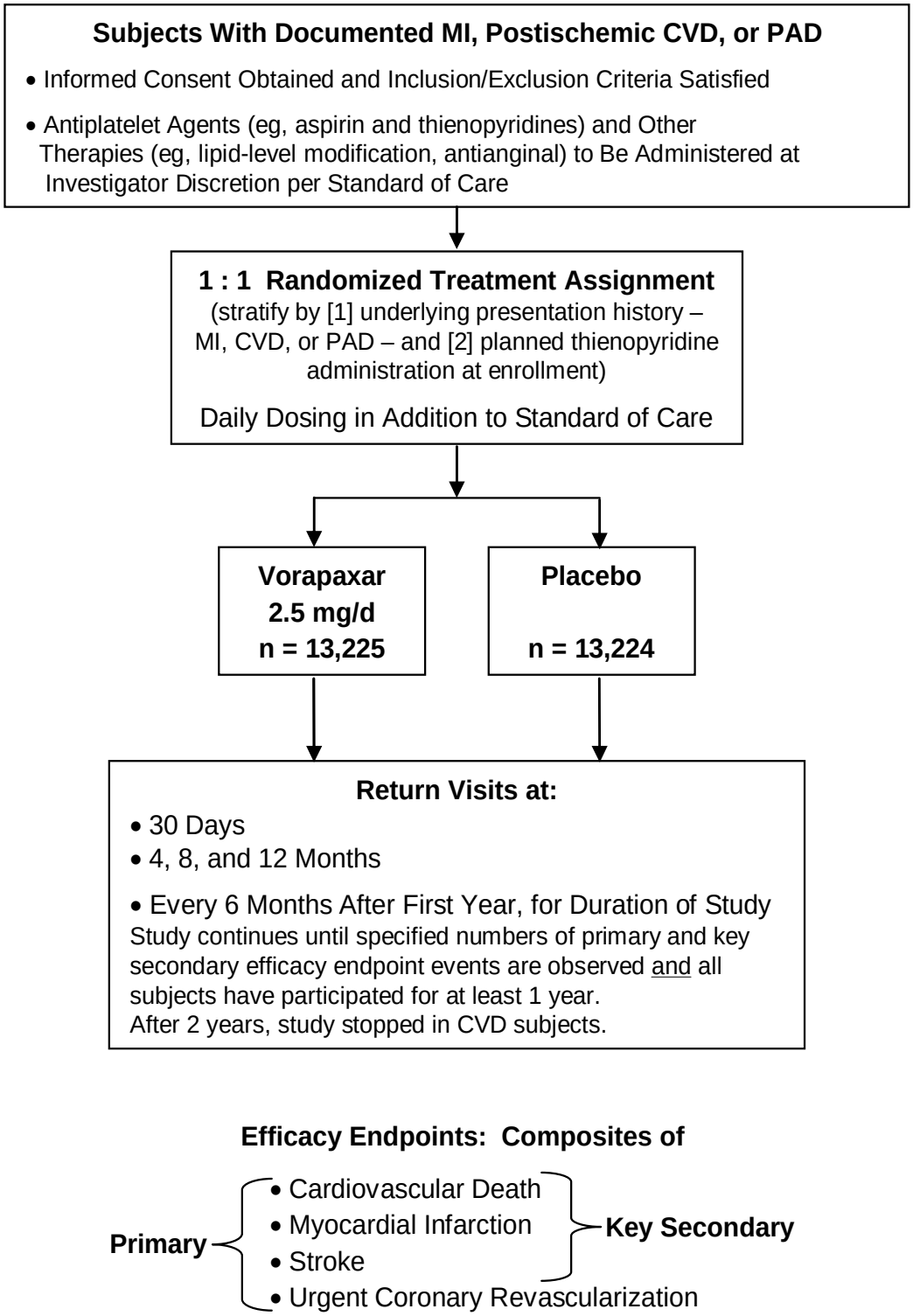


Figure 11 TRA 2°P-TIMI 50 Study Design (P04737)

8.1 TRA 2°P - TIMI 50 Overview of Statistical Methodology

The primary and key secondary efficacy endpoints and associated population and methodology for the TRA 2°P - TIMI 50 trial is as defined in the initial protocol and associated initial data analysis plan. The initial Data Analysis Plan (DAP) was finalized on November 3, 2009 to provide more detail on the proposed statistical analysis that was included in the initial protocol.

The primary efficacy analysis in TRA 2°P - TIMI 50 was based on the time from randomized treatment assignment until the first occurrence of one of the following events: CV death, MI, stroke, or UCR in the Overall Population. Data from the three strata from all randomized subjects were the basis for the primary efficacy analysis in the Overall Population.

A Cox proportional hazard (PH) model with covariates of treatment and two stratification factors (i.e. qualifying condition of CAD, stroke, or PAD, and planned thienopyridine use at the time of enrollment) was used to perform the analysis in the Overall Population. Estimates of the hazard ratios and associated 95% confidence intervals comparing placebo with vorapaxar were summarized. The key secondary efficacy endpoint (i.e. the first occurrence of CV death, MI, or stroke) was evaluated using similar methodology. Kaplan-Meier (KM) estimates for the time to the primary and key secondary efficacy endpoints were plotted. The annualized event rates were also provided.

Subgroup analyses were conducted for demographic and baseline characteristic variables such as, but not limited to, age, sex, race, and prior therapy.

The protocol-specified interim efficacy analysis was the responsibility of the Independent Statistical Group for the Data Safety Monitoring Board (DSMB) at Duke University. The final analysis was the joint responsibility of the Biostatistics group of the Sponsor and the TIMI group. The trial would have one interim analysis for overwhelming efficacy which would be performed when approximately 50% of the primary and 50% of the key secondary efficacy endpoints required for the completion of the study were available. Summaries were prepared for the DSMB by the independent statistical group. The data reviewed by the DSMB included both adjudicated and total “best available” (adjudicated plus unadjudicated) events. The Fleming-Harrington-O’Brien methodology was implemented to preserve the overall Type I error of 0.05. As calculated using software East 4, a nominal alpha level of 0.003 was pre-specified for the interim analysis. In the final analysis, at the completion of the trial both the primary and key secondary efficacy endpoints were to be tested at a level of α=0.049.

There was a single primary efficacy endpoint (composite of cardiovascular death, MI, stroke, or UCR) and one primary comparison (placebo vs. vorapaxar) defined in the primary hypothesis. Therefore, no additional adjustment for multiplicity was needed for the associated primary hypothesis testing paradigm, other than the adjustment for protocol-specified interim efficacy analysis. There was one key secondary efficacy endpoint (composite of cardiovascular death, MI, or stroke) in this study. The key secondary hypothesis was to be tested only if the primary analysis was statistically significant, and

therefore, no additional multiplicity adjustment was needed for the key secondary efficacy endpoint.

8.2 Operational Events that Affected Study Conduct

8.2.1 Data Safety Monitoring Board Recommendation

In early January 2011, the Study Chairs of P04737 (TRA 2ºP –TIMI 50) and the companion study in acute coronary syndrome P04736 (TRACER) received a communication from the DSMB dated January 8, 2011. The body of the letter was as follows:

The combined Data Safety and Monitoring Board (DSMB) of the TRACER and TRA 2ºP – TIMI 50 studies met face-to-face January 8, 2011. After considering all data of both trials the DSMB recommended the following:

1. Discontinuation of study drug in subjects with a history of stroke in the TRA 2ºP – TIMI 50 trial and continuation of the study drug as planned in all other subjects in TRA 2ºP –TIMI 50 due to increased risk of ICH. Discontinuation of study drug in subjects with prior stroke in TRA 2ºP –TIMI 50 includes stroke occurring pre and post randomization.
2. Discontinuation of study drug in all subjects in TRACER, and close-out of the trial.

The Executive Committee and the Sponsor accepted the recommendation of the DSMB, and, beginning on January 13, 2011, a series of communications was sent to the study sites to guide them on treatment discontinuation, follow-up, and communication of new risk information to subjects.

The DSMB recommended that subjects with any stroke prior to or post randomization discontinue study treatment as a result of a disproportionate number of ICHs observed in the vorapaxar group in these subjects without evidence of sufficient benefits to outweigh this risk. The Executive Committee determined that subjects randomized and stratified to the CVD stratum would also have their participation in the trial discontinued, with the exception of those subjects who experienced a stroke endpoint during the trial. Subjects in the CVD Stratum who had a new stroke during the trial were followed until the completion of the trial. For the remaining subjects with a history of stroke or stroke endpoint randomized and stratified to the CAD and PAD strata, study drug was discontinued but the subjects continued to be followed in the trial. As will be presented later in this document **(Section 8.5)**, an analysis of the data as it existed on February 1, 2011, demonstrated that if the study had been terminated in all subjects at that time, the final study conclusions would not differ.

8.2.2 Protocol Amendment and Associated Data Analysis Plan Amendment

The original Data Analysis Plan (DAP) was finalized on November 3, 2009 to provide more detail on the proposed statistical analysis. On May 13, 2011 the DAP was amended in

association with General Protocol Amendment #3. The protocol and DAP amendments occurred after the last DSMB meeting that took place in January 2011, but prior to database lock on January 9, 2012. **The protocol amendment did not alter the original pre-specified primary and key secondary endpoints, nor the approach that all randomized subjects would be included in the analysis of these endpoints.** In the protocol amendment and associated revised DAP, additional populations to examine were identified, given the information from the DSMB that subjects with a history of stroke did not display a positive benefit/risk ratio.

General Amendment #3 to the protocol, and the associated DAP amendment described the following changes:

- Defined Supplementary Secondary Objectives/Endpoints Related to Efficacy.
- Defined an on-treatment analysis for primary and key secondary efficacy endpoints.
- Defined TIMI major CABG related bleeding, GUSTO severe CABG related bleeding and intracranial hemorrhage exploratory safety endpoints.

While this amendment did not alter the primary or key secondary objectives of the study, it did describe changes related to the DSMB recommendation.

Supplementary Secondary Objectives Related to Efficacy were described in the amendment, and included evaluation of the risk of the original primary (cardiovascular death, MI, stroke, and urgent coronary revascularization) and secondary (cardiovascular death, MI, and stroke) composite endpoints in each of the following subsets of subjects:

- 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
- 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

The amendment included the restructuring of the other secondary endpoints to include the following individual components: cardiovascular death; MI; urgent coronary revascularization; all-cause death; and stroke.

The amendment also included the addition of more exploratory endpoints, including TIMI major CABG related bleeds, GUSTO severe CABG related bleeds, and Intracranial hemorrhage, subarachnoid hemorrhage, and subdural/epidural.

Further, the amendment described an on-treatment analysis to be performed using the same method for the primary and key secondary efficacy variables. For the purpose of this analysis, "on-treatment" is the interval from the first dose to the last recorded dose + 3 days.

8.2.3 Additional CEC Adjudication of ICH

Due to the concern communicated by the DSMB in January 2011 regarding the incidence of ICH associated with vorapaxar in the stroke population, the events of ICH reported in the trial were evaluated in greater depth. Therefore, prior to database lock, the following additional details pertaining to ICH were adjudicated by the CEC: location of intracranial bleed, associated potential provoking factors, and whether the ICH was fatal.

8.2.4 Pre-specification of Analyses and Associated Coverage under the Multiple Testing Plan

For the purpose of clarity, in the TRA 2ºP –TIMI 50 Clinical Summary Report submitted by the Sponsor, the efficacy analyses were categorized into three groups based on the level of pre-specification of the analyses and coverage under the pre-specified multiple testing paradigm.

Group 1: Analyses were pre-specified in the original study protocol and initial data analysis plan (DAP) and were covered under a multiplicity adjustment procedure:

- The primary efficacy endpoint: composite of CV death, MI, stroke or UCR.
- The key secondary efficacy endpoint: the composite of CV death, MI or stroke.

Other secondary efficacy endpoints included the evaluation of the occurrence of the following composites or individual components as indicated below, to be tested in a step down fashion:

- all-cause death, MI, stroke, and urgent coronary revascularization
- cardiovascular death and MI
- cardiovascular death, MI, stroke, urgent coronary revascularization, or urgent hospitalization for vascular cause of ischemic nature
- all-cause death, MI, stroke, any revascularization (including amputation for ischemic limb)
- cardiovascular death, MI, stroke, any revascularization (including amputation for ischemic limb), or urgent hospitalization for vascular cause of ischemic nature
- the individual components of the composite primary efficacy endpoint
    - cardiovascular death
    - MI
    - stroke
    - urgent coronary revascularization
- all-cause death

Group 2: Analyses were covered in the original study DAP unless described above as included with the amendment. Group 2 analyses were not covered under a multiplicity adjustment procedure. Significance levels associated with these analyses were to be interpreted in this context.

a) The primary and key secondary endpoints (as defined in Group 1) among subpopulations of subjects

b) Exploratory efficacy endpoints that included the first occurrence for various composite endpoints

c) The primary and key secondary endpoints for various subgroups

Group 3: Analyses that were not discussed in the initial or amended study DAP, and not covered under a multiplicity adjustment procedure. Inferential results (e.g., p-values) based on these analyses should be interpreted with caution.

8.2.5 Temporal Description of Study Events

Important milestones in the TRA 2°P-TIMI 50 study are described in **Table 8**.

The original protocol was completed on May 31, 2007 and the first subject was enrolled into the study in September 2007. There were three general amendments to the protocol as outlined below:

- General Amendment 1 was finalized on January 21, 2009. The major provision of this amendment was to allow the CEC to recommend stopping enrollment of subjects with a primary diagnosis of CAD, CVD, or PAD when the total of the subset reached the anticipated proportion of the planned total enrollment (70%, 15%, and 15%, respectively).

- General Amendment 2 was finalized on March 23, 2009. The major provision of this amendment was to allow for an increase in the proposed sample size on the basis of evaluation of the blinded overall event rate before the end of enrollment of subjects into the study. This sample size adjustment was based on an estimated pooled event rate of 3.15% for one year. The placebo event rate was predicted to be 3.4% and the treatment rate to 2.9%, which is equivalent to a risk reduction of 15%. The calculations and forward looking assumptions led to a recalculation of 24,322 subjects with 1402 major secondary endpoints needed.
- General Amendment 3 was finalized on March 10, 2011 after the DSMB meeting that recommended discontinuation of study drug in subjects with a history of stroke in the trial and continuation of the study drug as planned in all other subjects in this trial. Also, discontinuation of study drug in subjects with prior stroke included stroke occurring pre and post randomization. The major provisions were to formalize discontinuation of treatment in subjects with a prerandomization history or postrandomization occurrence of stroke (following a recommendation by the DSMB), identify follow-up procedures for these subjects, and add supplementary endpoints related to efficacy and supporting analyses.

The Data Analysis Plan was finalized on November 03, 2009 to provide more detail on the proposed statistical analysis, and was amended on July 22, 2011 following the DSMB recommendations.

The other notable milestones below involved the unscheduled DSMB review on January 8 2011 (discussed in **Section 8.2.1**) and the subsequent EC decision to discontinue and complete the CVD stratum on January 13, 2011. The final visit phase began on August 1, 2011 for the CAD/PVD strata with study end December 23, 2011.

Table 8 TRA 2°P-TIMI 50 Key Study Milestones

Key Study Milestone	Date Achieved
Study Initiation	09/26/2007
Enrollment Cap (CAD/CVD/ PAD- 70:15:15) Protocol Amendment #1	1/21/2009
Sample Size Increase	03/06/2009
Protocol Amendment #2	03/23/2009
Data Analysis Plan finalized	11/03/2009
Full Enrollment	11/12/2009
Planned Interim Analysis scheduled to occur when 50% of potential endpoints accrued)	02/24/2010
Unplanned DSMB Safety Review	12/15/2010
DSMB recommendation to terminate TRACER and discontinue study therapy in TRA 2ºP - TIMI50 subjects with history of stroke	01/13/2011
Protocol Amendment #3	03/10/2011
Data Analysis Plan Amendment	07/22/2011
Study Close-out Phase begins	08/01/2011
Last Visit for Last Subject for TRA 2ºP – TIMI 50	12/23/2011
Database Lock	01/09/2012

8.3 Overall Population Baseline Characteristics

The Overall Population is the ITT population that was randomized to the vorapaxar or placebo groups. The study included subjects with evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems in the hierarchical order as listed.

26,449 subjects were allocated to randomized treatment assignment: 13,224 placebo and 13,225 vorapaxar. Included were 20,123 men (76%) and 6,326 (24%) women aged 21 to 95 years. There were 17,779 (67%) subjects with CAD, 4,883 (18%) with CVD, and 3,787 (14.3%) with PAD as the qualifying condition. These numbers approximated the enrollment targets for the three strata CAD (70%), CVD (15%) and PAD (15%) specified in the trial design.

In TRA 2°P-TIMI 50, subjects were stratified by qualifying condition at entry –CAD, CVD, or PAD – and planned use of a thienopyridine. Fifty-eight percent of subjects were assigned to the 'planned thienopyridine administration during the study' stratum. In the study, the qualifying and stratifying conditions were well balanced between the treatment groups at entry.

As noted in **Table 9**, subjects were predominantly white (87%), male (approximately 76%), and a median age of 61 years. Additionally, 11% were over 75 years old. Median body weight for subjects was 81 kg with 92% of subjects having a weight ≥ 60 kg. Median body mass index was 27.6 kg/m^2, in the midrange of 'overweight' (25 to <30 kg/m^2).

Population characteristics were well balanced between the two treatment groups. Approximately 69% of subjects had a history of hypertension and approximately 83% had a history of hyperlipidemia. Subjects were well treated at randomization; mean blood pressure was 133/78 mm Hg and the mean calculated LDL-Cholesterol (LDL-C) was 84 mg/dL. Approximately 70% of the subjects reported an MI within the past year, 22% of subjects had a prior history of stroke, approximately 4% of subjects had a prior TIA, and 19% of subjects had a history of PAD. Twenty- five percent of subjects had a history of diabetes. More than 57% of subjects had a prior PCI procedure and 13% of subjects had a prior CABG procedure.

Table 9 TRA 2°P – TIMI 50 Baseline Demographics, Disease Characteristics, and Concomitant Medications: All Randomized Subjects

(Protocol No. P04737)

Characteristic[a]	Placebo (n=13224)	Vorapaxar (n=13225)	Total (n=26449)
Primary Enrollment Stratum			
Coronary Artery Disease (CAD)[b]	8881 (67.2)	8898 (67.3)	17779 (67.2)
Cerebrovascular Disease (CVD)[c]	2448 (18.5)	2435 (18.4)	4883 (18.5)
Peripheral Arterial Disease (PAD)[d]	1895 (14.3)	1892 (14.3)	3787 (14.3)
Planned Thienopyridine Administration			
No	5545 (41.9)	5548 (42.0)	11093 (41.9)
Yes	7679 (58.1)	7677 (58.0)	15356 (58.1)
Sex			
Male	10052 (76.0)	10071 (76.2)	20123 (76.1)
Female	3172 (24.0)	3154 (23.8)	6326 (23.9)
Age (y)			
Mean (SD)	60.9 (10.84)	61.0 (10.90)	60.9 (10.87)
Median	61.0	61.0	61.0
25th to 75th Percentile	53 - 69	53 - 69	53 - 69
Min – Max	21 - 93	24 - 95	21 - 95
Age Category			
<65 y	8273 (62.6)	8188 (61.9)	16461 (62.2)
65-<75 y	3445 (26.1)	3523 (26.6)	6968 (26.3)
≥75 y	1506 (11.4)	1514 (11.4)	3020 (11.4)
Race			
White	11524 (87.1)	11562 (87.4)	23086 (87.3)
Non-White	1695 (12.8)	1656 (12.5)	3351 (12.7)
Missing	5 (<0.1)	7 (0.1)	12 (<0.1)
Weight (kg)			
Mean (SD)	82.75 (17.27)	82.29 (16.88)	82.52 (17.08)
Median	81.0	81.0	81.00
25th to 75th Percentile	71.0 - 92.6	71.0 - 92.0	71.0 - 92.1
Min – Max	30.0 - 197.3	34.8 - 188.0	30.0 - 197.3
Missing	32 (0.2)	19 (0.1)	51 (0.2)
Weight Category			
<60 kg	921 (7.0)	931 (7.0)	1852 (7.0)
≥60 kg	12271 (92.8)	12275 (92.8)	24546 (92.8)

Table 9 TRA 2°P – TIMI 50 Baseline Demographics, Disease Characteristics, and Concomitant Medications: All Randomized Subjects

(Protocol No. P04737)

Characteristic[a]	Placebo (n=13224)	Vorapaxar (n=13225)	Total (n=26449)
Systolic Blood Pressure (mm Hg)			
Mean (SD)	133.4 (19.42)	133.5 (19.53)	133.5 (19.48)
Median	131.0	131.0	131.0
25th to 75th Percentile	120 - 145	120 - 146	120 - 145
Min – Max	70 - 221	68 - 221	68 - 221
Missing (n)	40	29	69
Diastolic Blood Pressure (mm Hg)			
Mean (SD)	78.1 (10.81)	78.0 (10.87)	78.0 (10.84)
Median	79.0	79.0	79.0
25th to 75th Percentile	70 - 85	70 - 85	70 - 85
Min – Max	35 - 130	10 - 122	10 - 130
Missing (n)	40	33	73
Renal Insufficiency			
CrCl <60 mL/min	1735 (13.1)	1803 (13.6)	3538 (13.4)
CrCl ≥60 mL/min	11295 (85.4)	11234 (84.9)	22529 (85.2)
Not Able to Calculate CrCl	194 (1.5)	188 (1.4)	382 (1.4)
eGFR <60 mL/min•1.73m^2	1972 (14.9)	2112 (16.0)	4084 (15.4)
eGFR ≥60 mL/min•1.73m^2	11085 (83.8)	10944 (82.8)	22029 (83.3)
Not Able to Calculate eGFR	167 (1.3)	169 (1.3)	336 (1.3)
Geographic Region			
North America	3920 (29.6)	3916 (29.6)	7836 (29.6)
Latin America	1646 (12.4)	1648 (12.5)	3294 (12.5)
Europe 1	5604 (42.4)	5612 (42.4)	11216 (42.4)
Europe 2	1319 (10.0)	1317 (10.0)	2636 (10.0)
Asia/Pacific	389 (2.9)	388 (2.9)	777 (2.9)
Australia/New Zealand	346 (2.6)	344 (2.6)	690 (2.6)
Diabetes Mellitus			
No	9864 (74.6)	9856 (74.5)	19720 (74.6)
Yes	3356 (25.4)	3368 (25.5)	6724 (25.4)
Missing	4 (<0.1)	1 (<0.1)	5 (<0.1)

Table 9 TRA 2°P – TIMI 50 Baseline Demographics, Disease Characteristics, and Concomitant Medications: All Randomized Subjects

(Protocol No. P04737)

Characteristic[a]	Placebo (n=13224)	Vorapaxar (n=13225)	Total (n=26449)
Hypertension			
No	4092 (30.9)	4178 (31.6)	8270 (31.3)
Yes	9127 (69.0)	9047 (68.4)	18174 (68.7)
Missing	5 (<0.1)	0	5 (<0.1)
Hyperlipidemia			
No	2209 (16.7)	2241 (16.9)	4450 (16.8)
Yes	11011 (83.3)	10983 (83.0)	21944 (83.2)
Missing	4 (<0.1)	1 (<0.1)	5 (<0.1)
Prior Stroke			
No	10344 (78.2)	10355 (78.3)	20699 (78.3)
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 Myocardial Infarction			
No	3631 (27.5)	3654 (27.6)	7284 (27.5)
Yes	9586 (72.5)	9570 (72.4)	19156 (72.4)
Prior ACS			
No	3309 (25.0)	3333 (25.2)	6642 (25.1)
Yes	9907 (74.9)	9891 (74.8)	19798 (74.9)
Prior PCI			
No	5566 (42.1)	5623 (42.5)	11189 (42.3)
Yes	7652 (57.9)	7600 (57.5)	15252 (57.7)
Prior CABG			
No	11467 (86.7)	11447 (86.6)	22914 (86.6)
Yes	1749 (13.2)	1776 (13.4)	3525 (13.3)
Vascular "Beds" Involved Based on Cardiovascular History[e]			
Coronary Bed	10362 (78.4)	10329 (78.1)	20691 (78.2)
Cerebrovascular Bed	3669 (27.7)	3674 (27.8)	7343 (27.8)
Peripheral Bed	2944 (22.3)	2901 (21.9)	5845 (22.1)
Only One Bed	10091 (76.3)	10157 (76.8)	20248 (76.6)
Only Two Beds	2503 (18.9)	2451 (18.5)	4954 (18.7)
All Three Beds	626 (4.7)	615 (4.7)	1241 (4.7)
No Beds	0	2 (<0.1)	2 (<0.1)

Table 9 TRA 2°P – TIMI 50 Baseline Demographics, Disease Characteristics, and Concomitant Medications: All Randomized Subjects

(Protocol No. P04737)

Characteristic[a]	Placebo (n=13224)	Vorapaxar (n=13225)	Total (n=26449)
Missing/Unable to Determine	4 (<0.1)	0	4 (<0.1)
History of Cigarette Smoking			
No	3936 (29.8)	3914 (29.6)	7850 (29.7)
Yes	9284 (70.2)	9311 (70.4)	18595 (70.3)
Missing	4 (<0.1)	0	4 (<0.1)
Any Thienopyridine[f]	8238 (62.3)	8204 (62.0)	16442 (62.2)
Any Clopidogrel	8124 (61.4)	8076 (61.1)	16200 (61.2)
Any Aspirin	12363 (93.5)	12371 (93.5)	24734 (93.5)
Aspirin Plus a Thienopyridine	7659 (57.2)	7504 (56.7)	15073 (57.0)
Aspirin and Any Other Antiplatelet Agent[g]	8242 (62.3)	8174 (61.8)	16416 (62.1)
Any Beta-adrenergic Antagonist	9232 (69.8)	9128 (69.0)	18360 (69.4)
Any Angiotensin Converting Enzyme Inhibitor or Combination	7953 (60.1)	7852 (59.4)	15805 (59.8)
Any Angiotensin II Receptor Antagonist or Combination	2123 (16.1)	2051 (15.5)	4174 (15.8)
Any Lipid Medication	12131 (91.7)	12032 (91.0)	24163 (91.4)
Any Statin	11927 (90.2)	11810 (89.3)	23737 (89.7)

[a] Data presented as number (%) of subjects unless otherwise noted

[b] 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

[c] Ischemic (presumed thrombotic) CVD as indicated by a history of ischemic stroke (hospitalized with final diagnosis of non-hemorrhagic 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

[d] 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

[e] Definitions of "beds" based on stated cardiovascular history
Coronary bed includes history of known coronary stenosis, angina, MI, PCI, or CABG.
Cerebrovascular bed includes history of known carotid stenosis, TIA, stroke type non-hemorrhagic or unknown, percutaneous carotid intervention, or carotid endarterectomy.
Peripheral bed includes history of PAD, claudication, peripheral arterial revascularization, or amputation related to limb ischemia.

[f] Any thienopyridine could have included clopidogrel, ticlopidine, prasugrel; clopidogrel was the most common thienopyridine used in this trial.

[g] Any other antiplatelet agent could have included any thienopyridine, dipyridamole, cilostazol, glycoprotein IIb/IIIa inhibitor.

8.4 Disposition, Permanent Discontinuation of Study Drug, Lost to Follow-up in the Overall Population

The disposition of the Overall Population is shown in the CONSORT diagram below **(Figure 12)**. Subjects in the CVD stratum were discontinued early (7-8 months before all other patients were called in for their last visit) at the direction of the Executive Committee and were counted as having completed the study if they had a final visit. After the DSMB recommendation to discontinue treatment in subjects with a history of stroke, the Executive Committee decided to discontinue subjects with a history of stroke from the trial if they did not have a stroke endpoint during the trial. Any subject (from any strata) who had a stroke during the study was followed until the end of the study. Although subjects whose final study visit were possibly impacted by DSMB/EC action consist of nearly 16% of the Overall Population, in January of 2011, the total duration (patient-years) of the potentially missed study follow-up for these subjects were expected to be only about 3% of the total study exposure for the overall study. As will be presented later in this document (**Section 8.5**), an analysis of the data as it existed on February 1, 2011, before Protocol Amendment 3 took effect, demonstrated that if the study had been terminated in all subjects at that time, the final study conclusions would not differ.

Importantly, discontinuations from the study were well balanced between groups. Slightly more subjects discontinued study drug prematurely in the vorapaxar group (n=3145) compared to placebo (n=2948), with the specific reasons provided in the diagram below.

Of the 26,449 subjects enrolled, 32 (0.1%) were lost to follow-up, and 532 (2.0%) withdrew consent for follow-up at a median of 9 months from randomization. Of the remaining 25,885 subjects who completed follow-up according to the protocol, 98.2% had ascertainment for end point events through their final study contact, whereas 461 (1.8%) had vital status assessment only.

An alternative approach to subject accounting that addresses the consequences of Amendment 3 (DSMB/EC action regarding CVD stratum) and the specific accounting within each stratum is depicted in **Figure 13**. In this diagram, it can be seen that 87% of subjects in the CVD stratum had their final visit between January of 2011 and August 1, 2011, when the EC issued notice to sites that the trial was to end and all subjects should be contacted for their final visit. This EC action defines August 1, 2011 as the date when all final visits should be initiated. Therefore, subjects that either died during the study or had their last visit after August 1, 2011 would be classified as having completed the study, even though a large number of patients in the CVD stratum were affected by this administrative decision (to have subjects in the CVD stratum complete their last visit prior to August 1, 2011), this represented only about 3% of total potential patient exposure in the trial. In the lowest box on the table, “Other” represents patients who had a final visit before August 1, 2011 for non-administrative reasons, such as the need for trial medication replenishment within weeks of anticipated study end.

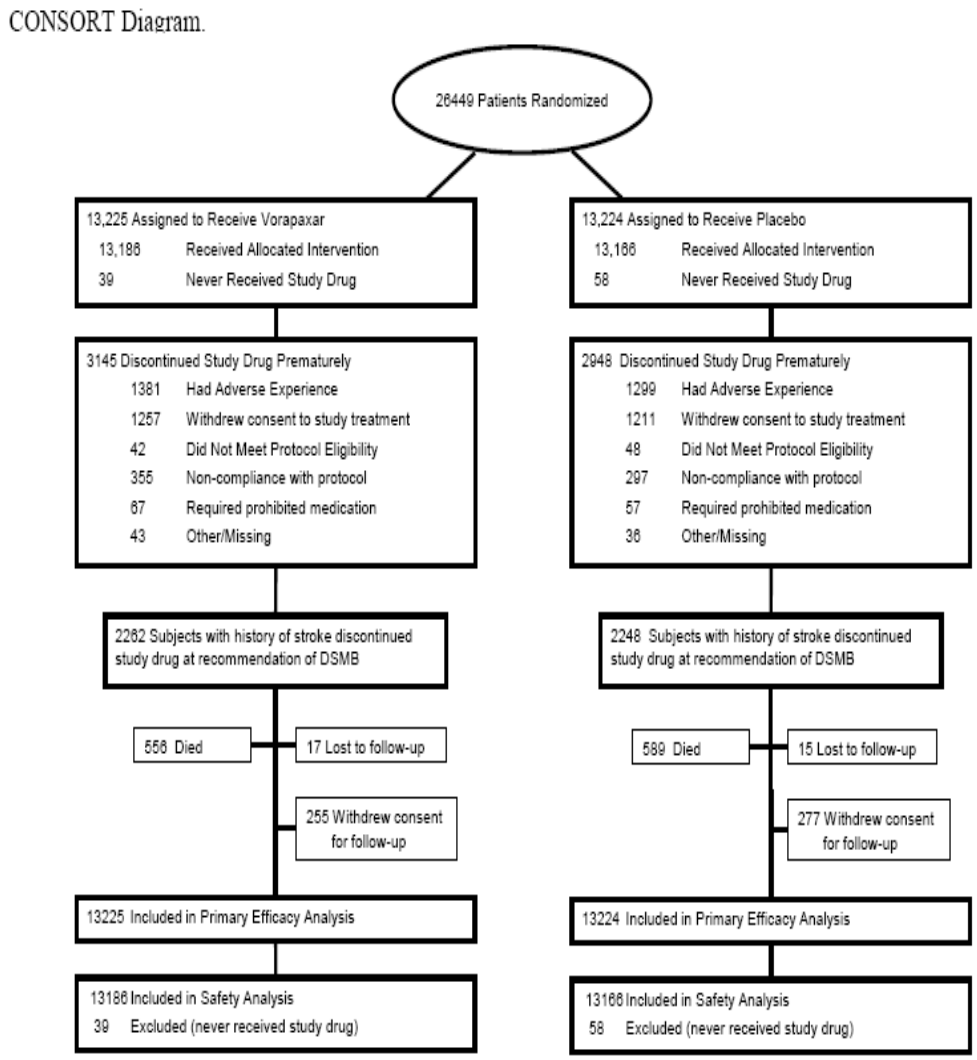


Figure 12 CONSORT Diagram for the Overall Population
Protocol No. P04737

Note: Subjects in CVD stratum were considered to have completed the study if they had a final visit.

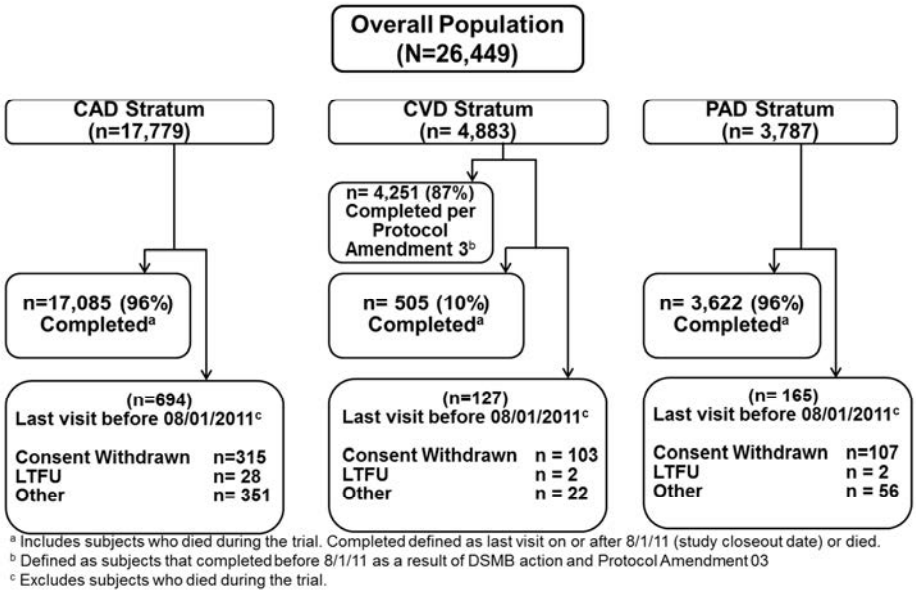


Figure 13 TRA 2°P – TIMI 50 Subject Accounting by Strata| Protocol No. P04737

8.5 Clinical Efficacy

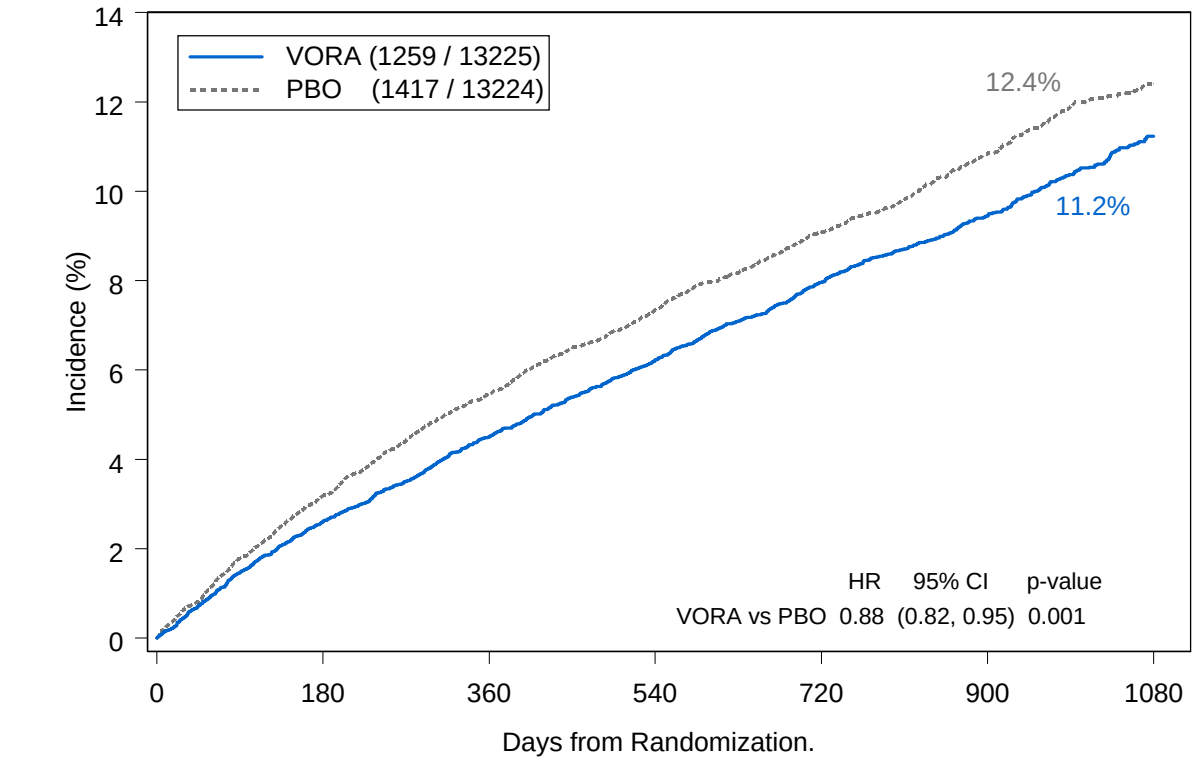
8.5.1 Clinical Efficacy in the Overall Population

The Overall Population is described in the CONSORT diagram **(Figure 12)**. When added on top of standard of care, vorapaxar resulted in 12% reduction in the primary efficacy endpoint (first occurrence of CV death, MI, stroke or UCR; HR 0.88; 95% CI 0.82 - 0.95; p=0.001) **(Figure 14 and Table 10)**. The treatment effect of vorapaxar on the key efficacy endpoints persisted throughout the entire TRA 2°P-TIMI 50 trial duration. This is supported by the continued separation of the KM estimates of the cumulative hazard rates of key clinical events over time. A similar significant and durable reduction of 13% was observed in the key secondary efficacy composite endpoint (CV death, MI, or stroke; HR 0.87; 95% CI 0.80 - 0.94; p <0.001) (**Figure 15 and Table 10**).

For both the primary and secondary endpoints, vorapaxar reduced all of the components of the composite except stroke where the rate of ischemic stroke was reduced by vorapaxar but the rate of hemorrhagic stroke was increased, resulting in a net lack of effect on total strokes. The 3-year KM event rate of MI event was 5.2% in the vorapaxar group compared with 6.1% in the placebo group (HR 0.83; 95 CI% 0.74 – 0.93; p=0.001) **(Table 11)**. The individual component of the composite endpoints that contributed most to the difference between vorapaxar and placebo was the reduction in the rate of MI (4.1% vorapaxar vs. 4.8% placebo in the primary endpoint and (4.2% vorapaxar vs. 5.0% placebo in the secondary endpoint).

The annualized event rates for the Overall Population are presented in **(Table 12)**.

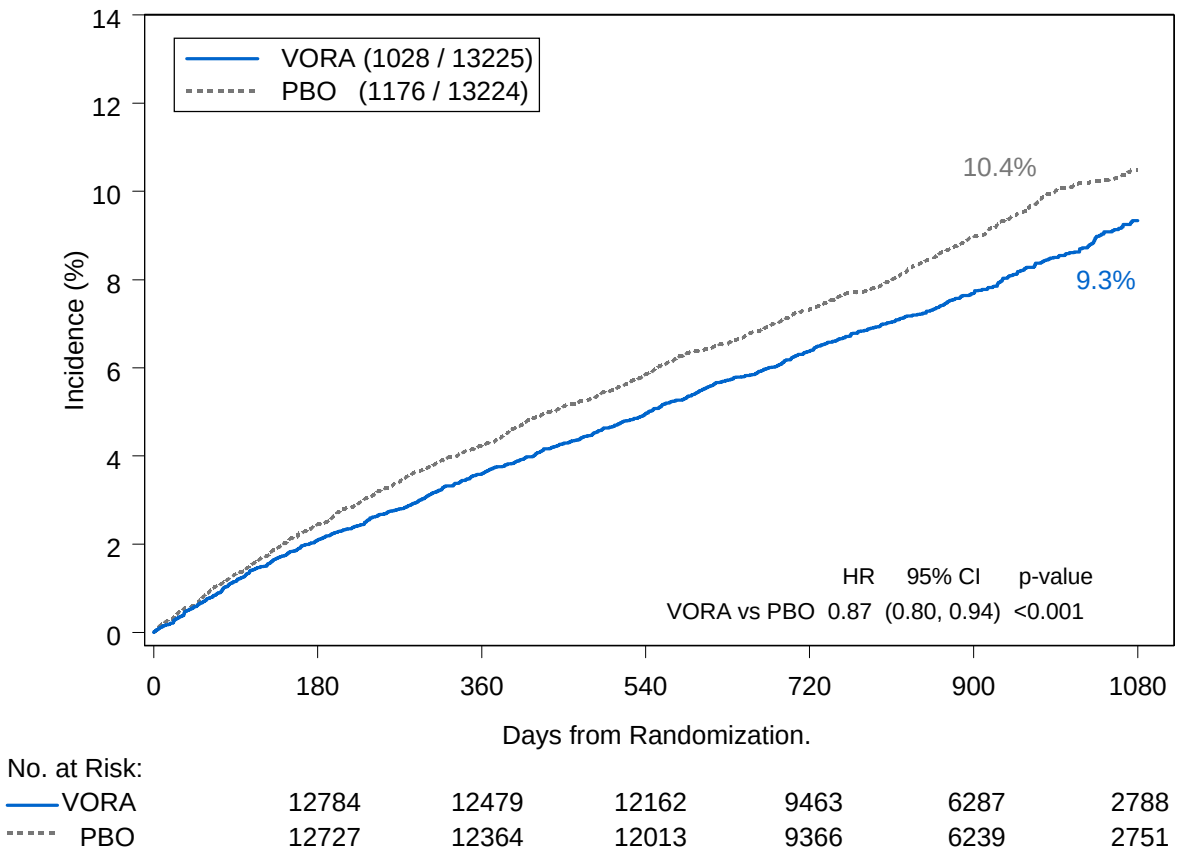
As mentioned above in **Section 8.4**, all subjects in the CVD stratum who had not had a stroke during the study received the final visit beginning in January of 2011 as specified in Protocol Amendment #3. This is in contrast to the final study visit for the remaining subjects in the study who had their final visit beginning on August 1. This represents a gap in follow-up of 6-7 months compared to patients in the CAD and PAD strata and amounts to estimated loss of about 3% total patient exposure in the trial. In order to help understand the impact of this decision, and to provide an assessment of efficacy unbiased by the discontinuation of the CVD stratum, a post-hoc analysis of efficacy endpoints using a data cut of February 1, 2011 was performed. The results are shown in Table 13. Had the study been terminated at this point, with close out of all strata, the Hazard Ratios (and p-values) for both the primary and secondary composite endpoints would have been similar to those presented in **Figure 14, Figure 15 and Table 10**.



No. at Risk:

VORA	12720	12364	12003	9296	6147	2706
PBO	12631	12207	11824	9180	6104	2686

Figure 14 Kaplan-Meier Estimate of Time to the First Occurrence of the Primary Efficacy Endpoint for All Subjects in the Overall Intent to Treat Population (Event Accrual Period: Randomization to Last Visit)



No. at Risk:						
VORA	12784	12479	12162	9463	6287	2788
PBO	12727	12364	12013	9366	6239	2751

Figure 15 Kaplan-Meier Estimate of Time to First Occurrence of Key Secondary Efficacy Endpoint for All Subjects in the Overall ITT Population (Event Accrual Period: Randomization to Last Visit)

Table 10 Primary and Key Secondary Composite Efficacy Endpoints and Contributing Components Overall ITT Population (Event Accrual Period: Randomization to Last Visit)

(Protocol No. P04737)

	Placebo		Vorapaxar			
	(n =13224)		(n =13225)			
Endpoint and	Subjects With		Subjects With		Hazard Ratio[b, c] (95%	
Contributing Component	Events (%)	KM%[a]	Events (%)	KM%[a]	Confidence Interval)	P Value[c]
Primary Efficacy Endpoint	1417 (10.7%)	12.4%	1259 (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	1176 (8.9%)	10.5%	1028 (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%)			

a Kaplan-Meier estimate at 1080 days

b Hazard ratio is vorapaxar group vs. placebo group

c Hazard ratio and p-value were calculated based on Cox PH model with covariates treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use)

Note: The primary composite efficacy endpoint is the first occurrence of any component: cardiovascular death, myocardial infarction, stroke, or urgent coronary revascularization. The key secondary composite efficacy endpoint is the first occurrence of any component: cardiovascular death, myocardial infarction, or stroke

Table 11 Secondary Efficacy Endpoints From Randomization To Last Visit: Overall ITT Population

(Protocol No. P04737)

Endpoints[d]	Placebo (n =13224) Subjects With Events (%)	Placebo KM%[c]	Vorapaxar (n = 13225) Subjects With Events (%)	Vorapaxar KM%[c]	Hazard Ratio[a,b] (95% Confidence Interval)	P Value[b]
All-Cause Death / MI / Stroke / UCR	1614 (12.2%)	14.2%	1481 (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	1681 (12.7%)	14.7%	1481 (11.2%)	13.1%	0.87 (0.81 - 0.93)	<0.001
All-Cause death/MI/Stroke/Any Revasc	2594 (19.6%)	22.6%	2395 (18.1%)	20.7%	0.91 (0.86 - 0.96)	0.001
CV Death / MI / Stroke / Any Revasc / UH-VCIN	2542 (19.2%)	22.1%	2314 (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 Revasc	1768 (13.5%)	15.5%	1583 (12.0%)	13.6%	0.89 (0.83 - 0.95)	<0.001

Note: For composite endpoints, the endpoint is the first occurrence of any component of the composite.

[a] Vorapaxar versus placebo; a hazard ratio <1 indicates lower hazard associated with vorapaxar relative to placebo.

[b] Cox proportional hazard model with covariates treatment and stratification factors.

[c] Kaplan-Meier estimate at 1080 days.

[d] All events were counted in the case of multiple events.

Table 12 Annualized Event Rates for Primary, Key Secondary and Other Secondary Efficacy Endpoints-Overall ITT Population- Event Accrual Period: Randomization to Last Visit

(Protocol No. P04737)

	Overall Population			
	Placebo (n=13224)		Vorapaxar (n=13225)	
	Subjects with Events (%)	Annualized Event Rate[a]	Subjects with Events (%)	Annualized Event Rate[a]
Primary Efficacy Endpoint (CV Death / MI / Stroke / UCR)[b]	1417 (10.7%)	4.6%	1259 (9.5%)	4.1%
CV Death	199 (1.5%)		172 (1.3%)	
MI	629 (4.8%)		536 (4.1%)	
Stroke	297 (2.2%)		297 (2.2%)	
UCR	292 (2.2%)		254 (1.9%)	
Key Secondary Efficacy Endpoint[b] (CV Death / MI / Stroke)	1176 (8.9%)	3.8%	1028 (7.8%)	3.3%
CV Death	207 (1.6%)		175 (1.3%)	
MI	665 (5.0%)		554 (4.2%)	
Stroke	304 (2.3%)		299 (2.3%)	
Other Secondary Efficacy Endpoint[b]				
CV Death	319 (2.4%)	1.0%	285 (2.2%)	0.9%
All-Cause Death	565 (4.3%)	1.8%	540 (4.1%)	1.7%
MI	673 (5.1%)	2.1%	564 (4.3%)	1.8%

a. Event Rate is expressed as number of subjects with events per 100 patient-years of exposure

b. Each subject was counted only once (first component event) in the component summary that contributed to each composite efficacy endpoint

Table 13 Sensitivity Analysis Primary and Key Secondary Efficacy Endpoints : Overall Population Event Accrual Period: Randomization to 01February 2011 Timepoint When 2281 Primary Events had Occurred

	Placebo (n=13224)	Vorapaxar (n=13225)		
	Subjects with Events (%)	Subjects with Events (%)	Hazard Ratio (95% CI)[a,b]	p-value[b]
Primary efficacy endpoint (CV death/MI/stroke/UCR)	1211 (9.2%)	1070 (8.1%)	0.87 (0.81-0.95)	0.001
CV death	156 (1.2%)	134 (1.0%)		
MI	527 (4.0%)	451 (3.4%)		
Stroke	266 (2.0%)	264 (2.0%)		
UCR	262 (2.0%)	221 (1.7%)		
Key secondary efficacy endpoint (CV death/MI/stroke)	989 (7.5%)	869 (6.6%)	0.87 (0.80-0.96)	0.003
CV death	163 (1.2%)	137 (1.0%)		
MI	555 (4.2%)	466 (3.5%)		
Stroke	271 (2.0%)	266 (2.0%)		

a. Vorapaxar versus placebo; a hazard ratio <1 indicates lower hazard associated with vorapaxar relative to placebo.
b. Cox proportional hazard model with covariates treatment and stratification factors.

8.5.2 Clinical Efficacy within Individual Strata

Table 14 illustrates the breakdown by the prespecified strata. Overall Population results appeared to be independent of planned thienopyridine use in favor of vorapaxar. Only the CAD stratum demonstrated a reduction in the HR (upper limit of the 95% CI less than one) for both the primary and secondary endpoints in favor of vorapaxar. Vorapaxar was not associated with a meaningful reduction in risk the CVD and PAD strata.

Table 14 Primary and Key Secondary Efficacy Endpoints-Event Accrual Period: Randomization to Last Visit-ITT Overall Population and By Stratum

	Placebo n=13224		Vorapaxar n=13225		
Enrollment Stratum	Subjects with Events m/n (%)	KM % [a]	Subjects with Events m/n (%)	KM % [a]	Hazard Ratio [b,c] (95% CI)
Primary Endpoint[d]					
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)
Planned Administration of Thienopyridine					
Yes	870/7679 (11.3%)	12.9%	782/7677 (10.2%)	11.7%	0.89 (0.81 – 0.98)
No	547/5545 (9.9%)	11.8%	477/5548 (8.6%)	10.6%	0.86 (0.76 – 0.97)
Secondary Endpoint[d]					
CAD	750/8881 (8.4%)	9.7%	610/8898 (6.9%)	8.1%	0.80 (0.72 - 0.89)
CVD	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)
Planned Administration of Thienopyridine					
Yes	679/7679 (8.8%)	10.3%	602/7677 (7.8%)	9.2%	0.88 (0.79 - 0.99)
No	497/5545 (9.0%)	10.8%	426/5548 (7.7%)	9.6%	0.85 (0.74 - 0.96)

[a]: Kaplan-Meier estimate at 1080 days
[b]: Hazard Ratio is vorapaxar group versus placebo group
[c]: Hazard Ratio is calculated based on Cox PH model with covariates treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use), with the exception for those subgroup variables related to the stratification factors. For subgroup variable of stratification factor, qualifying atherosclerotic disease (or planned thienopyridine use), hazard ratio is calculated from Cox PH model with covariates treatment and the other stratification factor, planned thienopyridine use (or qualifying atherosclerotic disease).
[d]:Primary Efficacy Endpoint: CV Death / MI / Stroke / UCR Key Secondary Efficacy Endpoint: CV Death / MI / Stroke

8.5.3 Key Subgroups

The consistency of the treatment effects in subgroups was assessed for the primary and key secondary efficacy endpoints. A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. The TRA 2°P – TIMI 50 trial was not powered to examine hypotheses on individual subgroups, and therefore such analyses must be interpreted cautiously, as differences (and lack of differences) can reflect the lack of power and/or play of chance among a large number of analyses.

8.5.3.1 Efficacy Results in Subgroups of the Overall Population

In the TRA 2°P – TIMI 50 Overall Population, the effect of vorapaxar relative to placebo was shown to be consistent across the majority of subgroups for the primary endpoints **(Figure 16)** and key secondary endpoints **(Figure 17)**. The only interaction term that attained an α of 0.05 was body weight (median was 81 kg) observed for the primary efficacy endpoint (p=0.024). The magnitude of the benefit of vorapaxar on the primary endpoint was greater in subjects with a body weight greater than the median compared to those subjects with a body weight less than the median. This pattern was also evident for the secondary efficacy endpoint and was consistent using different cut points for weight. The basis for this difference is unknown.

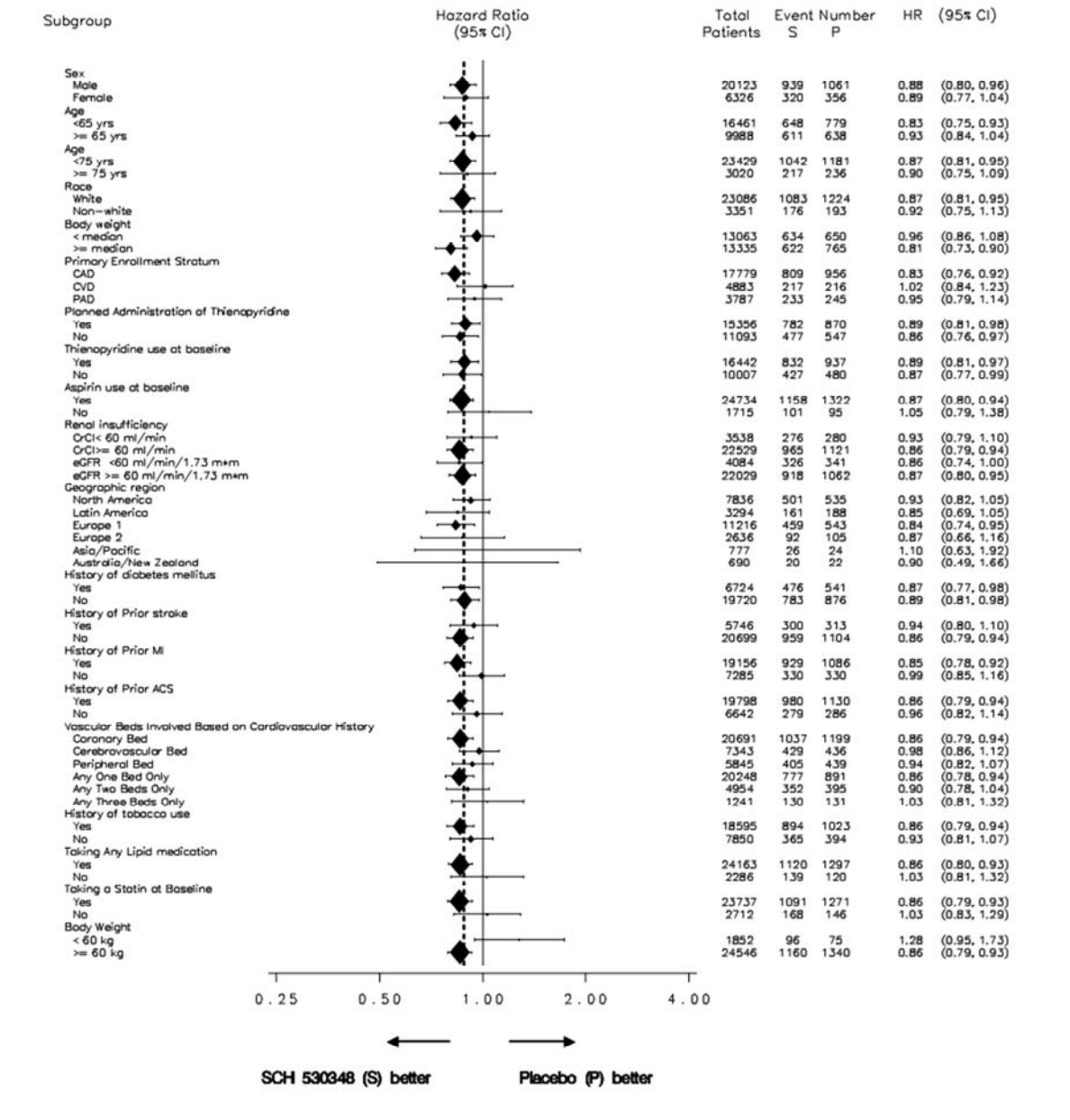


Figure 16 TRA 2°P – TIMI 50 Primary Efficacy Endpoint during the Study by Subgroup: ITT Population (Event Accrual Period: Randomization to Last Visit) (Protocol No. P04737)

Note: the < 60 kg/≥ 60 kg subgroup was an exploratory analysis

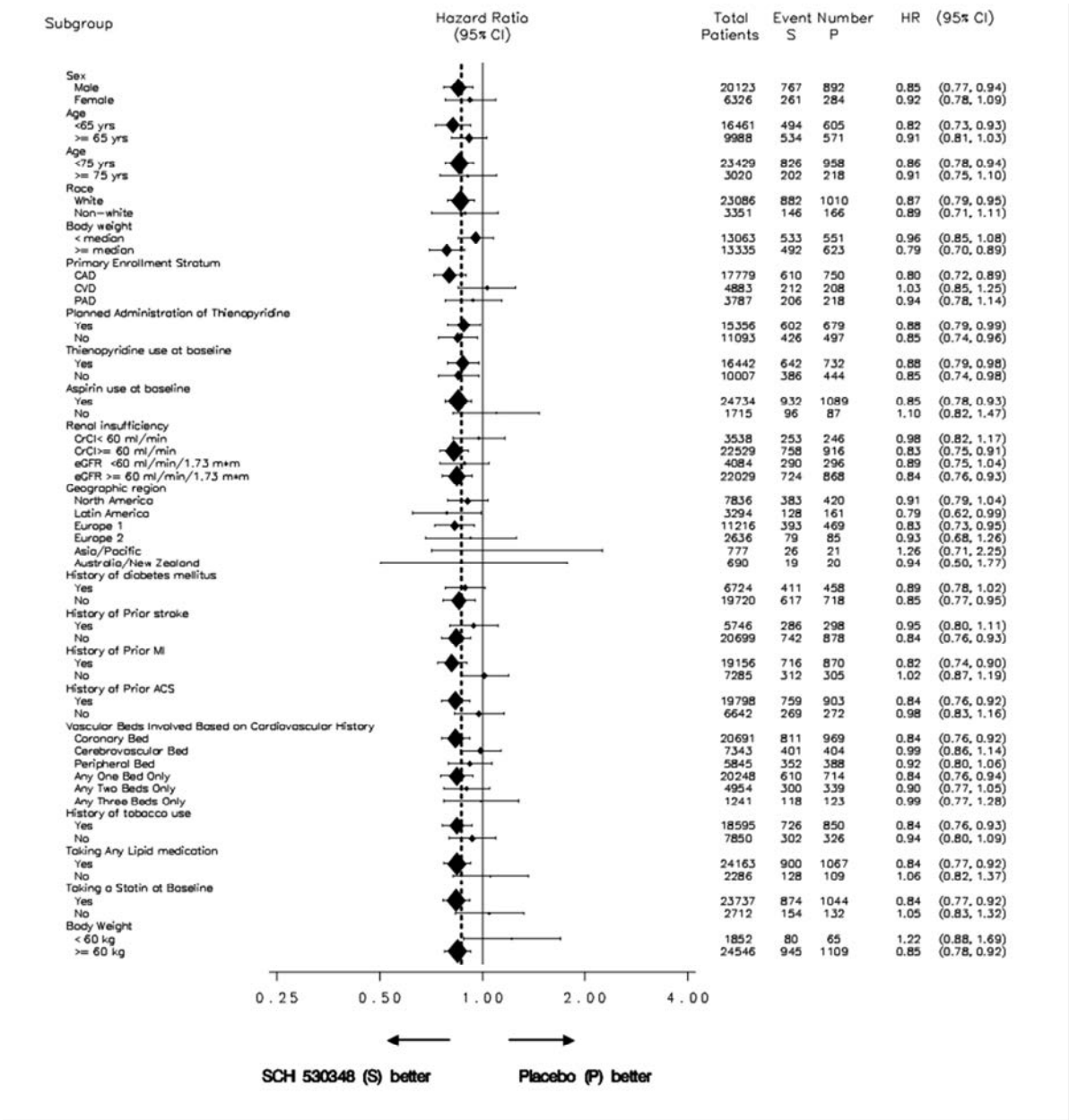


Figure 17 TRA 2°P – TIMI 50 Key Secondary Efficacy Endpoint during the Study by Subgroup: ITT Population (Event Accrual Period: Randomization to Last Visit) (Protocol No. P04737)

Note: the < 60 kg/≥ 60 kg subgroup was an exploratory analysis

8.6 TRA 2°P - TIMI 50 Safety Results in the Overall Population

The safety results for the Overall Population and the Proposed Label Population are presented in **Sections 8.6 and 9.4**, respectively. The analyses of the CEC adjudicated bleeding endpoints are presented first including ICH events. Subsequently, analyses of the CEC adjudicated bleeding endpoints in subgroups of subjects are presented in Forest Plots. Investigator assessments of unadjudicated adverse events follow, beginning with individual bleeding events and adverse bleeding events that led to treatment discontinuation. 'Other' (Non Bleeding) adverse events are then presented, as well as 'Other' adverse events that led to treatment discontinuation. These analyses are followed by an analysis of Deaths as reported by the Investigator. A discussion of the management of bleeding is included for both the Overall and Proposed Label Populations.

8.6.1 Adjudicated Bleeding Endpoints

Adjudicated bleeding endpoints for the Overall Population in the TRA 2°P - TIMI 50 trial are displayed in **Table 15**. For all adjudicated bleeding endpoints with the exception of CABG-related bleeding, the risk of bleeding was greater for subjects on vorapaxar compared to placebo. The 3-year KM estimates for GUSTO severe or moderate bleeding were 4.2% in the vorapaxar group (severe 1.7% and moderate 2.6%) and 2.9% in the placebo group (severe 1.4% and moderate 1.6%) (HR 1.51; 95% CI 1.31 - 1.74; p<0.001). Fatal bleeding event rates were 0.4% for vorapaxar vs. 0.3% for placebo (HR: 1.40; 95% CI 0.86-2.30; p=0.179). ICH rates were 1.0 % for vorapaxar vs. 0.6% for placebo (HR: 1.70; 1.25 - 2.32, p<0.001) (Table 15).

The most frequently reported category of CEC adjudicated GUSTO moderate or severe bleeding endpoints were Gastrointestinal disorders **(Table 16)**.

Table 15 TRA 2ºP-TIMI 50 Bleeding Endpoints Rates with Annualized Event Rates: Overall Population: Event Accrual Period Randomization to Last Visit

(Protocol No. P04737)

Endpoints	Placebo (n =13166)			Vorapaxar (n = 13186)			Hazard Ratio[a,b] (95% Confidence Interval)	p-value[b]
	Subjects With Events (%)	KM%[c]	Annualized Event Rate[d]	Subjects With Events (%)	KM%[c]	Annualized Event Rate[d]		
GUSTO Bleeding Categories								
Severe or Moderate[e]	313 (2.4%)	2.9%	1.0%	471 (3.6%)	4.2%	1.5%	1.51 (1.31 - 1.74)	<0.001
Severe	146 (1.1%)	1.4%	0.5%	192 (1.5%)	1.7%	0.6%	1.31 (1.06 - 1.63)	0.013
Moderate	179 (1.4%)	1.6%	0.6%	290 (2.2%)	2.6%	0.9%	1.62 (1.35 - 1.96)	<0.001
CABG-Related Severe or Moderate	13 (0.1%)	0.1%	<0.1%	11 (0.1%)	0.1%	<0.1%	0.84 (0.38 - 1.88)	0.675
TIMI Bleeding Categories								
Major or Minor[e]	337 (2.6%)	3.0%	1.1%	498 (3.8%)	4.5%	1.6%	1.48 (1.29 - 1.70)	<0.001
Major	243 (1.8%)	2.2%	0.8%	321 (2.4%)	2.9%	1.0%	1.32 (1.12 - 1.56)	0.001
Minor	105 (0.8%)	0.9%	0.3%	192 (1.5%)	1.7%	0.6%	1.83 (1.44 - 2.32)	<0.001
Clinically Significant[f]	1324 (10.1%)	11.3%	4.4%	1816 (13.8%)	15.4%	6.2%	1.41 (1.31 - 1.51)	<0.001
Non CABG-Related Major or Minor[e]	323 (2.5%)	2.9%	1.0%	486 (3.7%)	4.3%	1.5%	1.51 (1.31 - 1.74)	<0.001
Non CABG-Related Major	229 (1.7%)	2.1%	0.7%	309 (2.3%)	2.8%	1.0%	1.35 (1.14 - 1.60)	<0.001
CABG-Related Major	14 (0.1%)	0.1%	<0.1%	13 (0.1%)	0.1%	<0.1%	0.92 (0.43 - 1.97)	0.838
Other Categories								
Intracranial Hemorrhage	64 (0.5%)	0.6%	0.2%	109 (0.8%)	1.0%	0.3%	1.70 (1.25 - 2.32)	<0.001
Fatal ICH	11 (0.1%)	0.1%	<0.1%	26 (0.2%)	0.2%	0.1%	2.36 (1.16-4.77)	0.017
Fatal Bleeding	27 (0.2%)	0.3%	0.1%	38 (0.3%)	0.4%	0.1%	1.40 (0.86 - 2.30)	0.179

Table 15 TRA 2ºP-TIMI 50 Bleeding Endpoints Rates with Annualized Event Rates: Overall Population: Event Accrual Period Randomization to Last Visit

(Protocol No. P04737)

Endpoints	Placebo (n =13166)			Vorapaxar (n = 13186)			Hazard Ratio[a,b] (95% Confidence Interval)	p-value[b]
	Subjects With Events (%)	KM%[c]	Annualized Event Rate[d]	Subjects With Events (%)	KM%[c]	Annualized Event Rate[d]		

Note: Only TIMI major is an appropriate categorization in the context of CABC (in the Clinical Endpoints Committee Manual of Operations).

a. Vorapaxar vs. placebo; a hazard ratio <1 indicates lower hazard associated with vorapaxar relative to placebo.

b. Cox proportional hazards model with covariates of treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use).

c. Kaplan-Meier estimate at 1080 days.

d. Event rate is expressed as number of patients with events per 100 patient-years of exposure

e. Subcategories are mutually exclusive; each subject appears only in the highest intensity subcategory observed for that subject.

f. TIMI Major or Minor bleeding, or bleeding that requires unplanned medical or surgical treatment, or unplanned evaluation via laboratory test.

Table 16 Subjects (n %) with Bleeding Events Classified as CEC GUSTO Severe or Moderate Bleeding Endpoints by System Organ Class Randomization to Last Visit: Overall Population

(Protocol No. P04737)

	Placebo (n=13166)	Vorapaxar (n=13186)
System Organ Class[a]	n (%)	n (%)
Subjects Reporting Any Bleeding Event	313 (2.4)	471 (3.6)
Gastrointestinal Disorders	144 (1.1)	194 (1.5)
Injury, Poisoning, and Procedural Complications	66 (0.5)	91 (0.7)
Nervous System Disorders	49 (0.4)	91 (0.7)
Respiratory, Thoracic and Mediastinal Disorders	8 (0.1)	20 (0.2)
Vascular Disorders	25 (0.2)	41 (0.3)

a. System Organ Class reported if at least 20 subjects with events in either treatment group

8.6.2 Intracranial Hemorrhage

In the TRA 2ºP-TIMI 50 Overall Population, ICH occurred in 173 subjects, 109 (0.8%) on vorapaxar and 64 (0.5%) on placebo with annualized event rates of 0.3 and 0.2 events per 100 subject-years of exposure, respectively **(Table 15)**. Subjects who experienced ICH during the study had a median age of 68 years compared to a median age of 61 years for the Overall Population. Blood pressure at baseline in this group trended slightly higher than the rest of the Overall Population with median blood pressure of 140/80 mmHg (compared to 134/78 mm Hg in the Overall Population). Median body weight for subjects who experienced ICH was 75 kg (lower than the 81 kg median body weight for the Overall Population), with the majority (88%) of subjects having a weight ≥60 kg. ICH was more frequent in subjects weighing < 60 kg (3 yr KM for vorapaxar 1.7% vs. 0.9% placebo) compared to subjects weighing 60 kg or greater (3 yr KM vorapaxar 0.9% vs. 0.6% placebo).

Table 17 describes the causes and outcomes for subjects in the Overall Population who experienced ICH. Forty-five percent of the ICH events were spontaneous in etiology (61 vorapaxar vs. 17 placebo). Non-fatal ICH occurred in 131 (0.50%) subjects, 80 (0.61%) on vorapaxar and 51 (0.39%) on placebo, with an annualized event rate of 0.2 events per 100 subject-years of exposure for both treatment groups. Fatal ICH occurred in 37 (0.14%)

subjects, 26 (0.2%) on vorapaxar and 11 (0.08%) on placebo, with an annualized event rate of 0.1 events per 100 subject-years of exposure.

Table 17 Cause and Outcome of Intracranial Hemorrhage From Randomization Through Last Visit: Overall Population (As Treated)

(Protocol No. P04737)

	Subjects With Events (%)					
	Placebo (n = 13166)		Vorapaxar (n =13186)		Total (n =26352)	
Event	**n (%)**	**Event Rate[d]**	**n (%)**	**Event Rate[d]**	**n (%)**	**Event Rate[d]**
Intracranial Hemorrhage[e]	64 (0.49)	0.2%	109 (0.83)	0.3%	173 (0.66)	0.3%
Cause						
Spontaneous	17 (0.13)	0.1%	61 (0.46)	0.2%	78 (0.30)	0.1%
Without Stroke	6 (0.05)	<0.1%	11 (0.08)	<0.1%	17 (0.06)	<0.1%
With Stroke	11 (0.08)	<0.1%	50 (0.38)	0.2%	61 (0.23)	0.1%
Hemorrhagic Conversion	1 (<0.01)	<0.1%	3 (0.02)	<0.1%	4 (0.02)	<0.1%
Primary Intracranial Hemorrhage	9 (0.07)	<0.1%	46 (0.35)	0.1%	55 (0.21)	0.1%
Subarachnoid Hemorrhage	1 (<0.01)	<0.1%	1 (<0.01)	<0.1%	2 (<0.01)	<0.1%
Traumatic	24 (0.18)	0.1%	24 (0.18)	0.1%	48 (0.18)	0.1%
Surgery/Procedure	2 (0.02)	<0.1%	4 (0.03)	<0.1%	6 (0.02)	<0.1%
Fibrinolysis	3 (0.02)	<0.1%	3 (0.02)	<0.1%	6 (0.02)	<0.1%
Mass/Tumor	4 (0.03)	<0.1%	2 (0.02)	<0.1%	6 (0.02)	<0.1%
Intracranial Vascular	4 (0.03)	<0.1%	2 (0.02)	<0.1%	6 (0.02)	<0.1%
Other	16 (0.12)	<0.1%	19 (0.14)	0.1%	35 (0.13)	0.1%
Outcome						
Fatal[a]	11 (0.08)	<0.1%	26 (0.20)	0.1%	37 (0.14)	0.1%
Non-fatal[b]	51 (0.39)	0.2%	80 (0.61)	0.2%	131 (0.50)	0.2%
Contributing to death[c]	2 (0.02)	<0.1%	3 (0.02)	<0.1%	5 (0.02)	<0.1%

(Protocol No. P04737)						
	Subjects With Events (%)					
Event	**Placebo (n = 13166)**		**Vorapaxar (n =13186)**		**Total (n =26352)**	
	n (%)	**Event Rate[d]**	**n (%)**	**Event Rate[d]**	**n (%)**	**Event Rate[d]**

a. ICH that leads directly to death generally within 7 days (e.g. mass effect and herniation leading directly to death.
b. ICH without death within 30 days or death from causes not related to ICH (e.g.: subject with subdural hematoma following fibrinolytic for STEMI. Subject dies 7 days later of shock from progressive CHF following MI.
c. ICH was part of a chain of events in the causal pathway leading to death generally within 30 days without immediately or directly causing the death (e.g.: ICH without immediate death, but death following infectious complications of prolonged ventilation.
d. Event Rate is expressed as number of patients with events per 100 patient-years exposure.
e. First ICH event is counted

8.6.2.1 Intracranial Hemorrhage in TRA 2ºP-TIMI 50 Subjects with a Prior Stroke History

The potential harm, including ICH, of intensive antiplatelet therapy for secondary prevention in patients with a history of ischemic stroke has become apparent in several trials [17][18][19][3]. Because early phase trials indicated a low bleeding risk of vorapaxar in the stroke population, the TRA 2°P - TIMI 50 trial enrolled subjects with a history of stroke to determine the drug's efficacy and confirm its safety in this population. In the Overall Population, approximately 22% of subjects had a prior history of stroke. Eighty-five per cent of these subjects were enrolled in the CVD strata. The remaining subjects with a history of stroke also had history of MI or PAD and therefore were enrolled based on hierarchy in the CAD or PAD strata, respectively.

Importantly, subjects with a history of stroke had a 3-year KM rate for ICH was 2.7% in the vorapaxar group and 0.9% in the placebo group (HR 2.55; 95% CI 1.56 - 4.18; p<0.001). The observed difference between the treatment groups was predominantly due to an increase in spontaneous ICH. In contrast, subjects with no prior stroke history presented a lower overall 3-year KM estimate of 0.6% for vorapaxar vs. 0.5% for placebo (HR 1.25; 95% CI 0.84-1.88; p=0.273) **(Table 18)**.

Table 18 Summary of Intracranial Hemorrhage Endpoints by Population TRA 2ºP-TIMI 50

(Protocol No. P04737)

	Placebo		Vorapaxar			
	n/N (%)	KM%[c]	n/N (%)	KM%[c]	HR (95% CI)[a,b]	p-value[b]
Overall Population	64/13166 (0.5)	0.6%	109/13186 (0.8)	1.0%	1.70 (1.25-2.32	<0.001
Prior Stroke History	22/2864 (0.8)	0.9%	56/2855 (2.0)	2.7%	2.55 (1.56-4.18)	<0.001
No Prior Stroke History (NSH)[d]	42/10302 (0.4)	0.5%	53/10331 (0.5)	0.6%	1.25 (0.84-1.88)	0.273

[a] Vorapaxar versus placebo,; a HR < 1 indicates lower hazard associated with vorapaxar relative to placebo
[b] Cox proportional hazard model with covariates of treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use
[c] Kaplan-Meier estimate at 1080 days
[d] Includes subjects with TIA

8.6.3 Adjudicated Bleeding Endpoints in Subgroups Identified by Baseline Characteristics in the TRA 2ºP-TIMI 50 Overall Population

In the TRA 2ºP-TIMI 50 Overall Population, the effect of vorapaxar relative to placebo was shown to be consistent across the majority of subgroups. Consistent with the trial overall, there was an increase in adjudicated bleeding endpoints associated with vorapaxar treatment compared with placebo treatment across the subgroups examined **(Figure 18)**.

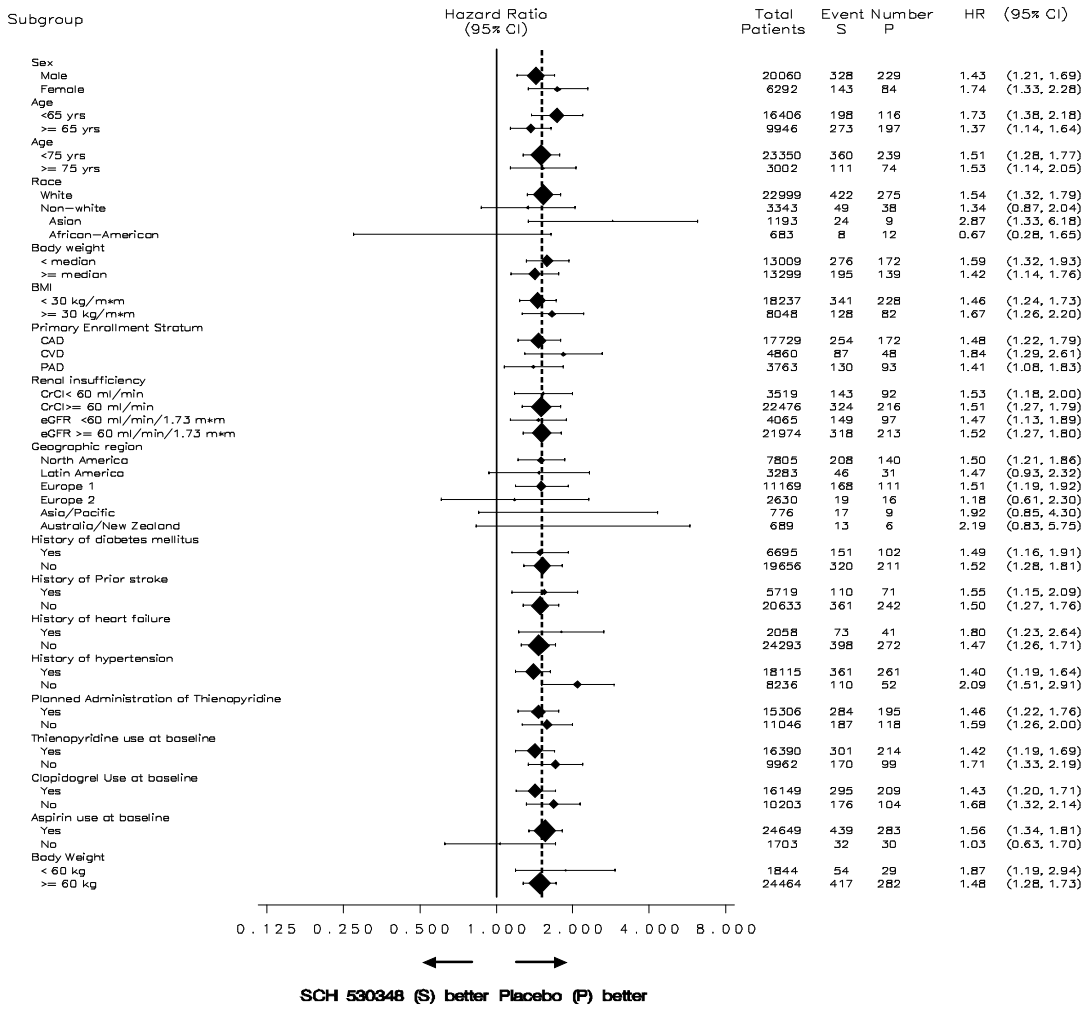


Figure 18 GUSTO Severe or Moderate Bleeding Events by Subgroups for As-Treated Population (Randomization to Last Visit) (P04737)

8.6.4 Individual Adverse Bleeding Events in the TRA 2°P–TIMI 50 Overall Population

Results of the analyses of unadjudicated Investigator assessments of Bleeding Events for the Overall Population are presented below.

More subjects reported bleeding events in the vorapaxar group (24.4%) compared to the placebo group (17.2%) with annualized event rates of 13.8 and 9.0 events per 100 subject-years of exposure, respectively.

The most frequently reported individual bleeding event was epistaxis, 6.2% for vorapaxar group compared to 3.1% for the placebo group, with an annualized event rate of 3.1 and 1.5 events per 100 subject-years of exposure, respectively. Contusion (2.9% for vorapaxar and 2.2% for placebo), hematuria (2.6% for vorapaxar and 2.0% for placebo), and 'increased tendency to bruise' (2.4% for vorapaxar and 1.4% for placebo) were more common with vorapaxar.

8.6.4.1 Adverse Bleeding Events Leading to Discontinuation in the TRA 2ºP-TIMI 50 Overall Population

For the TRA 2ºP-TIMI 50 Overall Population, more subjects in the vorapaxar group (3.0%) discontinued treatment due to bleeding events compared to subjects in the placebo group (1.8%). Epistaxis was the most frequently reported individual bleeding event resulting in treatment discontinuation in both treatment groups (0.4% for vorapaxar and 0.2% for placebo). Additional frequently reported bleeding events that led to discontinuation of study treatment included: melena (0.2% for vorapaxar and 0.1% for placebo), rectal hemorrhage (0.2% for vorapaxar and 0.1% for placebo), intracranial hemorrhage (0.3% for vorapaxar and 0.1% for placebo), hematuria (0.2% for vorapaxar and 0.1% for placebo) and increased tendency to bruise (0.2% for vorapaxar and <0.1% for placebo).

8.6.5 Other (Non-Bleeding) Serious Adverse Events in the TRA 2ºP-TIMI 50 Overall Population

Serious adverse events other than bleeding were reported in approximately 25% of subjects in both treatment groups. The most frequently reported SAEs for the Overall Population are summarized in **Table 19**. There was no clinically important difference in the incidence of these events between the two treatment groups.

Table 19 Most Frequently Reported Serious Other (Non Bleeding) Adverse Events: As Treated: Overall Population: Event Accrual Period: Randomization to Last Visit

(Protocol No. P04737)

	Number (%) of Subjects			
	Placebo		Vorapaxar	
	(n =13166)		(n = 13186)	
Event	n	(%)	n	(%)
Subjects Reporting Any Serious Other Adverse Event	3255	(24.7)	3250	(24.6)
Non-Cardiac Chest Pain	428	(3.3)	411	(3.1)
Cardiac Failure	136	(1.0)	146	(1.1)
Pneumonia	138	(1.0)	142	(1.1)
Atrial Fibrillation	86	(0.7)	112	(0.8)
Syncope	48	(0.4)	71	(0.5)
Cardiac Failure Congestive	63	(0.5)	73	(0.6)
Osteoarthritis	79	(0.6)	65	(0.5)

8.6.6 Other (Non-Bleeding) Adverse Events Leading to Discontinuation TRA 2ºP-TIMI 50 Overall Population

For the TRA 2ºP-TIMI 50 Overall Population, the numbers of non-bleeding adverse events that resulted in discontinuation of treatment over the course of the study were similar between both treatment groups; 7.0% in the vorapaxar group and 7.3% in the placebo group.

Most events leading to discontinuation occurred at a low frequency of 0.1% or less for either of the treatment groups. Of the individual events reported, anemia was the most frequently reported event with a higher incidence observed between vorapaxar and placebo (0.3% for vorapaxar and 0.1% for placebo). In subjects with an event of ‘anemia,’ approximately 49% of vorapaxar subjects and 38% of subjects on placebo also reported a bleeding event. This is consistent with the observed increased proportions of subjects with any bleeding event in the vorapaxar compared to the placebo treatment groups.

8.6.7 All-Cause Death in the TRA 2ºP-TIMI 50 Overall Population

There were fewer deaths from all causes associated with the vorapaxar treatment group than with placebo. Of the 26,449 subjects who received randomized treatment assignment (Overall Population), 1190 (4.4%) died during the course of the study. Of these, 580 (4%) were assigned to vorapaxar and 610 (4.6%) were assigned to placebo **(Table 20)**. Per protocol, deaths were to be reported up to 30 days after the final visit. All deaths in the database were adjudicated as to whether or not they were considered cardiovascular in nature. When spontaneous events were reported even if they occurred later than required per protocol they were not removed from the database. Deaths recorded after the last visit were 40 in the vorapaxar group and 45 in the placebo group.

Table 20 All-Cause Death Reported in TRA 2ºP-TIMI 50 Intent-to-Treat Overall Population

Protocol No. P04737

	During Study	
	Placebo	**Vorapaxar**
	(n=13224)	**(n=13225)**
	n (%)	n (%)
Total No. of Deaths	610 (4.6)	580 (4.4)
CV Death[c]	329 (2.5)	298 (2.3)
Non-CV death[c]	250 (1.9)	240 (1.8)
Unknown[c]	31 (0.2)	42 (0.3)
Total No. Of Deaths On or Before the Last Visit[a,b]	565 (4.3)	540 (4.1)
Total No. of Deaths After the Last Visit	45 (0.3)	40 (0.3)

a. Death Date recorded by Adjudicator is used, if different from the one recorded by Investigator.

b. For subjects with partial death date, the death date is estimated

c. Categories as determined by CEC adjudication

8.6.8 Management of Bleeding: Bleeding Duration and Impact of Intervention

In order to better understand the extent and severity of bleeding associated with vorapaxar, we compared how bleeding was managed for bleeding associated with placebo vs. vorapaxar. Interventions used to stop bleeding events experienced by the subjects were approximated by procedures performed or transfusions administered in temporal proximity to a bleeding event. Specifically, the analysis assessed procedures performed following the start of the subject's first CEC adjudicated GUSTO moderate or severe bleed event.

8.6.8.1 Procedures to Manage Bleeding in the TRA 2ºP-TIMI 50 Overall Population

In the Overall Population, 475 subjects on vorapaxar and 317 subjects on placebo experienced a CEC-adjudicated GUSTO moderate or severe bleeding event from the time of randomization onward[3]. In this population, 260/475 (55%) vorapaxar subjects and 189/317 (60%) placebo subjects had a procedure following the bleeding event. The most common therapeutic procedure reported in proximity to the first GUSTO severe/moderate event for a given subject was GI endoscopy (126/260 [49%] subjects in the vorapaxar group and 87/189 [46%] subjects in the placebo group). The median duration of the bleeding event was 3.0 (1.0-6.0) days in the vorapaxar group and 3.0 (1.0-5.0) days in the placebo group and similar for the events requiring GI endoscopy [3.0 days (1.0-5.0) vorapaxar; 2.0 days (1.0-5.0) placebo]. Additionally, of those hospitalized for such bleeding, duration of hospitalization was similar (6 days) for both treatment groups. The similarity in time to resolution and

[3] This analysis did not truncate the bleeding events at the subjects' last visit, so there is an excess of 4 vorapaxar and 4 placebo events compared with the primary bleeding analysis.

hospitalization period in patients with bleeding events randomized to vorapaxar or placebo, suggests that conventional supportive measures are effective in controlling bleeding events associated with vorapaxar.

Management of the most common individual bleeding event as reported by the Investigators, epistaxis, was also reviewed. In general, events of epistaxis were not GUSTO severe or moderate, or TIMI major or minor bleeds. The most common procedures initiated following epistaxis were 'cautery to nose' in 3.4% of subjects in the vorapaxar group who had a first report of epistaxis and 3.0% of subjects in placebo and 'nasal cavity packing' in 1.7% of subjects reporting this event in the vorapaxar group and 3.0% in the placebo group.

8.6.8.2 Transfusions in the TRA 2ºP-TIMI 50 Overall Population

Approximately 70% of subjects with a CEC-adjudicated GUSTO moderate or severe bleed event received a transfusion. The number of transfusions recorded for CEC-adjudicated GUSTO moderate or severe bleed events for the Overall Population is displayed in **Table 21.** There were 473 subjects on vorapaxar and 316 subjects on placebo who had a GUSTO moderate or severe bleeding event. The most common transfusions recorded were whole blood transfusion and/or packed red blood cells (PRBC) transfusion in 316/473 subjects (66.8%) in the vorapaxar group and 213/316 subjects (67.4%) in the placebo group. Platelet transfusion was recorded in 44/473 subjects (9.3%) in the vorapaxar group and 30/316 subjects (9.5%) in the placebo group. Fresh-frozen plasma (FFP) transfusion was recorded in 44/476 subjects (9.3%) in the vorapaxar group and 35/316 subjects (11.1%) in the placebo group. Among subjects who had bleeding events, approximately the same percentage received transfusions regardless of treatment groups. In addition, the distribution of the number of units of transfused products received was similar in both treatment arms. The use of FFP and platelet transfusions was relatively infrequent and generally did not occur without PRBC transfusion.

Table 21 Subjects with CEC-Adjudicated GUSTO Moderate/Severe Bleeding Receiving Transfusion within 2 days of Any Bleeding Event TRA 2ºP-TIMI 50 Overall Populations

(Protocol No. P04737)

	TRA 2ºP-TIMI 50 Overall Population	
	Placebo N (%)	**Vorapaxar N (%)**
Number of Subjects with a Bleeding Event	316	473
Any Transfusion	221 (69.9)	332 (70.2)
Whole Blood Transfusion	46 (14.6)	71 (15.0)
Packed Red Blood Cell Transfusion	170 (53.8)	254 (53.7)
Whole Blood and/or PRBC Transfusion	213 (67.4)	316 (66.8)
<3 Units	113 (35.8)	175 (37.0)
3-5 Units	67 (21.2)	108 (22.8)
>5 Units	25 (7.9)	26 (5.5)
Missing	8 (2.5)	7 (1.5)
Platelet Transfusion	30 (9.5)	44 (9.3)
Fresh-Frozen Plasma Transfusion	35 (11.1)	44 (9.3)
Cryoprecipitate Transfusion	1 (0.3)	7 (1.5)
Missing	0	3 (0.6)

Note: Table represents summary results for subjects who had a bleeding event, that began (per Investigator) on or after randomization during the study, and received one or more transfusions that began within 2 days after any bleeding event for subjects with CEC-Adjudicated GUSTO Moderate/Severe Bleeding Events.
This analysis did not truncate the bleeding events at the subjects' last visit, so there is an excess of 3 placebo and 2 vorapaxar events compared with the primary bleeding analysis.
Number of units is total for two consecutive calendar days, beginning with first day of transfusion(s). Subsequent transfusions, if any, begin a new 2-day transfusion record. Units represent the single largest 2-day total for the indicated transfusate.
Note: Subject may have had more than one type of transfusion and can be counted in multiple rows.

8.6.8.3 Effectiveness of Interventions to Terminate Bleeding Events in the TRA 2ºP-TIMI 50 Overall Population

In the TRA 2ºP-TIMI 50 Overall Population, the analysis of the duration from the first procedure to the end of the first bleeding event (as defined by the investigator on case report forms) was performed to estimate the effectiveness of the interventions. Although bleeding was more common in the vorapaxar treatment group, the duration of bleeding was similar between treatment groups. The median (25th to 75th percentile) duration was 3.0 days (1.0 – 5.0) for both treatment groups **(Table 22)**. The effectiveness of standard therapy for treatment of bleeding associated with the placebo group appears to be adequate for the treatment of vorapaxar-associated bleeding.

Table 22 Duration from the First Procedure to the End of First Bleed Event Subjects with CEC-Adjudicated GUSTO Moderate/Severe Bleeding TRA 2ºP-TIMI 50 Overall Population

(Protocol No. P04737)

	TRA 2ºP-TIMI 50 Overall	
	Placebo n (%)	**Vorapaxar n (%)**
Number of Subjects with a Bleeding Event	180	292
	Duration from First Procedure/Surgery/Revasc/PCI to End of First Bleeding (Days)	
Number of Subjects	113	182
Mean(SD)	9.4 (30.60)	7.8 (22.40)
Median (25th to 75th Percentile)	3.0 (1.0-5.0)	3.0 (1.0-5.0)

Note: Subject may have had more than one type of procedure/surgery and can be counted in multiple rows.

8.7 TRA 2°P –TIMI 50 Efficacy and Safety Conclusions in the Overall Population

The efficacy of vorapaxar at a daily dose of 2.5 mg was demonstrated in the TRA 2°P - TIMI 50 trial by the robust results for the primary and secondary endpoints for the Overall Population as well as the pre-specified subgroups.

In the Overall Population, a daily dose of 2.5 mg of vorapaxar significantly reduced the primary and key secondary efficacy composite endpoints compared to placebo on the background of standard of care. While all components of the composite endpoint, except stroke, were reduced by vorapaxar compared to placebo, the largest treatment effect of vorapaxar was observed in the reduction of Type I spontaneous MIs. There was a consistency of effect of vorapaxar among the subgroups examined, including medically important subgroups at potentially higher risk due to other underlying disease such as subjects with diabetes mellitus. The treatment effect of vorapaxar on the key efficacy endpoints persisted throughout the entire TRA 2°P-TIMI 50 trial duration.

There was an increased risk of GUSTO severe or moderate bleeding in the vorapaxar compared to the placebo group, as well as an increased risk of ICH, a component of GUSTO severe bleeding. The differences between the treatment groups were statistically significant for most GUSTO and TIMI categories including GUSTO moderate and severe, clinically significant bleeding, and intracranial hemorrhage. Fatal bleeding rates were comparable for both treatment groups. Based on analyses of management of bleeding events, the severity of bleeds in the vorapaxar group were generally similar to those occurring on placebo and resulted in similar treatments.

In the Overall Population, there was an increase in ICH events among subjects taking vorapaxar in addition to standard of care. The risk of ICH was greater in subjects with a history of stroke. In contrast, subjects with no prior stroke history demonstrated a smaller

increase in incidence of ICH and a smaller increase in risk associated with vorapaxar compared with placebo.

As a result of the increased risk of ICH observed by the trial DSMB in subjects with a history of stroke, additional subpopulations without a history of stroke were identified by the Executive Committee and the Sponsor prior to unblinding and database lock in Protocol Amendment 3. Assessment in these additional populations led to the ***Proposed Label Population*** (Post MI with no history of stroke or TIA) in which the Sponsor is seeking approval for the use of vorapaxar. Analyses of both efficacy and safety in the Proposed Label Population are presented in the following sections.

9 TRA 2ÁP ï TIMI 50
PROPOSED LABEL
POPULATION

9 TRA 2°P –TIMI 50 PROPOSED LABEL POPULATION

9.1 Rationale for the Proposed Label Population

In the context of robust efficacy results in the Overall Population, benefit-risk assessment resulted in refinement of the Overall Population to the Proposed Label Population. Subjects with a history of stroke are not candidates for vorapaxar given that the risk of ICH outweighs the potential benefits. This increased risk of ICH in subjects with a history of stroke was recognized by the DSMB and confirmed by analysis of the final results. Given that it is difficult in some clinical situations to distinguish stroke and TIA, subjects with a history of TIA were also excluded from the proposed label population. Removing subjects with a history of stroke and TIA reduced the risk of ICH with vorapaxar.

The subjects enrolled in the PAD stratum, which excluded patients with recent MI (<1 year), did not demonstrate an adequate benefit-risk profile. The demonstrable risks in this stratum without more definitive evidence of benefit argues for excluding such patients from the Proposed Label Population.

As a result of such assessments, the benefit-risk was best substantiated in the Post MI (CAD stratum) with no history of stroke or TIA (Proposed Label Population). Given that the Sponsor seeks an indication in patients with history of MI with no history of stroke or TIA, the remainder of the document summarizes the efficacy, safety, and benefit-risk in this Proposed Label Population.

9.2 TRA 2°P –TIMI 50 Baseline Characteristics and Concomitant Medications in the Proposed Label Population

In the TRA 2°P-TIMI 50 Proposed Label Population (n=16,897 (64%) of the n=26,449 in the Overall Population), (i.e., post MI with no history of stroke or TIA) the two treatment groups were well balanced in terms of demographic characteristics at baseline, with no apparent differences **(Table 23)**. Subjects were predominantly white (88%) and male (79.9%). Compared to the Overall Population, Proposed Label Population subjects were slightly younger and had a slightly greater body weight and body mass index (BMI). Median age was 58 years and 7.3% were over 75 years old. Median body weight for subjects was approximately 83 kg with 94.8% of subjects having a weight ≥ 60 kg. Median BMI was 27.8 kg/m^2 and approximately one quarter of the subjects were obese (≥30 kg/m^2). Mean systolic blood pressure in the Proposed Label Population was approximately 130 mmHg and diastolic blood pressure was 78 mmHg.

In the Proposed Label Population, 61.2% of subjects in the vorapaxar group had a history of hypertension and 84.5% had a history of hyperlipidemia. Approximately 28% of subjects had a prior history of MI less than one month prior to randomization and 5% of subjects had prior PAD. Approximately 79% of subjects had a prior PCI procedure and 13% of subjects had a prior CABG.

Approximately 21% percent of subjects in the vorapaxar group had a history of diabetes. Nine percent of subjects had impaired renal function defined as an estimated GFR of <60 mL/min based on calculated creatinine clearance (CrCl) at baseline.

For the Proposed Label Population, the baseline history of CAD resulted in the near universal administration of aspirin (98.3%) with the vast majority of the subjects (77.6%) taking clopidogrel. As expected in a post-MI population, approximately 77% of subjects were taking dual antiplatelet therapy (thienopyridine in addition to aspirin) at the time of study enrollment, a percentage that is greater than in the Overall Population (57%).

Table 23 TRA 2°P – TIMI 50 Baseline Demographics, Disease Characteristics, and Concomitant Medications in the Proposed Label Population

(Protocol No. P04737)

Characteristic[a]	Placebo (n=8439)	Vorapaxar (n=8458)	Total (n=16897)
Planned Thienopyridine Administration			
No	2232 (26.4)	2255 (26.7)	4487 (26.6)
Yes	6207 (73.6)	6203 (73.3)	12410 (73.4)
Sex			
Male	6763 (80.1)	6735 (79.6)	13498 (79.9)
Female	1676 (19.9)	1723 (20.4)	3399 (20.1)
Age (y)			
Mean (SD)	58.5 (10.46)	58.7 (10.58)	58.6 (10.52)
Median	58.0	59.0	58.0
25th to 75th Percentile	51 - 66	51 - 66	51 - 66
Min – Max	22 - 92	24 - 92	22 - 92
Age Category			
<65 y	6052 (71.7)	5960 (70.5)	12012 (71.1)
65-<75 y	1781 (21.1)	1864 (22.0)	3645 (21.6)
≥75 y	606 (7.2)	634 (7.5)	1240 (7.3)
Race			
White	7415 (87.9)	7481 (88.4)	14896 (88.2)
Non-White	1021 (12.1)	971 (11.5)	1992 (11.8)
Missing	3 (<0.1)	6 (0.1)	9 (0.1)
Weight (kg)			
Mean (SD)	84.67 (17.30)	83.99 (16.8)	84.33 (17.0)
Median	83.00	82.50	83.00
25th to 75th Percentile	73.0 - 94.7	73.0 - 93.4	73.0 - 94.0
Min – Max	37.0 - 197.3	36.2 - 188.0	36.2 - 197.3
Missing	14 (0.2)	10 (0.1)	24 (0.1)
Weight Category			
<60 kg	429 (5.1)	432 (5.1)	861 (5.1)
≥60 kg	7996 (94.8)	8016 (94.8)	16012 (94.8)
Systolic Blood Pressure (mm Hg)			
Mean (SD)	130.2 (18.63)	130.3 (18.76)	130.2 (18.69)
Median	129.0	130.0	129.0
25th to 75th Percentile	118 - 141	118 - 141	118 - 141
Min – Max	82 - 221	70 - 210	70 - 221
Missing (n)	24	18	42

Table 23 TRA 2°P – TIMI 50 Baseline Demographics, Disease Characteristics, and Concomitant Medications in the Proposed Label Population

(Protocol No. P04737)

Characteristic[a]	Placebo (n=8439)	Vorapaxar (n=8458)	Total (n=16897)
Diastolic Blood Pressure (mm Hg)			
Mean (SD)	77.8 (10.72)	77.6 (10.66)	77.7 (10.69)
Median	78.0	78.0	78.0
25th to 75th Percentile	70 - 85	70 - 85	70 - 85
Min – Max	35 - 130	10 - 122	10 - 130
Missing (n)	24	19	43
Renal Insufficiency			
CrCl <60 mL/min	716 (8.5)	801 (9.5)	1517 (9.0)
CrCl ≥60 mL/min	7608 (90.2)	7548 (89.2)	15156 (89.7)
Not Able to Calculate CrCl	115 (1.4)	109 (1.3)	224 (1.3)
eGFR <60 mL/min•1.73m^2	926 (11.0)	1049 (12.4)	1975 (11.7)
eGFR ≥60 mL/min•1.73m^2	7411 (87.8)	7310 (86.4)	14721 (87.1)
Not Able to Calculate eGFR	102 (1.2)	99 (1.2)	201 (1.2)
Geographic Region			
North America	2620 (31.0)	2630 (31.1)	5250 (31.1)
Latin America	1019 (12.1)	1022 (12.1)	2041 (12.1)
Europe 1	3577 (42.4)	3593 (42.5)	7170 (42.4)
Europe 2	814 (9.6)	815 (9.6)	1629 (9.6)
Asia/Pacific	145 (1.7)	141 (1.7)	286 (1.7)
Australia/New Zealand	264 (3.1)	257 (3.0)	521 (3.1)
Diabetes Mellitus			
No	6625 (78.5)	6648 (78.6)	13273 (78.6)
Yes	1814 (21.5)	1809 (21.4)	3623 (21.4)
Missing	0	1 (<.1)	1 (<0.1)
Hypertension			
No	3227 (38.2)	3282 (38.8)	6509 (38.5)
Yes	5211 (61.7)	5176 (61.2)	10387 (61.5)
Missing	1 (<0.1)	0	1 (<0.1)
Hyperlipidemia			
No	1323 (15.7)	1307 (15.5)	2630 (15.6)
Yes	7116 (84.3)	7151 (84.5)	14267 (84.4)

Table 23 TRA 2°P – TIMI 50 Baseline Demographics, Disease Characteristics, and Concomitant Medications in the Proposed Label Population

(Protocol No. P04737)

Characteristic[a]	Placebo (n=8439)	Vorapaxar (n=8458)	Total (n=16897)
Prior ACS			
No[b]	5 (0))	4 (0)	9 (0)
Yes	8434 (100)	8454 (100)	16888 (100)
Prior PCI			
No	1727 (20.5)	1746 (20.6)	3473 (20.6)
Yes	6712 (79.5)	6711 (79.3)	13423 (79.4)
Prior CABG			
No	7352 (87.1)	7356 (87.0)	14708 (87.0)
Yes	1083 (12.8)	1101 (13.0)	2184 (12.9)
Vascular "Beds" Involved Based on Cardiovascular History[c]			
Coronary Bed	8438 (100)	8456 (100)	16894 (100)
Cerebrovascular Bed	261 (3.1)	234 (2.8)	495 (2.9)
Peripheral Bed	716 (8.5)	692 (8.2)	1408 (8.3)
Only One Bed	7528 (89.2)	7585 (89.7)	15113 (89.4)
Only Two Beds	846 (10.0)	819 (9.7)	1665 (9.9)
All Three Beds	65 (0.8)	53 (0.6)	118 (0.7)
No Beds	0	1 (<0.1)	1 (<0.1)
History of Cigarette Smoking			
No	2409 (28.5)	2473 (29.2)	4882 (28.9)
Yes	6030 (71.5)	5985 (70.8)	12015 (71.1)
Any Thienopyridine[d]	6631 (78.6)	6604 (78.1)	13235 (78.3)
Any Clopidogrel	6572 (77.9)	6538 (77.3)	13110 (77.6)
Any Aspirin	8298 (98.3)	8315 (98.3)	16613 (98.3)
Aspirin Plus Any Other Antiplatelet Agent(s)[e]	6544 (77.5)	6493 (76.8)	13037 (77.2)
Aspirin Plus a Thienopyridine	6531 (77.4)	6482 (76.6)	13013 (77.0)
Any Beta-adrenergic Antagonist	7209 (85.4)	7194 (85.1)	14403 (85.2)
Any Angiotensin converting Enzyme Inhibitor or Combination	5586 (66.2)	5586 (66.0)	11172 (66.1)
Any Angiotensin II Receptor Antagonist or Combination	1105 (13.1)	1002 (11.8)	2107 (12.5)

Table 23 TRA 2°P – TIMI 50 Baseline Demographics, Disease Characteristics, and Concomitant Medications in the Proposed Label Population

(Protocol No. P04737)

Characteristic[a]	Placebo (n=8439)	Vorapaxar (n=8458)	Total (n=16897)
Any Lipid Medication	8184 (97.0)	8132 (96.1)	16316 (96.6)
Any Statin	8086 (95.8)	8031 (95.0)	16117 (95.4)

a. Data presented as number (%) of subjects unless otherwise noted

b. These subjects were misstratified to the CAD stratum.

c Definitions of "beds" based on stated cardiovascular history
Coronary bed includes history of known coronary stenosis, angina, MI, PCI, or CABG.
Cerebrovascular bed includes history of known carotid stenosis, TIA, stroke type non-hemorrhagic or unknown, percutaneous carotid intervention, or carotid endarterectomy.
Peripheral bed includes history of PAD, claudication, peripheral arterial revascularization, or amputation related to limb ischemia.

d Any thienopyridine could have included clopidogrel, ticlopidine, prasugrel; clopidogrel was the most common thienopyridine used in this trial.

e Any other antiplatelet agent could have included any thienopyridine, dipyridamole, cilostazol, glycoprotein IIb/IIIa inhibitor.

9.3 TRA 2°P –TIMI 50 Clinical Efficacy Results in the Proposed Label Population

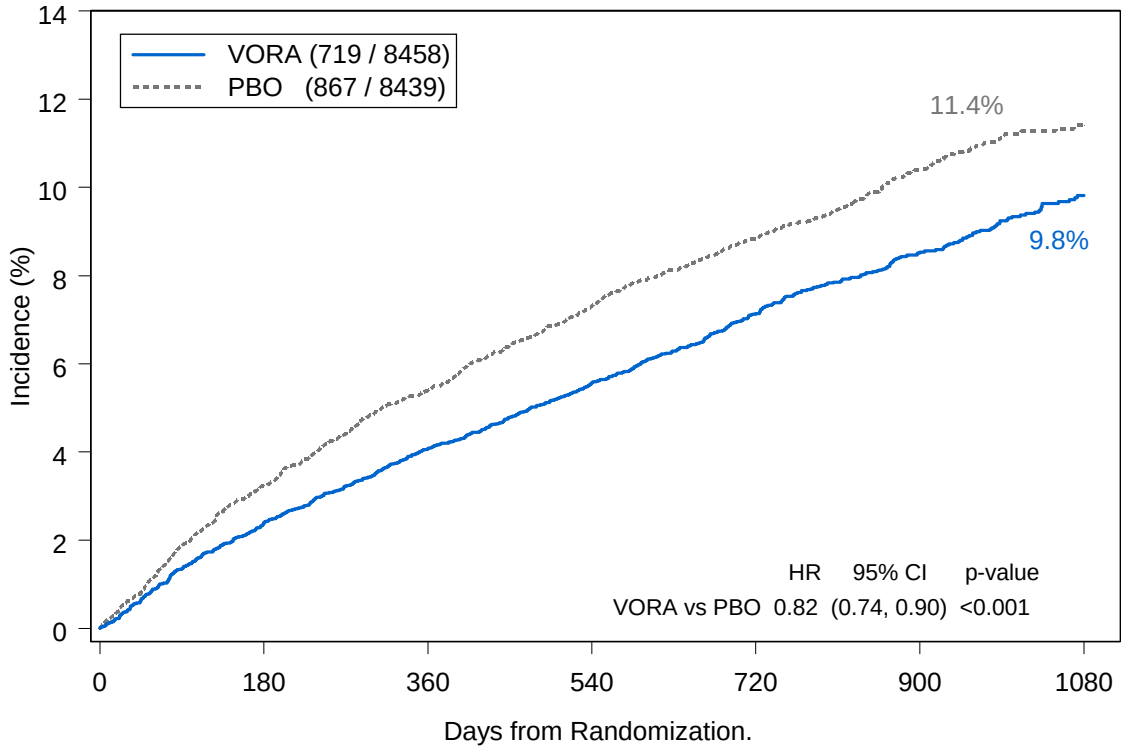
The Proposed Label Population was not pre-specified and therefore all p-values should be viewed as nominal. The results in the Proposed Label Population supported a clinically important benefit **(Figure 19, Figure 20, and Table 24)**, consistent with the Overall Population. There was an 18% reduction in the primary efficacy endpoint (HR 0.82; 95% CI 0.74-0.90) and a 22% reduction in the composite key secondary endpoint (HR 0.78; 95% CI 0.70 - 0.88). The treatment effect of vorapaxar on the key efficacy endpoints persisted throughout the entire TRA 2°P-TIMI 50 trial duration. This is supported by the continued separation of the KM estimates of the cumulative hazard rates of key clinical events over time.

All components of the composite endpoints (first event in the case of multiple events) were reduced by vorapaxar compared with placebo. As with the Overall Population, the individual component of the composite endpoints that most contributed to the difference between vorapaxar and placebo was the reduction in the rate of MI 4.4% vorapaxar vs. 5.3% placebo in the primary endpoint and 4.6% vorapaxar vs. 5.7% placebo in the secondary endpoint **(Table 24)**.

The 3-year KM event rate of MI event was 5.4% in the vorapaxar group compared with 6.6% in the placebo group **(Table 25)**. In the Overall Population, the 3 yr KM event rates of stroke as an endpoint were similar for vorapaxar (2.8%) and placebo (2.8%) HR 0.97 (95% CI 0.83 - 1.14). In the Proposed Label Population (i.e., in subjects without a prior history of stroke or TIA), 3 yr KM event rates of stroke as an endpoint were substantially lower than in the Overall Population (which included patients with a history of stroke). In the Proposed Label Population, vorapaxar was associated with an important reduction in the rate of first stroke: vorapaxar (0.9%) vs. placebo (1.4%) HR 0.62 (95% CI 0.45 - 0.85) (**Table 25**).

Several other secondary endpoints were analyzed; of these CV-Death and all-cause death showed a favorable trend **(Table 25)**.

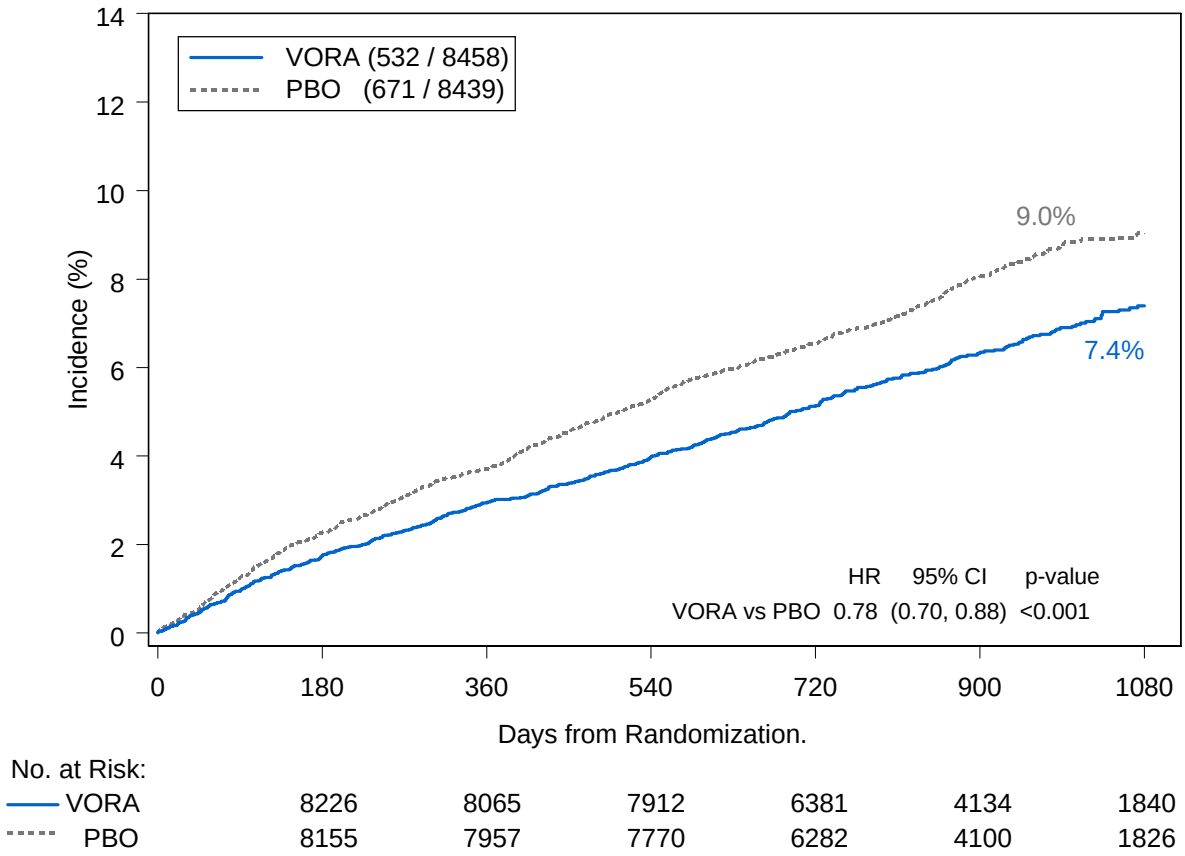
The annualized event rates for the Proposed Label Population are presented in **(Table 26)**. Annualized event rates can provide an estimate of the number of excess events prevented.



No. at Risk:

VORA	8175	7974	7784	6245	4026	1779
PBO	8073	7819	7606	6124	3994	1775

Figure 19 Kaplan-Meier Estimate of Time to the First Occurrence of CEC-Adjudicated Primary Efficacy Endpoint: in the Proposed Label Population (Event Accrual Period: Randomization to Last Visit) (P04737)



No. at Risk:

VORA	8226	8065	7912	6381	4134	1840
PBO	8155	7957	7770	6282	4100	1826

Figure 20 Kaplan-Meier Estimate of Time to the First Occurrence of CEC-Adjudicated Secondary Efficacy Endpoint: Proposed Label Population (Event Accrual Period: Randomization to Last Visit) (P04737)

Table 24 Primary and Key Secondary Composite Efficacy Endpoints and Contributing Components in the Proposed Label Population (Event Accrual Period: Randomization to Last Visit)

(Protocol No. P04737)

	Placebo n=8439		Vorapaxar n=8458			
	Subjects with Events (%)	KM %[c]	Subjects with Events (%)	KM %[c]	Hazard Ratio [a, b] (95% CI)	P-Value[b]
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%)			

a. Vorapaxar versus placebo; a hazard ratio <1 indicates lower hazard associated with vorapaxar relative to placebo

b. Cox PH model with covariates treatment and stratification factors

c. Kaplan-Meier estimate at 1080 days

Note: The primary composite efficacy endpoint is the first occurrence of any component: cardiovascular death, myocardial infarction, stroke, or urgent coronary revascularization. The key secondary composite efficacy endpoint is the first occurrence of any component: cardiovascular death, myocardial infarction, or stroke

Table 25 Other Secondary Efficacy Endpoints in the Proposed Label Population (Event Accrual Period: Randomization to Last Visit)

(Protocol No. P04737)

Endpoints[d]	Placebo (n =8583) Subjects With Events (%)	Placebo KM%[c]	Vorapaxar (n =8608) Subjects With Events (%)	Vorapaxar KM%[c]	Hazard Ratio[a,b] (95% Confidence Interval)	P Value[b]
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 Revasc	1424 (16.9%)	18.7%	1294 (15.3%)	17.2%	0.90 (0.83 - 0.97)	0.005
CV death/MI/Stroke/Any Revasc/UH-VCIN	1398 (16.6%)	18.2%	1269 (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 Revasc	1027 (12.2%)	13.5%	939 (11.1%)	12.5%	0.91 (0.83 - 0.99)	0.029

Note: For composite endpoints, the endpoint is the first occurrence of any component of the composite.

[a] Vorapaxar versus placebo; a hazard ratio <1 indicates lower hazard associated with vorapaxar relative to placebo.

[b] Cox proportional hazard model with covariates treatment and stratification factors.

[c] Kaplan-Meier estimate at 1080 days.

[d] All events were counted in the case of multiple events.

Table 26 Annualized Event Rates for Primary, Key Secondary and Other Secondary Efficacy Endpoints Proposed Label Population Event Accrual Period: Randomization to Last Visit

Protocol No. (P04737)

	Proposed Labeled Population			
	Placebo (n=8439)		Vorapaxar (n=8458)	
	Subjects with Events (%)	Annualized Event Rate[a]	Subjects with Events (%)	Annualized Event Rate[a]
Primary Efficacy Endpoint (CV Death / MI / Stroke / UCR)[b]	867 (0.3%)	4.4%	719 (8.5%)	3.6%
CV Death	96 (1.1%)		82 (1.0%)	
MI	451 (5.3%)		374 (4.4%)	
Stroke	84 (1.0%)		60 (0.7%)	
UCR	236 (2.8%)		203 (2.4%)	
Key Secondary Efficacy Endpoint[b] (CV Death / MI / Stroke)	671 (8.0%)	3.3%	532 (6.3%)	2.6%
CV Death	101 (1.2%)		84 (1.0%)	
MI	481 (5.7%)		387 (4.6%)	
Stroke	89 (1.1%)		61 (0.7%)	
Other Secondary Efficacy Endpoint[b]				
CV Death	159 (1.9%)	0.8%	131 (1.5%)	0.6%
All-Cause Death	259 (3.1%)	1.2%	238 (2.8%)	1.1%
MI	486 (5.8%)	2.4%	393 (4.6%)	1.9%

a. Event rate is expressed as number of subjects with events per 100 patient-years of exposure

b. Each subject was counted only once (first component event) in the component summary that contributed to each composite efficacy endpoint

9.3.1 Multiple Occurrences of Adjudicated Endpoints

The results presented below indicate that subjects in the vorapaxar group showed a reduced hazard for total events (including first and recurrent events) for both primary and key secondary composite endpoints compared to the subjects in the placebo group in the Proposed Label Population **(Table 27)**. In this analysis, each event (first or recurrent) is considered an endpoint; a subject who has an MI followed by a stroke would have both events counted (in contrast to other analyses where a patient is censored after the first event). In this analysis, vorapaxar was associated a significant reduction in total events defined in the primary efficacy endpoint (HR 0.80; 95% CI 0.74 – 0.88). A similar result was observed for the reduction of total events defined in the secondary efficacy endpoint.

Table 27 Analysis of Multiple Occurrences of Adjudicated Primary and Secondary Composite Endpoint Component Events in the Proposed Label Population

(Protocol No.P04737)

	Placebo (n=8439)	Vorapaxar (n=8458)	Hazard Ratio[a,b] (95% CI)	P-Value[b]
Primary Efficacy Endpoint*(CV Death / MI / Stroke / UCR)				
Total Events	1160	936	0.80 (0.74 - 0.88)	<0.001
Subjects with only one Event	666	572		
Subjects with two Events	150	106		
Subjects with >= 3 Events	51	41		
Key Secondary Efficacy Endpoint*(CV Death / MI / Stroke)				
Total Events	862	689	0.80 (0.72 - 0.88)	<0.001
Subjects with only one Event	540	424		
Subjects with two Events	97	79		
Subjects with >= 3 Events	34	29		

a. Hazard Ratio is vorapaxar group versus placebo group

b. Hazard Ratio and P-value were calculated based on Andersen-Gill model with covariates treatment and stratification factor (planned thienopyridine use).

In the Proposed Label Population and as shown in **Table 28**, a reduction in total MI events was observed with vorapaxar versus placebo (HR 0.82; 95% CI 0.72 – 0.92). Fewer subjects receiving vorapaxar experienced one or two MI events than subjects receiving placebo. These results suggest that vorapaxar in addition to standard of care, effectively prevented recurrent MI events in the Proposed Label Population.

Table 28 Analysis of Multiple Occurrences of MI in Efficacy Endpoints in the Proposed Label Population
Event Accrual Period: Randomization to Last Visit

(Protocol No. P04737)

	Placebo (n=8439)	Vorapaxar (n=8458)	Hazard Ratio[a,b] (95% CI)	P-Value[b]
Efficacy Endpoint - MI				
Total Events	598	491	0.82 (0.72 - 0.92)	<0.001
Subjects with only one Event	414	333		
Subjects with two Events	49	37		
Subjects with >= 3 Events	23	23		

a. Hazard Ratio is vorapaxar group versus placebo group

b. Hazard Ratio and P-value were calculated based on Andersen-Gill model with covariates treatment and stratification factors (planned thienopyridine use).

9.3.2 Efficacy Results in Subgroups of the Proposed Label Population

As with the Overall Population **(Sec. 8.5.3.1)**, the effect of vorapaxar relative to placebo was shown to be consistent across the majority of subgroups (gender, age, race, and thienopyridine use at baseline) in the Proposed Label Population. These analyses are depicted in **Figure 21** for the primary endpoint and **Figure 22** for the secondary endpoints. As was seen in the Overall Population, the benefit of vorapaxar on both the primary and secondary endpoint appeared greater in subjects with a body weight greater than the median compared to those with a body weight less than the median.

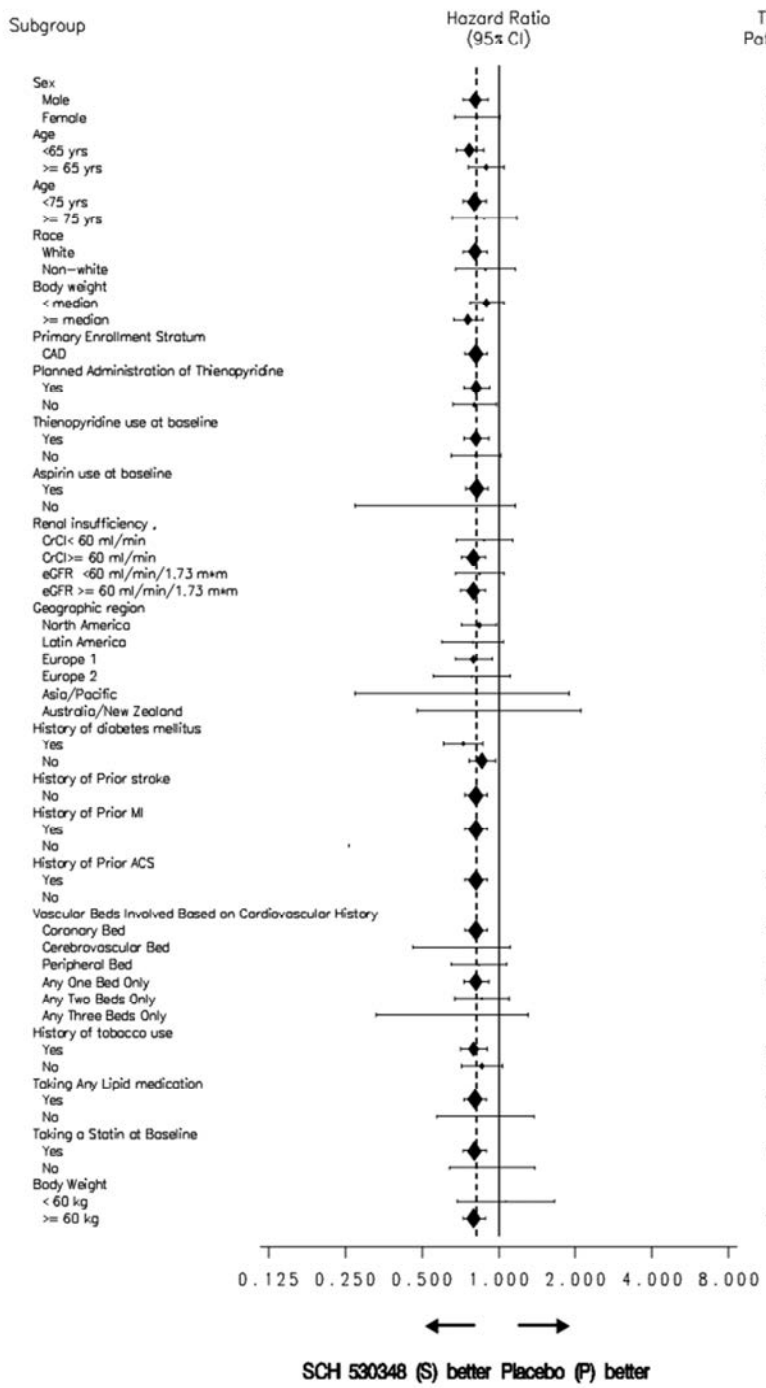


Figure 21 Plot of Hazard Ratio and 95% CI for Primary Efficacy Endpoint in Subjects with No History of Stroke or TIA Whose Qualifying Condition Was CAD by Subgroup ITT Population (Forest Plot)

Note: the < 60 kg/≥ 60 kg subgroup was an exploratory analysis

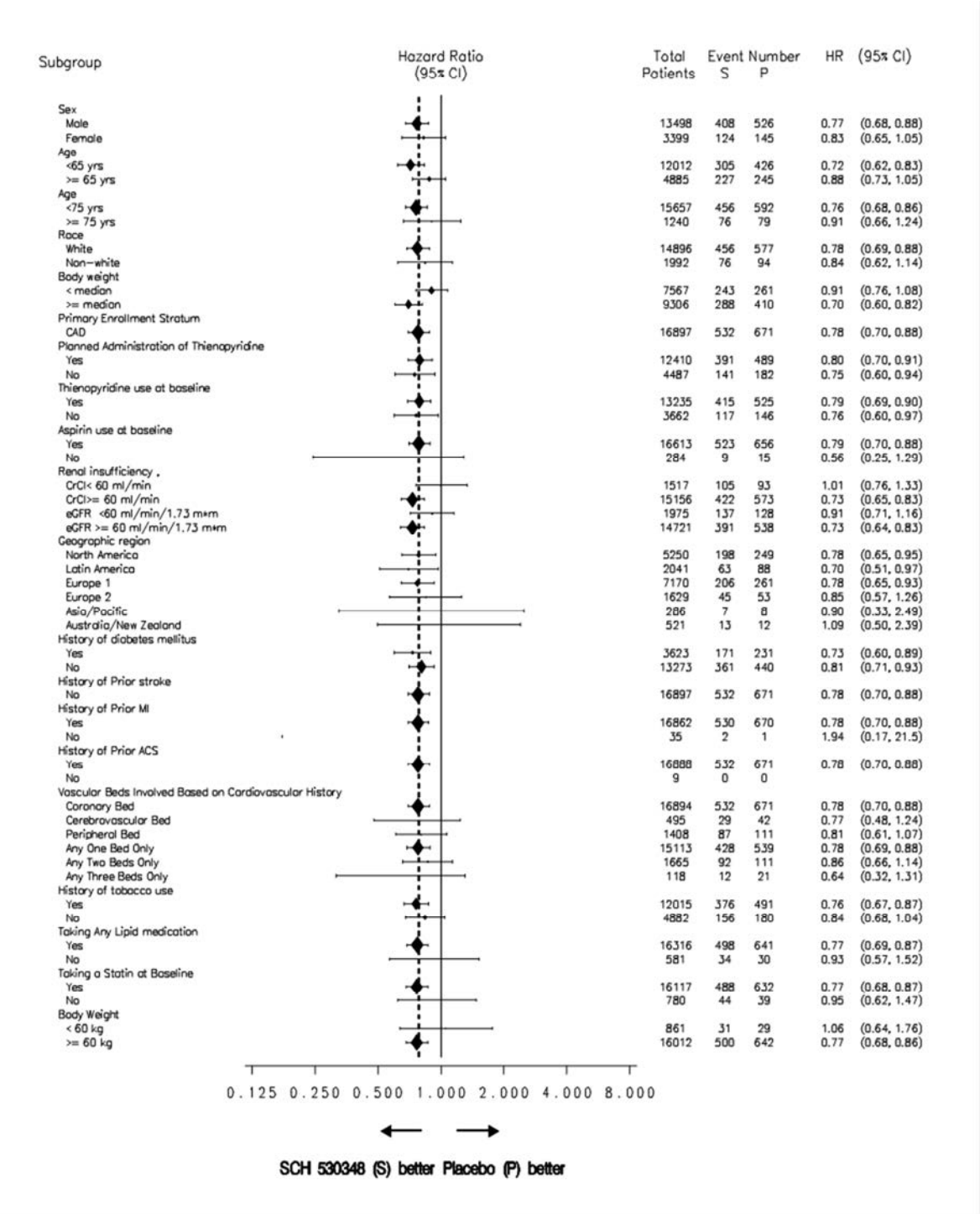


Figure 22 Plot of Hazard Ratio and 95% CI for Key Secondary Efficacy Endpoint in Subjects with No History of Stroke or TIA Whose Qualifying Condition Was CAD by Subgroup: ITT Population (Forest Plot)

Note: the < 60 kg/≥ 60 kg subgroup was an exploratory analysis

9.3.3 Stent Thrombosis

The CEC adjudicated the occurrence of stent thrombosis in subjects with PCI and a stent placement. Stent thrombosis was adjudicated according to the Academic Research Consortium definitions using the cardiac catheterization and intervention reports as a surrogate for angiographic review. The results of the occurrence of stent thrombosis in Proposed Label Population are summarized in **Table 29**. Vorapaxar appeared to reduce the rate of definite, definite or probable, and definite or probable or possible stent thrombosis vs. placebo in subjects receiving any stent before or during the study.

Table 29 Coronary Stent Thrombosis in Subjects in the Proposed Label Population Undergoing PCI with Stent Implanted Prior to, as well as, Prior to or During the Study (TRA 2°P-TIMI 50)

(Protocol No. P04737)

	Placebo (n=8439)		Vorapaxar (n=8458)			
Endpoints[d]	Subjects with Events (%)	KM %[a]	Subjects with Events (%)	KM %[a]	Hazard Ratio[b,c] (95% CI)	p-Value[c]
Subjects receiving any stent prior to randomization or during study	6460		6464			
Definite	80 (1.2%)	1.4%	56 (0.9%)	1.1%	0.70 (0.50 - 0.98)	0.040
Definite or Probable	87 (1.3%)	1.5%	63 (1.0%)	1.2%	0.72 (0.52 - 1.00)	0.050
Definite or Probable, or Possible	145 (2.2%)	2.6%	113 (1.7%)	2.0%	0.78 (0.61 - 0.99)	0.045

a. Kaplan-Meier estimate at 1080 days
b. Hazard Ratio is vorapaxar group versus placebo group
c. Hazard Ratio and P-value were calculated based on Cox PH model with covariates treatment and stratification factors (planned thienopyridine use)
d ARC (Academic Research Consortium) definition

9.4 TRA 2°P –TIMI 50 Safety Results in the Proposed Label Population

9.4.1 Adjudicated Bleeding Endpoints

Table 30 describes the GUSTO, TIMI, and other adjudicated bleeding endpoints that occurred in the Proposed Label Population. Excluding patients with history of stroke or TIA in the Proposed Label Population, reduced the occurrence of ICH and associated GUSTO severe endpoints associated with vorapaxar. The 3 year KM estimates for GUSTO severe or moderate bleeding endpoints were 3.1% in the vorapaxar group (severe 1.2% and moderate 2.1%) and 2.2% in the placebo group (severe 1.0% and moderate 1.2%) (HR 1.48; 95% CI, 1.21 to 1.82; p<0.001). Annualized event rates were 1.1 events per 100 subject-years of exposure in the vorapaxar group and 0.8 events per 100 subject-years of exposure in the placebo group. Fatal bleeding event rates were 0.2% for the vorapaxar and placebo groups (HR, 0.99; 95% CI, 0.47 to 2.09; p=0.989).

For clinically significant bleeding (i.e., TIMI major or minor bleeding, or bleeding that required unplanned treatment or evaluation) the 3 year KM estimate was 14.6% for vorapaxar vs. 10.2% for placebo (HR 1.46; 95% CI, 1.34 to 1.60; p<0.001).

Despite the recommendation to continue study drug during CABG, CABG-related TIMI major bleeding occurred at the same event rate (0.1%) in both treatment groups (HR; 1.00: 95% CI 0.37-2.66; p=0.996). This is further discussed in **Section 10.2.1**.

The most common GUSTO moderate or severe bleeding endpoints were gastrointestinal events **(Table 31)**.

Table 30 TRA 2ºP-TIMI 50 Bleeding Endpoints with Annualized Event Rates in the Proposed Label Population: Event Accrual Period Randomization to Last Visit

(Protocol No. P04737)

Endpoints	Placebo (n =8412)			Vorapaxar (n =8444)			Hazard Ratio[a,b] (95% Confidence Interval)	p-value[b]
	Subjects With Events (%)	KM%[c]	Annualized Event Rate[d]	Subjects With Events (%)	KM%[c]	Annualized Event Rate[d]		
GUSTO Bleeding Categories								
Severe or Moderate[e]	156 (1.9%)	2.2%	0.8%	231 (2.7%)	3.1%	1.1%	1.48 (1.21-1.82)	<0.001
Severe	73 (0.9%)	1.0%	0.4%	85 (1.0%)	1.2%	0.4%	1.16 (0.85-1.59)	0.352
Moderate	88 (1.0%)	1.2%	0.4%	152 (1.8%)	2.1%	0.7%	1.73 (1.33-2.25)	<0.001
CABG-Related Severe or Moderate	8 (0.1%)	0.1%	<0.1%	6 (0.1%)	0.1%	<0.1%	0.75 (0.26-2.16)	0.591
TIMI Bleeding Categories								
Major or Minor[e]	175 (2.1%)	2.4%	0.8%	259 (3.1%)	3.5%	1.3%	1.48 (1.22 - 1.80)	<0.001
Major	133 (1.6%)	1.8%	0.6%	161 (1.9%)	2.2%	0.8%	1.21 (0.96 - 1.52)	0.108
Minor	47 (0.6%)	0.6%	0.2%	105 (1.2%)	1.4%	0.5%	2.23 (1.58 - 3.15)	<0.001
Clinically Significant[f]	785 (9.3%)	10.2%	4.0%	1120 (13.3%)	14.6%	5.9%	1.46 (1.34 - 1.60)	<0.001
Non CABG-Related Major or Minor[e]	167 (2.0%)	2.3%	0.8%	251 (3.0%)	3.4%	1.2%	1.50 (1.24 - 1.83)	<0.001
Major	125 (1.5%)	1.7%	0.6%	153 (1.8%)	2.1%	0.7%	1.22 (0.96 - 1.55)	0.098
CABG-Related Major	8 (0.1%)	0.1%	<0.1%	8 (0.1%)	0.1%	<0.1%	1.00 (0.37 - 2.66)	0.996
Other Categories								
Intracranial Hemorrhage	30 (0.4%)	0.5%	0.1%	38 (0.5%)	0.5%	0.2%	1.26 (0.78 - 2.03)	0.348
Fatal ICH	8 (0.1%)	0.1%	<0.1%	10 (0.1%)	0.2%	<0.1%	1.24 (0.49-3.14)	0.649

Table 30 TRA 2ºP-TIMI 50 Bleeding Endpoints with Annualized Event Rates in the Proposed Label Population: Event Accrual Period Randomization to Last Visit

(Protocol No. P04737)

Endpoints	Placebo (n =8412)			Vorapaxar (n =8444)			Hazard Ratio[a,b] (95% Confidence Interval)	p-value[b]
	Subjects With Events (%)	KM%[c]	Annualized Event Rate[d]	Subjects With Events (%)	KM%[c]	Annualized Event Rate[d]		
Fatal Bleeding	14 (0.2%)	0.2%	0.1%	14 (0.2%)	0.2%	0.1%	0.99 (0.47 - 2.09)	0.989

Note: Only TIMI major is an appropriate categorization in the context of CABG (in the Clinical Endpoints Committee Manual of Operations).

[a] Vorapaxar vs. placebo; a hazard ratio <1 indicates lower hazard associated with vorapaxar relative to placebo.

[b] Cox proportional hazards model with covariates of treatment and stratification factors.

[c] Kaplan-Meier estimate at 1080 days.

[d] Event rate is expressed as number of patients with events per 100 patient-years of exposure

[e] Subcategories are mutually exclusive; each subject appears only in the highest intensity subcategory observed for that subject.

[f] TIMI Major or Minor bleeding, or bleeding that requires unplanned medical or surgical treatment, or unplanned evaluation via laboratory test.

Table 31 Subjects (n %) with Bleeding Events Classified as CEC GUSTO Severe or Moderate Bleeding Endpoints by System Organ Class Randomization to Last Visit: Proposed Label Population

(Protocol No. P04737)

	Placebo (n=8412)	Vorapaxar (n=8444)
System Organ Class[a]	n (%)	n (%)
Subjects Reporting Any Bleeding Event	156 (1.9)	231 (2.7)
Gastrointestinal Disorders	75 (0.9)	109 (1.3)
Injury, Poisoning, and Procedural Complications	27 (0.3)	48 (0.6)
Nervous System Disorders	24 (0.3)	30 (0.4)
Renal and Urinary Disorders	7 (0.1)	13 (0.2)
Vascular Disorders	11 (0.1)	20 (0.2)

a. System Organ Class reported if at least 20 subjects with events in either treatment group

9.4.2 Intracranial Hemorrhage in the TRA 2ºP-TIMI 50 Proposed Label Population

As discussed above, the rates of ICH were higher in subjects with a history of stroke compared to subjects without a history of stroke **(Table 18)**. In subjects randomized to placebo, the 3 year KM rates for ICH were 0.9% in subjects with a history of stroke compared to 0.5% in subjects without a history of stroke. Not only are the rates of ICH higher in patients with a history of stroke, but also the risk of ICH associated with vorapaxar is significantly higher in subjects with a prior history of stroke. In patients with a history of stroke, the 3 year KM event rates for ICH were 2.7% for vorapaxar and 0.9% for placebo (HR 2.55; 95% CI 1.56 to 4.18; p<0.001). In contrast, in subjects without a history of stroke or TIA (Proposed Label Population), the 3 year KM event rates for ICH were 0.5% for vorapaxar and 0.5% for placebo (HR 1.26; 95% CI 0.78 to 2.03; p=0.348). The annualized rates for ICH were 0.2% for vorapaxar and 0.1% for placebo.

Subjects in the Proposed Label Population who experienced ICH had a median age of 65 years, and were predominantly white (85.7%) and male (72%). Median body weight was 75.3 kg, with 89.8% of subjects having a weight ≥60 kg. Median systolic blood pressure was 137 mmHg and median diastolic pressure was 79 mmHg. There was no clinically meaningful difference in demographics between the treatment groups. **Figure 23** displays Forest plots for the CEC adjudicated ICH in subgroups of the Proposed Label Population.

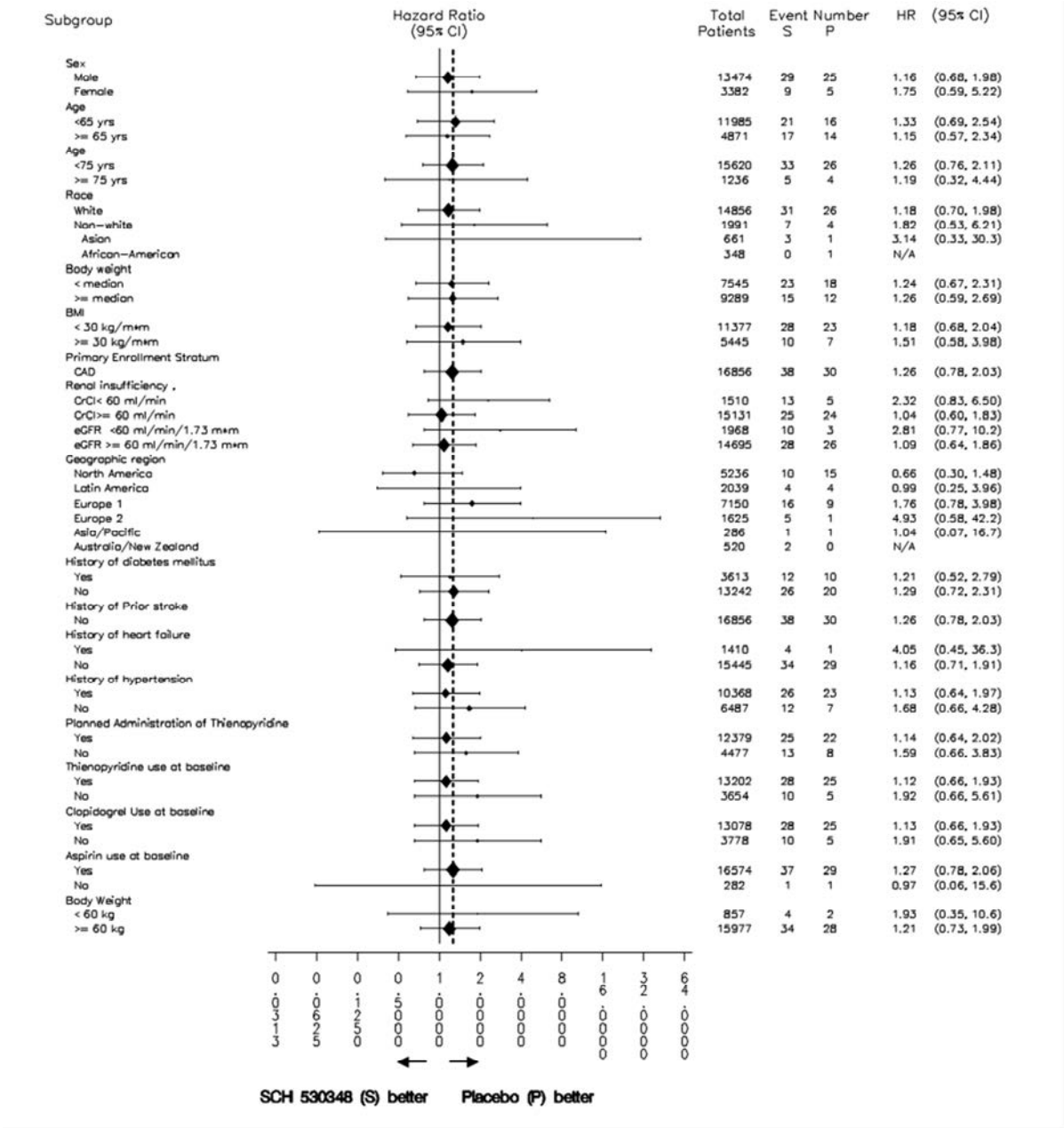


Figure 23 Plot of Hazard Ratio (95% CI) and Event Rate for ICH by Subgroup in Proposed Label Population Event Accrual Randomization to Last Visit

Table 32 includes the associated causes of the 68 events of ICH reported in the Proposed Label Population. Of the 38 cases of ICH in the vorapaxar group, 16/38 were spontaneous, with an annualized event rate of 0.1 events per 100 subject-years of exposure. Of the 30 cases of ICH in the placebo group, 7/30 were spontaneous, with an annualized event rate of 0.1 events per 100 subject-years of exposure. Traumatic ICH accounted for 25 of the 68 cases: 14 in the vorapaxar group and 11 in the placebo group. Non-fatal ICH occurred in 49 subjects, 27 on vorapaxar and 22 on placebo. Fatal ICH occurred in 18 subjects, 10 on vorapaxar and 8 on placebo.

Table 32 Intracranial Hemorrhage Etiology and Outcome: TRA 2ºP – TIMI 50 Proposed Label Population As Treated Population: Event Accrual Period: Randomization to Last Visit

(Protocol No. P04737)

	Subjects With Events (%)					
	Placebo (n=8412)		Vorapaxar (n=8444)		Total (n=16856)	
Event	n (%)	Event Rate[a]	n (%)	Event Rate[a]	n (%)	Event Rate[a]
Intracranial Hemorrhage	30 (0.36)	0.1%	38 (0.45)	0.2%	68 (0.40)	0.2%
Cause[e]						
Spontaneous	7 (0.08)	0.1%	16 (0.19)	0.1%	23 (0.13)	0.1%
Traumatic	11 (0.13)	0.1%	14 (0.17)	0.1%	25 (0.15)	0.1%
Surgery/Procedure	1 (0.01)	0.1%	2 (0.02)	<0.1%	3 (0.02)	<0.1%
Mass/Tumor	2 (0.02)	<0.1%	1 (0.01)	<0.1%	3 (0.02)	<0.1%
Intracranial Vascular	0	0	0	0	0	0
Fibrinolysis	2 (0.02)	<0.1%	2 (0.02)	<0.1%	4 (0.02)	<0.1%
Other	9 (0.11)	<0.1%	5 (0.06)	<0.1%	14 (0.08)	<0.1%
Outcome						
Fatal[b]	8 (0.10)	<0.1%	10 (0.12)	<0.1%	18 (0.10)	<0.1%
Non-fatal[c]	22 (0.26)	0.1%	27 (0.32)	0.1%	49 (0.29)	0.1%
Contributing to death[d]	0	0	1 (0.01)	<0.1%	1(<0.1)	<0.1%

a. Event rate is expressed as number of patients with events per 100 patient-years exposure

b. ICH that leads directly to death generally within 7 days (e.g. mass effect and herniation leading directly to death.

c. ICH without death within 30 days or death from causes not related to ICH (e.g.: subject with subdural hematoma following fibrinolytic for STEMI. Subject dies 7 days later of shock from progressive CHF following MI.

d. ICH was part of a chain of events in the causal pathway leading to death generally within 30 days without immediately or directly causing the death (e.g.: ICH without immediate death, but death following infectious complications of prolonged ventilation.

e. First ICH event is counted

9.4.3 Bleeding Endpoints in Subgroups Identified by Baseline Characteristics in the TRA 2ºP-TIMI 50 Proposed Label Population

Subgroup analyses based on demographic and other baseline characteristics are displayed for GUSTO severe or moderate bleeding for the Proposed Label Population **(Figure 24)**. Consistent with the trial overall, in this population there was an increase in bleeding endpoints associated with vorapaxar treatment compared with placebo treatment across the subgroups examined. The effect of vorapaxar on the bleeding endpoints relative to placebo was shown to be consistent across the majority of subgroups. Concomitant medical conditions or medical history of diabetes mellitus, and history of heart failure or hypertension did not significantly impact the bleeding risk.

In addition, the concomitant use of antiplatelet treatments did not appear to have a clear impact on bleeding risk. The risk of GUSTO severe or moderate bleeding was similar in the stratum of subjects who had planned administration of thienopyridines as well as in those subjects using thienopyridines at baseline. An assessment of bleeding risk relative to the use of aspirin is limited by the very small number of subjects (282/16,856) who were not taking aspirin at baseline.

Based on subgroup analysis in the Overall Population, a higher rate of ICH was observed in subjects weighing <60 kg who were treated with vorapaxar compared to subjects weighing 60 kg or greater. Most of the affected subjects had a history of stroke or TIA and hence in the Proposed Label Population, from which these subjects were excluded, the GUSTO severe bleeding rates, which include ICH were similar in subjects above and below the 60 kg cutpoint.

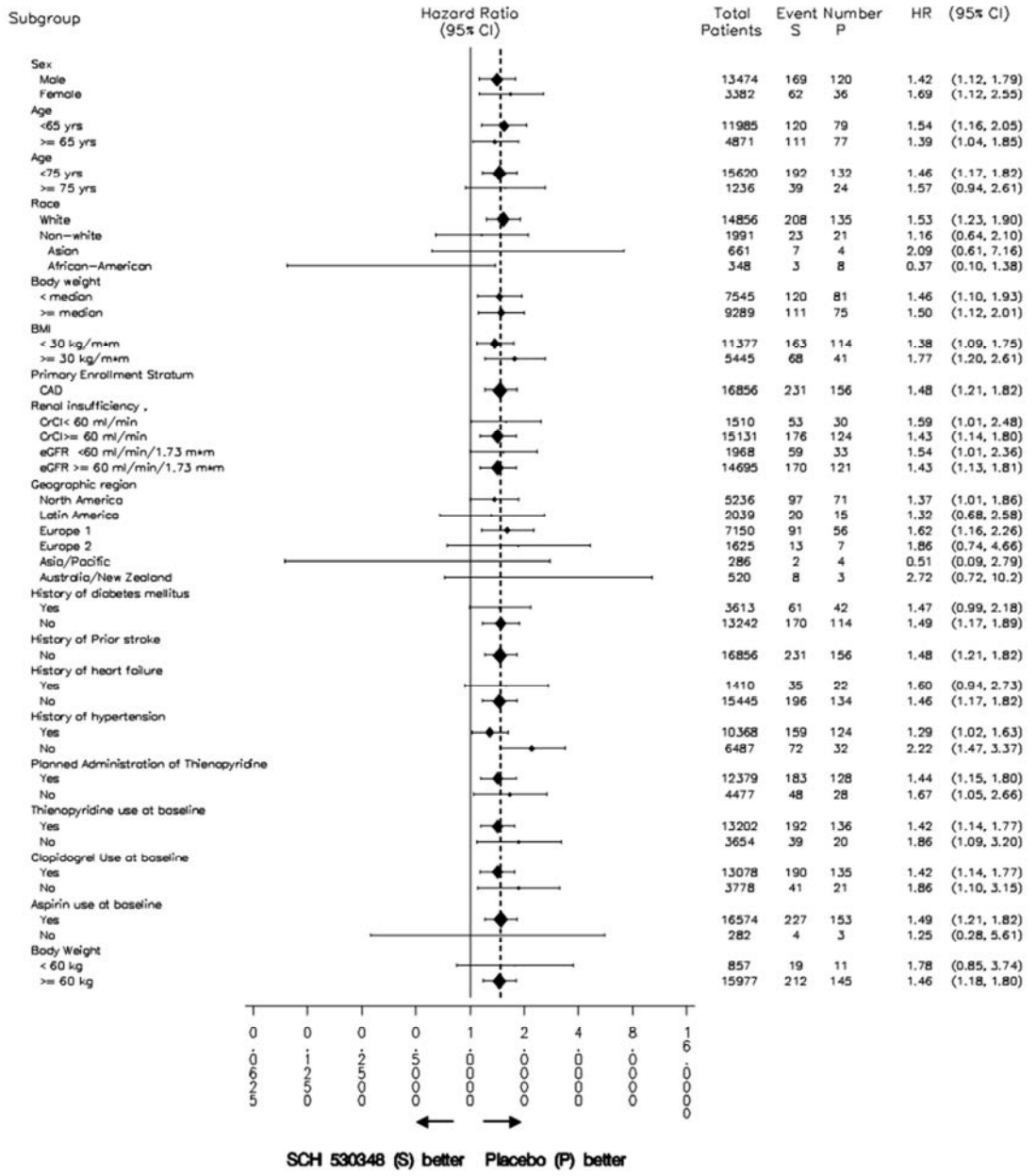


Figure 24 Plot of Hazard Ratio (95% CI) and Event Rate for GUSTO-Severe or Moderate Bleeding Events by Subgroups for Proposed Label Population (Randomization to Last Visit)

9.4.4 Individual Bleeding Events in the TRA 2ºP-TIMI 50 Proposed Label Population

Unadjudicated Investigator assessments of Bleeding Events for the Proposed Label Population were similar to the Overall Population:

More subjects reported bleeding events in the vorapaxar group (25.7%) compared to the placebo group (18.1%) with annualized event rates of 14.2 and 9.3 events per 100 subject-years of exposure, respectively.

The most frequently reported bleeding event was epistaxis, 7.2% for vorapaxar group compared to 3.6% for placebo with an annualized event rate of 3.4 and 1.7 events per 100 subject-years of exposure, respectively.

The other most frequently reported bleeding events were contusion (3.5% vorapaxar vs. 2.6% placebo), increased tendency to bruise (2.6% vorapaxar vs. 1.6% placebo) and hematuria (2.5% vorapaxar vs. 2.0% placebo).

9.4.5 Adverse Bleeding Events Leading to Discontinuation in the TRA 2ºP-TIMI 50 Proposed Label Population

For the Proposed Label Population, discontinuation due to bleeding events was similar to that in the Overall Population. More subjects in the vorapaxar group (2.9%) discontinued treatment due to bleeding events compared to subjects in the placebo group (1.7%).

A large proportion of bleeding events leading to treatment discontinuation were categorized in the gastrointestinal System Organ Class (SOC) (80 [0.9%] subjects in the vorapaxar group and vs. 53 [0.6%] subjects in the placebo group). The most frequently reported single bleeding event resulting in treatment discontinuation in both treatment groups was epistaxis (40 [0.5%] in the vorapaxar group and 16 [0.2%] in the placebo group).

9.4.6 Other (Non-Bleeding) Serious Adverse Events in the TRA 2ºP-TIMI 50 Proposed Label Population

Non-bleeding Serious Adverse Events are presented in order of decreasing frequency based on the vorapaxar treatment group in **Table 33**. The incidence of these events was similar in the two treatment groups.

Table 33 Most Frequent Reported Serious Other (Non Bleeding) Adverse Events by Subject Population: As Treated: Proposed Label Population: Event Accrual Period: Randomization to Last Visit

(Protocol No. P04737)

Event	Number (%) of Subjects			
	Proposed Label Population			
	Placebo		Vorapaxar	
	(n =8412)		(n =8444)	
	n	(%)	n	(%)
Subjects Reporting Any Serious Other Adverse Event	1772	(21.1)	1702	(20.2)
Non-Cardiac Chest Pain	365	(4.3)	338	(4.0)
Cardiac Failure	86	(1.0)	87	(1.0)
Pneumonia	71	(0.8)	74	(0.9)
Atrial Fibrillation	49	(0.6)	67	(0.8)
Syncope	29	(0.3)	41	(0.5)
Cardiac Failure Congestive	37	(0.4)	36	(0.4)
Osteoarthritis	50	(0.6)	37	(0.4)

9.4.7 Other (Non-Bleeding) Adverse Events Resulting in Discontinuation in the TRA 2ºP-TIMI 50 Proposed Label Population

Other (non-bleeding) adverse events resulting in treatment discontinuation were assessed for the Proposed Label Population**.**

As with the Overall Population, a proportion of subjects reported an 'other' AE that resulted in discontinuation of treatment (6.0% for vorapaxar and 6.2% for placebo). Similarly, of the individual events reported, anemia was the most frequently reported event with a higher incidence observed with vorapaxar than with placebo (0.3% for vorapaxar and 0.1% for placebo). In subjects with an event of ‘anemia,’ approximately 51.0% of vorapaxar subjects and 32.9% of subjects on placebo also reported a bleeding event. This is consistent with the observed increased proportions of subjects with any bleeding event in the vorapaxar compared to the placebo treatment groups.

9.4.8 All- Cause Death in the TRA 2ºP-TIMI 50 Proposed Label Population

As described previously, all deaths that occurred at any time during the trial were analyzed. There were fewer deaths from any cause in the vorapaxar treatment group than in the placebo group. In the Proposed Label Population, a small proportion of subjects were reported to have died following their last study visit **(Table 34)**.

Table 34 All-Cause Death Recorded in TRA 2ºP-TIMI 50 Intent-to-Treat Proposed Label Population[a,b]

Protocol No. P04737

	During the Study	
	Proposed Label Population	
	Placebo	**Vorapaxar**
	(n=8439)	**(n=8458)**
	n (%)	n (%)
Total No. Of Deaths	278 (3.3)	253 (3.0)
CV Death	163 (1.9)	138 (1.6)
Non-CV Death	103 (1.2)	98 (1.2)
Unknown	12 (0.1)	17 (0.2)
Total No. Of Deaths On or Before the Last Visit	259 (3.1)	238 (2.8)
Total No. of Deaths After the Last Visit	19 (0.2)	15 (0.2)

a. Death Date recorded by Adjudicator is used, if different from the one recorded by Investigator.
b. For subjects with partial death date, the death date is estimated
c. Categories as determined by CEC adjudication

9.4.9 Management of Bleeding: Bleeding Duration and Impact of Intervention

9.4.9.1 Therapeutic Procedures to Control Bleeding in the Proposed Label Population

In the Proposed Label Population, there were 234 subjects on vorapaxar and 157 subjects on placebo who experienced a CEC-adjudicated GUSTO moderate or severe bleeding event[4] with 132/234 vorapaxar subjects and 94/157 placebo subjects having a procedure to stop the bleeding. The most common therapeutic procedures were GI endoscopies (74/132 subjects in the vorapaxar group and 47/94 subjects in the placebo group). For the TRA 2ºP-TIMI 50 Proposed Label Population, the analysis of the duration from the first procedure to the end of first bleed event was performed. As with the TRA 2ºP-TIMI 50 Overall Population, although bleeding was more common in the vorapaxar treatment group, the duration of bleeding was similar between treatment groups. The median (25th to 75th percentile) duration in days was 3.0 (1.0 – 6.0) in the vorapaxar group and 3.0 (1.0 – 5.0) in the placebo group **(Table 35)**. Thus, standard supportive care, including interventions provided resolution of bleeds in the vorapaxar arm in a manner similar to that in the placebo group.

[4] This analysis did not truncate the bleeding events at the subjects' last visit, so there is an excess of 3 vorapaxar and 1 placebo event compared with the primary bleeding analysis.

Table 35 Duration from the First Procedure to the End of First Bleed Event TRA 2ºP-TIMI 50 Proposed Label Populations

(Protocol No. P04737)

	TRA 2ºP-TIMI 50 Proposed Label Population	
	Placebo n (%)	**Vorapaxar n (%)**
Number of Subjects with a Bleeding Event	157	234
	Duration from First Procedure/Surgery/Revasc/PCI to End of First Bleeding (Days)	
Number of Subjects	84	128
Mean(SD)	4.9 (10.40)	8.7(24.80)
Median (25th to 75th Percentile)	3.0(1.0-5.0)	3.0(1.0-6.0)

Subject may have had more than one type of procedure/surgery and can be counted in multiple rows.
This analysis did not truncate the bleeding events at the subjects' last visit, so there is an excess of 3 vorapaxar and 1 placebo event compared with the primary bleeding analysis.

9.4.9.2 Transfusions in the TRA 2ºP-TIMI 50 Proposed Label Population

In the Proposed Label Population, 233 subjects on vorapaxar and 157 subjects on placebo had a bleeding event. The most common transfusions recorded were whole blood transfusion and/or packed red blood cells (PRBC) transfusion in 170 subjects (73.0%) in the vorapaxar group and 106 subjects (67.5%) in the placebo group. **(Table 36)** Platelet transfusion was recorded in 24 subjects (10.3%) in the vorapaxar group and 13 subjects (8.3%) in the placebo group. Fresh-frozen plasma (FFP) transfusion was recorded in 27 subjects (11.6%) in the vorapaxar group and 13 subjects (8.3%) in the placebo group. Among subjects who had bleeding events, approximately the same percentage received transfusions regardless of treatment groups. In addition, the distribution of the number of units of transfused products received was similar in both treatment arms. The use of FFP and platelet transfusions was relatively infrequent and generally did not occur without PRBC transfusion.

There were 8 subjects who received platelet transfusions alone (4 subjects in the vorapaxar group and 4 subjects in the placebo group). The 4 subjects on vorapaxar who received platelet transfusions did so following traumatic or spontaneous ICH. All four subjects survived; however, sufficient data was not collected to indicate whether or not the platelet transfusions were beneficial.

Table 36 Summary Results for Subjects Who Received One or More Transfusions within 2 Days after a Bleeding Event for Subjects with CEC-Adjudicated GUSTO Moderate/Severe Bleeding TRA 2ºP-TIMI 50 Proposed Label Populations

(Protocol No. P04737)

	TRA 2ºP-TIMI 50 Proposed Label Population	
	Placebo n (%)	**Vorapaxar n (%)**
Number of Subjects with a Bleeding Event	157	233
Any Transfusion	109 (69.4)	178 (76.4)
Whole Blood Transfusion	26 (16.6)	39 (16.7)
Packed Red Blood Cell Transfusion	81 (51.6)	135 (57.9)
Whole Blood and/or PRBC Transfusion	106 (67.5)	170 (73.0)
<3 Units	57 (36.3)	84 (36.1)
3-5 Units	34 (21.7)	64 (27.5)
>5 Units	11 (7.0)	19 (8.2)
Missing	4 (2.5)	3 (1.3)
Platelet Transfusion	13 (8.3)	24 (10.3)
Fresh-Frozen Plasma Transfusion	13 (8.3)	27 (11.6)
Cryoprecipitate Transfusion	1 (0.6)	6 (2.6)
Missing	0	1 (0.4)

Note: Units represent the single largest 2-day total for the indicated transfusate.

Note: Table summarizes all subjects who received one or more transfusions that began within 2 Days after any bleeding event for subjects with CEC-Adjudicated GUSTO Moderate/Severe Bleeding

Note: Subject may have had more than one type of transfusion and can be counted in multiple rows.

9.5 TRA 2°P –TIMI 50 Efficacy and Safety Conclusions for the Proposed Label Population

The Proposed Label Population substantiated an already robust treatment effect observed in the Overall Population. In the Proposed Label Population (post MI subjects with no history of stroke or TIA), a daily dose of 2.5 mg vorapaxar reduced the primary and key secondary efficacy endpoints by 18 and 22%, respectively relative to placebo. There was a reduction in all components of the composite endpoints; the individual component that most contributed to the difference between vorapaxar and placebo was the reduction in the rate of MIs. The incidence of stroke was higher in the Overall Population than in the Proposed Label Population; placebo events were 2.5% vs. 1.2%, respectively. Importantly, in the Proposed Label Population where patients with a prior history of stroke or TIA are excluded, the relative risk of a subject's first stroke was 38% less (0.7% vs. 1.2%) in the vorapaxar group compared to the placebo group.

The treatment effect of chronic dosing with vorapaxar 2.5 mg/day on the primary and key secondary endpoints was shown to be durable and can be viewed as constant and persistent over the length of the study, as demonstrated by continuous separation of the KM curves. In addition to the reduction of the first event within a composite endpoint (CV death, MI, stroke), an exploratory analysis of multiple occurrences of adjudicated endpoints indicated that vorapaxar was associated with a reduction in the incidence of recurrent events. The effect of vorapaxar was consistent among the subgroups examined. In addition, an exploratory analysis suggested that vorapaxar reduced the risk of coronary stent thrombosis.

In the Proposed Label Population, the risk of GUSTO moderate or severe bleeding was greater in the vorapaxar group compared to placebo (KM 3-yr rate 3.1% vs. 2.2%; $p < 0.001$), but the difference was driven principally by GUSTO moderate bleeding. The most frequent bleeding site was gastrointestinal. Although of greater frequency, the need for intervention as well as for transfusions and the median time from procedure to bleeding resolution were similar between vorapaxar and placebo, with a few outliers in the vorapaxar group. Thus, standard supportive care, including interventions, provided resolution of bleeds in both the vorapaxar and placebo group.

In the Proposed Label Population where patients with a history of stroke or TIA were excluded, the critical components of GUSTO severe bleeding, namely the risk of ICH and fatal bleeds, were reduced compared to the Overall Population. The incidence rate of ICH in the vorapaxar group was similar to that in the placebo group (0.5% vs. 0.4%, respectively) and fatal bleeding rates were the same in both treatment groups (0.2 %).

The most frequently reported reason for discontinuation of treatment due to bleeding, which was higher in the vorapaxar group, was epistaxis. The effect of vorapaxar relative to placebo on bleeding risk was consistent across the majority of subgroups in both the Overall and the Proposed Label Populations, including most demographic and baseline characteristics on the bleeding endpoints (GUSTO severe or moderate bleeding, GUSTO severe bleeding only, TIMI major or minor bleeding, non CABG TIMI major or minor bleeding, and clinically significant bleeding).

Taken together, in patients post MI that do not have a history of stroke or TIA, the robust benefits of vorapaxar outweigh the risk of bleeding. More formal assessments of the benefit-risk profile of vorapaxar in this population are discussed in greater detail in **Section 12**.

10 AREAS OF SPECIAL INTEREST

10 AREAS OF SPECIAL INTEREST

The following section presents analyses of other important areas that were examined in the clinical development of vorapaxar. These include potential for rebound, follow-up on ocular safety, and the use of vorapaxar in CABG and other major surgery.

10.1 Potential for Rebound

The withdrawal of antiplatelet agents such as clopidogrel have been implicated in an increase in inflammatory biomarkers and platelet activation 1 month after drug discontinuation, which in turn has been associated with an increase in adverse clinical endpoints [20]. This ‘‘rebound phenomenon’’ is also well established with agents such as heparin [21]. The potential for rebound was thus explored in the vorapaxar development program.

As described in **Section 5.5.1**, TRAP-induced platelet aggregation was evaluated in healthy volunteers and in patients. Upon cessation of dosing to steady state, inhibition of TRAP-induced platelet aggregation remains at target levels for up to 4 weeks while normalization of TRAP-induced platelet aggregation occurs between 4 to 8 weeks after dosing, depending on the assumed EC50 (**Section 5.5.1**). The reduction in vorapaxar plasma concentrations is gradual due to the long half-life of vorapaxar (187 hours) and is the basis for a relatively long period before there is rapid normalization in platelet function.

To support the hypothesis that rebound hypercoagulability does not occur following discontinuation of vorapaxar, the clinical data from the Phase 3 program were examined. Subjects who discontinued study drug and continued to be followed in the trial may provide the best representation of withdrawal events. **Table 37** includes the analysis of the primary and secondary endpoints that occurred within 30 days after the final dose of study drug for subjects who discontinued the TRA 2ºP-TIMI 50 trial prematurely but continued in follow up. Consistent with a lack of rebound, there was no excess of observed atherothrombotic events (as defined by the primary efficacy endpoints) in the vorapaxar vs. the placebo groups in these subjects.

Table 37 Assessment of Primary and Key Secondary Endpoints 30 Days After Off Treatment in Subjects Who Discontinued Treatment Prematurely: Overall Population[a,b]

(Protocol No. P04737)

	Placebo (n=2746)	**Vorapaxar (n=2933)**
	Subjects with Events[c] (%)	**Subjects with Events[c] (%)**
Primary Efficacy Endpoint (CV Death / MI / Stroke / UCR)[c,d]	73 (2.7%)	68 (2.3%)
CV Death	37 (1.3%)	39 (1.3%)
MI	20 (0.7%)	14 (0.5%)
Stroke	14 (0.5%)	13 (0.4%)
Ischemic (Non- hemorrhagic* Cerebral Infarction)	12 (0.4%)	10 (0.3%)
Hemorrhagic Stroke[e]	2 (0.1%)	3 (0.1%)
Uncertain	0	0
UCR	2 (0.1%)	2 (0.1%)
Key Secondary Efficacy Endpoint (CV Death / MI / Stroke)[c,d]	71 (2.6%)	66 (2.3%)
CV Death	37 (1.3%)	39 (1.3%)
MI	20 (0.7%)	14 (0.5%)
Stroke	14 (0.5%)	13 (0.4%)
Ischemic (Non- hemorrhagic Cerebral Infarction)	12 (0.4%)	10 (0.3%)
Hemorrhagic Stroke[e]	2 (0.1%)	3 (0.1%)
Uncertain	0	0

a. Includes treated subjects with last visit day > the on-treatment period.

b. On-treatment is defined as from first dose date to last recorded dose date + 3 days. The event accrual period is defined as from the first day post the on-treatment period to 30 days later to the last visit day, whichever came first.

c. The endpoint of interest will be the first clinical events during the event accrual period. It means that subjects may have already had clinical events during the period that the subject was treated, and this analysis will only include new clinical events (first or subsequent) during the event accrual period.

d. Each subject was counted only once (first component event) in the component summary that contributed to each composite efficacy endpoint.

e. Includes primary intracerebral hemorrhage, non-hemorrhagic infarction with hemorrhagic conversion, and subarachnoid hemorrhage.

10.2 Vorapaxar Use in Major Surgery

10.2.1 Coronary Artery Bypass Graft (CABG) Surgery

In both TRA 2ºP-TIMI 50 and TRACER trials, CABG surgeries were undertaken following routine standard of care, as deemed appropriate by the investigators and the treating physicians. Data available at the time (including specific CABG experience in TRA-PCI Phase II study) supported the continuation of vorapaxar during surgical procedures such as CABG. As a result, during the conduct of the study, discontinuation of study drug treatment for CABG was not recommended. However, at the discretion of the investigators and the treating physicians or surgeons, study drug treatment could be temporarily interrupted; 31 subjects on placebo and 36 subjects on vorapaxar interrupted therapy prior to CABG

(Table 40). Use or interruption of other common concomitant medications, such as aspirin or thienopyridine, was per routine standard of care.

The analyses that follow did not evaluate the effect of interruption or termination of other concomitant medications such as aspirin or clopidogrel that might have influenced the bleeding outcomes.

10.2.1.1 CABG Surgery in the TRA 2ºP-TIMI 50 Overall Population

During the study, among the Overall Population, 419 subjects underwent CABG surgery (230 on placebo vs. 189 on vorapaxar). The bleeding rates were low in this population. Only 25 subjects had confirmed TIMI major CABG related bleeding, 13 on placebo, and 12 on vorapaxar (HR 1.06; CI 0.48-2.33) **(Table 38 and Table 39)**. There was only one CABG-related fatal bleeding, and it was in the placebo group.

Table 38 TRA 2ºP-TIMI 50 Bleeding Endpoints in Subjects who Underwent CABG: Event Accrual Period; From Randomization to Last Visit: Overall Population

(Protocol No. P04737)

Endpoint	Subjects With Events (%)		
	Placebo (n =230)	Vorapaxar (n = 189)	Hazard Ratio (95% Confidence Interval)
CABG-Related TIMI Major[a]	13 (5.7%)	12 (6.3%)	1.06 (0.48 - 2.33)
CABG-Related Fatal Bleeding	1 (0.4%)	0	

Note: Subjects who had > 1 CABG during the interval, bleeding associated with 1st CABG is used.

Only TIMI Major is an appropriate categorization in the context of CABG.

a. CABG-related fatal bleeding is defined as having 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.

Blood product transfusion is common with CABG surgery. However, In the TRA 2ºP-TIMI 50 trial, the transfusion rate was low; approximately 30% of the subjects who underwent CABG received any transfusion, with similar distribution between treatment groups. Similarly, there was no significant difference observed in the volume of chest tube drainage or need for reoperation for bleeding between groups.

Table 39 TRA 2ºP-TIMI 50 Other Measures of Bleeding Associated With CABG from Randomization to Last Visit: Overall Population

(Protocol No. P04737

Endpoint	No. of Subjects with Events (Percentage)		Absolute Difference[a] (95% Confidence Interval)	p-value[b]
	Placebo (n =230)	Vorapaxar (n =189)		
Any Blood Product Transfusion	70 (30.4%)	59 (31.2%)	0.78% (-8.11%-9.67%)	0.863
Packed Red Blood Cell Transfusion	56 (24.3%)	48 (25.4%)	1.05% (-7.27%-9.37%)	0.805
Platelet Transfusion	25 (10.9%)	25 (13.2%)	2.36% (-3.93%-8.64%)	0.459
Need for Re-operation for Bleeding	8 (3.5%)	6 (3.2%)	-0.30% (-3.75%-3.14%)	0.863
Endpoint	**Mean Value in mL**		**Absolute Difference[a] (95% Confidence Interval)**	**p-value[b]**
	Placebo (n =230)	Vorapaxar (n =189)		
Chest Tube Drainage After 8 Hours	415.7	411.7	-3.97 (-85.66, 77.73)	0.924
Chest Tube Drainage After 24 Hours[c]	873.7	872.8	-0.87 (-137.56, 135.8)	0.990
Total Drainage	1241.1	1239.2	-1.90 (-212.82, 209.0)	0.986

Note: For subjects who have more than one CABG, data from the first CABG are used. Transfusions are within 2 days after CABG surgery.

a Difference is vorapaxar minus placebo.

b Pearson's $\chi 2$ test.

c If time of chest tube removal is <24 hours from placement, then total drainage will be used also for drainage at 24 hours

10.2.1.2 Treatment Interruption Prior to CABG Surgery

During the study, 31 subjects in the placebo group and 36 subjects in the vorapaxar group interrupted study treatment prior to surgery. The results for CABG-related bleeding endpoints (TIMI major, GUSTO severe or moderate and GUSTO severe bleeding) are presented in **Table 40**. The number of bleeding events is very small and therefore no conclusions can be derived from these data.

Table 40 Bleeding Endpoints Associated with CABG in Subjects Whose Treatment Was or Was Not Interrupted Prior to Surgery: As-Treated Population

(Protocol No. P04737)

Subjects with Bleeding Endpoint	Number of Subjects (%)	
	Placebo (n =157)	Vorapaxar (n =140)
Treatment Interrupted[a]	# Subjects 31	# Subjects 36
CABG-Related GUSTO Severe or Moderate	0	2 (5.6)
CABG-Related GUSTO Severe	0	1 (2.8)
CABG-Related TIMI Major[b]	0	2 (5.6)
Treatment Not Interrupted[a]	# Subjects 126	# Subjects 104
CABG-Related GUSTO Severe or Moderate	8 (6.3)	5 (4.8)
CABG-Related GUSTO Severe	2 (1.6)	2 (1.9)
CABG-Related TIMI Major[b]	8 (6.3)	6 (5.8)

Note: Subjects who permanently discontinued study medication prior to CABG were excluded from this table.

a "Treatment interruption" is defined as an interruption of >2 days prior to CABG.

b Only TIMI Major is an appropriate categorization in the context of CABG

10.2.1.3 CABG Surgery in the TRA 2ºP-TIMI 50 Proposed Label Population

Although the numbers are smaller, similar results were observed for bleeding endpoints among the 288 total subjects who underwent CABG surgery within the Proposed Label Population. The bleeding rate was similarly low; there were only 14 TIMI major CABG-related bleeding, 7 on placebo vs. 7 on vorapaxar (HR 1.17; 95% CI 0.41-3.34). In general, rates for transfusion and chest tube drainage volume were similar between treatment groups. Only 1 CABG-related fatal bleeding event occurred and was in the placebo group.

10.2.2 Other Major Surgery

Bleeding was also examined in 578 subjects who underwent non-CABG cardiac or major thoracic or vascular surgery during treatment in the TRA 2ºP-TIMI 50 trial. GUSTO severe or moderate bleeding occurred in more subjects in the vorapaxar group (n=17, 6.3%) compared to the placebo group (n=13, 4.2%). GUSTO severe bleeding occurred in more subjects in the placebo group (n=9, 2.9%) compared to the vorapaxar group (n=5, 1.9%).

Blood product transfusions occurred in 44/269 (16.3%) vorapaxar subjects and 48/309 (15.5%) placebo subjects. PRBC transfusions occurred in 32/269 (11.9%) vorapaxar and 34/309 (11.0%) placebo subjects. Platelet transfusions occurred in 15 (5.6%) vorapaxar and 7/309 (2.3%) placebo subjects.

10.3 Ocular Safety

10.3.1 Ocular Safety Studies

Preclinical studies identified a low incidence of vacuoles in the inner nuclear layer of the retina of the eye (bilateral) in rats administered ≥10 mg/kg of vorapaxar. This phenomenon has not been observed in mice or monkeys. To address the potential safety concerns raised by the preclinical ocular findings, the Sponsor conducted two clinical studies examining potential ocular effects of vorapaxar. One Phase 1 study (P05185) in mostly healthy volunteers indicated no ocular safety signal for vorapaxar relative to placebo with respect to any of the measures assessed.

The second study (P05183) was conducted as a substudy of the TRA 2ºP-TIMI 50 trial designed to determine the long-term ocular safety of vorapaxar when administered in addition to the standard of care for 1 year, with respect to any changes occurring in the retina, both anatomic and functional, in subjects with documented atherosclerotic disease. Core facilities read Optical Coherence Tomography (OCT) scans and fundus photography to give consistent evaluation of the primary endpoint. The Safety Review Committee (SRC) was composed of retinal specialists who reviewed all data in a blinded manner. Comparing patients on vorapaxar and placebo, no differences in any of the ocular safety parameters assessed in this study were identified.

11 RELEVANCE OF TRACER IN UNDERSTANDING THE USE OF VORAPAXAR IN PATIENTS AFTER A MYOCARDIAL INFARCTION

11 RELEVANCE OF TRACER IN UNDERSTANDING THE USE OF VORAPAXAR IN PATIENTS AFTER A MYOCARDIAL INFARCTION

The relevance of TRACER to our understanding of how vorapaxar should be used and how it will perform in the Proposed Label Population is not straightforward. The TRACER and TRA 2°P - TIMI 50 studies enrolled distinctly different populations. TRACER enrolled subjects in the early hours of an acute coronary syndrome whereas TRA 2°P - TIMI 50 enrolled stable subjects that were > 2 weeks post MI. The impact of selecting subjects at different stages of the atherothrombotic disease process is evident in differences in baseline characteristics and in the natural history of these two populations (described in the placebo arms of the two studies). With these differences in mind, the Sponsor maintains that the effects of vorapaxar in each study should be interpreted in the context of the specific population defined in each trial and should not be pooled. The sections that follow describe these differences and then outline how this information should be used by the clinician to select the appropriate patient for treatment with vorapaxar.

11.1 Important Differences in the Evaluation of Therapeutic Interventions at Different Stages of the Atherothrombotic Disease Process

The vorapaxar Phase 3 clinical program was designed to assess the safety and efficacy of vorapaxar in two mutually exclusive patient populations, during two separate disease presentations, at different stages in the disease process for two separate indications. TRACER enrolled hospitalized subjects in the midst of an acute coronary syndrome. These subjects invariably received parenteral anti-coagulants and loading dose regimens of both anti-coagulants and antiplatelet agents. In an emergency setting these agents are aggressively and often concomitantly initiated in subjects whose susceptibility to bleeding is unknown. In contrast, the post MI stratum of the TRA 2°P - TIMI 50 enrolled subjects that were clinically stable as they were 2 weeks to 1 year post the index event (median 77 days). While both studies included subjects with atherothrombotic coronary artery disease, these two studies evaluated a therapeutic intervention at distinctly different stages in the evolution of the disease process. In order to put the results of the two studies into context, it is important to understand (1) differences in the pathobiology, events, treatments, and procedures that occur at these two stages in the atherothrombotic coronary artery disease process, (2) differences in the design of the TRACER and TRA 2°P-TIMI 50 studies, and (3) differences in the selection of subjects at these two points in time.

Patients presenting with ACS are inherently unstable. The integrity of the coronary artery endothelium may be disrupted and there may be active clot in the artery. As a result of this pathobiology, patients are treated acutely and aggressively with antiplatelet agents that will include aspirin and some combination of oral and/or IV formulations of an antithrombin agent, GPIIb/IIIa antagonists, and $P2Y_{12}$ antagonists. Many patients will undergo PCI and may receive a stent to restore and maintain flow in the coronary artery, a procedure which in-and-of-itself is pro-thrombotic. The design of the TRACER study took these issues into account and utilized a 40 mg loading dose of vorapaxar to ensure complete inhibition of thrombin induced platelet aggregation at this unstable, pro-thrombotic stage of the disease process.

As one would expect, the baseline characteristics of the patients at these two stages of the disease will differ. At a minimum, one important difference is that by definition, ALL patients in the chronic stable stage of the disease will have a history of MI and therefore will have been exposed to a number of medications used to treat an MI before entering the trial. In contrast, for some patients, the presentation of NSTEACS will be their first presentation with coronary artery disease or their first MI. These so-called naïve patients may not have had experience with the medications used to treat patients with an MI.

In the time between when a patient presents with ACS and when they are stable outpatients many things can happen that will influence their subsequent course. Some patients will not survive the ACS event. Others may undergo CABG, PCI or both. Depending on the location and size of the infarct, age of the patient, renal status and other factors, some patients may develop or exacerbate existing heart failure or new or worsening arrhythmias. The vast majority of patients will also receive antiplatelet and anti-thrombotic therapy, some for the first time. Some patients will have bleeding of various degrees as a consequence of receiving these therapies.

Understanding these differences is important when comparing the results of TRACER and TRA 2°P – TIMI 50 where vorapaxar was initiated at these two distinct phases of the disease process.

11.2 Differences in Subject Characteristics and Event Rates

Differences in specific aspects of the subject characteristics are detailed in **Section 7** and **Appendix 1**. TRACER subjects were older than subjects in the Proposed Label Population of the TRA 2°P – TIMI 50, with more than the twice the number of subjects over the age of 75. Essentially all subjects in the Proposed Label Population had a prior MI history at baseline while only 29.3% of TRACER subjects presented with a history of MI prior to the qualifying ACS event. Only 5.9% of patients in TRACER had a PCI within the year prior to randomization compared to 76.6% in the Proposed Label Population of the TRA 2°P-TIMI 50 study. Not surprisingly, relatively few TRACER subjects (9.8%) had prior experience with dual antiplatelet therapy with both ASA and a thienopyridine. In contrast to this relative lack of prior experience with aggressive antiplatelet therapy, more than 75% of subjects selected for the TRA 2°P-TIMI 50 were taking dual antiplatelet therapy with ASA and a thienopyridine at the time of presentation and randomization.

The clinical course and outcomes of patients enrolled in TRACER were significantly different from the outcomes of patients in TRA 2°P - TIMI 50. **Figure 25** provides Kaplan-Meier plots of the secondary composite endpoint (CV death, MI and stroke) in the placebo groups of both trials. Placebo subjects in the TRACER study had a much higher event rate in the early portion of the study and the lines continue to separate for months. In addition, TRACER subjects underwent a more invasive course of therapy (with more PCIs and CABGs) during the study including both the initial hospitalization and the period following hospital discharge (See **Table 5 in Appendix 1**). These differences in event rates and procedures for revascularization, extending well beyond the acute ACS admission for TRACER, emphasize the relevance of the differences in patients selected at different phases of the disease process.

It is important to recognize that the different event rates of patients selected for TRACER compared to those patients selected for TRA 2°P – TIMI 50 are not limited to the early period after an MI. Even if the first 30 days of data are removed from the TRACER analysis **(Figure 26)**, a substantial difference in GUSTO moderate or severe bleeding rates for placebo subjects persists for the duration of the TRACER trial compared to the placebo subjects in the TRA 2°P – TIMI 50 trial. The observation that the difference in bleeding rates persists well beyond the acute ACS event in TRACER suggests that this difference is not explained by the procedures and concomitant medications that occur in the first 30 days after an ACS event. A more likely explanation for the difference in bleeding rates in TRACER beyond 30 days after the index ACS event is related to the inability to identify an underlying predisposition to bleeding when patients are selected in the early phase of an acute coronary syndrome before their susceptibility to bleeding is fully understood.

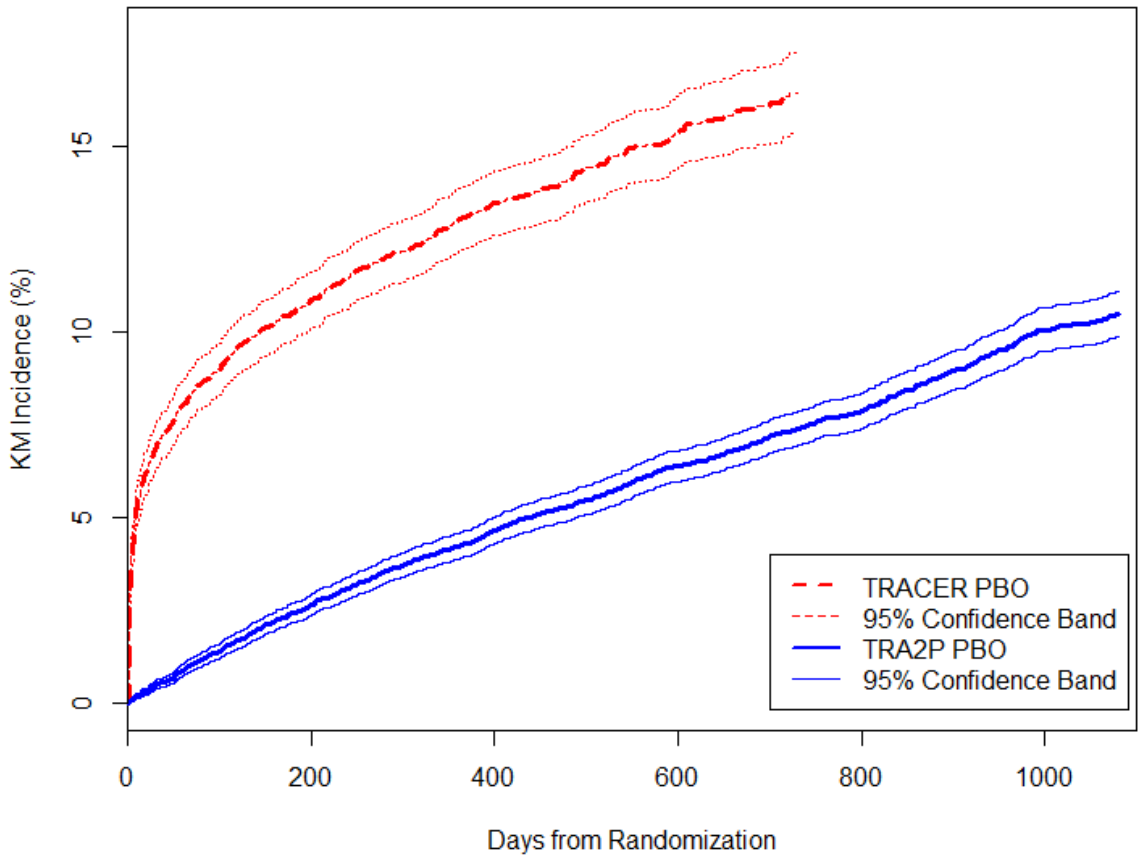


Figure 25 Comparison of Secondary Composite Endpoint Placebo Event Rates CV Death/MI/Stroke TRACER/TRA 2°P - TIMI -50 Event Accrual Period: Randomization to Last Visit (P04736, P04737)

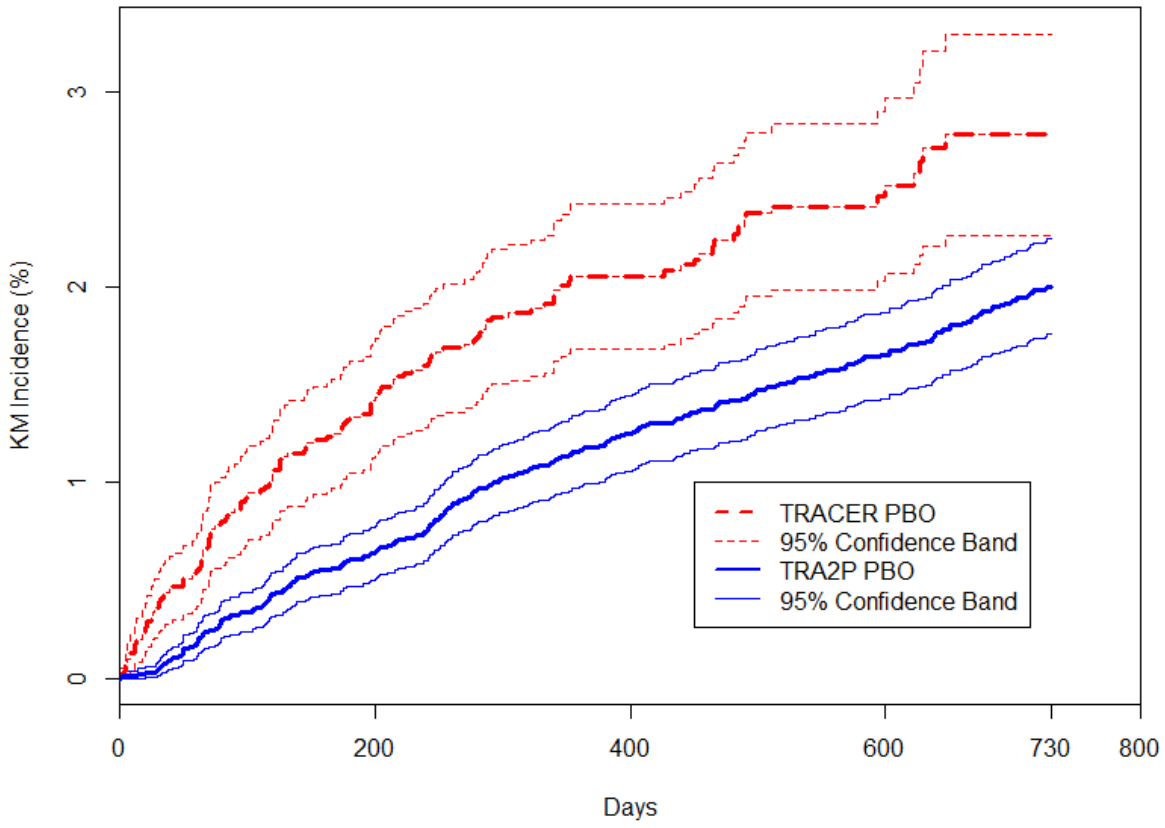


Figure 26 Comparison of GUSTO Severe/Moderate Cumulative Placebo Event Rates Over Time: Treated Population
Event Accrual Period: Day 31 to last Visit for TRACER, Randomization to Last Visit for TRA 2°P – TIMI 50
(P04736, P04737)

11.3 Relevance of TRACER in the Context of the TRA 2°P-TIMI 50

Prior sections of this document outline important differences in the clinical characteristics and outcomes of subjects selected in the midst of an acute episode during hospitalization compared to clinically stable patients selected at least 2 weeks after an MI. Given these differences, the relevance of the data generated in TRACER in the context of TRA 2°P-TIMI 50 is unclear. When administered on top of standard of care, both studies demonstrated the anti-thrombotic effects of vorapaxar, and both studies demonstrated an increased risk of bleeding as would be expected from more aggressive antiplatelet therapy. However, the estimates of the magnitude of the benefit and the magnitude of the risk of vorapaxar from TRACER may not be relevant in understanding how vorapaxar will perform when given to stable patients 2 weeks after an MI.

The greater increase in the risk of bleeding in TRACER subjects represents the results of committing patients to triple antiplatelet therapy with ASA, a $P2Y_{12}$ inhibitor, and vorapaxar prior to knowing whether the subject will be susceptible to bleeding. The magnitude of the risk of bleeding in TRACER does not incorporate what a physician would learn about a patient following weeks of therapy on antiplatelet agents, after the acute phases of an MI. With this in mind, the Sponsor concludes that pooling of bleeding safety data from the two trials is not appropriate to describe the risk of bleeding in the Proposed Label Population. In the case of the vorapaxar clinical development program, there are sufficient data in each study to identify and characterize the risk of bleeding in each patient population.

11.4 Selecting the Appropriate Patient for Vorapaxar

Selecting the appropriate patient likely to benefit from vorapaxar should be based on two sources of information: specific information from the vorapaxar clinical development program and more general information generated from more than 2 decades of using antiplatelet agents in patients after an MI.

The vorapaxar clinical development program provides a substantial amount of data to guide the selection of the patients who are expected to benefit from the reduction in the risk of atherothrombotic events associated with vorapaxar treatment with an acceptable safety profile.

- Vorapaxar should be prescribed to appropriate post-MI patients who are at risk for secondary atherothrombotic events as a complement to standard risk prevention measures and therapies

- Vorapaxar should be prescribed to patients after an MI who are stable, at least 2 weeks post-MI, and tolerating evidence based antiplatelet therapy which may include aspirin or aspirin plus clopidogrel when indicated and tolerating other cardiovascular evidence based therapy (e.g., statins, beta blockers, and RAAS inhibitors as indicated)

- Vorapaxar should not be given to patients with a history of stroke or TIA

- Vorapaxar should not be given to patients using potent CYP3A4 inhibitors or inducers

Vorapaxar should be used with caution in older aged patients and low body weight. As with other antiplatelet agents, vorapaxar should be used with caution in patients with a prior history of clinically significant bleeding.

12 BENEFIT RISK ASSESSMENT

12 BENEFIT RISK ASSESSMENT

12.1 Introduction

TRA 2°P-TIMI 50 was designed to assess the effectiveness of vorapaxar on top of contemporary standard of care. At baseline, risk factors for secondary atherothrombotic events among subjects that comprised the Proposed Label Population in the TRA 2°P-TIMI 50 trial were well addressed and in accordance to the standard of care (Table 23). Nearly all of the subjects received aspirin therapy (98.3%), 78.3% received a thienopyridine, and 77% received aspirin plus a thienopyridine. Statin therapy was used in nearly all of the subjects (95.4%), and blood pressure was in general well-controlled (median blood pressure 129/78 mmHg). Despite this comprehensive approach to secondary prevention, the rate of CV death, MI or stroke remains high in the post-MI with no history of stroke or TIA population, as assessed in the placebo group. In the placebo group of TRA 2°P-TIMI 50, the 3-year KM rate of CV death, MI, or stroke was 8.0%. Adjusting for exposure, the annualized event rate is 3.3 events per 100 patient-years in this population. In other words, of the 50 year old patients who have an MI, one-third are likely to have a recurrent MI, stroke, or die from a cardiovascular cause.

Extensive evaluation of the efficacy, safety, PK and PD profile of vorapaxar has been assessed by studying approximately 40,000 subjects in two Phase III clinical outcome studies designed to evaluate different populations in distinct clinical settings for separate indications. When administered on a standard of care background, both studies demonstrated the anti-thrombotic effects of vorapaxar, and both studies demonstrated an increased risk of bleeding as would be expected from more aggressive antiplatelet therapy. Taken together, the goal of the clinical development program was to identify a clearly defined population of patients in whom the anti-thrombotic benefits outweigh the increased risk of bleeding. In the TRACER study, patients were enrolled during the early phase of a hospitalization for a non-ST segment elevation ACS event, and had not been exposed to prior aggressive antiplatelet therapy. The full analysis of the TRACER study demonstrates that the initiation of vorapaxar (administered with a loading dose of 40 mg and then maintained at 2.5 mg/day) in subjects selected during the early stages of a non-ST segment elevation acute coronary syndrome, was associated with unacceptably high risk for ICH that was not balanced by sufficient efficacy in this acute population.

In contrast, the TRA-2°P - TIMI 50 study evaluated stable patients who were enrolled at least 2 weeks after an MI, and in whom the vast majority were on and were tolerating dual antiplatelet therapy. The results from the TRA 2°P - TIMI 50 clinical trial have established the efficacy and safety profile of vorapaxar in the Proposed Label Population. The use of vorapaxar reduced the rates of the primary (CV death/MI/stroke/UCR) and secondary (CV death/MI/stroke) endpoints compared to placebo. Notably, as discussed elsewhere, the efficacy was durable and consistent among the subgroups examined. The efficacy of vorapaxar was offset by a higher rate of GUSTO moderate or severe bleeding with vorapaxar compared to placebo. However, in patients post MI without a history of stroke or TIA (Proposed Label Population), the rates of serious bleeds (GUSTO severe, ICH, and fatal bleeding) were reduced compared to the Overall Population. In the Proposed Label

Population, the rates of GUSTO severe bleeding were similar in subjects randomized to vorapaxar or placebo.

The benefit-risk assessments described in this section integrate the efficacy and safety results in the Proposed Label Population to enable a determination of the therapeutic utility of vorapaxar. The results of these assessments support the use of vorapaxar 2.5 mg once daily to prevent atherothrombotic events in post-MI patients who have no history of stroke or TIA. In this population, the balance between benefits and risks strongly and consistently supports the use of vorapaxar for secondary prevention of atherothrombotic events.

12.2 Measurements of Benefits and Risks

Consistent with contemporary benefit-risk assessments, the key measurements that assess benefits associated with the use of a drug are hard clinical endpoints, whose reductions prevent irreversible tissue damage or death [16]. Considering the mechanism of action of vorapaxar and the clinical setting in which benefit-risk was assessed, these events are CV death, MI, and stroke. MI and stroke, both of which result in irreversible tissue damage with acute and chronic functional limitations and whose reductions are associated with durable gain, along with CV death were analyzed for benefit in the Proposed Label Population. As shown previously, vorapaxar reduced first and recurrent (i.e., total) atherothrombotic events (Table 27). The following assessments of benefit-risk focus on first events, in parallel with the primary and key secondary endpoints.

To balance benefit created by reducing the risks of irreversible tissue damage, risk is assessed by measuring the rates of events of irreversible harm. When considering the mechanism of action of vorapaxar, indicators of the risk of irreversible harm include life threatening or fatal bleeding events, specifically GUSTO severe bleeding, fatal bleeding, and ICH.

Some of the outcome endpoint events, such as CV death, ICH, and fatal bleeding occurred in more than one efficacy and/or safety endpoint. For example, a procedure performed for a confirmed coronary ischemic event that led to fatal bleeding would be recorded as both a CV death and fatal bleed. A hemorrhagic stroke event would be recorded as both a stroke and ICH. To avoid double-counting in order to assess the balance of benefit to risk, events were assigned to only one mutually-exclusive category. Specifically, benefit is assessed by the rates of CV death excluding fatal bleed, MI excluding CV death, and ischemic stroke excluding CV death. Risk is assessed with the endpoints of fatal bleed, non-fatal ICH, and GUSTO severe (non-fatal non-ICH).

12.3 Methodology

The primary analytical approach used to assess the balance between benefit and risk is focused on evaluation of risk differences based on exposure-adjusted event rates and cumulative hazards and hazard ratios using time-to-event analysis for the first occurrences of the endpoint events. The event accrual period for the primary analysis is from randomization to the date of last visit, for each subject. The statistical evaluations of benefit and risk are presented in terms of summary statistics, risk differences, number needed to treat (NNT),

number needed to harm (NNH), hazards ratios, Kaplan-Meier estimates, and the associated 95% confidence intervals.

The risk difference (RD) of vorapaxar compared to placebo is defined as the absolute difference in incidence rates in the two treatment groups (placebo rates minus vorapaxar rates) calculated as the number of events per 10,000 patient-years of exposure. A negative RD indicates that the event favors vorapaxar; and positive value indicates that the event favors placebo. The exposure-adjusted event rate is calculated as follows:

Exposure-adjusted Event Rate =

$$10{,}000 \times \frac{total\ n\ with \geq 1\ event\ post\ randomization}{total\ patient\ years\ of\ exposure}$$

For subjects with one or more events, the exposure was calculated based on the number of days from the randomization to the date of the first event. As discussed in detail below, the primary analysis of benefit-risk is based on time-to-first event. In addition, it is possible to evaluate benefit-risk for all events (first and recurrent). To calculate the exposure-adjusted total event rate, the numerator is the total number of events (first and recurrent) during the event accrual period and the denominator is the total patient-years during the accrual period. For subjects without an event, the exposure was calculated based on the number of days from the randomization to the date of the last visit. The 95% confidence interval for risk difference was based on the method by Miettinen and Nurminen [22]. The exposure-adjusted event rate may be converted to 1,000 patient-years by multiplying the rates by 0.1. Alternatively, to parallel the descriptions of the 3-year KM event rates in TRA 2°P-TIMI 50, the exposure-adjusted event rate may be converted to 1,000 patients per 3 years by multiplying the RD per 10,000 PY by 0.033.

The NNT and NNH were calculated as the reciprocals of the risk differences. In terms of efficacy, a negative number expresses the number of patient-years exposure with vorapaxar instead of placebo to prevent 1 additional harmful event (NNT). In terms of safety, a positive number expresses the number of patient-years treatment with vorapaxar instead of placebo to observe 1 additional bleeding event (NNH). Interpreting NNT and NNH between endpoints with differing baseline risk, differential follow-up or treatment duration must be done with caution, as NNT and NNH values are best compared when such factors are similar among the populations, subgroups, or endpoints of interest for cross study comparisons. It should also be noted that the significance of small risk differences with confidence intervals that overlap zero should be cautiously interpreted, as this is a limitation of NNT (or NNH) methodology [23]. For example, when the difference in the number of events per 10,000 patient-years is close to zero, the values of NNT or NNH can become excessively large, rendering the results not interpretable.

For selective endpoints, the plots of cumulative excess numbers of events per 10,000 patients based on Kaplan-Meier method were also provided to demonstrate the temporal course of benefit vs. risk.

12.3.1 Benefit-Risk Assessment Expressed as the Balance between Number Needed to Treat and Number Needed to Harm

The examination of the rates of first unique events in the Proposed Label Population confirms that the use of vorapaxar resulted in meaningful benefit by reducing the rate of CV death, MI, or stroke. Adjusting for exposure in the TRA 2°P-TIMI 50 study, there were 250 CV death (excluding fatal bleed), MI (excluding CV death), or ischemic stroke (excluding CV death) events in the vorapaxar-treated group compared to 322 events in the placebo treated group per 10,000 PY. The RD between the two groups is -71 (95% CI -104, -38): there were 71 excess events in placebo-treated subjects **(Table 41)**. The NNT, the inverse of the RD, to prevent one CV death (excluding fatal bleed), MI (excluding CV death), or ischemic stroke (excluding CV death) is 140. The largest difference occurred in the time to first MI (excluding CV death) element: the RD was -42 (95% CI -69,-15).

The risk of irreversible damage from bleeding events was slightly increased in vorapaxar treated subjects compared to placebo treated subjects. Given the small risk differences, it is difficult to interpret the NNH. Nonetheless, there were 41 GUSTO severe bleeding events (including ICH and fatal bleed events) per 10,000 PY in the vorapaxar group compared to 35 per 10,000 PY in the placebo group (RD 6; 95% CI -6, 18), thus the NNH is 1,798. Considering the key elements of GUSTO severe bleeding that infer risk, the RD for fatal bleeding was zero (95% CI -5, 5), the RD for non-fatal ICH was 2 (95% CI -4, 9), and RD for GUSTO severe non-fatal, non-ICH bleeding was 1 (95% CI -7, 10). The NNHs were -266,599 for fatal bleeding, 4300 for non-fatal ICH, and 7488 for GUSTO severe non-fatal, non-ICH bleeding.

In balance, the benefits of vorapaxar outweigh the risks. The ratio of overall benefit (first event of CV death (excluding fatal bleed), MI (excluding CV death), or ischemic stroke (excluding CV death) to overall risk (all GUSTO severe bleeding) is 71:6 when vorapaxar is used instead of placebo on top of standard of care. This ratio implies that the use of vorapaxar is 12 times more likely to result in a benefit event than a risk event. The following analyses confirm the direction of this balance and demonstrate that vorapaxar elicits early and sustained benefits over risks compared to placebo.

Table 41 Risk Differences and NNT or NNH of Main Efficacy and Safety Endpoints in the Proposed Label Population: ITT/As-treated Population ~ Event Accrual Period: Randomization to Last Visit.

	No. of Events per 10,000 PY		RD (95% CI)[a]	NNT/NNH[b]
	Placebo	Vorapaxar		
Efficacy endpoints ITT Population	n=8349	n=8458		
CV death excluding fatal bleed/ MI excluding CV death/ Ischemic stroke excluding CV death	322	250	-71 (-104 , -38)	-140
CV death excluding fatal bleed	72	57	-15 (-30 , 1)	-686
MI excluding CV death	216	174	-42 (-69 , -15)	-238
Ischemic stroke excluding CV death	34	18	-15 (-26 , -6)	-647
	Placebo	Vorapaxar	RD (95% CI)[a]	NNT/NNH[b]
Safety Endpoints: As-Treated Population	n=8412	n=8444		
GUSTO severe bleeding	35	41	6 (-6 , 18)	1798
Fatal Bleeding	7	7	0 (-5 , 5)	-266599
Non-Fatal ICH	11	13	2 (-4 , 9)	4300
GUSTO severe non-fatal non-ICH	19	20	1 (-7 , 10)	7488

a. The risk difference and 95% confidence intervals on Vorapaxar vs. Placebo are based on M&N method (Miettinen and Numinen 1985).
b. NNT=number needed to treat; NNH=number needed to harm; NNT and NNH are calculated as the reciprocal of the corresponding risk differences. A negative number denotes the number of patient-years treatment with vorapaxar plus standard of care instead of Standard care alone to prevent 1 additional harmful event (NNT), while a positive number denotes the number of patient-years treatment with vorapaxar plus standard of care instead of standard of care alone to observe 1 additional harmful event (NNH). Interpreting NNT/NNH between endpoints with differing baseline risks, differential follow-up, or treatment duration must be done with caution, as NNT/NNH values are best compared when such factors are similar among the populations, subgroups, or endpoints of interest.

12.3.2 Temporal Course of Benefit-Risk

In order to understand the temporal course of the benefits and risks, the key efficacy and safety events were characterized over time using the Kaplan-Meier method to plot the risk difference between vorapaxar and placebo. In this assessment, the temporal course of benefits of vorapaxar over placebo was measured by the accumulation of the risk difference of the composite of the mutually-exclusive efficacy endpoints CV death excluding fatal bleed, MI excluding CV death, and ischemic stroke excluding CV death, expressed per 10,000 PY, between the two arms of the study. The temporal course of risk was assessed by assessing the accumulation of risk difference between vorapaxar and placebo groups of all GUSTO severe bleeding events, which includes fatal bleeding, non-fatal ICH, and GUSTO severe non-fatal, non-ICH bleeding events, per 10,000 PY.

The use of vorapaxar in the Proposed Label Population resulted in early and durable benefit-risk effects compared to placebo **(Figure 27)**. The cumulative excess number of benefit events vs. placebo has a negative slope, indicating a cumulative risk difference in favor of vorapaxar compared to placebo over time, that begins soon after initiation of treatment. There was a small, persistent increase in the cumulative excess number of harm events (GUSTO severe) over time. The risk of GUSTO severe bleeding remained low, particularly after the first year of study. In sum, the magnitude of the benefit compared to risk increased steadily over time, without any apparent loss of effectiveness.

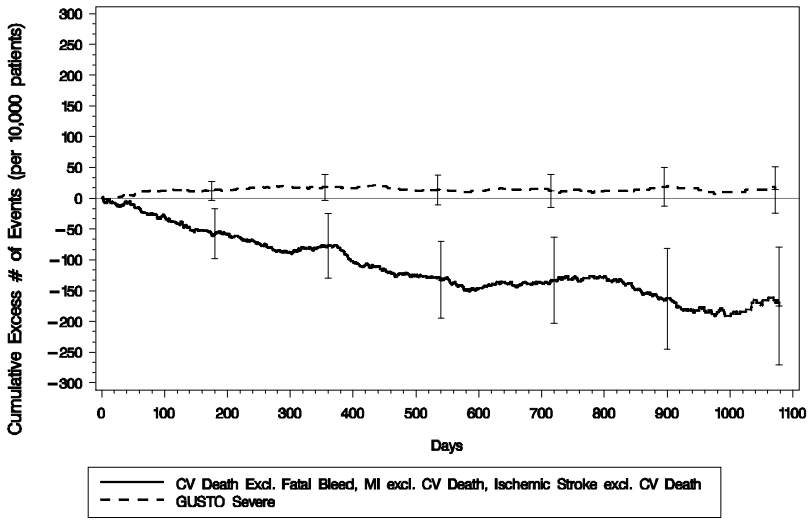


Figure 27 Cumulative Excess Number of Benefit and Harm Events. Benefits are the Composite of CV Death excluding Fatal Bleed, MI excluding CV Death and Ischemic Stroke excluding CV Death versus Risk of GUSTO Severe Bleeding. Vorapaxar versus Placebo: Proposed Label Population: ITT and As-Treated Populations ~ Event Accrual Period: Randomization to Last Visit.
Protocol No. P04737

12.3.3 Net Clinical Outcome

Net benefit of vorapaxar was compared to placebo by assessing the arithmetic difference in net clinical efficacy plus safety outcome events. Because equal weight is applied to each of the components of the composite, the most appropriate components to include are those of similar severity: the efficacy endpoints of CV death, MI, and stroke and the safety endpoints of GUSTO severe bleeding (which includes non-fatal ICH and bleeding death). Therefore, the most robust composite endpoint to assess net clinical outcome would include CV death, MI, stroke, and GUSTO severe bleeding. This composite endpoint balances the benefits associated with reducing the risks of irreversible tissue damage, and risks associated with events that lead to irreversible harm.

In the Overall Population, vorapaxar reduced the rate of the net clinical outcome using this composite by 12% (95% CI 0.81-0.95). Restricting the population to patients post MI who do not have a history of stroke or TIA (Proposed Label Population), improved the benefit risk profile. In the Proposed Label Population, vorapaxar reduced the rate of the net clinical outcome by 19% (95% CI 0.72 - 0.90). Estimates of net clinical outcome using All-Cause Death (rather than CV death) yields similar results. **(Table 42 and Table 43).**

An alternative approach might define the net clinical outcome composite endpoint to include less severe risks and less durable benefits. The protocol defined net clinical outcome to include non-severe bleeding and urgent coronary revascularization. In this analysis, the composite endpoint included CV death, MI, stroke, UCR, and both GUSTO severe and GUSTO moderate bleeding. However, this endpoint erroneously assumes that UCR and GUSTO moderate bleeding have the same weight or clinical relevance as CV death, MI, stroke, or GUSTO severe bleeding. While it is possible to estimate the relative degree of severity of these endpoints, appropriate weighting factors are not universally accepted. Nonetheless, using this composite endpoint, the reduction of the rate of net clinical outcome was directionally similar to the reduction of the composite restricted to more severe events. In the Overall Population, vorapaxar reduced the composite that includes CV death, MI, stroke, UCR, and GUSTO severe and GUSTO moderate bleeding (with equal weight applied to each endpoint) by 5% (95% CI 0.0.89-1.02). In the Proposed Label Population, vorapaxar reduced this composite endpoint by 11% (95% CI 0.82-0.98). Taken together, these results confirm the net benefit of vorapaxar vs. placebo and further support the selection of the Proposed Label Population.

Table 42 Time-to-Event Analyses of the Net Clinical Outcome in the Proposed Label Population: As-Treated Population ~ Event Accrual Period: Randomization to Last Visit

(Protocol No. P04737)

Net Clinical Outcome Endpoints	Subjects With Events (%)				Hazard Ratio[a,b] (95% CI)[b]	
	Placebo (n = 8412)		Vorapaxar (n = 8444)			
CV death / MI / Stroke / UCR / GUSTO Severe / GUSTO Moderate	966/8412	(11.5%)	873/8444	(10.3%)	0.89	(0.82 - 0.98)
CV death / MI / Stroke / GUSTO Severe	714/8412	(8.5%)	583/8444	(6.9%)	0.81	(0.72 - 0.90)
All-Cause Death / MI / Stroke / GUSTO Severe	792/8412	(9.4%)	674/8444	(8.0%)	0.84	(0.76 - 0.93)

a. Hazard ratio is vorapaxar group versus placebo group

b. Hazard ratio was calculated based on Cox PH model with covariates treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use)

Table 43 Time-to-Event Analyses of the Net Clinical Outcome in the Overall Population: As-Treated Population ~ Event Accrual Period: Randomization to Last Visit

(Protocol No. P04737)

Net Clinical Outcome Endpoints	Subjects With Events (%)				Hazard Ratio[a,b] (95% CI)[b]	
	Placebo (n = 13166)		Vorapaxar (n = 13186)			
CV death / MI / Stroke / UCR / GUSTO Severe / GUSTO Moderate	1612/13166	(12.2%)	1537/13186	(11.7%)	0.95	(0.89 – 1.02)
CV death / MI / Stroke / GUSTO Severe	1257/13166	(9.5%)	1110/13186	(8.4%)	0.88	(0.81 - 0.95)
All-Cause Death / MI / Stroke / GUSTO Severe	1439/13166	(10.9%)	1318/13186	(10.0%)	0.91	(0.84 - 0.98)

a. Hazard ratio is vorapaxar group versus placebo group

b. Hazard ratio was calculated based on Cox PH model with covariates treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use)

12.4 Benefit-Risk Conclusion

Novel medications are needed to address the unacceptably high, unmet need to reduce the risk of secondary events after myocardial infarction. Despite the extensive experience of using antiplatelet therapy in an ACS setting, the data supporting the use of antiplatelet agents for the secondary prevention of cardiovascular events in chronic stable high-risk patients is sparse. With the exception of aspirin, the current use of other antiplatetet treatments is this setting is based on post-hoc analyses of one or two studies that does not allow for an appropriate benefit risk assessment The TRA 2°P-TIMI 50 clinical trial definitively demonstrates the effectiveness of vorapaxar for secondary prevention in the Proposed Label Population: the balance of benefit-risk favors vorapaxar on top of standard of care vs. standard of care alone.

The analysis of benefit-risk supports a new therapeutic paradigm for the prevention of secondary atherothrombotic events in post-myocardial infarction patients. To date, definitive therapy has not been established for any treatment other than aspirin. The TRA 2°P-TIMI 50 study is the first clinical trial to establish that long term therapy (greater than one year) in patients post-MI provides substantial benefit with an acceptable level of risk.

The primary analysis to assess benefit risk demonstrated that the balance of benefit-risk favors the use of vorapaxar over placebo. The risk difference of first, unique efficacy events, assessed here as benefit, strongly favored vorapaxar. The risk difference of serious bleeding events, assessed here as risk, leaned towards vorapaxar, but in balance, vorapaxar is more likely to result in a benefit event than a risk event. The temporal course analysis shows that the benefit of vorapaxar is realized early, is durable, and appears to increase over time. In contrast, the risk of serious bleeding associated with vorapaxar is small and does not appear to change over time. The net benefit consistently favors the use of vorapaxar and this net benefit persists over time. The comparison of net clinical outcome realized by vorapaxar in the Proposed Label Population compared to the overall population in TRA 2°P-TIMI 50 supports the selection of the Proposed Label Population and the indication.

13 OVERALL SUMMARY

13 OVERALL SUMMARY

For the 6-700,000 patients in the US who will have an MI in the next year, the risk of future cardiovascular events remains unacceptably high. Over the past 30 years, a number of different treatments -- beta blockers, renin – angiotensin – aldosterone system blockers, lipid lowering medication, anti-hypertension medication and aspirin -- have improved the outcome of patients with atherosclerotic cardiovascular disease. However, for these patients, the only established antithrombotic treatments are aspirin and, for the 6 – 12 month period after a PCI, a $P2Y_{12}$ inhibitor. In the patients who have had an MI, there is a clear opportunity to further reduce the risk of future cardiovascular events through more aggressive antiplatelet therapy.

Vorapaxar is a selective antagonist of the protease-activated receptor 1 (PAR 1), the primary thrombin receptor on human platelets, which mediates the downstream effects of thrombin, a critical coagulation factor in hemostasis and thrombosis. Thrombin-induced platelet activation has been implicated in a variety of cardiovascular disorders including thrombosis, atherosclerosis, and restenosis following percutaneous coronary intervention (PCI). As an antagonist of PAR-1, vorapaxar blocks thrombin-mediated platelet activation and thereby has the potential to reduce the risk of atherothrombotic complications of coronary disease.

The vorapaxar clinical development program included two cardiovascular outcome studies with > 40,000 subjects. The two studies evaluated different populations in distinct clinical settings for separate indications. When administered on a standard of care background, both studies demonstrated the anti-thrombotic effects of vorapaxar, and both studies demonstrated an increased risk of bleeding as would be expected from more aggressive antiplatelet therapy. Taken together, the goal of the clinical development program was to identify a clearly defined population of patients in whom the anti-thrombotic benefits outweigh the increased risk of bleeding. In the TRACER study, subjects were enrolled early in the hospitalization for a non-ST elevation ACS event. Relatively few of these subjects had been previously exposed to aggressive antiplatelet therapy. In this population of patients, selected in the early phases of their ACS, the risk of bleeding outweighed the potential reduction of atherothrombotic events over the 2 years of follow-up. In contrast, the TRA-2°P - TIMI 50 study evaluated stable subjects enrolled > 2 weeks after an MI. The vast majority of these subjects were on, and were tolerating aggressive dual antiplatelet therapy. In this study, the benefits of vorapaxar, on top of standard of care, clearly exceeded the risk of bleeding.

The TRA2°P - TIMI 50 study enrolled subjects with atherosclerotic cardiovascular disease that qualified based on three specific conditions, nearly all of whom were already on optimal evidence-based therapies. Subjects were randomized to vorapaxar on top of standard of care, which in 78% of patients included dual antiplatelet therapy. By design, the majority of subjects were enrolled within one year of an MI. Subjects also qualified for the study based on a recent stroke or peripheral arterial disease. In this diverse population, the study achieved the primary hypothesis and demonstrated a statistically significant and clinically meaningful reduction of cardiovascular events. This result was robust and consistent across multiple subgroups for both the primary and secondary endpoints. However, the study highlighted the importance of identifying the right patients for aggressive antiplatelet therapy. Importantly, subjects in this study with a prior history of stroke had an unacceptably high risk of intracranial hemorrhage. Subjects with PAD did not demonstrate an adequate

benefit-risk profile in the context of the risks of vorapaxar without more definitive evidence of benefit in these subjects. In the final analysis, the balance of benefits and risks was greatest in those subjects who qualified for the study based on a recent MI without a prior history of stroke or TIA. With this in mind, the Sponsor seeks the following indication for vorapaxar:

Patients with History of Myocardial Infarction (MI)

Vorapaxar, an antagonist of the protease-activated receptor-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.

Vorapaxar use will be contraindicated in patients with a history of stroke, TIA, intracranial hemorrhage, or active pathological bleeding.

In this distinct and easily identifiable population of patients, vorapaxar provides a clinically important option for reducing the substantial residual risk remaining following an MI.

14 LIST OF REFERENCES

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Appendix 1 - Comparative Safety Analysis of TRACER and TRA 2ÁP ï TIMI 50

Appendix 1
Comparative Safety Analysis of TRACER and TRA 2°P – TIMI 50

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1 COMPARATIVE SAFETY ANALYSIS OF TRACER AND TRA 2°P – TIMI 50

1.1 Overview

As described in **Section 11** of the Briefing Document (RELEVANCE OF TRACER IN UNDERSTANDING THE USE OF VORAPAXAR IN PATIENTS AFTER A MYOCARDIAL INFARCTION), this Appendix provides additional discussion of the relevant features that account for the differences in the TRACER and the TRA 2°P - TIMI 50 populations. The two studies evaluated different populations in distinct clinical settings for separate indications. When administered on standard of care background, both studies demonstrated the antithrombotic effects of vorapaxar, and an increased risk of bleeding as would be expected from more aggressive antiplatelet therapy. In addition, this Appendix will include a discussion on the appropriateness of pooling the bleeding data from these two Phase 3 studies.

1.2 Relevance and Key Features of the Patient Populations

Comparisons of key baseline characteristics and medical history between TRACER and TRA 2°P - TIMI 50 are shown in **Table 1 and Table 2**. Many of the baseline characteristics that differ (prior history of MI, history of PAD and history of stroke) are the result of the different designs of the two studies. TRACER subjects were older than subjects in the Proposed Label Population of the TRA 2°P – TIMI 50, with more than the twice the number of subjects over the age of 75. Essentially all subjects in the Proposed Label Population had a prior MI history at baseline while only 29.3% of TRACER subjects presented with a history of MI prior to the qualifying ACS event. Only 5.9% of patients in TRACER had a PCI within the year prior to randomization compared to 79% in the Proposed Label Population of the TRA 2°P-TIMI 50 study. TRACER enrolled relatively few subjects with a history of stroke (4.3%) which contrasts the Overall Population of TRA 2°P – TIMI 50 (21.7%) and which is similar to the Proposed Label Population which by definition excluded patients with a history of stroke.

Table 1 Summary of Key Baseline Characteristics TRACER and TRA 2°P-TIMI 50- Medical History

	TRACER P04736 (N=12944)	**TRA 2°P-TIMI 50 P04737 Overall Population (N=26449)**	**TRA 2°P-TIMI 50 P04737 Proposed Label Population (N=16897)**
Baseline Characteristics			
Female (%)	28.1	23.9	20.1
Age (mean, year)	64.4	60.9	58.6
Age (≥ 75 years, %))	17.0	11.4	7.3
Weight (mean, kg)	82.5	82.5	84.3
Race			
White	85.3	87.3	88.2
Non-white	14.4	12.7	11.8

Table 2 Summary of Key Medical History Findings TRACER and TRA 2°P-TIMI 50- Medical History

	TRACER P04736 (N=12994) % subjects	TRA 2°P-TIMI 50 P04737 Overall Population (N=26449) % subjects	TRA 2°P-TIMI 50 P04737 Proposed Label Population (N=16897) % subjects
Medical History			
Hypertension	70.5	68.7	61.5
History of Smoking	59.7	70.3	71.1
Current Smoker	27.3	20.8	19.7
Hyperlipidemia	62.3	83.2	84.4
Diabetes Mellitus	31.4	25.4	21.4
Family History of Premature CAD	27.5	30.1	35.4
Prior Myocardial Infarction	29.3	72.4	99.8
Type Most Recent			
STEMI	7.8	36.0	52.8
NSTEMI	10.0	29.0	41.0
Unknown	11.5	7.4	5.9
Prior Angina	51.7	34.3	39.9
Prior Stroke	4.3	21.7	0
Timing of Most Recent			
≤3 Months	0.1	11.7	0
>3 Months to ≤6 Months	0.1	3.7	0
>6 Months to ≤ 12 Months	0.2	3.6	0
> 12 Months	3.5	2.4	0
Missing/Unknown	0.3	0.4	0
Prior Transient Ischemic Attack	2.5	4.2	0
Timing Most Recent			
≤ 12 Months	0.5	1.6	0
> 12 Months	1.9	2.5	0
Missing/Unknown	0.2	0.1	0
Prior Peripheral Arterial Disease	7.2	18.9	5.0
Claudication	3.1	20.5	6.9
Heart Failure	9.3	7.8	8.4
Prior PCI	23.9	57.7	79.4
Timing of Most Recent			
≤ 12 Months	5.9	52.0	76.6

	TRACER P04736 (N=12994) % subjects	**TRA 2°P-TIMI 50 P04737 Overall Population** (N=26449) % subjects	**TRA 2°P-TIMI 50 P04737 Proposed Label Population** (N=16897) % subjects
> 12 Months	17.8	5.2	2.4
Prior CABG	11.9	13.3	12.9
Timing of Most Recent			
≤ 12 Months	1.0	5.9	8.1
> 12 Months	10.8	7.4	4.8
Prior Peripheral Arterial Revascularization	2.9	10.7	1.9
Prior Amputation related to Limb Ischemia	0.5	0.9	0.2
Hepatic Function at Baseline			
ALT ≥2xULN	3.6	1.9	2.2
AST ≥2xULN	18.5	0.9	0.9
Alkaline phosphatase ≥ 2xULN	0.2	0.2	0.2
GGT ≥2XULN	7.2	5.9	6.0
Total Bilirubin ≥1.5xULN	1.6	0.6	0.6
Calculated Creatinine Clearance at Baseline[a]			
<60 mL/min	12.9	13.4	9.0
a. Cockcroft-Gault equation			

Importantly, as referenced in **Section 7.4**, many of the patients who received anti-platelet therapy in TRACER were receiving this therapy for the first time (60%) as part of the acute treatment with PCI associated with NSTEACS (**Table 3**). Relatively few TRACER subjects (9.8%) had prior experience with dual anti-platelet therapy with both ASA and a thienopyridine. In contrast to this relative lack of prior experience with aggressive anti-platelet therapy in TRACER, more than 75% of subjects selected for the TRA 2°P-TIMI 50 were taking dual anti-platelet therapy with ASA and a thienopyridine at the time of presentation and randomization. Thus, subjects in TRA 2P-TIMI-50 were almost always experienced with antiplatelet therapy and because of this had already demonstrated a lack of propensity to bleed when placed on such medications (**Table 4**).

Table 3 Use of Antiplatelet Therapy Prior to Index Hospitalization in the TRACER Trial (All Randomized Subjects)

	Placebo (N=6471)	Vorapaxar (N=6473)	Total (N=12994)
Dual Antiplatelet Therapy (Aspirin and Thienopyridine)	636 (9.8)	642 (9.9)	1278 (9.9)
Single Antiplatelet Therapy (Aspirin or Thienopyridine)	1970 (30.4)	1966 (30.4)	3936 (30.4)
Naïve to Antiplatelet Therapy (None)	3865 (59.7)	3865 (59.7)	7730 (59.7)

Table 4 shows the major concomitant medications used in the two studies. It is apparent from the differences between the two columns for the TRACER study, (Concomitant Medications from Initial Hospitalization through Randomization and Concomitant Medications at Discharge for Index Hospitalization) that medication usage changed during the qualifying hospitalization with anti-thrombin agents used frequently during the initial hospitalization. Almost double the number of patients in TRA 2°P - TIMI 50 had aspirin only usage compared to TRACER.

Table 4 Concomitant Medications in TRACER and TRA 2°P-TIMI 50

	TRACER P04736 **Concomitant Medications from Initial Hospitalization through Randomization** **(N=12944)** **% subjects**	**TRACER P04736** **Concomitant Medications at Discharge for Index Hospitalization** **(N=12944)** **% subjects**	**TRA 2°P-TIMI 50 P04737** **Overall Population Baseline Medications** **(N=26449)** **% subjects**	**TRA 2°P-TIMI 50 P04737** **Proposed Label Population Baseline Medications** **(N=16897)** **% subjects**
Any Antiplatelet Agent(including Aspirin)	99.0	95.0	99.2	99.6
Any Aspirin	96.7	92.6	93.5	98.3
Any Thienopyridine[a]	87.4	77.5	62.2	78.3
Any Clopidogrel	86.2	76.1	61.2	77.6
Any Ticlopidine	0.7	0.6	0.8	0.5
Any Prasugrel	0.8	0.9	0.2	0.2
Any Dipyridamole	0.4	0.2	4.1	0.1
Any Cilostazol	0.5	0.4	2.3	0.3
Aspirin Only	9.3	17.3	31.4	21.2
Aspirin Plus a Thienopyridine	85.2	75.1	57.0	77.0
Aspirin plus Any Other Antiplatelet Agent[b]	87.4	75.2	62.1	77.2
Any Antiplatelet Agent other than Aspirin or Clopidogrel[d]	Not reported	Not reported	0.8	0.1
Any Oral Anticoagulant[c]	0.2	1.5	0.1	0.1
Warfarin	0.2	1.1	0.1	<0.1
Any Fibrinolytic	0.2	0	0	0
Any Glycoprotein IIb/IIIa Inhibitor	18.3	Not reported	Not reported	Not reported

	TRACER P04736 **Concomitant Medications from Initial Hospitalization through Randomization** **(N=12944)** **% subjects**	**TRACER P04736** **Concomitant Medications at Discharge for Index Hospitalization** **(N=12944)** **% subjects**	**TRA 2°P-TIMI 50 P04737** **Overall Population Baseline Medications** **(N=26449)** **% subjects**	**TRA 2°P-TIMI 50 P04737** **Proposed Label Population Baseline Medications** **(N=16897)** **% subjects**
Any Antithrombin Agent	86.1	Not reported	0.4	0.2
Unfractionated Heparin	45.6	Not reported	0.1	0.1
Low Molecular Weight Heparin	47.5	Not reported	0.2	0.1
Direct Thrombin Inhibitor	4.8	Not reported	<0.1	<0.1
Fondaparinux	9.7	Not reported	0	<0.1
Any Beta-adrenergic Antagonist[e]	76.5	78.8	69.4	85.2
Any ACE-I or Combination	54.3	57.9	59.8	66.1
Any AIIA or Combination	15.1	14.8	15.8	12.5
Any Statin	84.3	87.1	89.7	95.4
Any Proton Pump Inhibitor	35.7	32.3	24.5	25.8
Any H2 Receptor Antagonist	14.1	9.1	4.9	4.8

[a]Any Thienopyridine includes Clopidogrel, Ticlopidine, Prasugrel, Ticagrelor
[b] Any other Antiplatelet includes any Thienopyridine, Dipyridamole, Cilostazol, Glycoprotein IIb/IIIa Inhibitor
[c] Any Oral Anticoagulant includes Warfarin, Phenoprocoumon, Acenocoumarol, Fluindone
[d] Subjects were not taking aspirin or Clopidogrel
[e] Excludes ophthalmic preps

The final important difference between TRACER and TRA 2°P - TIMI 50 relates to the different treatments subjects received during the studies. TRACER subjects underwent a much more invasive course of therapy, both during the initial hospitalization and the period following hospital discharge. These differences are shown in **Table 5**. The fact that TRACER subjects, as a percentage, had more revascularization procedures, underscores another differentiating characteristic from the TRA 2°P - TIMI 50 subjects.

Table 5 Patient Care and Management

	TRACER P04736 **Randomization through Discharge From Acute Care**	**TRACER P04736** **Post Index Hospitalization to Last Visit**	**2°P-TIMI 50 P04737** **Overall Population**
	(N=12944)	(N=12944)	(N=26449)
	n (%)	n (%)	n (%)
PCI	7479 (57.8)	1534 (11.9)	1929 (7.3)
CABG	1312 (10.1)	578 (4.5)	429 (1.6)

1.3 Abbreviated Integrated Summary of Safety for TRACER and TRA 2°P TIMI-50

The following section presents a condensed version of the Integrated Summary of Safety for the Phase 3 studies. The analysis reports on nearly 40,000 patients who received placebo or vorapaxar from 1:1 randomization in the two studies. Aside from the differences noted above for medical history, concomitant and historical medications and procedures, and qualifying diagnoses, median follow-up for the two studies differed by over one year: TRACER was 1.4 years versus TRA 2°P TIMI 50, which was 2.5 years.

The motivation behind the trial designs for TRACER and TRA 2°P - TIMI 50 was to study two different populations to seek two different indications. Though increased risk for major bleeding and ICH was common to vorapaxar treatment in both studies, it would be an oversimplification to assume that the absolute risk for bleeding presented by vorapaxar is the same for both populations studied. Combining the bleeding data from both studies would be similar to a meta-analysis of safety derived from studying two different populations, which would be useful only if both populations were potential targets for therapy and there was no attempt to distinguish them through the product label. The Sponsor is not seeking an indication to initiate vorapaxar treatment in the early stages of an acute NSTEMI, but rather is seeking an indication where vorapaxar is initiated for secondary prevention in the outpatient setting in patients who had an MI and no previous history of stroke or TIA.

All evidence points to an increased risk of severe bleeding in the NSTEACS subjects enrolled in TRACER compared to the Overall Population and more so the Proposed Label Population of TRA 2°P – TIMI 50. The Sponsor has provided a pooled analysis at the request of the FDA, but feels that the pooling diminishes the differences that exist in subject populations between the studies and therefore provides a potentially distorted estimate of bleeding risks in the population for which the Sponsor is seeking an indication i.e., patients

with a history of MI and no history of stroke or TIA. The Chronic Pool includes all bleeding events that occurred ≥ 30 days in TRACER and all bleeding events that occurred in TRA 2ºP-TIMI 50 (including patients with a history of stroke and all patients in the CVD stratum). The bleeding events from the first 30 days of subjects' participation in the TRACER trial are not included in this Chronic Pool, in consideration of: 1) the inherent differences in the bleeding rate in the control groups of the two studies attributable to the use of multiple concomitant antithrombotic therapies 2) the invasive procedures during the index hospitalization in TRACER and 3) the differences in the trial populations. The 30-day post randomization cut point, determined in agreement with FDA, is somewhat arbitrary , as the bleeding rates in the control groups of TRACER and TRA 2ºP-TIMI 50 do not begin to show overlap of the 95% CIs until day 600, when event rates are very low. (**Figure 26 of Briefing Document**)

1.3.1 Adverse Events Reported in TRACER and TRA 2°P - TIMI 50

Table 6 is an overall summary of bleeding events and other non-bleeding adverse events in TRACER and TRA 2°P - TIMI 50. The table displays counts as well as percent of total subjects. Underlying differences between the two studies are best discerned by comparing the placebo groups (%) for the two studies. As might be expected from a longer follow-up period, placebo percentages for non-bleeding treatment-emergent adverse events were slightly higher for the placebo group in TRA 2ºP TIMI 50 than in TRACER.

Bleeding events were approximately 25% higher in the placebo group of TRACER than TRA 2ºP TIMI 50 despite the fact that median follow-up of TRA 2°P - TIMI 50 was one year longer than TRACER. This difference in bleeding rates in the *placebo groups* of the two studies suggests a difference in the underlying predisposition to bleeding in the two populations. Consequently, bleeding occurred overall at a much higher rate in TRACER than in TRA 2°P - TIMI 50. In both studies, bleeding events were increased in the vorapaxar treatment groups.

In contrast to bleeding events, other treatment emergent adverse advents, and in particular treatment-related adverse events, were higher in the placebo group of TRA 2°P - TIMI 50 than TRACER, as might be expected from a longer median follow-up. There are no important differences between placebo and vorapaxar for either of the two studies with respect to other adverse events.

Table 6 Number (%) of Subjects With the Indicated Type of Adverse Event Reported During the Study: TRACER and TRA 2ºP-TIMI 50 Overall

(Protocol Nos. P04736, P04737)

	TRACER		TRA 2ºP-TIMI 50	
	Placebo	**Vorapaxar**	**Placebo**	**Vorapaxar**
	(n=6441)	**(n=6446)**	**(n=13166)**	**(n=13186)**
Any Bleeding Event				
Any Treatment-Emergent Bleeding Event	1555 (24.1)	2058 (31.9)	2420(18.4)	3358(25.5)
Any Treatment-Related Treatment Emergent Bleeding Event	949 (14.7)	1364 (21.2)	1450(11.0)	2251(17.1)
Any Serious Bleeding Event	365 (5.7)	518 (8.0)	475 (3.6)	692 (5.2)
Any Treatment-Related Serious Bleeding Event	216 (3.4)	330 (5.1)	221 (1.7)	395 (3.0)
Any Bleeding Event Resulting in Treatment Discontinuation[a]	125 (1.9)	255 (4.0)	234 (1.8)	401 (3.0)
Any Treatment-Related Bleeding Event Resulting in Treatment Discontinuation[a]	99 (1.5)	213 (3.3)	180 (1.4)	322 (2.4)
Any Bleeding Event Resulting in Study Discontinuation	130 (2.0)	258 (4.0)	240 (1.8)	409 (3.1)
Any Treatment-Related Bleeding Event Resulting in Discontinuation	101 (1.6)	214 (3.3)	181 (1.4)	326 (2.5)
Any Bleeding Event Resulting in Death	24 (0.4)	33 (0.5)	34 (0.3)	49 (0.4)
Any Treatment-Related Bleeding Event Resulting in Death	9 (0.1)	22 (0.3)	11 (0.1)	24 (0.2)
Any Treatment-Emergent Bleeding Event	1555 (24.1)	2058 (31.9)	2420(18.4)	3358(25.5)
Any Treatment-Related Treatment Emergent Bleeding Event	949 (14.7)	1364 (21.2)	1450(11.0)	2251(17.1)
Any Serious Bleeding Event	365 (5.7)	518 (8.0)	475 (3.6)	692 (5.2)
Any Treatment-Related Serious Bleeding Event	216 (3.4)	330 (5.1)	221 (1.7)	395 (3.0)
Any Bleeding Event Resulting in Treatment Discontinuation[a]	125 (1.9)	255 (4.0)	234 (1.8)	401 (3.0)
Any Other Adverse Event				
Any Treatment-Emergent Other Adverse Event	4651 (72.2)	4795 (74.4)	10227(77.7)	10208(77.4)
Any Treatment-Related Treatment Emergent Other Adverse Event	643 (10.0)	733 (11.4)	2070(15.7)	2124(16.1)
Any Serious Other Adverse Event	1561 (24.2)	1638 (25.4)	3255(24.7)	3250(24.6)
Any Treatment-Related Serious Other Adverse Event	75 (1.2)	63 (1.0)	93 (0.7)	83 (0.6)
Any Other Adverse Event Resulting in Treatment Discontinuation[a]	348 (5.4)	407 (6.3)	960 (7.3)	926 (7.0)
Any Treatment-Related Other Adverse Event Resulting in Treatment Discontinuation[a]	95 (1.5)	122 (1.9)	314 (2.4)	327 (2.5)
Any Other Adverse Event Resulting in Study Discontinuation	361 (5.6)	429 (6.7)	1007 (7.6)	981 (7.4)

(Protocol Nos. P04736, P04737)

	TRACER		TRA 2°P-TIMI 50	
	Placebo	**Vorapaxar**	**Placebo**	**Vorapaxar**
	(n=6441)	**(n=6446)**	**(n=13166)**	**(n=13186)**
Any Treatment-Related Other Adverse Event Resulting in Discontinuation	96 (1.5)	122 (1.9)	316 (2.4)	330 (2.5)
Any Other Adverse Event Resulting in Death	177 (2.7)	175 (2.7)	319 (2.4)	306 (2.3)
Any Treatment-Related Other Adverse Event Resulting in Death	3 (<0.1)	5 (0.1)	5 (<0.1)	7 (0.1)

Note: All categories reflect decisions made by the investigators, except for serious bleeding events, which were identified by the algorithm for serious bleeding events

Note: "Any Bleeding or Other Adverse Event" is a unique accounting, and is not the sum of the other two categories.

a. Subjects who died during treatment were considered to have completed

1.3.2 Bleeding in TRACER and TRA 2°P - TIMI 50

1.3.2.1 Pooled Bleeding Analysis

For the chronic pool, the risk of bleeding was greater for subjects on vorapaxar than for subjects on placebo for all bleeding endpoints, significantly different except for TIMI major CABG related bleeding (**Table 7)**. The table contains the annualized event rates for TRACER and TRA 2°P TIMI 50 so that placebo rates for bleeding can be compared between the two studies. Because bleeding rates in the placebo groups are so different between the two studies (**Section 11.2**), the pooled analysis yields event rates that are likely to be higher than would be observed in the intended label population; patients with a history of MI and no history of stroke or TIA. The Chronic Pooled Bleeding rates are likely to reflect worst case scenarios, seen only if substantial numbers of NSTEACS patients had vorapaxar initiated in the acute stage of an NSTEACS. In the briefing document, the Sponsor has indicated that vorapaxar should not be initiated at this acute stage of an NSTEACS.

- GUSTO severe or moderate bleeding annualized event rates were 1.7 events per 100 subject-years of exposure in the vorapaxar group and 1.1 events per 100 subject-years of exposure in the placebo group (HR 1.48; 95% CI 1.32 -1.67; p< 0.001).
- Clinically significant bleeding annualized event rates were 6.6 events per 100 subject-years of exposure for vorapaxar vs. 4.5 events per 100 subject-years of exposure for placebo (HR 1.45; 95% CI 1.36 - 1.54; p< 0.001).
- TIMI major CABG related bleeding annualized event rates were 0.1 events per 100 subject-years of exposure in both treatment groups (HR 1.29; 95% CI 0.75-2.19; p= 0.354)

A total of 229 cases of ICH were reported: 150 (0.8%) subjects in the vorapaxar group and 79 (0.4%) subjects in the placebo group. Annualized event rates were 0.4 events per 100

subject-years of exposure in the vorapaxar group and 0.2 events per 100 subject-years of exposure in the placebo group (HR 1.89; 95% CI 1.44 -2.48; p< 0.001).

A total of 96 fatal bleeding events were reported: 58 (0.3%) subjects in the vorapaxar group and 38 (0.2%) subjects in the placebo group. The annualized event rate was 0.1 events per 100 subject-years of exposure in both groups (HR 1.52; 95% CI 1.01 - 2.29; p= 0.044). Results in the chronic pool exclude 9 of the total 29 fatal bleeds in the vorapaxar group and 5 of the total 16 fatal bleeds in the placebo group occurring during the first 30 days of the TRACER trial, consistent with the definition of the chronic pool.

The chronic pool bleeding event rates were in general slightly higher than those of the TRA 2ºP-TIMI 50 overall population, for all categories, in both the vorapaxar and placebo treatment groups. The annualized event rates for the Proposed Label Population were generally lower than those of the chronic pool for most bleeding endpoints. In the vorapaxar group, the GUSTO severe or moderate bleeding event rate was 1.1 events per 100 subject-years of exposure in the Proposed Label Population versus 1.7 events per 100 subject-years of exposure in the chronic pool. The ICH event rate was 0.2 events per 100 subject-years of vorapaxar exposure in the Proposed Label Population versus 0.4 events per 100 subject-years of exposure in the chronic pool.

The TRACER bleeding rates were substantially higher than those of the TRA 2ºP-TIMI 50 Overall Population in both the vorapaxar and placebo treatment groups (e.g., nearly four times higher with respect to GUSTO moderate or severe annualized bleed rate of 4.0 events per 100 subject-years of exposure in the placebo group in TRACER vs. 1.1 events per 100 subject-years of exposure in the placebo group in the TRA 2ºP-TIMI 50 overall population). Exclusion of bleeds occurring during the first 30 day of TRACER in the chronic pooling mitigated the exaggerated early bleeding rates observed in TRACER but the bleeding rates for the remaining events in TRACER were still higher than the TRA 2ºP-TIMI 50 Overall Population. Importantly, in examining the chronic pool, no new signal with respect to these bleeding endpoints was observed, despite examination of over 19,000 subjects exposed to vorapaxar.

Table 7 Bleeding Endpoints with Annualized Event Rates in TRACER, TRA 2°P TIMI-50 Overall Population and Chronic Pool

	TRACER			TRA 2°P TIMI-50 Overall Population			Chronic Pool[f]		
	Placebo (n=6441)	Vorapaxar (n=6446)	Hazard Ratio [a,b] (95% CI)	Placebo (n =13166)	Vorapaxar (n = 13186)	Hazard Ratio [a,b] (95% CI)	Placebo (n=19393)	Vorapaxar (n=19434)	Hazard Ratio [a,b] (95% CI)
	Annualized Event Rate[c]	Annualized Event Rate[c]		Annualized Event Rate[c]	Annualized Event Rate[c]		Annualized Event Rate[c]	Annualized Event Rate[c]	
GUSTO Bleeding Categories									
Severe or Moderate	4.0%	5.5%	1.36 (1.18 - 1.57)	1.0%	1.5%	1.51 (1.31-1.74)	1 1%	1.7%	1.48 (1.32-1.67)
Severe	1.2%	2.0%	1.62 (1.27 - 2.06)	0.5%	0.6%	1.31 (1.06-1.63)	0.5%	0.7%	1.43 (1.19-1.72)
Moderate	2.8%	3.5%	1.26 (1.06 - 1.49)	0.6%	0.9%	1.62 (1.35-1.96)	0.7%	1.0%	1.50 (1.29-1.75)
TIMI Bleeding Categories									
Major or Minor	3.0%	4.5%	1.52 (1.29 - 1.78)	1.1%	1.6%	1.48 (1.29-1.70)	1.1%	1.7%	1.53 (1.35-1.72)
Major	1.9%	2.9%	1.49 (1.22 - 1.82)	0.8%	1.0%	1.32 (1.12-1.56)	0.8%	1.1%	1.41 (1.22-1.63)
Minor	1.1%	1.7%	1.56 (1.20 - 2.03)	0.3%	0.6%	1.83 (1.44-2.32)	0.4%	0.6%	1.74 (1.42-2.14)
Clinically Significant[d]	10.5%	15.2%	1.41 (1.29-1.54)	4.4%	6.2%	1.41 (1.31-1.51)	4.5%	6.6%	1.45 (1.36-1.54)
Non CABG Major or Minor	2.2%	3.5%	1.61 (1.34 - 1.94)	1.0%	1.5%	1.51 (1.31-1.74)	1.0%	1.6%	1.55 (1.37-1.75)
TIMI Major CABG Related	0.8%	1.0%	1.31 (0.95 - 1.79)	<0.1%	<0.1%	0.92 (0.43-1.97)	0.1%	0.1%	1.29 (0.75-2.19)
Other categories									
Intracranial Hemorrhage	0.2%	0.6%	2.52 (1.48 - 4.29)	0.2%	0.3%	1.70 (1.25-2.32)	0.2%	0.4%	1.89 (1.44-2.48)
Fatal Bleeding[e]	0.2%	0.3%	1.81 (0.98 - 3.34)	0.1%	0.1%	1.40 (0.86-2.30)	0 1%	0.1%	1.52 (1.01-2.29)

a. Vorapaxar vs. placebo; a hazard ratio <1 indicates lower hazard associated with vorapaxar relative to placebo
b. Cox proportional hazards model with covariates of treatment and stratification factors
c. Event rate is expressed as number of patients with events per 100 patient years of exposure
d. TIMI Major or Minor bleeding or bleeding that requires unplanned medical or surgical treatment, laboratory evaluation
e. TRACER subject 520303 in the vorapaxar group had a fatal bleed event that occurred after the last visit. As a result, the event was not counted in this analysis. When this event is included the HR is 1.87 (1.02-3.44)
f. Chronic Pool accrual period is Day 31 to Last visit for TRACER and Randomization to Last visit for TRA 2 P TIMI-50

1.3.3 Other (non-bleeding) Serious Adverse Events (SAEs) in Phase 3

Table 8 presents pooled other (non-bleeding) SAEs by combining TRA 2°P TIMI 50 with the entire TRACER population (Overall Pool). Overall SAEs (seen in at least 20 subjects) presented in this table are markedly similar between placebo and vorapaxar, with few exceptions. Notably, anemia was reported more frequently for vorapaxar than for placebo as would be expected for a drug that increases bleeding tendency. Pulmonary embolism was reported twice as frequently for placebo than for vorapaxar and this contributed to the numerically increased event rate for placebo in the SOC of Respiratory, Thoracic and Mediastinal Disorders. Rates for the SOC of Neoplasms Benign, Malignant and Unspecified were nearly identical between the vorapaxar and placebo groups.

Table 8 Summary of Serious Adverse Events - Other Adverse Events for at Least 20 Subjects - During Treatment for Overall Pool[a]

	Placebo n=19607		Vorapaxar n=19632	
	Subjects with Events (%)	Event Rate[b]	Subjects with Events (%)	Event Rate[b]
SUBJECTS REPORTING ANY ADVERSE EVENT	**4301(21.9)**	**(14.0)**	**4312(22.0)**	**(14.1)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**87 (0.4)**	**(0.2)**	**139 (0.7)**	**(0.4)**
ANAEMIA	25 (0.1)	(0.1)	62 (0.3)	(0.2)
THROMBOCYTOPENIA	33 (0.2)	(0.1)	33 (0.2)	(0.1)
CARDIAC DISORDERS	**868 (4.4)**	**(2.5)**	**878 (4.5)**	**(2.6)**
ATRIAL FIBRILLATION	165 (0.8)	(0.5)	192 (1.0)	(0.5)
ATRIAL FLUTTER	31 (0.2)	(0.1)	42 (0.2)	(0.1)
ATRIOVENTRICULAR BLOCK COMPLETE	20 (0.1)	(0.1)	24 (0.1)	(0.1)
BRADYCARDIA	43 (0.2)	(0.1)	29 (0.1)	(0.1)
CARDIAC FAILURE	264 (1.3)	(0.7)	265 (1.3)	(0.8)
CARDIAC FAILURE CONGESTIVE	87 (0.4)	(0.2)	106 (0.5)	(0.3)
CARDIOGENIC SHOCK	33 (0.2)	(0.1)	25 (0.1)	(0.1)
SICK SINUS SYNDROME	23 (0.1)	(0.1)	23 (0.1)	(0.1)
SUPRAVENTRICULAR TACHYCARDIA	29 (0.1)	(0.1)	17 (0.1)	(<.1)
VENTRICULAR FIBRILLATION	36 (0.2)	(0.1)	36 (0.2)	(0.1)
VENTRICULAR TACHYCARDIA	62 (0.3)	(0.2)	49 (0.2)	(0.1)
EAR AND LABYRINTH DISORDERS	**38 (0.2)**	**(0.1)**	**37 (0.2)**	**(0.1)**
VERTIGO	22 (0.1)	(0.1)	27 (0.1)	(0.1)
GASTROINTESTINAL DISORDERS	**397 (2.0)**	**(1.1)**	**421 (2.1)**	**(1.2)**
ABDOMINAL PAIN	24 (0.1)	(0.1)	16 (0.1)	(<.1)
GASTRITIS	28 (0.1)	(0.1)	37 (0.2)	(0.1)
GASTROOESOPHAGEAL REFLUX DISEASE	39 (0.2)	(0.1)	28 (0.1)	(0.1)

Table 8 Summary of Serious Adverse Events - Other Adverse Events for at Least 20 Subjects - During Treatment for Overall Pool[a]

	Placebo n=19607		Vorapaxar n=19632	
	Subjects with Events (%)	Event Rate[b]	Subjects with Events (%)	Event Rate[b]
INGUINAL HERNIA	38 (0.2)	(0.1)	52 (0.3)	(0.1)
PANCREATITIS	20 (0.1)	(0.1)	22 (0.1)	(0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**663 (3.4)**	**(1.9)**	**661 (3.4)**	**(1.9)**
CHEST PAIN	44 (0.2)	(0.1)	39 (0.2)	(0.1)
NON-CARDIAC CHEST PAIN	527 (2.7)	(1.5)	530 (2.7)	(1.5)
HEPATOBILIARY DISORDERS	**141 (0.7)**	**(0.4)**	**137 (0.7)**	**(0.4)**
CHOLECYSTITIS	37 (0.2)	(0.1)	35 (0.2)	(0.1)
CHOLECYSTITIS ACUTE	24 (0.1)	(0.1)	22 (0.1)	(0.1)
CHOLELITHIASIS	53 (0.3)	(0.1)	49 (0.2)	(0.1)
INFECTIONS AND INFESTATIONS	**812 (4.1)**	**(2.3)**	**816 (4.2)**	**(2.4)**
APPENDICITIS	24 (0.1)	(0.1)	27 (0.1)	(0.1)
BRONCHITIS	34 (0.2)	(0.1)	41 (0.2)	(0.1)
CELLULITIS	50 (0.3)	(0.1)	56 (0.3)	(0.2)
DIVERTICULITIS	26 (0.1)	(0.1)	20 (0.1)	(0.1)
ERYSIPELAS	21 (0.1)	(0.1)	17 (0.1)	(<.1)
GASTROENTERITIS	39 (0.2)	(0.1)	43 (0.2)	(0.1)
LOBAR PNEUMONIA	20 (0.1)	(0.1)	21 (0.1)	(0.1)
PNEUMONIA	197 (1.0)	(0.6)	221 (1.1)	(0.6)
SEPSIS	36 (0.2)	(0.1)	26 (0.1)	(0.1)
SEPTIC SHOCK	18 (0.1)	(0.1)	12 (0.1)	(<.1)
URINARY TRACT INFECTION	61 (0.3)	(0.2)	71 (0.4)	(0.2)
UROSEPSIS	7 (<0.1)	(<0.1)	28 (0.1)	(0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**322 (1.6)**	**(0.9)**	**341 (1.7)**	**(1.0)**
FALL	18 (0.1)	(0.1)	22 (0.1)	(0.1)
FEMUR FRACTURE	24 (0.1)	(0.1)	18 (0.1)	(0.1)
HIP FRACTURE	16 (0.1)	(<0.1)	21 (0.1)	(0.1)
METABOLISM AND NUTRITION DISORDERS	**173 (0.9)**	**(0.5)**	**183 (0.9)**	**(0.5)**
DEHYDRATION	29 (0.1)	(0.1)	26 (0.1)	(0.1)
DIABETES MELLITUS	21 (0.1)	(0.1)	24 (0.1)	(0.1)
HYPERGLYCAEMIA	22 (0.1)	(0.1)	21 (0.1)	(0.1)
HYPOGLYCAEMIA	22 (0.1)	(0.1)	28 (0.1)	(0.1)

Table 8 Summary of Serious Adverse Events - Other Adverse Events for at Least 20 Subjects - During Treatment for Overall Pool[a]

	Placebo n=19607		Vorapaxar n=19632	
	Subjects with Events (%)	Event Rate[b]	Subjects with Events (%)	Event Rate[b]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**402 (2.1)**	**(1.1)**	**331 (1.7)**	**(1.0)**
ARTHRITIS	21 (0.1)	(0.1)	18 (0.1)	(0.1)
BACK PAIN	21 (0.1)	(0.1)	14 (0.1)	(<.1)
INTERVERTEBRAL DISC PROTRUSION	38 (0.2)	(0.1)	21 (0.1)	(0.1)
MUSCULOSKELETAL CHEST PAIN	44 (0.2)	(0.1)	47 (0.2)	(0.1)
MUSCULOSKELETAL PAIN	20 (0.1)	(0.1)	22 (0.1)	(0.1)
OSTEOARTHRITIS	96 (0.5)	(0.3)	76 (0.4)	(0.2)
SPINAL COLUMN STENOSIS	22 (0.1)	(0.1)	14 (0.1)	(<0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**478 (2.4)**	**(1.4)**	**471 (2.4)**	**(1.4)**
BLADDER CANCER	21 (0.1)	(0.1)	30 (0.2)	(0.1)
COLON CANCER	26 (0.1)	(0.1)	38 (0.2)	(0.1)
LUNG CANCER METASTATIC	22 (0.1)	(0.1)	9 (<0.1)	(<0.1)
LUNG NEOPLASM MALIGNANT	24 (0.1)	(0.1)	27 (0.1)	(0.1)
PROSTATE CANCER	56 (0.3)	(0.2)	39 (0.2)	(0.1)
NERVOUS SYSTEM DISORDERS	**306 (1.6)**	**(0.9)**	**329 (1.7)**	**(0.9)**
CONVULSION	24 (0.1)	(0.1)	16 (0.1)	(<0.1)
PRESYNCOPE	24 (0.1)	(0.1)	21 (0.1)	(0.1)
SYNCOPE	89 (0.5)	(0.3)	105 (0.5)	(0.3)
PSYCHIATRIC DISORDERS	**96 (0.5)**	**(0.3)**	**98 (0.5)**	**(0.3)**
DEPRESSION	22 (0.1)	(0.1)	25 (0.1)	(0.1)
RENAL AND URINARY DISORDERS	**235 (1.2)**	**(0.7)**	**246 (1.3)**	**(0.7)**
NEPHROLITHIASIS	32 (0.2)	(0.1)	26 (0.1)	(0.1)
RENAL FAILURE	63 (0.3)	(0.2)	76 (0.4)	(0.2)
RENAL FAILURE ACUTE	61 (0.3)	(0.2)	60 (0.3)	(0.2)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**57 (0.3)**	**(0.2)**	**71 (0.4)**	**(0.2)**
BENIGN PROSTATIC HYPERPLASIA	28 (0.1)	(0.1)	41 (0.2)	(0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**380 (1.9)**	**(1.1)**	**331 (1.7)**	**(0.9)**
ACUTE RESPIRATORY FAILURE	23 (0.1)	(0.1)	19 (0.1)	(0.1)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	101 (0.5)	(0.3)	95 (0.5)	(0.3)
DYSPNOEA	31 (0.2)	(0.1)	27 (0.1)	(0.1)

Table 8 Summary of Serious Adverse Events - Other Adverse Events for at Least 20 Subjects - During Treatment for Overall Pool[a]

	Placebo n=19607		Vorapaxar n=19632	
	Subjects with Events (%)	Event Rate[b]	Subjects with Events (%)	Event Rate[b]
PLEURAL EFFUSION	32 (0.2)	(0.1)	31 (0.2)	(0.1)
PULMONARY EMBOLISM	54 (0.3)	(0.2)	26 (0.1)	(0.1)
RESPIRATORY FAILURE	22 (0.1)	(0.1)	25 (0.1)	(0.1)
VASCULAR DISORDERS	**285 (1.5)**	**(0.8)**	**256 (1.3)**	**(0.7)**
AORTIC ANEURYSM	18 (0.1)	(0.1)	20 (0.1)	(0.1)
DEEP VEIN THROMBOSIS	20 (0.1)	(0.1)	22 (0.1)	(0.1)
HYPERTENSION	43 (0.2)	(0.1)	42 (0.2)	(0.1)
HYPERTENSIVE CRISIS	41 (0.2)	(0.1)	30 (0.2)	(0.1)
HYPOTENSION	49 (0.2)	(0.1)	50 (0.3)	(0.1)
ORTHOSTATIC HYPOTENSION	23 (0.1)	(0.1)	17 (0.1)	(<.1)

a. The overall pooled experience is the pooling of all data in P04736 and p04737.

b. Event Rate is expressed as number of patients with events per 100 patient-years of exposure.

1.4 Conclusion

Inclusion of the Chronic Pool from TRACER with the Overall Population from the TRA 2°P TIMI-50 trial results in increased event rates and Hazard Ratios for most bleeding events. These types of pooled analyses are influenced by virtue of the inherent differences that exist between a hospitalized ACS population, largely naïve to anti-platelet therapy and the events surrounding ACS, and a population of patients who are post MI secondary prevention patients with no history of stroke or TIA, such as the Proposed Label Population. Therefore, a pooled analysis of bleeding events does not represent the risk of bleeding in the population of patients for which an indication is being sought. Other adverse event rates are similar between vorapaxar and placebo.