EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2016
EMA/CHMP/500315/2016
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment Assessment report

Invented name: Zontivity

International non-proprietary name: vorapaxar

Procedure No. EMEA/H/C/002814/II/0005

Marketing authorisation holder (MAH): Merck Sharp & Dohme Limited

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

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
ACC	American College of Cardiology
AHA	American Heart Association
ALI	acute limb ischemia
AMI	acute myocardial infarction
aPTT	accelerated partial thromboplastin time
ARB	angiotensin II receptor blocker
ASA	aspirin
AUC	area under the curve
BB	beta blockers
BCS	Biopharmaceutics Classification System
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
DAPT	dual anti-platelet therapy
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
ESC	European Society of Cardiology
EU	European Union
F	female
GCP	good clinical practice
GMR	geometric mean ratio
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries cooperative group; a classification system for degree of bleeding
HR	hazard ratio
HC	Health Canada
ICH	intracranial hemorrhage
INR	international normalized ratio
ITT	intent to treat-refers to a study data set for statistical analysis
KM, K-M	Kaplan-Meier
LDL-C	low-density-lipoprotein cholesterol
M	male
MACE	major adverse cardiac event

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 (BR analysis)
NNT	number needed to treat (BR analysis)
P	Placebo (used as abbrev in many of the statistical figures)
PAD	peripheral artery(arterial) disease
PAR-1	protease-activated receptor 1 (the "thrombin receptor")
PCI	percutaneous coronary intervention
PD	pharmacodynamics
PH	proportional hazard
PK	pharmacokinetics
PMF	Preliminary Marketing Formulation
PT	prothrombin time
RAAS	renin-angiotensin aldosterone system
RIR	recurrent ischemia with rehospitalization
RD	risk difference
RRR	relative risk reduction
RR	risk reduction
Revasc	revascularization
S	SCH 530348 (used in many of the statistical figures)
SAE	serious adverse event
STEMI	ST segment elevation myocardial infarction
TIA	transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction Study Group
TRA	thrombin-receptor antagonist; specifically SCH 530348, as used in this study
TRAP	thrombin receptor agonist peptide
TRA 2ºP-TIMI 50	Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events; the present study
TRACER	acronym for study under Protocol P04736 (A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard of Care in Subjects With Acute Coronary Syndrome: Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome)
TT	thrombin time
TQT	thorough QT
UA	unstable angina
UCR	urgent coronary revascularization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme Limited submitted to the European Medicines Agency on 1 September 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include treatment of patients with Peripheral Arterial Disease (PAD) and as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the contact details of local representative in Luxembourg in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 9.1. Moreover, revised RMP version 2.0 was provided as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0222/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of this application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	1 September 2015
Start of procedure:	19 September 2015
CHMP Rapporteur Assessment Report	13 November 2015
PRAC Rapporteur Assessment Report	21 November 2015
PRAC members comments	25 November 2015
Updated PRAC Rapporteur Assessment Report	26 November 2015
PRAC Outcome	3 December 2015
CHMP members comments	7 December 2015
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 December 2015
Request for supplementary information (RSI)	17 December 2015
CHMP Rapporteur Assessment Report	2 March 2016
PRAC Rapporteur Assessment Report	4 March 2016
PRAC members comments	9 March 2016
Updated PRAC Rapporteur Assessment Report	10 March 2016
PRAC Outcome	17 March 2016
CHMP members comments	17 March 2016
Updated CHMP Rapporteur Assessment Report	23 March 2016
Request for supplementary information (RSI)	1 April 2016
PRAC Rapporteur Assessment Report	30 May 2016
PRAC members comments	3 June 2016
CHMP Rapporteur Assessment Report	8 June 2016
PRAC Outcome	9 June 2016
CHMP members comments	13 June 2016
Updated CHMP Rapporteur Assessment Report	15 June 2016
Opinion	23 June 2013

2. Scientific discussion

2.1. Introduction

Zontivity (vorapaxar) is an antiplatelet agent, the first-in-class selective antagonist of the protease-activated receptor 1 (PAR-1), the primary thrombin receptor on human platelets, which mediates the

downstream effects of this critical coagulation factor in haemostasis and thrombosis. As an antagonist of PAR-1, vorapaxar blocks thrombin-mediated platelet aggregation and thereby has the potential to reduce the risk of atherothrombotic complications.

Zontivity received a marketing authorisation (MA) in the EU in January 2015 for the reduction of atherothrombotic events in adult patients with a history of myocardial infarction (co-administered with acetylsalicylic acid and, where appropriate, clopidogrel) but without history of stroke or TIA (absolute contraindications). Zontivity was also approved in the US in May 2014 with a broader indication i.e. for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease.

The MAH now seeks an extension of the indications for use of Zontivity in patients with peripheral arterial disease (similar to the US label). The *initially* proposed wording for section 4.1 of the SmPC is as follows (additional text shown as bold/italics/underlined):

> *Zontivity, co-administered with acetylsalicylic acid (ASA) and**/or**, where appropriate, clopidogrel, is indicated for the reduction of atherothrombotic events in adult patients with a history of myocardial infarction (MI)* ***or with peripheral arterial disease (PAD)***

The posology remains unchanged to one tablet (2.08 mg vorapaxar) once daily.

This variation application is based to a large extent on the same dossier as the initial MA application (MAA). There are no additional non-clinical or clinical pharmacology data and no new clinical studies. The application is mainly supported by data from the same pivotal study assessed during the initial MAA i.e. the TRA 2ºP-TIMI 50 (Study P04737; 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). However, in this application, the focus is on the population of patients with PAD who were included in the pivotal trial, complemented by additional analyses.

Background information

During the review of the MAA, the MAH requested an amendment of the originally proposed indications (which concerned only patients with a history of myocardial infarction) to include also patients with PAD. This followed the FDA licensing decision to grant a broad indication encompassing PAD patients. The CHMP considered the MAH's request and agreed that the changes to extend the indications should be submitted either as a post-authorisation variation or as separate standalone MAA. This would allow time for a more thorough assessment of the data related to the PAD population which had not been specifically presented and discussed in the original submission.

Following the CHMP advice (as well as comments from Rapporteurs during a pre-submission meeting) the MAH is now applying for an extension of the indications through a type II variation.

Peripheral Arterial Disease

Atherosclerosis is a polyarterial disease that can manifest as coronary artery disease (CAD), cerebrovascular disease (CVD), and/or PAD. The risk factors for the development of coronary and peripheral artery atherosclerosis are the same; namely, diabetes mellitus, hyperlipidaemia, hypertension, age, family history and smoking. Also the pathophysiology of atherothrombosis is the same in PAD and CAD; only the diagnostic site differs.

Atherothrombotic stimulation of platelet aggregation is inhibited with aspirin and clopidogrel (or other P2Y12 inhibitors) through different mechanisms, but there is evidence that both mechanisms are associated with varying degrees of preventing MACE in patients with either PAD or CAD. Similarly,

vorapaxar an inhibitor of the platelet PAR-1 receptor, blocks platelet aggregation induced by thrombin and may reduce MACE in CAD and PAD patients via a common pharmacologic action.

The REACH registry is the most recent large compilation of outcomes in patients with atherothrombosis manifested as CAD, CVD, PAD, or with multiple risk factors. Among nearly 65,000 patients with one year follow-up, CV death, MI, or stroke rates were 4.52% for patients with CAD, 6.47% for patients with CVD, and 5.35% for patients with PAD. Patients with multiple atheromatous sites had higher event rates. Thus, patients with atherothrombosis have high rates of MACE regardless of original presentation. Disease in any vascular bed increases the risk to a similar degree suggesting that the site of disease is not as important, with respect to future MACE events, as the presence of atherothrombotic disease itself.

The European Society of Cardiology (ESC) guidelines describe PAD as occurring in the following vascular sites; carotid, vertebral, upper extremity, mesenteric, renal and lower extremity vessels (LEAD or lower extremity arterial disease). *For the purpose of this application, the term PAD refers to the LEAD component of peripheral arterial disease as described by the ESC*. Most studies of PAD use the criterion of ankle brachial index (ABI) <0.90 as indicative of the presence of disease and this cut point has largely been established based on outcomes of patients with measured ABIs. There is a large increment in risk when ABI is less than 0.90 compared to an ABI of 0.90-1.1. Pain does not always accompany impaired limb perfusion, as defined by an ABI<0.90. Thus, PAD and its accompanying increased risk of CV events and mortality may go undetected. PAD in the presence of other sites of atheromatous disease is associated with further increased risk for MACE, as demonstrated from follow-up of the REACH registry. Critical limb ischemia (CLI), the peripheral equivalent of acute coronary syndrome, represents the most serious manifestation of PAD. Though only 1%–2% of patients will develop CLI, this condition is associated with a high rate of limb amputation and mortality (~25% 1-year outcomes for each).

Evidence for the high risk and the unmet medical need in the PAD population was also seen in the TRA-2°P TIMI 50 study. All placebo subjects in the trial received background therapy with aspirin and/or clopidogrel. Yet the placebo rates of the primary and secondary composite efficacy endpoints were highest for those patients qualifying for the trial on the basis of established PAD: the 3-year KM rates for the primary endpoint were CAD, 12.1%; CVD, 12.1%; PAD, 13.4% and for the secondary endpoint were CAD, 9.7%; CVD, 11.7%; PAD, 11.9%, indicating an unmet medical need at least as great in patients with PAD as it is in CAD.

In general, the residual risk in patients with documented atherothrombotic disease remains high as documented in the REACH registry and in the control group of the TRA 2°P -TIMI 50 trial, despite recommended guideline therapy. There is a need for further treatment in this vulnerable population, which should not exclude patients with PAD.

Peer-reviewed guidelines note the paucity of evidence-based medicine supporting antiplatelet therapy for PAD patients. Guidelines currently support aspirin therapy (75-325mg) to reduce MACE risk in atherosclerotic lower extremity PAD. However, a recent meta-analysis of aspirin therapy for PAD disclosed no benefit [Berger et al. JAMA 2009]. Guidelines mention clopidogrel monotherapy as an alternative to aspirin at “B” level of evidence citing the CAPRIE trial.

The 2011 European Society of Cardiology (ESC) Guideline on the diagnosis and treatment of peripheral artery diseases notes, in relation to PAD epidemiology, that in a recent study in a population aged 60–90 years in Sweden, the prevalence of Lower Extremity Arterial Disease (LEAD) was 18% and that of intermittent claudication was 7%. Typically, one-third of all LEAD patients in the community are symptomatic but the prevalence of critical limb ischaemia is much less. The frequency of LEAD is strongly age related: uncommon before 50 years, rising steeply at older ages. In a recent study in Germany the prevalence of symptomatic and asymptomatic LEAD in men aged 45–49 years was 3.0%, rising to 18.2% in those aged 70–75 years. Corresponding rates for women were 2.7% and 10.8%.

Risk factors for PAD are similar to those in the aetiology of CAD i.e. the typical risk factors for atherosclerotic disease. However, for some peripheral sites the evidence linking certain factors to the development of atherosclerosis is limited. Also, specific risk factors may be more important for the development of the disease at certain sites, but there are few comparative studies. For LEAD the evidence appears to support a stronger link with smoking and diabetes.

The ESC guideline also notes that all patients with LEAD are at increased risk of CVD events and secondary prevention measures are mandatory to improve prognosis. Further to pharmacological approaches aimed at improving exercise capacity in patients with intermittent claudication (such as naftidrofuryl, cilostazol, pentoxifylline and others) as well as antihypertensive and lipid-lowering therapy, where relevant, the Guideline suggests the use of antiplatelets (generally antiplatelet therapy is a Class I recommendation for patients with symptomatic PAD). Mainly this advice concerns low dose aspirin with clopidogrel recommended in case of intolerance. In LEAD patients with co-existing stable CAD, the Guideline advises that clopidogrel may be considered as an alternative to aspirin for long-term antiplatelet therapy (Class IIa recommendation).

The most recent (2011) ACCF/AHA Guideline on the management of patients with PAD also advises (Class I recommendation) use of antiplatelet therapy to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic LEAD, including those with intermittent claudication or CLI, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia (Level of Evidence: A). The Guideline recommends aspirin, typically in daily doses of 75 to 325 mg, as safe and effective therapy to reduce the CV risk in symptomatic LEAD (Level of Evidence: B). Clopidogrel (75 mg per day) is recommended as alternative therapy to aspirin (Level of Evidence: B).

For asymptomatic patients with LEAD antiplatelet therapy is also recommended (Class IIa) in case of an ABI $\leq$ 0.90 (Level of Evidence: C). For those with ABI of 0.91 to 0.99, the Guideline states that the usefulness of antiplatelet therapy is not well established. The concomitant use of aspirin and clopidogrel is generally not recommended.

It should be noted here the clopidogrel is the only antiplatelet agent currently licensed for prevention of atherothrombotic events in patients with established PAD.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Problem statement -Rationale for the proposed indication

Atherothrombosis frequently occurs in multiple vascular beds within the same patient. The pivotal TRA 2°P -TIMI 50 trial enrolled subjects with atherothrombosis in the coronary, cerebral and peripheral arteries based on a hierarchy defined by which vascular bed was affected in the prior 12 months (with randomization stratified by qualifying condition at entry i.e. CAD, CVD, or PAD) and was designed to evaluate the efficacy and safety of vorapaxar in reducing atherothrombotic events in patients receiving standard therapy.

Subjects with a recent history (< 12 months) of MI were randomized in the CAD stratum regardless of disease presence in the other two vascular beds. Subjects without a recent history of MI (as defined in the CAD stratum), regardless of disease presence of PAD, who had a recent stroke (< 12 months) were

randomized in the CVD stratum. Finally, subjects randomized to the PAD stratum had symptomatic peripheral arterial disease (history of intermittent claudication and resting ABI <0.85, or amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia) but did not have a history of recent MI or recent stroke. As expected, there was a considerable overlap in between the three strata in the TRA 2°P TIMI 50 population: in the CAD stratum, 1604 subjects had peripheral vascular bed involvement and 585 subjects had a history of stroke. Likewise, 986 subjects in the PAD stratum had a prior MI (>12 months from randomization) and 304 subjects had a history of stroke (253 subjects > 12 months from randomization).

The results of the study in the *Overall Population* were significantly in favour of vorapaxar and the findings in the specific CAD population were the basis of the initial MAA approval. The MAH notes that the success or failure of a trial should be determined by the prespecified analyses based on its original, overall population. Having excluded patients with cerebrovascular disease (as established during the original MAA, due to safety issues; please see below), the analysis of the remaining cohorts (CAD or PAD) should be considered together as the TRA 2°P - TIMI 50 study was not powered to demonstrate statistical significance in the PAD population or any of the other individual qualifying strata. The pooled results in those two strata (as shown in the efficacy/safety below), complemented with additional analyses in the PAD population can support the expended indication.

Based on the common pathophysiology associated with CAD and PAD, the substantial unmet medical need especially in patients with PAD, and the strength of the benefit – risk assessment in TRA 2°P -TIMI 50, the MAH seeks the new indication based on the pooled data from those patients with a previous MI or PAD with no history of stroke or TIA. This population and its corresponding analyses best maintain the integrity of the original trial.

CHMP comments

The MAH suggests that patients with atherosclerosis, irrespective of whether it is manifested as CAD, CVD, or PAD, share a common pathophysiology and poor prognosis and this was the basis of the population selection in the pivotal TRA 2ºP-TIMI 50 trial. They note that during the evaluation of the vorapaxar application in the US, the FDA expressed the view that, to maintain best the scientific integrity of the trial, the only patient group(s) that should be excluded from analysis should be those with a safety concern, in this case patients with previous history of stroke. The remaining patients from either the CAD (recent history of MI) or the PAD stratum could be examined together.

In line with this view, the MAH's position for this application is that the primary evidence comes from the pooled data of the CAD (post-MI) and PAD populations. Although there are additional analyses focused on the PAD group, as discussed in the clinical part below, these have a secondary role in the presentation of the results.

In this context, a key issue in the review of the current application is the validity of the MAH's argument that, based on the common atherosclerotic background, patients with CAD and/or PAD can be considered as a single population and if this is sufficient justification for a pooled analysis of the two TRA 2ºP-TIMI 50 strata. This is an important question since, as suggested by the MAH, the PAD stratum alone was not powered to establish vorapaxar efficacy and safety.

It is agreed that both CAD and PAD populations often overlap and share underlying risk factors and a high risk of future events. However, the question is whether the two populations represent a sufficiently homogeneous group to permit extrapolations from one to the other and to draw conclusions for either of them based on a pooled analysis.

This approach, to examine together patients with different manifestations of atherosclerotic vascular disease, is not unique to TRA 2ºP-TIMI 50. CAPRIE (a randomised trial of clopidogrel versus aspirin in patients at risk of ischaemic events; Lancet 1996) randomised 19,185 patients with a history of recent

MI (≤35 days before randomisation; n=6,302), ischaemic stroke (n=6,431) or symptomatic PAD (n=6,452) to aspirin (325 mg) or clopidogrel (75 mg). After a mean follow-up of 1.9 years the overall results showed a statistically significant (p=0.043) relative-risk reduction of 8.7% in favour of clopidogrel in the primary endpoint of ischaemic stroke, myocardial infarction or vascular death. The group of patients with PAD showed the greatest benefit with clopidogrel; the average event rate/year in the clopidogrel group was 3.71% compared with 4.86% in the aspirin group, a relative-risk reduction of 23.8% (8.9 to 36.2; p=0.0028). Vascular deaths appeared to have contributed most to the differences between treatments in the PAD group. In contrast to PAD, no clear benefit of clopidogrel vs aspirin was seen in the MI population alone. Therefore, in CAPRIE there was some evidence of heterogeneity between the PAD and MI populations, although following a post-hoc analysis in the subgroup of patients who had both MI and PAD (+stroke) the results showed more consistency across the three patients groups. Based on this the investigators suggested that the observed heterogeneity does not invalidate the underlying concept of CAPRIE to study all atherosclerotic patients together.

Following CAPRIE, the CHARISMA trial (Bhatt et al. NEJM 2006) again investigated a range of patients with atherosclerotic disease i.e. with documented CAD, CVD, symptomatic PAD, or multiple atherothrombotic risk factors. A total of 15,603 patients were assigned to receive either DAPT with clopidogrel plus aspirin (n=7,802) or aspirin alone (n=7,801). After a median of 28 months of follow-up, the rate of the primary event (MI, stroke, or death from cardiovascular causes) was not statistically different between treatments (relative risk, 0.93; 95%CI, 0.83 to 1.05; P=0.22) while bleedings were more common with dual therapy. In a subsequent analysis of CHARISMA (Cacoub et al. European Heart Journal 2009) including only the PAD population, the investigators reported that in general the overall rate of CV death (as well as deaths from any cause), MI, or stroke was significantly higher in patients with PAD than the rest. Yet, in line with the overall CHARISMA results there were no significant differences between DAPT with clopidogrel plus aspirin compared to aspirin alone, although the trend was in favour of clopidogrel. The rate of severe bleeding was similar between groups (but in general the data suggested that PAD patients were at higher risk of bleeding than non-PAD patients).

The above indicate that indeed the model of studying together patients with different expressions of atherosclerosis has been put to the test before, but the findings (especially of CAPRIE) do not seem to provide much support that this is a clinically and/or methodologically valid concept. The fact also that in TRA 2ºP-TIMI 50 one of the atherosclerotic populations, patients with history of stroke (CVD stratum), were found to be at much higher risk of bleeding and ICH and were forced to discontinue from the study casts some doubts on the principle that the common pathophysiological background and risk factors are sufficiently strong determinants of the homogeneity of the disease to allow pooled analyses with consistent findings across the different patients groups.

This issue is further discussed in the efficacy and safety sections below.

Overview of the clinical data

In the initial MAA, the "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)".

Study No	Methodology	Study Population			Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Results
		M	F	Age Range				
P04737	Multinational, randomized, double-blind, placebo-controlled, fixed-dose, balanced-parallel-groups study	20123	6326	21-95	men/women, aged ≥18y with evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems	vorapaxar 2.5 mg tablet or placebo tablet to match vorapaxar 2.5 mg tablet; 1 tablet taken orally each day; Duration of treatment: ~3.5-4y	Primary efficacy endpoint: time from randomized treatment assignment to the first occurrence of any component of the composite of CV death, MI, stroke, and UCR. The key secondary endpoint of the study was the time from randomized treatment assignment to the first occurrence of any component of the composite of CV death, MI, and stroke.	-The addition of daily dose of 2.5 mg of vorapaxar to standard therapy (including ASA and thienopyridine) reduced the risk of CV death, MI, stroke or UCR among subjects with stable atherosclerosis in the overall population. -Vorapaxar increased the risk of GUSTO moderate or severe bleeding, including intracranial haemorrhage in the overall population while in the proposed label population the rates of ICH and fatal bleeding were similar in both treatment groups.

GCP

The trial was conducted following appropriate Good Clinical Practice (GCP) standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed. Three site closures occurred during the trial due to GCP compliance issues and are detailed in the TRA 2°P-TIMI 50 CSR.

No GCP issues were identified during the review of TRA 2ºP-TIMI 50 at the time of the initial MAA.

2.4. Clinical Pharmacology

No new clinical pharmacology data have been submitted with this variation. The pharmacokinetic and pharmacodynamic profile of vorapaxar was established during the initial MAA.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No new dose response studies have been submitted.

2.5.2. Main study

Methods

The **TRA 2°P-TIMI 50** trial was extensively discussed during the initial MAA; therefore, only the aspects of the study that are relevant to the current application are presented in detail in this report.

In brief, TRA 2°P-TIMI 50 was a multicenter, randomized, double-blind, placebo-controlled, balanced-parallel-groups trial that included subjects with evidence or a history of atherosclerosis as follows:

a) CAD as indicated by a history of presumed spontaneous myocardial infarction (MI) ≥2 weeks but ≤ 12 months or

b) ischaemic (presumed thrombotic) CVD as indicated by a history of ischemic stroke ≥2 weeks but ≤12 months or

c) PAD as indicated by a history of intermittent claudication and

- a resting ankle/brachial index (ABI) of <0.85, or
- amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia

Treatments

Upon enrolment, subjects were to receive the randomized allocated treatment with vorapaxar or placebo in a 1:1 ratio. All doses were to be taken by the subject orally, once daily, with or without food, as follows:

- one tablet of vorapaxar 2.5 mg, or
- one tablet of matching placebo

Investigators were encouraged to follow applicable clinical guidelines for subjects with established atherosclerosis, including antiplatelet therapy (eg, aspirin, thienopyridine), lipid-modification therapy, cardiac remodelling therapy, and antianginal therapies. If aspirin was used, it was recommended that it be administered in the range of 75 to 325 mg daily.

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; that is, when a pre-specified defined number of subjects had efficacy endpoint events and every subject had the opportunity to participate in the study for at least 1 year.

Outcomes/endpoints

The primary efficacy endpoint of the study was the time from randomized treatment assignment to the first occurrence of any component of the composite of cardiovascular death, MI, stroke, and urgent coronary revascularization.

The key secondary endpoint of the study was the time from randomized treatment assignment to the first occurrence of any component of the composite of cardiovascular death, MI, and stroke. Additional secondary efficacy endpoints and exploratory endpoints comprising various combinations of components and individual components were addressed.

Secondary safety endpoints were based on measures of bleeding, including composite of moderate and severe bleeding events according to GUSTO classification, and clinically significant bleeding, defined as TIMI major or TIMI minor bleeding, or bleeding that requires unplanned medical treatment, surgical treatment, or laboratory evaluation.

Sample size

The initial plan was to recruit 19,500 subjects, but following a blinded sample size re-estimation in March 2009, up to 25,000 subjects were to be recruited at approximately 1000 centres in North America, Latin America, Eastern and Western Europe, Israel, South Africa, Asia/Pacific, and Australia/New Zealand; 1032 study sites in 32 countries. This sample size was required to provide adequate power to test the hypothesis of a 15% relative risk reduction with vorapaxar relative to placebo, each added to the existing standard of care, for occurrence of the primary and key secondary composite efficacy endpoints, plus adjust for potential dropouts during the study.

Randomisation

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).

Blinding

Treatment assignment was blinded for subjects, investigators and staff who evaluated subjects and their responses or made decisions about subject care, and Sponsor personnel who had direct contact with subject records or were involved with study contact or data review. Unblinding during the study was to occur only in the event of an emergency or adverse event for which it was necessary to know the study treatment to determine an appropriate course of therapy for the subject.

Statistical methods

An "Intent-to-Treat" (ITT) population was used for analyses and evaluations of efficacy, whereas an "As Treated" population was used for analyses and evaluations of safety.

Analyses of the primary efficacy endpoint and key secondary endpoint were accomplished via the Cox proportional hazards model with covariates of treatment and stratification factors. Subjects who did not have any endpoint event before the last visit or subjects who were lost to follow-up and had no event, were censored at the time of last available information (last study visit). If a subject had a fatal event that was not part of a specific endpoint for analysis, the subject was censored at the time of death. Treatment differences were tested at alpha=0.049 to account for one interim analysis. P-values and estimates of the hazard ratios and 95% confidence intervals were provided. Similar analyses were performed for other secondary and exploratory efficacy endpoints at alpha=0.05. 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 primary hypothesis other than the 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. Therefore, no additional multiplicity adjustment was needed for the key secondary efficacy endpoint other than the adjustment for protocol-specified interim efficacy analysis.

The efficacy analyses were categorized into 3 groups based on the level of pre-specification of the analyses

Group 1: Analyses were pre-specified in the study 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:

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

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

Group 2: Analyses were pre-specified in the study DAP, and were not covered under a multiplicity adjustment procedure. Significance levels associated with these analyses were to be interpreted in this context including potential elevation of both type I and type II error rates.

a) The primary and key secondary endpoints (as defined above among the following subpopulations of subjects:

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

b) Exploratory efficacy endpoints include the first occurrence of any component of the following composites:

- All-cause death, MI, and stroke in subjects undergoing PCI during the study
- All-cause death, MI, and stroke in subjects undergoing CABG during the study
- CV death, MI, stroke, and UCR in association with use of thienopyridine
- CV death, MI, stroke, and UCR in subjects taking aspirin but not thienopyridine
- CV death, MI and stroke in subjects taking aspirin but not thienopyridine

c) The primary and key secondary endpoints within category of the following subgroups:

- Sex, age: <65 vs ≥65 and < 75 vs. ≥75, race: Caucasian, vs non-Caucasian
- Geographic Regions: North America, Latin America, Europe I, Europe II, Asia, Australia/New Zealand.
- Body weight: < median (81 kg) vs. ≥median
- Stratification factor of atherosclerosis history at time of enrolment: CAD, CVD, PAD
- Planned use of thienopyridine, aspirin use, history of diabetes, renal insufficiency, tobacco use,
- Prior stroke, prior MI, prior ACS (MI or hospitalization for unstable angina), lipid medication, statin therapy

Group 3: Analyses that were NOT pre-specified in the study DAP, and NOT covered under a multiplicity adjustment procedure were considered exploratory and post hoc in nature. Inferential results (e.g p-values) based on these analyses were interpreted with caution as these analyses were subject to biases and confounding associated with post-hoc analyses including potentially elevated false discovery rates and potential inflation of both the type I and type II error rates. The p values presented in this group were not adjusted p-values and were used only to support hypothesis-generating purposes. Examples include subgroups including but not limited to subgroup by body weight, exposure to PPI, exposure to H2A, systemic exposure to CYP34P inducer and subgroups based on time from MI or stroke qualifying

events to randomization.

Pre-specified bleeding endpoints were analysed via the Cox proportional hazards model with covariates of treatment and stratification factors for time-to-event analyses. Pearson's Chi-squared test and analysis of variance models, as appropriate, were used for other variable measures.

CHMP comments

The TRA 2ºP-TIMI 50 methodology has previously been reviewed and considered adequate.

The statistical methods presented above are those for the initial submission. In particular, references to the DAP and analysis groups apply to the original application only. The methods were considered adequate in the original submission. It is assumed that the analysis methods for the new submission and newly defined population are the same and therefore adequate. As discussed throughout this document, the patient population on which this application is based was defined post hoc.

Results

- **Conduct of the study and participant flow**

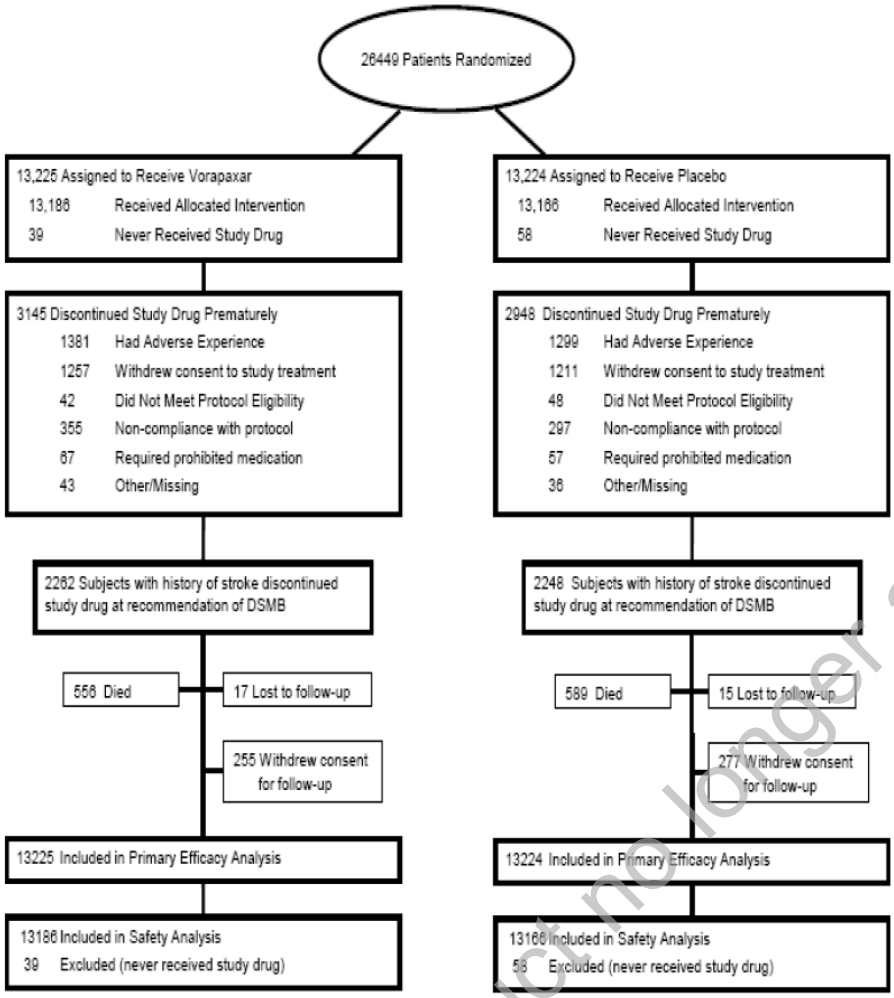
A total of 26,449 received randomized treatment assignment: 13,224 placebo and 13,225 vorapaxar (Intent to Treat population). There were 20,123 men (76%) and 6,326 (24%) women aged 21 to 95 years.

The ITT population comprised:

- 17,779 subjects with CAD,
- 4,883 with CVD, and
- 3,787 with PAD as the qualifying condition.

The patients' disposition in the whole TRA 2ºP-TIMI 50 is shown in the diagram below.

Figure E.1. Subject Disposition



In January 2011 (approximately 3.5 years after initiation of the trial) the DSMB recommended that all subjects with a stroke either prior to or during the study discontinue study medication while the remaining subjects continue the study drug as planned. This was due to an increased number of intracranial haemorrhages (ICH) reported in subjects with a prior history of stroke. A communication was sent to all study sites to inform about discontinuing subjects with a prior history of stroke, conduct follow-up visits and inform subjects. Patients with MI and PAD who also had a stroke were to discontinue treatment but continue their follow-up visits.

The initial plan for the primary efficacy analysis in the overall population involved data from subjects in all three strata, based on their qualifying atherosclerotic disease presentation, in their entirety.

Following the recommendation of the DSMB and prior to database lock, the Executive Committee and Sponsor pre-specified populations that excluded the group identified by the DSMB. While not part of the pre-specified populations of interest, the Sponsor in conjunction with the Executive Committee also decided that a history of TIA should be granted the same level of consideration as stroke for it is clinically difficult to distinguish between history of TIA or stroke. This led to the further restriction of the population to subjects with no history of stroke or TIA.

During the initial MAA the findings in the following subpopulations of TRA 2ºP-TIMI 50 were submitted and reviewed (Note: the numbers reflect the ITT population):

- *'Overall population'* (n =26,449) – subjects, regardless of the qualifying condition, who received randomized treatment assignment.
- *'NSH population'* (n = 20,699) – subjects with no stroke history (NSH) – regardless of the qualifying condition, who received randomized treatment assignment.
- *'CAD (Post MI) and no history of stroke'* (n = 17,191) – subjects whose qualifying condition was CAD and did not have a documented history of stroke prior to randomization.

as well as the post-hoc defined:

- *'Proposed Label Population'* (n = 16,897) – subjects whose qualifying condition was CAD (post MI) who did not have documented history of stroke or TIA prior to randomization.

The results in this population were the basis of the currently approved indication.

In support of this variation application, the MAH has now submitted the results for a new post-hoc cohort, an expanded version of the previous *'Proposed Label Population',* termed:

- ***'Intended Label Population'*** (n = 20,170) – subjects whose qualifying condition was CAD or PAD with no history of stroke or TIA prior to randomization.

In addition, the MAH has also provided the results in the following groups that include only patients diagnosed with PAD:

- ***PAD stratum and no history of stroke or TIA*** (n = 3,273) - subjects with no history of stroke or TIA whose qualifying condition was PAD at entry;
- ***Clinical PAD Population*** (n = 3,945) **–** Subjects with:
    - Subjects with no history of stroke or TIA whose qualifying condition was PAD at entry or
    - Subjects with baseline ABI ≤0.90 and Fontaine category >1; or
    - Subjects with a history of peripheral arterial revascularization

The rationale for this *Clinical PAD* group is that many subjects fulfilled the diagnostic criteria for PAD but, based on the hierarchical definition, were assigned to the CAD stratum (because they had a recent MI < 12 months prior to enrolling); thus they were excluded from the PAD stratum. For this population a clinically relevant and well-accepted definition of PAD was used. These criteria may miss some patients with PAD because even though they satisfy ABI criteria, they did not include symptoms and might therefore be undiagnosed. The population for these sensitivity analyses fit with accepted definitions of PAD, and more likely represent patients with clinically relevant PAD.

- ***Aspirin-Only PAD Population*** (n = 2,087):
    - Subjects with no history of stroke or TIA whose qualifying condition was PAD at entry and
    - Had aspirin use at baseline with no planned use of a thienopyridine

This sample was analyzed to be consistent with typical background treatment in Europe.

CHMP comments

It needs to be noted again here that the MAH considers the ***'Intended Label Population'*** as the primary population for this application with the results in the other groups mainly presented as supporting evidence.

This is based, according to the MAH, on the original objective and design of TRA 2ºP-TIMI 50 aiming at the atherosclerotic population as a whole. Having excluded patients with CVD (due to safety issues),

the analysis of the remaining cohorts (CAD or PAD) should be considered together, as the TRA 2°P - TIMI 50 study was not powered to demonstrate statistical significance in the PAD population or any of the other individual qualifying strata.

The *'Intended Label Population'* mainly comprises patients with CAD and prior MI and only approximately 16%-19% patients with evidence of PAD (as defined by the PAD stratum or Clinical PAD population criteria). Therefore, the findings in the *'Intended Label Population'* still reflect primarily the post-MI population that was reviewed in the initial MAA.

Certainly, it is essential to evaluate also the efficacy and safety of vorapaxar in the PAD population separately; therefore, the data in the ***PAD stratum*** are also presented here and discussed in detail with more information on the *Clinical PAD* and *Aspirin-only PAD* groups shown where relevant.

Of note, Unless otherwise stated, all TRA 2ºP-TIMI 50 populations mentioned in the remaining sections of this report concern patients "with no history of stroke or TIA" (not repeated for the sake of simplicity); for example, "*PAD stratum"* refers to patients in *PAD stratum and no history or stroke of TIA*. Also the terms "CAD stratum", "post-MI patients", "patients with recent MI" all referring to TRA 2ºP-TIMI 50 *CAD stratum (Post MI) and no history of stroke or TIA*, are used interchangeably.

- **Baseline data**

- ***Intended Label Population***

In the *Intended Label Population*, subjects were predominantly white (89%), male (78%), with a median age of 60 years; 9% were over 75 years old. Median body weight was 82 kg. Overall, the use of concomitant medications was similar between the two treatment groups. There was near universal use of aspirin (97%), 71% of subjects were treated with clopidogrel and 70% were treated with dual antiplatelet therapy. The two treatment groups were well balanced in terms of relevant medical history. Overall, 65% of the subjects had hypertension, 85% had hyperlipidaemia, and 24% had diabetes mellitus. Approximately 82% of subjects with hyperlipidaemia were being treated with lipid medications, of those 93% were receiving statins. Antihypertensive agents were also commonly used: 80% of subjects were taking a beta blocker, 63% an ACE inhibitor or combination, and 14% an ARB or combination.

Table E.1. TRA 2ºP-TIMI 50 Baseline Demographics, Disease Characteristics, and Concomitant Medications in Subjects With No History of Stroke or TIA Whose Qualifying Condition was CAD or PAD

Characteristic	Placebo (N=10090)	Vorapaxar (N=10080)	Total (N=20170
Age (y)			
Mean (SD)	59.7 (10.66)	59.9 (10.73)	59.8 (10.70)
Median	60.0	60.0	60.0
Age (n (%))			
<65 y	6787(67.3)	6649 (66.0)	13436 (66.6)
65-<75 y	2378(23.6)	2502 (24.8)	4880 (24.2)
≥75 y	925 (9.2)	929 (9.2)	1854 (9.2)
Sex (n (%))			
Female	2165 (21.5)	2204 (21.9)	4369 (21.7)
Male	7925 (78.5)	7876 (78.1)	15801 (78.3)
Race (n (%))			
White	8924 (88.4)	8939 (88.7)	17863 (88.6)
Non-white	1163 (11.5)	1134 (11.3)	2297 (11.4)
Asian	353 (3.5)	332 (3.3)	685 (3.4)
Black/African American	238 (2.4)	231 (2.3)	469 (2.3)
Weight (kg)	(n=10071)	(n=10067)	(n=20138)
Mean (SD)	83.96 (17.312)	83.39 (16.857)	83.68 (17.088)
Median	82.10	82.00	82.00
Weight (n(%))			
<60 kg	580 (5.7)	597 (5.9)	1177 (5.8)
≥60 kg	9491 (94.1)	9470 (93.9)	18961 (94.0)

Characteristic	Placebo (N=10090)	Vorapaxar (N=10080)	Total (N=20170
Calculated Body Mass Index (kg/m2)a	(n=10065)	(n=10057)	(n=20122)
Mean (SD)	28.51 (5.028)	28.37 (4.871)	28.44 (4.951)
Median	27.80	27.80	27.80
Systolic Blood Pressure (mm Hg)	(n=10063)	(n=10060)	(n=20123)
Mean (SD)	131.8 (19.07)	132.0 (19.37)	131.9 (19.22)
Median	130.0	130.0	130.0
Diastolic Blood Pressure (mm Hg)	(n=10062)	(n=10057)	(n=20119)
Mean (SD)	77.6 (10.71)	77.5 (10.71)	77.5 (10.71)
Median	78.0	78.0	78.0
Ankle/Brachial Index	(n=9818)	(n=9830)	(n=19648)
Mean (SD)	1.027 (0.2248)	1.029 (0.2225)	1.028 (0.2236)
Median	1.040	1.050	1.040
Hypertension	6564 (65.1)	6520 (64.7)	13084 (64.9)
History of Cigarette Smoking	7411 (73.4)	7348(72.9)	14759(73.2)
Hyperlipidaemia	8573 (85.0)	8554 (84.9)	17127 (84.9)
Diabetes Mellitus	2377 (23.6)	2385 (23.7)	4762 (23.6)
Prior Peripheral Arterial Disease	2049 (20.3)	1980(19.6)	4029 (20.0)
Claudication	2230 (22.1)	2187 (21.7)	4417 (21.9)
Heart Failure	873 (8.7)	856 (8.5)	1729 (8.6)
Prior PCI	7153 (70.9)	7125 (70.7)	14278 (70.8)
Prior CABG	1471 (14.6)	1471 (14.6)	2942 (14.6)
Prior Percutaneous Carotid Intervention	55 (0.5)	59 (0.6)	114 (0.6)
Prior Carotid Endarterectomy	134 (1.3)	160 (1.6)	294 (1.5)
Peripheral Arterial Revascularization	1199 (11.9)	1171 (11.6)	2370 (11.8)
Prior Amputation Related to Limb Ischemia	83 (0.8)	93 (0.9)	176 (0.9)
Estimated eGFR at Baseline			
<60 mL/min·1.73m^2	1383 (13.7)	1476 (14.6)	2859 (14.2)
≥60 mL/min·1.73m^2	8591 (85.1)	8482 (84.1)	17073 (84.6)
Not Able to Calculate	116 (1.1)	122 (1.2)	238 (1.2)
Functional status			
NYHA Functional Classification	(n=10068)	(n=10055)	(n=20123)
I (no limitation of activities)	8678 (86.2)	8654 (86.1)	17332 (86.1)
II (slight, mild limitation of activities)	1307 (13.0)	1303 (13.0)	2610 (13.0)
III (marked limitation of activities)	76 (0.8)	89 (0.9)	165 (0.8)
IV (symptoms with any activity, or at rest)	7 (0.1)	9 (0.1)	16 (0.1)
Fontaine Classification	(n=10009)	(n=9991)	(n=20000)
I (asymptomatic)	8355 (83.5)	8343 (83.5)	16698 (83.5)
IIa (intermittent claudication walking >200 m)	998 (10.0)	1000 (10.0)	1998 (10.0)
IIb (intermittent claudication walking <200 m)	597 (6.0)	589 (5.9)	1186 (5.9)
III (pain at rest or at night)	46 (0.5)	39 (0.4)	85 (0.4)
IV (ulceration, necrosis, or gangrene)	13 (0.1)	20 (0.2)	33 (0.2)
Concomitant medication			
Any Antiplatelet Agent (including aspirin)	10005 (99.2)	10013 (99.3)	20018 (99.2)
Any Aspirin	9756 (96.7)	9746 (96.7)	19502 (96.7)
Any Clopidogrel	7137 (70.7)	7088 (70.3)	14225 (70.5)
Any Ticlopidine	64 (0.6)	72 (0.7)	136 (0.7)
Any Prasugrel	17 (0.2)	21 (0.2)	38 (0.2)
Any Thienopyridine	7215 (71.5)	7177 (71.2)	14392 (71.4)
Any Dipyridamole	9 (0.1)	11 (0.1)	20 (0.1)
Any Cilostazol	220 (2.2)	192 (1.9)	412 (2.0)
Any Antiplatelet Agent Other Than Aspirin or Clopidogrel	32 (0.3)	35 (0.3)	67 (0.3)
Aspirin Only	2642 (26.2)	2704 (26.8)	5346 (26.5)
Aspirin Plus a Thieopyridine	6983 (69.2)	6920 (68.7)	13903 (68.9)
Aspirin Plus Any Other Antiplatelet Agent	7114 (70.5)	7042 (69.9)	14156 (70.2)
Any Oral Anticoagulant	7 (0.1)	11 (0.1)	18 (0.1)
Warfarin	6 (0.1)	9 (0.1)	15 (0.1)
Any Beta-adrenergic Antagonist (excludes ophthalmic preps)	8065 (79.9)	8019 (79.6)	16084 (79.7)
Any Angiotensin Converting Enzyme Inhibitor or Combination	6367 (63.1)	6326 (62.8)	12693 (62.9)
Any Angiotensin II Receptor Antagonist or Combination	1484 (14.7)	1371 (13.6)	2855 (14.2)
Any Statin	9458 (93.7)	9329 (92.5)	18787 (93.1)

Characteristic	Placebo (N=10090)	Vorapaxar (N=10080)	Total (N=20170
Any Proton Pump Inhibitor	2542 (25.2)	2521 (25.0)	5063 (25.1)
Any H2-Receptor Antagonist	480 (4.8)	457 (4.5)	937 (4.6)
Any Thienopyridine includes Clopidogrel, Ticlopidine, Prasugrel, Ticagrelor Any Other Antiplatelet includes any Thienopyridine, Dipyridamole, Cilostazol, Glycoprotein IIb/IIIa Inhibitor Any Oral Anticoagulant includes Warfarin, Phenoprocoumon, Acenocoumarol, Fluindione Subjects were not taking aspirin or Clopidogrel			

CHMP comments

In general the TRA 2ºP-TIMI 50 patient characteristics are consistent with what is expected in a population with atherosclerotic disease and multiple risk factors. The groups were well balanced in terms of demographics, coexistent conditions and background therapies. Almost all patients were on aspirin and the majority were also receiving clopidogrel (i.e. double antiplatelet therapy) but there were very few patients on other antiplatelet agents like prasugrel or ticagrelor. This is a limitation identified in the previous round and currently reflected in the approved SmPC.

Of course, this population mainly reflects post-MI patients who represent the majority in this group. The baseline characteristics in patients with PAD (*PAD stratum*) are described below.

- ***PAD stratum***

The baseline data in the *PAD stratum* with no history of stroke or TIA are shown below.

Table E.2. TRA 2ºP-TIMI 50 Baseline Demographics, Disease Characteristics, and Concomitant Medications Subjects With No History of Stroke or TIA whose Qualifying Condition was PAD at Entry and Prior to Randomization

	Placebo (n=1651)	Vorapaxar (n=1622)	TOTAL (n=3273)
Age (years)			
Mean (SD)	66.0 (9.39)	65.8 (9.44)	65.9 (9.41)
Median	66.0	66.0	66.0
Age (n(%))			
<65	735(44.5)	689(42.5)	1424(43.5)
65 - <75	597(36.2)	638(39.3)	1235(37.7)
>=75	319(19.3)	295(18.2)	614(18.8)
Sex (n(%))			
Female	489(29.6)	481(29.7)	970(29.6)
Male	1162(70.4)	1141(70.3)	2303(70.4)
Race (n(%))			
White	1509(91.4)	1458(89.9)	2967(90.7)
Non-White	142 (8.6)	163(10.0)	305 (9.3)
Asian	13 (0.8)	11 (0.7)	24 (0.7)
Black or African American	61 (3.7)	59 (3.6)	120 (3.7)
Weight (kg)	(n=1646)	(n=1619)	(n=3265)
Mean (SD)	80.32 (16.921)	80.30 (16.818)	80.31 (16.867)
Median	78.45	78.90	78.70
Weight (n(%)			
< 60 kg	151 (9.1)	165(10.2)	316 (9.7)
>=60 kg	1495(90.6)	1454(89.6)	2949(90.1)
Missing	5 (0.3)	3 (0.2)	8 (0.2)
Calculated Body Mass Index (kg/m²)a	(n=1646)	(n=1616)	(n=3262)
Mean (SD)	27.94 (5.229)	27.82 (4.958)	27.88 (5.096)
Median	27.30	27.40	27.30
Systolic Blood Pressure (mm Hg)	(n=1648)	(n=1620)	(n=3268)
Mean (SD)	139.8 (19.26)	140.8 (20.13)	140.3 (19.70)
Median	140.0	140.0	140.0
Diastolic Blood Pressure (mm Hg)	(n=1647)	(n=1618)	(n=3265)
Mean (SD)	76.8 (10.59)	77.1 (10.97)	76.9 (10.78)
Median	78.0	78.0	78.0
Ankle/Brachial Index	(n=1595)	(n=1548)	(n=3143)

	Placebo (n=1651)	Vorapaxar (n=1622)	TOTAL (n=3273)
Mean (SD)	0.765 (0.2268)	0.767 (0.2269)	0.766 (0.2268)
Median	0.770	0.760	0.760
Missing	56	74	130
Hypertension	1353(82.0)	1344(82.9)	2697(82.4)
Hyperlipidaemia	1457(88.2)	1403(86.5)	2860(87.4)
Diabetes Mellitus	563(34.1)	576(35.5)	1139(34.8)
Prior Peripheral Arterial Disease	1610(97.5)	1572(96.9)	3182(97.2)
Claudication	1638(99.2)	1618(99.8)	3256(99.5)
Heart Failure	157 (9.5)	157 (9.7)	314 (9.6)
Prior PCI	441(26.7)	414(25.5)	855(26.1)
Prior CABG	388(23.5)	370(22.8)	758(23.2)
Prior Percutaneous Carotid Intervention	30 (1.8)	44 (2.7)	74 (2.3)
Prior Carotid Endarterectomy	97 (5.9)	126 (7.8)	223 (6.8)
Peripheral Arterial Revascularization	1024(62.0)	1022(63.0)	2046(62.5)
Prior Amputation for Limb Ischemia	63 (3.8)	79 (4.9)	142 (4.3)
Estimated eGFR at Baseline			
<60 mL/min·1.73m^2	457(27.7)	427(26.3)	884(27.0)
≥60 mL/min·1.73m^2	1180(71.5)	1172(72.3)	2352(71.9)
Not Able to Calculate	14 (0.8)	23 (1.4)	37 (1.1)
Functional status			
NYHA Functional Classification	(n=1648)	(n=1620)	(n=3268)
I (no limitation of activities)	1380(83.7)	1339(82.7)	2719(83.2)
II (slight, mild limitation of activities)	165(10.0)	166(10.2)	331(10.1)
III (marked limitation of activities)	87 (5.3)	95 (5.9)	182 (5.6)
IV (symptoms with any activity, or at rest)	15 (0.9)	19 (1.2)	34 (1.0)
Fontaine Classification	(n=1645)	(n=1615)	(n=3260)
I (asymptomatic)	442(26.9)	405(25.1)	847(26.0)
IIa (intermittent claudication walking >200 m)	672(40.9)	674(41.7)	1346(41.3)
IIb (intermittent claudication walking <200 m)	485(29.5)	485(30.0)	970(29.8)
III (pain at rest or at night)	35 (2.1)	32 (2.0)	67 (2.1)
IV (ulceration, necrosis, or gangrene)	11 (0.7)	19 (1.2)	30 (0.9)
Concomitant medication			
Any Antiplatelet Agent (including aspirin)	1607 (97.3)	1576 (97.2)	3183 (97.3)
Any Aspirin	1458 (88.3)	1431 (88.2)	2889 (88.3)
Any Clopidogrel	565 (34.2)	550 (33.9)	1115 (34.1)
Any Ticlopidine	20 (1.2)	24 (1.5)	44 (1.3)
Any Prasugrel	0	0	0
Any Thienopyridine	584 (35.4)	573 (35.3)	1157 (35.3)
Any Dipyridamole	7 (0.4)	3 (0.2)	10 (0.3)
Any Cilostazol	191 (11.6)	176 (10.9)	367 (11.2)
Any Antiplatelet Agent Other Than Aspirin or Clopidogrel	30 (1.8)	27 (1.7)	57 (1.7)
Aspirin Only	888 (53.8)	882 (54.4)	1770 (54.1)
Aspirin Plus a Thieopyridine	452 (27.4)	438 (27.0)	890 (27.2)
Aspirin Plus Any Other Antiplatelet Agent	570 (34.5)	549 (33.8)	1119 (34.2)
Any Oral Anticoagulant	3 (0.2)	4 (0.2)	7 (0.2)
Warfarin	3 (0.2)	4 (0.2)	7 (0.2)
Any Beta-adrenergic Antagonist (excludes ophthalmic preps)	856 (51.8)	825 (50.9)	1681 (51.4)
Any Angiotensin Converting Enzyme Inhibitor or Combination	781 (47.3)	740 (45.6)	1521 (46.5)
Any Angiotensin II Receptor Antagonist or Combination	379 (23.0)	369 (22.7)	748 (22.9)
Any Statin	1372 (83.1)	1298 (80.0)	2670 (81.6)
Any Proton Pump Inhibitor	374 (22.7)	338 (20.8)	712 (21.8)
Any H2-Receptor Antagonist	59 (3.6)	59 (3.6)	118 (3.6)

Any Thienopyridine includes Clopidogrel, Ticlopidine, Prasugrel, Ticagrelor
Any Other Antiplatelet includes any Thienopyridine, Dipyridamole, Cilostazol, Glycoprotein IIb/IIIa Inhibitor
Any Oral Anticoagulant includes Warfarin, Phenoprocoumon, Acenocoumarol, Fluindione
Subjects were not taking aspirin or Clopidogrel

CHMP comments

There are some interesting observations when the baseline characteristics of the PAD population are compared with their CAD counterparts. Compared to the previously considered "Proposed Label Population" comprising only CAD patients with no history of stroke or TIA, the PAD population was older (PAD: median 66yrs vs CAD: median 58 yrs), there was a higher percentage of diabetic patients (PAD: average 34.8% vs CAD: average 21.4%), as well as a higher rate of renal impairment as suggested by the percentage of patients with eGFR <60 mL/min·1.73m^2.

As expected, more PAD patients had a history of peripheral revascularisation procedures, but far less coronary revascularisations than their CAD counterparts. Also in terms of background therapy, although in the CAD population the use of aspirin was almost universal, in PAD a significant proportion of patients were receiving clopidogrel instead of aspirin as a sole antiplatelet. Also DAPT in CAD patients was common (more than 75%) but only half of that (around 34%) in PAD patients.

In general, treatment groups within the PAD stratum were again well balanced in terms of demographics, risk factors, functional status and therapies.

- **Outcomes and estimation**

Primary and Key Secondary Endpoints

- ***Intended Label Population***

In the *Intended Label Population* there was a 17% reduction in the primary efficacy endpoint (HR 0.83; 95% CI 0.76-0.90; p <0.001) and a 20 % reduction in the composite key secondary endpoint (HR 0.80; 95% CI 0.73 - 0.89; p <0.001). The rates of all components of the composite endpoints (first event in the case of multiple events) were reduced by vorapaxar compared with placebo. The individual component of the composite endpoint that most contributed to the difference between vorapaxar and placebo was the reduction in MI (Table E.3).

Table E.3. TRA 2ºP-TIMI 50 Primary and Key Secondary Efficacy Endpoints and Contributing Components With Stroke Sub-Categories Included, in Subjects With No History of Stroke or TIA Whose Qualifying Condition was CAD or PAD (Event Accrual Period: Randomization to Last Visit)

	Placebo (n=10090)			**Vorapaxar (n=10080)**				
	Subjects with Events (%)	KM %[a]	Event Rate [f]	Subjects with Events (%)	KM %[a]	Event rate [f]	Hazard Ratio (95% CI)[b,c]	P-Value[c]
Primary Efficacy Endpoint [d]	1073 (10.6%)	11.8%	4.4%	896 (8.9%)	10.1%	3.6%	0.83 (0.76-0.90)	<0.001
CV Death	154 (1.5%)			129 (1.3%)				
MI	531 (5.3%)			450 (4.5%)				
Stroke	123 (1.2%)			91 (0.9%)				
Ischemic	100 (1.0%)			60 (0.6%)				
Haemorrhagic [e]	16 (0.2%)			22 (0.2%)				
Uncertain	7 (0.1%)			9 (0.1%)				
UCR	265 (2.6%)			226 (2.2%)				
Key Secondary Efficacy Endpoint [d]	851 (8.4%)	9.5%	3.4%	688 (6.8%)	7.9%	2.8%	0.80 (0.73-0.89)	<0.001
CV Death	160 (1.6%)			132 (1.3%)				
MI	562 (5.6%)			464 (4.6%)				
Stroke	129 (1.3%)			92 (0.9%)				
Ischemic	104 (1.0%)			61 (0.6%)				
Haemorrhagic [e]	17 (0.2%)			22 (0.2%)				
Uncertain	8 (0.1%)			9 (0.1%)				

	Placebo (n=10090)			Vorapaxar (n=10080)				
	Subjects with Events (%)	KM %[a]	Event Rate [f]	Subjects with Events (%)	KM %[a]	Event rate [f]	Hazard Ratio (95% CI)[b,c]	P-Value[c]

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 (qualifying atherosclerotic disease and planned thienopyridine use)
d. Each patient was counted only once (first component event) in the component summary that contributed to the primary or key secondary efficacy endpoint
e. Haemorrhagic stroke includes primary intracerebral haemorrhage, non-haemorrhagic infarction with haemorrhagic conversion, and subarachnoid haemorrhage
f. Annualized Event Rate is expressed as number of patients with events per 100 patient-years of exposure
Note: UCR=recurrent ischemia leading to urgent coronary revascularization; MI=myocardial infarction; CV death=Cardiovascular death

Figure E.2. TRA 2°P – TIMI 50 Kaplan-Meier Estimate of Time to the First Occurrence of CEC-Adjudicated Primary Efficacy Endpoint: in Subjects With No History of Stroke or TIA Whose Qualifying Condition Was CAD or PAD (Event Accrual Period: Randomization to Last Visit)

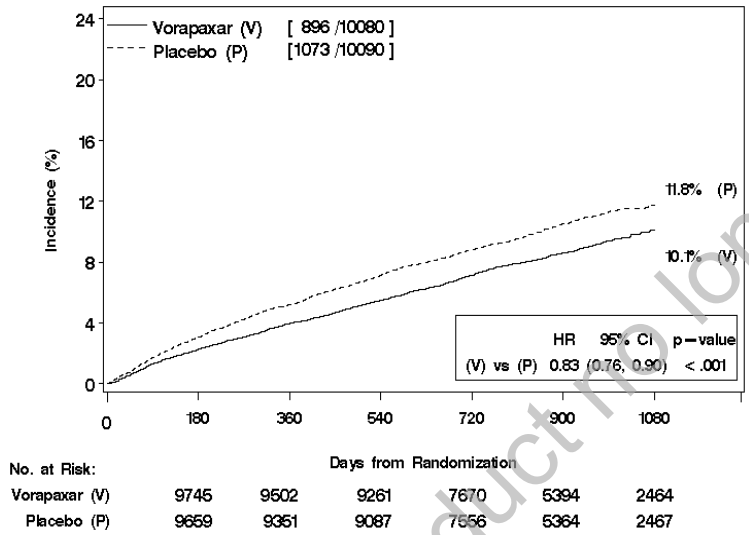
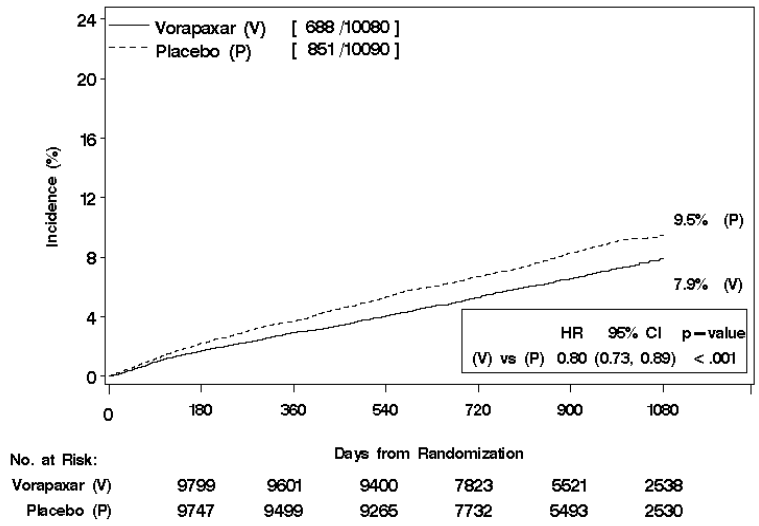


Figure E.3. TRA 2°P – TIMI 50 Kaplan-Meier Estimate of Time to the First Occurrence of CEC-Adjudicated Secondary Efficacy Endpoint: in Subjects With No History of Stroke or TIA Whose Qualifying Condition Was CAD or PAD (Event Accrual Period: Randomization to Last Visit)



- ***PAD stratum***

In the *PAD stratum* with no history of stroke or TIA, there was a 13% reduction in the primary efficacy endpoint (HR 0.87; 95% CI 0.71 – 1.06) and a 12% reduction in the composite key secondary endpoint (HR 0.88; 95% CI 0.71 – 1.09) (Table E.4).

Table E.4. TRA 2°P – TIMI 50 Primary and Key Secondary Composite Efficacy Endpoints and Contributing Components in Subjects With No History of Stroke or TIA Whose Qualifying Condition was PAD: ITT Event Accrual Period: Randomization to Last Visit

	Placebo (n=1651)			**Vorapaxar (n=1622)**				
	Subjects with Events (%)	KM %[a]	Event Rate [f]	Subjects with Events (%)	KM %[a]	Event rate [f]	Hazard Ratio (95% CI)[b,c]	P-Value[c]
Primary Efficacy Endpoint [d]	206 (12.5%)	12.8%	4.6%	177(10.9%)	11.1%	4.0%	0.87 (0.71-1.06)	0.167
CV Death	58 (3.5%)			47(2.9%)				
MI	80 (4.8%)			76 (4.7%)				
Stroke	39 (2.4%)			31 (1.9%)				
Ischemic	31 (1.9%)			22 (1.4%)				
Haemorrhagic [e]	5 (0.3%)			6 (0.4%)				
Uncertain	3 (0.2%)			3 (0.2%)				
UCR	29 (1.8%)			23(1.4%)				
Key Secondary Efficacy Endpoint [d]	180 (10.9%)	11.1%	4.0%	156 (9.6%)	9.8%	3.5%	0.88 (0.71-1.09)	0.229
CV Death	59 (3.6%)			48 (3.0%)				
MI	81 (4.9%)			77 (4.7%)				
Stroke	40 (2.4%)			31 (1.9%)				
Ischemic	32 (1.9%)			22 (1.4%)				
Haemorrhagic [e]	5 (0.3%)			6 (0.4%)				
Uncertain	3 (0.2%)			3 (0.2%)				

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 (qualifying atherosclerotic disease and planned thienopyridine use)
d. Each patient was counted only once (first component event) in the component summary that contributed to the primary or key secondary efficacy endpoint
e. Haemorrhagic stroke includes primary intracerebral haemorrhage, non-haemorrhagic infarction with haemorrhagic conversion, and subarachnoid haemorrhage.
f. Annualized Event Rate is expressed as number of patients with events per 100 patient-years of exposure
Note: UCR=recurrent ischemia leading to urgent coronary revascularization; MI=myocardial infarction; CV death=Cardiovascular death

Figure E.4. TRA 2°P – TIMI 50 Kaplan-Meier Estimate of Time to the First Occurrence of Primary Efficacy Endpoint: in Subjects With No History of Stroke or TIA Whose Qualifying Condition Was PAD: ITT Event Accrual Period: Randomization to Last Visit

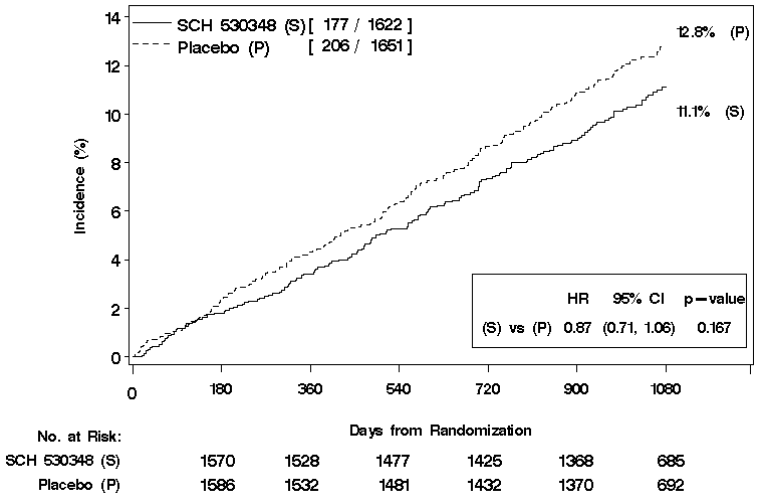
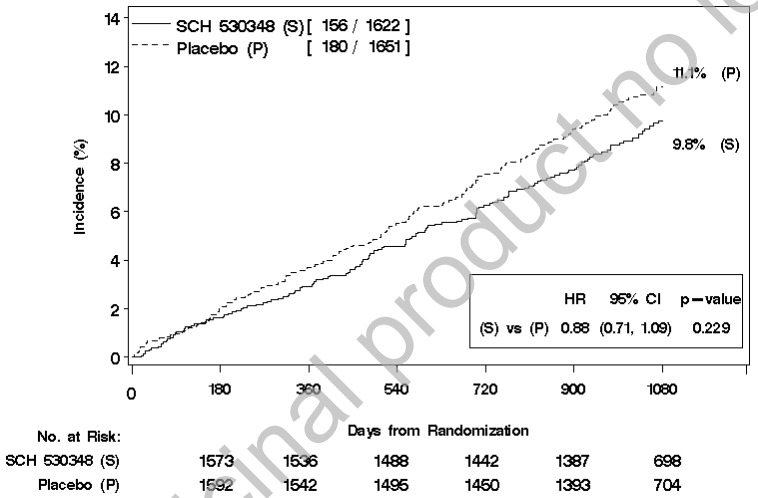


Figure E.5. TRA 2°P – TIMI 50 Kaplan-Meier Estimate of Time to the First Occurrence of Key Secondary Efficacy Endpoint in Subjects with No History of Stroke or TIA Whose Qualifying Condition Was PAD: ITT Event Accrual Period: Randomization to Last Visit



- ***Clinical PAD and Aspirin-Only PAD populations***

The results in the *Clinical PAD* and *Aspirin-Only PAD* populations were also consistent with the *PAD stratum*.

Table E.5. TRA 2°P – TIMI 50 Primary and Key Secondary Efficacy Endpoints in PAD Event Accrual-Randomization to Last Visit- ITT

					Hazard Ratio (95% CI)[b,c]	p-Value[c]
	Subjects With Events (%)	KM% [a]	Subjects With Events (%)	KM% [a]		

Clinical PAD Population [d]	**Placebo (n=2006)**		**Vorapaxar (n=1939)**			
CV death/MI/stroke/UCR†	282	14.6%	232	12.5%	0.84 (0.71-1.00)	0.052
CV death/MI/stroke‡	240	12.4%	200	10.7%	0.86 (0.71-1.03)	0.105
Aspirin Only PAD Population [e]	**Placebo (n=1053)**		**Vorapaxar (n=1034)**			
CV death/MI/stroke/UCR†	119	11.6%	94	9.3%	0.79 (0.60-1.04)	0.088
CV death/MI/stroke‡	106	10.3%	87	8.6%	0.82 (0.62-1.09)	0.180

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. Subjects With No History of Stroke or TIA Who Were NOT in the CVD Stratum AND Whose Qualifying Condition Was PAD OR (had ABI<= 0.9 with Symptoms~) OR History of Peripheral Arterial Revascularization Symptoms [Fontaine Stage II, III, or IV])

e. Subjects with no history of stroke or TIA whose qualifying condition was PAD who were on aspirin at baseline, and did not plan thienopyridine use during the study

†Primary Endpoint

‡Secondary Endpoint

CHMP comments

In the *Intended Label Population* the results showed a significant reduction in primary and key secondary efficacy endpoints by 17% and 20%, respectively compared to placebo with all components (CV deaths, MI, stroke and UCR) contributing almost to the same extent. These findings are similar to those in the previously considered "Proposed Label Population" (see table below) comprising only CAD patients with no history of stroke ort TIA, who also represent the majority of the *Intended Label Population.*

TRA 2oP – TIMI 50 Primary and Key Secondary Efficacy Endpoints and Contributing Components With Stroke Sub-Categories Included, in Subjects With No History of Stroke or TIA Whose Qualifying Condition was CAD (Event Accrual Period: Randomization to Last Visit) [*"Proposed Label Population"*]

	Placebo (n = 8439)		Vorapaxar (n = 8458)			
Endpoint and Contributing Component	Subjects With Events (%)	KM%[c]	Subjects With Events (%)	KM%[c]	Hazard Ratio[a,b] (95% Confidence Interval)	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%)			

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.

Abbreviations: CAD = coronary artery disease; CV = cardiovascular; KM = Kaplan-Meier; MI = myocardial infarction, TIA = transient ischemic attack; UCR = urgent coronary revascularization

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

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

[c] Kaplan-Meier estimate at 1080 days

In the *PAD stratum* a similar trend in favour of vorapaxar is also seen in the primary and secondary endpoints but without reaching statistical significance. The same applies also to the *Clinical PAD* and *Aspirin-Only PAD* populations.

Clearly, the key efficacy results appear very consistent across the different populations, but there are also some interesting qualitative differences. Compared to the CAD population (as captured in the "Proposed Label Population", shown in the table above) the rate of CV deaths among PAD patients was almost three times as high and the rate of strokes almost twice as high, while MIs and UCR were less common. Interestingly, while in the CAD population the results were mainly driven by a reduction in MIs, in the PAD group it is a reduction in CV mortality that appears to contribute more to the differences between vorapaxar and placebo.

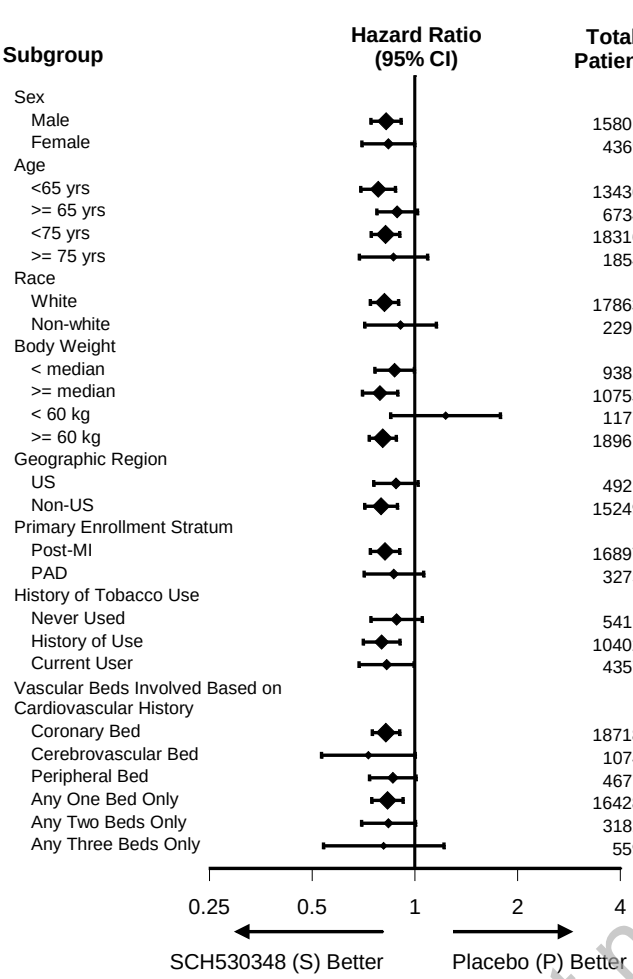
- **Ancillary analyses**

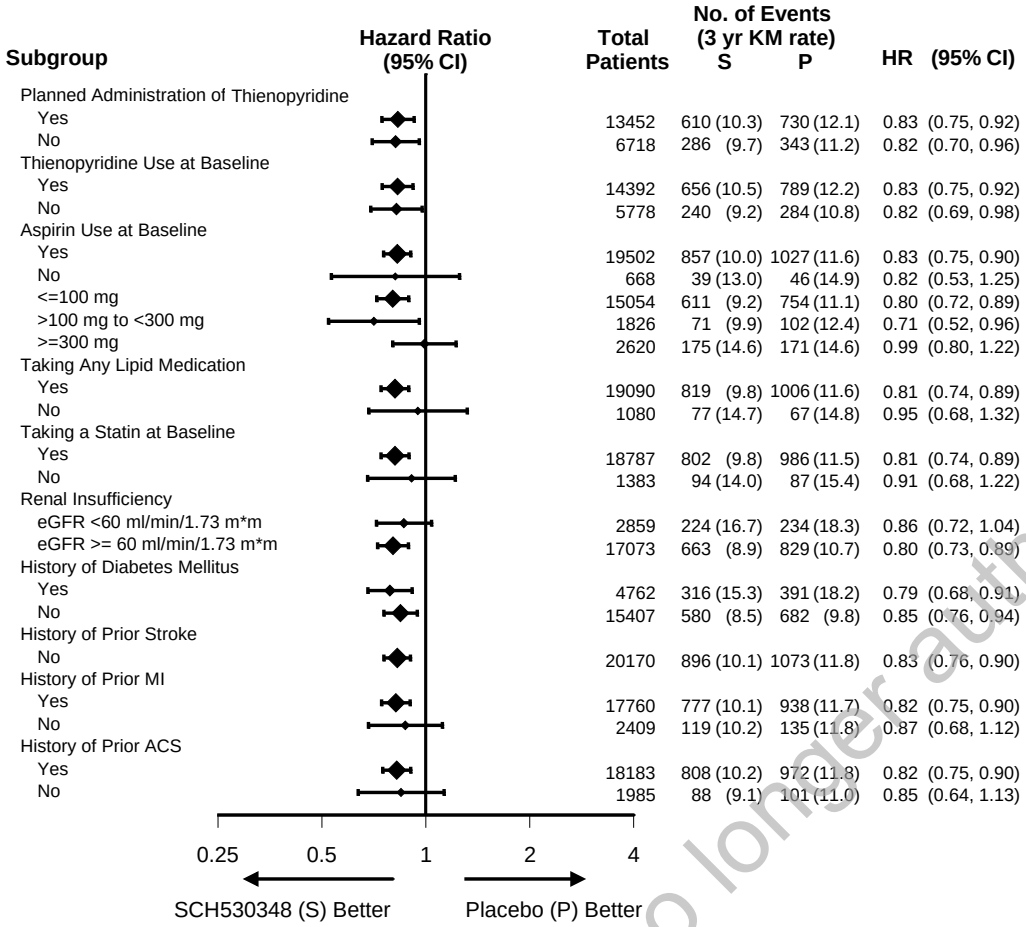
Efficacy in Subgroups

A wide range of demographic, concurrent baseline medications and other baseline characteristics were examined for their effect on outcome in the different populations. The results in specific subgroups for the primary endpoint are shown in Figures E.6a/b for the *Intended Label Population* and E.7a/b for the *PAD stratum*.

- ***Intended Label Population***

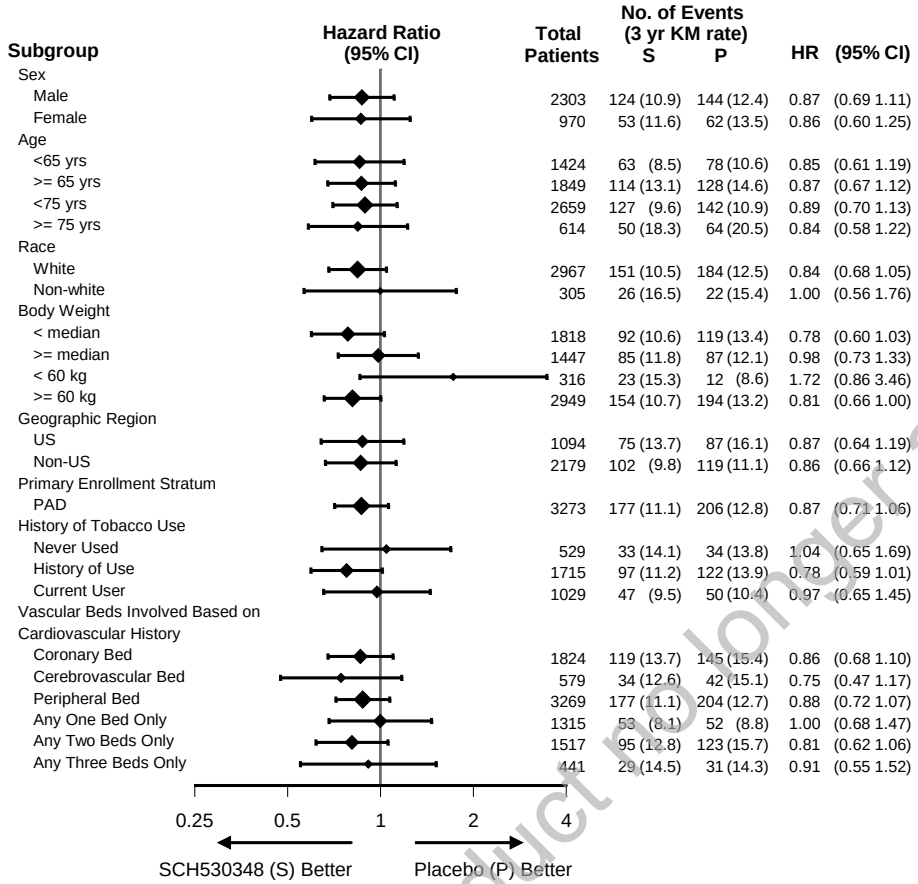
Figure E.6a/b. TRA 2°P – TIMI 50 Plot of Hazard Ratio and 95% CI for Primary Efficacy Endpoint in Subjects with No History of Stroke or TIA Whose Qualifying Condition Was CAD or PAD by Subgroup: ITT Population (Randomization to Last Visit)

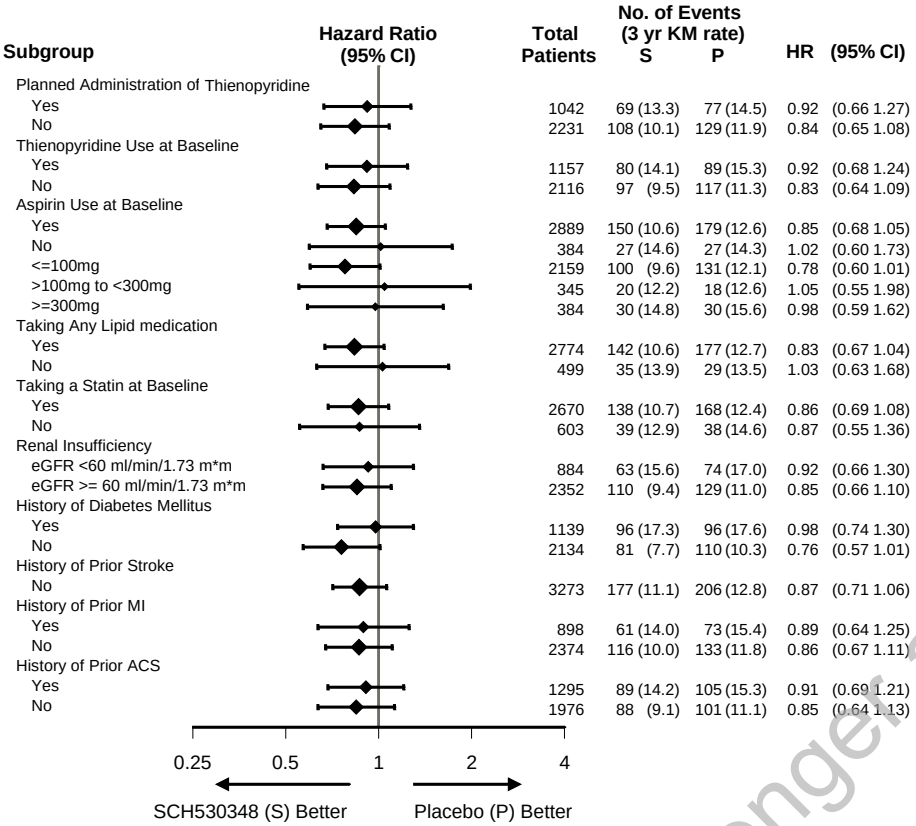




- ***PAD stratum***

Figure E.7a/b. TRA 2°P – TIMI 50 Plot of Hazard Ratio (95% CI) for Primary Efficacy Endpoint in Subjects With No History of Stroke or TIA Whose Qualifying Condition was PAD: ITT Population Event Accrual Period Randomization to Last Visit





CHMP comments

In both the *Intended Label Population* and *PAD stratum* the treatment effect of vorapaxar was generally consistent across most subgroups including sex, age, different risk factors and concomitant therapies at baseline including aspirin, thienopyridine and statins.

A subgroup identified during the initial MAA review, with uncertain efficacy findings which are confirmed in the current analyses, were patients weighing <60kg. Due also to some safety concerns, it was considered appropriate to include a warning in the SmPC advising use with caution in patients with a body weight <60 kg. The current subgroup analyses do not provide any significant new information.

In addition to the above, the MAH has provided a number of additional efficacy analyses exploring different aspects of the key endpoints in the ***Intended Label Population***, some of which are shown below:

Efficacy Endpoints in Subjects Following an ACS Event

As described above, vorapaxar was associated with a reduction in occurrence of MIs from time of randomization. This is a landmark analysis (i.e., events occurring after the first ACS event which serves as the "landmark") of the primary and key secondary endpoints in subjects with ACS during the study for the *Intended Label Population*. Such analyses allow for direct examination of subsequent event rates in subjects experiencing an ACS event while on study medication.

There were 114 more first ACS events in the placebo group than in the vorapaxar group. The results indicate that in those subjects who had an ACS event during the TRA 2°P – TIMI 50 study, vorapaxar was associated with 16% reduction in the primary endpoint and 20% reduction in the key secondary endpoint in those patients from the time of the ACS event to the end of the study [Table E.6]. Therefore, vorapaxar reduced first ACS events and also reduced the rate of the primary and secondary endpoints in subjects following an ACS event.

Table E.6. TRA 2°P – TIMI 50 [Landmark Analysis] Primary and Key Secondary Efficacy Endpoints in Subjects with ACS During the Study Whose CEC Adjudicated Efficacy Events During the Study Met Coronary Ischemic Criteria: ITT Population Subjects with No History of Stroke or TIA Whose Qualifying Condition Was CAD or PAD Event Accrual Period: First ACS to Last Visit

	Placebo (n=913)	**Vorapaxar (n=799)**		
	Subjects with Events (%)	Subjects with Events (%)	Hazard Ratio (95% CI)[a,b]	P-Value[b]
Since ACS				
CV Death / MI / Stroke / UCR	245 (26.8%)	179 (22.4%)	0.84 (0.69 - 1.01)	0.069
CV Death / MI / Stroke	199 (21.8%)	139 (17.4%)	0.80 (0.64 - 0.99)	0.040

Multiple Occurrences of Adjudicated Endpoints

Table E.7 below shows 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 Intended Label Population. Vorapaxar was associated with a significant reduction in total events defined in the primary efficacy endpoint (HR 0.83; 95% CI 0.76-0.89). A similar result was observed for the reduction of total events defined in the secondary efficacy endpoint.

Table E.7. TRA 2°P – TIMI 50 Analysis of Multiple Occurrences of Adjudicated Primary and Secondary Composite Endpoint Component Events in CAD or PAD Subjects with no History of Stroke or TIA ITT Population Event Accrual Period: Randomization to Last Visit

	Placebo (n=10090)	**Vorapaxar n=10080)**	**Hazard Ratio (95% CI)[a,b]**	**P-Value[b]**
Primary Efficacy Endpoint				
Total Events	1420	1174	0.83(0.76-0.89)	<0.001
Subjects with only one Event	832	706		
Subjects with two Events	181	138		
Subjects with >= 3 Events	60	52		
Key Secondary Efficacy Endpoint				
Total Events	1090	894	0.82 (0.75-0.89)	<0.001
Subjects with only one Event	684	544		
Subjects with two Events	125	106		
Subjects with >= 3 Events	42	38		

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 (qualifying atherosclerotic disease and planned thienopyridine use).
Note: UCR = recurrent ischemia leading to urgent coronary revascularization; MI = myocardial infarction;
CV death = Cardiovascular death

Multiple Occurrences of MI in Efficacy Endpoints

Table E.8 below shows total MI events (first and subsequent) in the *Intended Label Population* with vorapaxar versus placebo (HR 0.83; 95% CI 0.75-0.93). These results suggest that vorapaxar in addition to standard of care, reduced the total number of MI events in the Intended Label Population.

Table E.8. TRA 2°P – TIMI 50 Analysis of Multiple Occurrences of MI in Efficacy Endpoints in Subjects with No History of Stroke or TIA Whose Qualifying Condition Was CAD or PAD: ITT Population Event Accrual Period: Randomization to Last Visit

	Placebo (n=10090)	Vorapaxar n=10080)	Hazard Ratio (95% CI)[a,b]	P-Value[b]
Efficacy Endpoint - MI				
Total Events	699	585	0.83 (0.75 - 0.93)	0.001
Subjects with only one Event	482	398		
Subjects with two Events	61	46		
Subjects with >= 3 Events	26	26		

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 (qualifying atherosclerotic disease and planned thienopyridine use)
Note: MI = myocardial infarction

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table E.9. Summary of efficacy for trial TRA 2°P – TIMI 50

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Vorapaxar (SCH 530348) in Addition to Standard of Care in Subjects With a History of Atherosclerotic Disease: Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2ºP-TIMI 50)	
Study identifier	Protocol No. P04737
Design	A multicenter, international, randomized, double-blind, placebo-controlled, balanced-parallel-groups, events-driven investigation of orally administered vorapaxar in the secondary prevention of ischemic events in patients with a history of atherosclerotic disease
Hypothesis	Superiority
Primary objective	The primary objective was to evaluate the hypothesis that vorapaxar added to standard of care will reduce the incidence of atherothrombotic ischemic events relative to standard of care alone, as measured by the composite of cardiovascular (CV) death, myocardial infarction (MI), stroke, and urgent coronary revascularization (UCR) in subjects with established coronary artery disease (CAD), cerebrovascular disease (CVD), or peripheral artery disease (PAD)
Treatments groups	26,449 patients received randomized treatment: 13,224 placebo and 13,225 vorapaxar (Intent to Treat population; ITT) Subjects were enrolled in one of three strata: 17,779 subjects with CAD; 4,883 with CVD; 3,787 with PAD

	Following DSMB advice all subjects with a stroke either prior to or during the study discontinued study medication (due to an increased number of intracranial haemorrhages (ICH) reported in subjects with a prior history of stroke). Subjects with MI and PAD who had a stroke also discontinued treatment but continued their follow-up visits. Patients also with a history of TIA should were not included in the analyses as it is clinically difficult to distinguish between history of TIA or stroke. This led to the further restriction of the population to subjects with no history of stroke or TIA Data from subjects in the remaining two strata (CAD and PAD) were reviewed in the following populations of interest: • '*Intended Label Population*' (n=20,170): subjects whose qualifying condition was CAD or PAD with no history of stroke or TIA. • *PAD stratum and no history of stroke or TIA* (n=3,273): subjects with no history of stroke or TIA whose qualifying condition was PAD at entry • *'Clinical PAD Population'* (n=3,945): subjects with no history of stroke or TIA with PAD; or baseline ABI ≤0.90 and Fontaine category >1; or history of peripheral arterial revascularization • *'Aspirin-Only PAD Population'* (n=2,087): subjects with no history of stroke or TIA whose qualifying condition was PAD at entry and had aspirin at baseline with no planned use of a thienopyridine Note: results below are presented for the '*Intended Label Population*' and '*PAD stratum and no history of stroke or TIA'* only		
Duration of the study	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Median (participation in the study): 905 days for placebo; 906 days for vorapaxar not applicable not applicable	
Endpoints and definitions	Primary endpoint	Composite of CV death, MI, stroke or UCR	
	Key Secondary endpoint	Composite of CV death, MI or stroke	
	Other Secondary endpoints	- Different composite endpoints with combinations of all-cause death, MI, stroke, and urgent coronary revascularization, any revascularization. The individual components of the composite primary efficacy endpoint: a. cardiovascular death, b. MI, c. stroke, d. UCR, - All-cause death	
Database lock	09 January 2012		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat; Randomization to Last Visit		
Descriptive statistics and estimate variability	*Intended Label Population*		
		Placebo	Vorapaxar
	Number of subject	(n=10090)	(n=10080)
	Primary Efficacy Endpoint (Events %; KM%*)	1073 (10.6%); 11.8%	896 (8.9%); 10.1%
	CV Death MI Stroke UCR	154 (1.5%) 531 (5.3%) 123 (1.2%) 265 (2.6%)	129 (1.3%) 450 (4.5%) 91 (0.9%) 226 (2.2%)
	Key Secondary Endpoint (Events %; KM%*)	851 (8.4%); 9.5%	688 (6.8%); 7.9%
	PAD Stratum and no history of stroke or TIA		
	Number of subject	(n =1651)	(n =1622)
	Primary Efficacy Endpoint (Events %; KM%*)	206 (12.5%); 12.8%	177 (10.9%); 11.1%

	CV Death MI Stroke UCR	58 (3.5%) 80 (4.8%) 39 (2.4%) 29 (1.8%)	47 (2.9%) 76 (4.7%) 31 (1.9%) 23 (1.4%)
	Key Secondary Endpoint (Events %; KM%*)	180 (10.9%); 11.1%	156 (9.6%); 9.8%

Effect estimate per comparison	Primary endpoint	*Intended Label Population*	
		Hazard Ratio (95% CI)	0.83 (0.76 - 0.90)
		P-value	<0.001
		PAD Stratum and no history of stroke or TIA	
		Hazard Ratio (95% CI)	0.87 (0.71 - 1.06)
		P-value	0.167
	Key Secondary Endpoint	*Intended Label Population*	
		Hazard Ratio (95% CI)	0.80 (0.73 - 0.89)
		P-value	<0.001
		PAD Stratum and no history of stroke or TIA	
		Hazard Ratio (95% CI)	0.88 (0.71 - 1.09)
		P-value	0.229
*3-year Kaplan-Meier event rate			

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The current variation application is based entirely on the same pivotal trial TRA 2P – TIMI 50 (P04737) which supported the initial MAA for patients with a history of myocardial infarction. TRA 2P – TIMI 50 was a large trial in 26,449 patients with evidence of atherosclerosis from three categories: cerebral, coronary or peripheral disease, examined as three separate strata. After the discontinuation of patients with cerebrovascular disease, only patients with established CAD and PAD remained in the study.

Patients were randomized to vorapaxar and placebo and were followed-up for more than two years. The primary objective was to evaluate the hypothesis that vorapaxar can reduce the incidence of atherothrombotic events compared to standard of care alone, as assessed by the composite of cardiovascular death, myocardial infarction, stroke, and urgent coronary revascularization. The overall methodology and specific aspects of TRA 2P – TIMI 50 were considered in detail during the initial review and are not repeated again here as there are no new issues or significant new information.

In the previous review, only the results in the CAD stratum (recent MI) were considered in the benefit:risk analysis which resulted in the currently licensed indication. To support the extension of the indication to PAD patients, the MAH has submitted, as pivotal data, the results in the combined CAD and PAD strata i.e. patients presenting with CAD or PAD but with no history of stroke or TIA, the so-called *Intended Label Population*. Still, the majority of the *Intended Label Population* are primarily patients with CAD (~84%) with the PAD group representing a small percentage (~16%) of the pooled population. Nonetheless, analyses have also been provided separately for the PAD population alone (*PAD stratum*).

Efficacy data and additional analyses

A total of 20,170 subjects from the combined CAD/PAD strata were pooled together in the *Intended Label Population* that mainly included white (88.6%) males (78.3%), most of them < 65 years of age (66.6%) with cardiovascular comorbidities: high prevalence of hypertension (64.9%) and hyperlipidaemia (84.9%) and a significant percentage of diabetics (23.9%). However, when isolating the PAD population (*PAD stratum*) it appears that compared with their CAD counterparts, PAD patients were older (PAD: median 66yrs vs CAD: median 58 years), they had a higher prevalence of diabetes (PAD: average 34.8% vs CAD: average 21.4%), as well as a higher rate of renal impairment. Also in terms of background therapy, although in the CAD population the use of aspirin was almost universal, in PAD a percentage of patients

were receiving clopidogrel instead of aspirin as a sole antiplatelet. Also dual antiplatelet therapy in CAD patients was very common (more than 75%) but not so much (around 34%) among PAD patients. Still, across all populations, the treatment groups (vorapaxar and placebo) were well balanced in terms of key characteristics, risk factors and background therapies.

In the *Intended Label Population* the efficacy results showed a significant effect of active therapy on the primary efficacy composite endpoint with a 3-year KM event rate of 10.1% in the vorapaxar group compared to 11.8% in the placebo group (HR; 0.83; 95% CI 0.76-0.90, P<0.001) and all components of the composite showing a decrease with vorapaxar (although there was an unfavourable trend in haemorrhagic strokes).

In the PAD population alone (*PAD stratum*) the results were consistent with *Intended Label Population* showing a 3-year KM event rate of 11.1% in the vorapaxar group compared to 12.8% in the placebo group but without reaching statistical significance (HR; 0.87; 95% CI 0.71-1.06, P<0.167). Still, all individual components showed again a consistent trend in favour of vorapaxar. Of interest, when comparing the findings in the PAD group with CAD patients, it appears that in general PAD patients in TRA 2ºP-TIMI 50 were at notably higher risk of CV death as well as stroke (while MIs and urgent revascularisation were more common in the CAD stratum). In the same context, in the PAD group a reduction in CV mortality was found to have contributed most to the difference between vorapaxar and placebo whereas in the CAD stratum the results were mainly driven by a reduction in MIs.

Similar results were also observed in the other two analyses: the *Clinical PAD Population* which further to patients in the PAD stratum examined also those who, although classified in the CAD stratum, had evidence of PAD; and the *Aspirin-Only PAD Population* which included PAD patients who were only on aspirin and are thought to represent better the "Guideline-recommended" conditions (in terms of antiplatelet therapy).

With regard to subgroups or other analyses the results were in general consistent with the primary findings and there is no significant new information over and above what was assessed during the previous TRA 2P – TIMI 50 review, including the treatment effect in patients weighing <60Kg or efficacy differences in relation to other concomitant therapies. The approved SmPC already includes relevant information which is generally adequate.

Overall, the efficacy results across all populations comprising patients with PAD showed a clear consistent trend in favour of vorapaxar. However, only in the *Intended Label Population,* where post-MI and PAD patients were examined together as a single group the differences between treatments reached statistical significance. In the other analyses, when PAD patients were studied alone, there were no significant differences between vorapaxar and placebo. This could be explained by an insufficient number of PAD patients. Nonetheless, the evidence in favour of vorapaxar in PAD patients and the significance of the vorapaxar treatment effect depends on the validity of the claim that PAD and post-MI patients can be considered as one group, based on the common atherosclerotic background. As discussed above, although some of the arguments are valid, differences between the two populations in terms of the short- and longer-term risks, concomitant therapies (including revascularisation and other interventions) and natural history of the disease cast some doubts on the notion that this is a sufficiently homogenous population to permit conclusions for either patient group based on a single pooled analysis. However, in response, the MAH provided some further information and arguments suggesting that PAD patients may benefit to a similar degree as post-MI patients but the smaller population does not permit a more robust analysis. A calculation of the treatment-stratum interaction significance levels for the primary and key secondary endpoints indicated no significant heterogeneity.

In addition, it is noted that almost all PAD patients included in TRA 2ºP-TIMI 50 were symptomatic. The clinical guidelines make a relevant distinction, recommending antiplatelet therapy first to symptomatic patients (higher level of evidence in both ESC and AHA guidelines). Also in CHARISMA trial there was

some indication that symptomatic patients might benefit more than asymptomatic. The efficacy of vorapaxar in asymptomatic patients is uncertain; therefore, vorapaxar treatment should be limited to symptomatic PAD patients only.

Further to the efficacy results, there are also some points related to the initially proposed SmPC changes which deserve further consideration. They concern specific SmPC amendments aiming at incorporating the new wording related to PAD patients into the existing text that currently applies to CAD patients only. This led to alterations to the advice for post-MI patients that cannot be justified by the available data. For example, for section 4.1 it was initially proposed to amend the text to advise *"Zontivity, co-administered with acetylsalicylic acid (ASA) and/or, where appropriate, clopidogrel, is indicated for the reduction of atherothrombotic events in adult patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD)".* This means in practice that also patients with history of MI can be treated with *either* aspirin *or* clopidogrel, which goes against the previous CHMP decision for MI patients. No justification was provided to support this change. The need for background aspirin therapy in all post-MI patients, complemented by clopidogrel as appropriate, was established in the previous review. However, in PAD patients concomitant therapy with either aspirin or clopidogrel may be adequate (although most patients were on aspirin) and can possibly be supported by the TRA 2ºP-TIMI 50 results (depending also on safety; see below). Upon CHMP request, the MAH updated the SmPC wording to include information about PAD patients separately, so that the new proposal does not affect the current recommendations for MI patients.

2.5.4. Conclusions on the clinical efficacy

The efficacy results showed a positive trend for vorapaxar in most endpoints and subgroups in the primary and secondary analyses but did not reach statistical significance when PAD patients were examined as a distinct group. However, the TRA 2ºP-TIMI 50 efficacy results showed a clear consistency across all endpoints and populations, with the findings in PAD patients showing a trend in favour of vorapaxar similar to their CAD counterparts which suggests that PAD patients may benefit from therapy to a similar degree as post-MI patients. The amendment of the indication to include symptomatic patients with PAD is acceptable.

2.6. Clinical safety

Introduction

The safety of vorapaxar was evaluated in 19,632 subjects receiving the drug in the Phase 3 development program (13,186 subjects in TRA 2°P-TIMI 50 and 6,446 in TRACER trial in ACS patients). Of the 13,186 subjects exposed in TRA 2°P-TIMI 50, 2,187 received vorapaxar for more than 3 years.

Safety evaluations and bleeding analyses in TRA 2°P-TIMI 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. All bleeding events reported throughout the trial were adjudicated by the CEC to determine if each 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. GUSTO moderate bleeding required the presence of a transfusion without haemodynamic instability. The protocols did not specify criteria for transfusion. Thus GUSTO moderate bleeding was subject to potentially varying standards. Recent literature support greater emphasis on the incidence of GUSTO severe bleeding as it most accurately portrays the overall long-term risk of an antiplatelet agent.

It was recommended that subjects continue study treatment during the time of surgery (CABG or other). CABG related fatal bleeding is defined as death that occurred within 7 days among subjects with CABG related bleeding. CABG-related bleeding constitutes a provocative test for assessing surgical bleeding with antithrombotic agents. TIMI CABG major bleeding is the most specific and objective measurement of surgical bleeding risk associated with CABG.

TIMI major CABG-related bleeding was pre-defined and adjudicated, in accordance with the CEC charter as any haemorrhage that met any of the following criteria:

- Fatal bleeding (i.e., bleeding that directly results in death), or
- Peri-operative intracranial bleeding, or
- Re-operation following closure of the sternotomy incision for the purpose of controlling bleeding, or
- Transfusion of ≥5 units of whole blood or PRBCs within a 48 hour period, or
- Chest tube output >2 L within a 24 hour period.

As such, TIMI major CABG-related bleeding is the appropriate categorization for assessment of bleeding events due to CABG. Transfusions and re-operations, as well as the volume of chest tube drainage, was captured in the electronic case report forms to facilitate evaluation of the outcome of the bleeding events.

CHMP comments

The key aspects of the safety evaluation in TRA 2ºP-TIMI 50 were discussed in detail during the initial MAA review. As previously concluded, the general plan for integrating and presenting the key safety data of the TRA 2°P-TIMI 50 trial is acceptable.

Patient exposure

From the entire TRA 2°P-TIMI 50 population, in total 13,186 subjects received vorapaxar. In the *Overall* population (all strata), subjects randomized to vorapaxar received treatment for a median of 823 days with a range up to 1461 days. More than 76% of the subjects were on treatment for at least 2 years (720 days) and the median duration of treatment was 2.5 years (823 days for vorapaxar and 826 days for placebo).

In the ***Intended Label Population***, 10,059 subjects received at least one dose of active treatment which accounts for 76% of the overall TRA 2°P-TIMI 50 population exposed to vorapaxar. The duration of treatment and compliance are shown in Tables S.1 and S.2.

Table S.1. TRA 2°P – TIMI 50: Duration of Participation in Treatment Number (%) of Subjects With No History of Stroke or TIA Whose Qualifying Conditions Was CAD or PAD: All Randomized Subjects

	Placebo	**Vorapaxar**
Variable	(n=10049)	(n=10059)
Participation: Number (%) of Subjects		
Any Participation	10049 (99.6)	10059 (99.8)
≥30 Days	9820 (97.3)	9800 (97.2)
≥90 Days	9578 (94.9)	9535 (94.6)
≥180 Days	9264 (91.8)	922 7(91.5)
≥360 Days	8890 (88.1)	8851 (87.8)
≥540 Days	8558 (84.8)	8479 (84.1)
≥720 Days	7019 (69.6)	6884 (68.3)
≥900 Days	4833 (47.9)	473 0(46.9)

	Placebo	Vorapaxar
Variable	(n=10049)	(n=10059)
≥1080Days	2144 (21.2)	2103 (20.9)
Randomized, Not treated	41 (0.4)	21 (0.2)
Summary Statistics (Duration in Days)[a]		
Number of Subjects	10049	10059
Mean Participation (days)	831.1	820.3
Standard Deviation	321.90	326.21
Median Participation (days)	894.0	891.0
25th to 75th Percentile (days)	702.0 - 1071.0	694.0 - 1069.0
Minimum Participation (days)	1	1
Maximum Participation (days)	1461	1461

Note: "Duration of Participation in Treatment" is the interval from date of randomized treatment assignment to date of last dose, without regard to intervening days or intervals when a dose was not taken. For subjects with a partial date of last dose, date of last dose is estimated
a. Does not include subjects who received randomized treatment assignment but were not treated

Table S.2. TRA 2°P – TIMI 50: Compliance to Treatment: Number (%) of Subjects of Subjects With No History of Stroke or TIA Whose Qualifying Conditions Was CAD or PAD

	Placebo	Vorapaxar
Any Exposure	10049 (100)	10059 (100)
<= 10 %	4 (<.1)	0
>10 – 20 %	3 (<.1)	2 (<.1)
>20 – 30 %	5 (<.1)	6 (0.1)
>30 – 40 %	8 (0.1)	12 (0.1)
>40 – 50 %	19 (0.2)	28 (0.3)
>50 – 60 %	30 (0.3)	37 (0.4)
>60 – 70 %	61 (0.6)	73 (0.7)
>70 – 80 %	189 (1.9)	217 (2.2)
>80 – 90 %	632 (6.3)	608 (6.0)
> 90 %	8947 (89.0)	8894 (88.4)
Replacement[a]	149 (1.5)	181 (1.8)
Undeterminable[b]	2 (<.1)	1 (<.1)

a. Extent of exposure for subjects who were assigned replacement kit(s) could not be determined.
b. When Total Dispensed Quantity < Total Returned Quantity.

Patient exposure in terms of duration and compliance in the ***PAD stratum*** is shown in Tables S.3 and S.4 below.

Table S.3. TRA 2°P – TIMI 50: Duration of Participation in Treatment Number (%) of Subjects With No History of Stroke or TIA Whose Qualifying Conditions Was PAD: All Randomized Subjects

	Placebo	Vorapaxar
Variable	(n=1651)	(n=1622)
Participation: Number (%) of Subjects		
Any Participation	1637(99.2)	1615(99.6)
≥30 Days	1591(96.4)	1564(96.4)
≥90 Days	1547(93.7)	1510(93.1)
≥180 Days	1479(89.6)	1440(88.8)
≥360 Days	1403(85.0)	1368(84.3)
≥540 Days	1340(81.2)	1281(79.0)
≥720 Days	1276(77.3)	1209(74.5)
≥900 Days	1158(70.1)	1118(68.9)
≥1080Days	561(34.0)	538(33.2)
Randomized, Not treated	14 (0.8)	7 (0.4)
Summary Statistics (Duration in Days)[a]		
Number of Subjects	1637	1615
Mean Participation (days)	896.8	871.5

	Placebo	Vorapaxar
Variable	(n=1651)	(n=1622)
Standard Deviation	362.88	375.07
Median Participation (days)	1018.0	1002.0
25th to 75th Percentile (days)	789.0 - 1134.0	715.0 - 1107.0
Minimum Participation (days)	1	1
Maximum Participation (days)	1427	1446

Note: "Duration of Participation in Treatment" is the interval from date of randomized treatment assignment to date of last dose, without regard to intervening days or intervals when a dose was not taken. For subjects with a partial date of last dose, date of last dose is estimated

a. Does not include subjects who received randomized treatment assignment but were not treated

Table S.4. TRA 2°P – TIMI 50: Compliance to Treatment: Number (%) of Subjects of Subjects With No History of Stroke or TIA Whose Qualifying Conditions Was PAD

	Placebo	Vorapaxar
Any Exposure	1637 (100)	1615 (100)
<= 10 %	2 (0.1)	0
>10 - 20 %	0	0
>20 - 30 %	1 (0.1)	0
>30 - 40 %	2 (0.1)	4 (0.2)
>40 - 50 %	3 (0.2)	7 (0.4)
>50 - 60 %	5 (0.3)	5 (0.3)
>60 - 70 %	9 (0.5)	14 (0.9)
>70 - 80 %	34 (2.1)	37 (2.3)
>80 - 90 %	104 (6.4)	122 (7.6)
> 90 %	1452 (88.7)	1398 (86.6)
Replacement[a]	25 (1.5)	28 (1.7)

Note: "Extent of Exposure" is an estimate based on total tablets dispensed - total tablets returned, divided by duration of treatment. (interval from date of first dose to date of last dose, without regard to intervening days or intervals when a dose was not taken).

For subjects with a partial date of last dose, date of last dose is estimated.

a. Extent of exposure for subjects who were assigned replacement kit(s) could not be determined.

CHMP comments

The overall exposure to vorapaxar, in terms of numbers of patients included in the vorapaxar clinical program and duration of treatment, is sufficient to establish the key aspects of its safety profile and this was done in the previous review. In the *PAD stratum* the percentage of patients treated for more than 3 years was higher (>30%) than their CAD counterparts while compliance remained generally at high levels. Still, if this application is approved, vorapaxar for many PAD patients will be a chronic treatment and a point that needs to be considered is to what extent the available data are sufficient to establish its possible long-term safety in this setting.

Adverse events

BLEEDING

As bleeding represents the main safety issue with this product and is a key determinant of the benefit:risk, bleeding events are presented first here.

Adjudicated Bleeding Endpoints - Protocol Specified Analysis of Bleeding Endpoints (Randomization to Last Visit)

- ***Intended Label Population***

Table S.5 shows the GUSTO, TIMI, and other adjudicated bleeding endpoints in the *Intended Label Population* (using protocol specified randomization to last visit analysis). The rates of GUSTO severe bleeding were similar in the two groups with the 3 year KM estimates for GUSTO severe or moderate bleeding endpoints being 3.8% in the vorapaxar group and 2.7% in the placebo group (HR 1.45; 95% CI 1.23-1.71; p<0.001). This increase in GUSTO severe or moderate bleeding over placebo was driven largely by an increase in GUSTO moderate bleeding. Annualized event rates for GUSTO severe or moderate bleeding were 1.3 events per 100 subject-years of exposure in the vorapaxar group and 0.9 events per 100 subject-years of exposure in the placebo group. The 3 year KM event rate for fatal bleeding was 0.3% for both the vorapaxar and placebo groups (HR 0.95; 95% CI 0.51 – 1.78; p=0.872).

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 15.2% for vorapaxar vs. 11.1% for placebo (HR 1.42; 95% CI 1.31-1.54; p<0.001), or 6.1 events per 100 patient-years compared to 4.2 for placebo.

Table S.5. TRA 2°P – TIMI 50 Bleeding Endpoints in Subjects With No History of Stroke or TIA: As-Treated Population Whose Qualifying Condition was CAD or PAD (Event Accrual Period: Randomization to Last Visit)

Endpoints	Placebo (n =10049) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Vorapaxar (n =10059) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Hazard Ratio[a,b] (95% CI)	P-Value[b]
GUSTO Bleeding Categories								
Severe or Moderate[e]	233 (2.3%)	2.7%	0.9%	335 (3.3%)	3.8%	1.3%	1.45 (1.23 - 1.71)	<0.001
Severe	105 (1.0%)	1.3%	0.4%	115 (1.1%)	1.3%	0.5%	1.09 (0.84 - 1.43)	0.503
Moderate	138 (1.4%)	1.6%	0.5%	229 (2.3%)	2.6%	0.9%	1.67 (1.35 - 2.07)	<0.001
CABG-Related Severe or Moderate	10 (0.1%)	0.1%	<0.1%	10 (0.1%)	0.1%	<0.1%	1.00 (0.42 - 2.41)	0.996
TIMI Bleeding Categories								
Major or Minor[e]	253 (2.5%)	2.9%	1.0%	356 (3.5%)	4.1%	1.4%	1.42 (1.21 - 1.66)	<0.001
Major	183 (1.8%)	2.1%	0.7%	219 (2.2%)	2.5%	0.9%	1.20 (0.99 - 1.46)	0.069
Minor	80 (0.8%)	0.9%	0.3%	150 (1.5%)	1.7%	0.6%	1.88 (1.44 - 2.47)	<0.001
Clinically Significant[f]	1016 (10.1%)	11.1%	4.2%	1403(13.9%)	15.2%	6.1%	1.42 (1.31 - 1.54)	<0.001
Non CABG-Related Major or Minor[e]	242 (2.4%)	2.8%	1.0%	345 (3.4%)	3.9%	1.4%	1.43 (1.22 - 1.69)	<0.001
Major	172 (1.7%)	2.0%	0.7%	208 (2.1%)	2.4%	0.8%	1.21 (0.99 - 1.48)	0.062
CABG-Related Major	11 (0.1%)	0.1%	<0.1%	12 (0.1%)	0.1%	<0.1%	1.09 (0.48 - 2.48)	0.830
Other Categories								
Intracranial Haemorrhage	39 (0.4%)	0.5%	0.2%	49 (0.5%)	0.6%	0.2%	1.25 (0.82 - 1.91)	0.294
Fatal ICH	10 (0.1%)	0.1%	<0.1%	13 (0.1%)	0.2%	0.1%	1.30 (0.57 - 2.95)	0.538
Fatal Bleeding	20 (0.2%)	0.3%	0.1%	19 (0.2%)	0.3%	0.1%	0.95 (0.51 - 1.78)	0.872

Note: Only TIMI major is an appropriate categorization in the context of CABG (in the Clinical Endpoints Committee Manual of Operations).
a. Hazard Ratio is vorapaxar group vs placebo group
b. 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)
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
Note: 5 subjects included in the overall population were incorrectly stratified to the CVD stratum and had no qualifying condition for the study.

- ***PAD stratum***

The magnitude of the increased risk of bleeding in the *PAD stratum* with no history of stroke or TIA was consistent with the *Intended Label Population*.

Table S.6. TRA 2°P – TIMI 50: Bleeding Endpoints with Annualized Event Rates in Subjects With No History of Stroke or TIA Whose Qualifying Condition was PAD: As-treated Population Event Accrual Period Randomization to Last Visit

Endpoints	Placebo (n =1637) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Vorapaxar (n =1615) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Hazard Ratio[a,b] (95% CI)	P-Value[b]
GUSTO Bleeding Categories								
Severe or Moderate[e]	77 (4.7%)	4.9%	1.7%	104(6.4%)	6.8%	2.3%	1.38 (1.03 - 1.85)	0.033
Severe	32 (2.0%)	2.1%	0.7%	30 (1.9%)	2.0%	0.7%	0.94 (0.57 - 1.54)	0.799
Moderate	50 (3.1%)	3.1%	1.1%	77 (4.8%)	5.0%	1.7%	1.58 (1.11 - 2.25)	0.012
CABG-Related Severe or Moderate	2 (0.1%)	0.1%	<0.1%	4 (0.2%)	0.3%	<0.1%	2.02 (0.37 - 11.0)	0.416
TIMI Bleeding Categories								
Major or Minor[e]	78 (4.8%)	5.0%	1.7%	97 (6.0%)	6.3%	2.2%	1.26 (0.94 - 1.70)	0.123
Major	50 (3.1%)	3.2%	1.1%	58 (3.6%)	3.7%	1.3%	1.17 (0.80 - 1.71)	0.407

Endpoints	Placebo (n =1637) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Vorapaxar (n =1615) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Hazard Ratio[a,b] (95% CI)	P-Value[b]
Minor	33 (2.0%)	2.1%	0.7%	45 (2.8%)	3.0%	1.0%	1.39 (0.88 - 2.17)	0.155
Clinically Significant[f]	231(14.1%)	14.6%	5.4%	283(17.5%)	18.0%	6.9%	1.28 (1.07 - 1.52)	0.006
Non CABG-Related Major or Minor[e]	75 (4.6%)	4.8%	1.7%	94 (5.8%)	6.1%	2.1%	1.27 (0.94 - 1.73)	0.118
Major	47 (2.9%)	3.0%	1.0%	55 (3.4%)	3.5%	1.2%	1.18 (0.80 - 1.75)	0.396
CABG-Related Major	3 (0.2%)	0.2%	<0.1%	4(0.2%)	0.3%	<0.1%	1.35 (0.30 - 6.02)	0.696
Other Categories								
Intracranial Haemorrhage	9 (0.5%)	0.6%	0.2%	11 (0.7%)	0.7%	0.2%	1.24 (0.51 - 2.98)	0.638
Fatal ICH	2 (0.1%)	0.1%	<0.1%	3 (0.2%)	0.2%	<0.1%	1.52 (0.25 - 9.09)	0.647
Fatal Bleeding	6 (0.4%)	0.4%	0.1%	5 (0.3%)	0.4%	0.1%	0.84 (0.26 - 2.77)	0.780

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. Hazard Ratio and p-value were calculated based on 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 subjects 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..

The results in the *Clinical PAD* and *Aspirin-Only PAD* populations were generally consistent with the results in the *PAD stratum*.

- ***Clinical PAD***

Table S.7. TRA 2°P – TIMI 50: Bleeding Endpoints in the Clinical PAD Population: As-Treated; Event Accrual Period: Randomization to Last Visit

Endpoints	Placebo (n =1992) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Vorapaxar (n =1931) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Hazard Ratio[a,b] (95% CI)	P-Value[b]
GUSTO Bleeding Categories								
Severe or Moderate[e]	96 (4.8%)	5.2%	1.8%	123(6.4%)	6.8%	2.4%	1.33 (1.02 - 1.74)	0.036
Severe	40 (2.0%)	2.3%	0.7%	35 (1.8%)	2.0%	0.7%	0.89 (0.56 - 1.40)	0.608
Moderate	63 (3.2%)	3.3%	1.2%	91 (4.7%)	5.0%	1.7%	1.51 (1.09 - 2.08)	0.012
CABG-Related Severe or Moderate	2 (0.1%)	0.1%	<0.1%	5 (0.3%)	0.3%	<0.1%	2.58 (0.50-13.28)	0.258
TIMI Bleeding Categories								
Major or Minor[e]	96 (4.8%)	5.2%	1.8%	118(6.1%)	6.5%	2.3%	1.27 (0.97 - 1.67)	0.078
Major	60 (3.0%)	3.3%	1.1%	68 (3.5%)	3.7%	1.3%	1.17 (0.82 - 1.65)	0.386
Minor	42 (2.1%)	2.3%	0.8%	56 (2.9%)	3.1%	1.1%	1.38 (0.93 - 2.06)	0.112
Clinically Significant[f]	279(14.0%)	14.8%	5.5%	343(17.8%)	8.5%	7.2%	1.31 (1.12 - 1.54)	<.001
Non CABG-Related Major or Minor[e]	93 (4.7%)	5.0%	1.7%	114(5.9%)	6.3%	2.2%	1.27 (0.97 - 1.67)	0.087
Major	57 (2.9%)	3.1%	1.1%	64 (3.3%)	3.5%	1.2%	1.15 (0.81 - 1.65)	0.429
CABG-Related Major	3 (0.2%)	0.2%	<0.1%	5 (0.3%)	0.3%	<0.1%	1.71 (0.41 - 7.17)	0.460
Other Categories								
Intracranial Haemorrhage	11 (0.6%)	0.6%	0.2%	12 (0.6%)	0.7%	0.2%	1.12 (0.49 - 2.53)	0.794
Fatal ICH	3 (0.2%)	0.17%	<0.1%	3 (0.2%)	0.17%	<0.1%	1.02 (0.21 - 5.07)	0.978
Fatal Bleeding	8 (0.4%)	0.5%	0.1%	6 (0.3%)	0.4%	0.1%	0.77 (0.27 - 2.21)	0.621

Endpoints	Placebo (n =1992) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Vorapaxar (n =1931) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Hazard Ratio[a,b] (95% CI)	P-Value[b]
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. Hazard Ratio and p-value were calculated based on 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 subjects 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.								

- ***Aspirin-Only PAD Population***

Table S.8. TRA 2°P – TIMI 50: Bleeding Endpoints: in Aspirin-Only PAD Population~ Event Accrual Period: As-Treated: Randomization to Last Visit

Endpoints	Placebo (n =1044) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Vorapaxar (n =1030) Subjects With Events (%)	KM%[c]	Annual. Event Rate[d]	Hazard Ratio[a,b] (95% CI)	P-Value[b]
GUSTO Bleeding Categories								
Severe or Moderate[e]	41 (3.9%)	4.1%	1.4%	53 (5.1%)	5.5%	1.9%	1.32 (0.88 - 1.98)	0.186
Severe	20 (1.9%)	2.2%	0.7%	20 (1.9%)	2.1%	0.7%	1.01 (0.54 - 1.88)	0.977
Moderate	24 (2.3%)	2.2%	0.8%	36 (3.5%)	3.8%	1.3%	1.53 (0.91 - 2.56)	0.108
CABG-Related Severe or Moderate	1 (0.1%)	0.1%	<0.1%	1 (0.1%)	0.1%	<0.1%	1.01 (0.06 - 6.12)	0.995
TIMI Bleeding Categories								
Major or Minor[e]	41 (3.9%)	4.1%	1.4%	47 (4.6%)	4.7%	1.7%	1.16 (0.76 - 1.76)	0.485
Major	28 (2.7%)	2.9%	1.0%	27 (2.6%)	2.7%	0.9%	0.98 (0.58 - 1.66)	0.931
Minor	14 (1.3%)	1.3%	0.5%	21 (2.0%)	2.1%	0.7%	1.52 (0.77 - 2.98)	0.228
Clinically Significant[f]	124(11.9%)	12.3%	4.5%	148(14.4%)	14.9%	5.6%	1.23 (0.97 - 1.56)	0.087
Non CABG-Related Major or Minor[e]	39 (3.7%)	3.9%	1.4%	46 (4.5%)	4.6%	1.6%	1.19 (0.78 - 1.83)	0.413
Major	26 (2.5%)	2.7%	0.9%	26 (2.5%)	2.6%	0.9%	1.01 (0.59 - 1.75)	0.961
CABG-Related Major	2 (0.2%)	0.2%	<0.1%	1 (0.1%)	0.1%	<0.1%	0.50 (0.05 - 5.56)	0.576
Other Categories								
Intracranial Haemorrhage	4 (0.4%)	0.4%	0.1%	8 (0.8%)	0.8%	0.3%	2.02 (0.61 - 6.71)	0.250
Fatal ICH	2 (0.2%)	0.19%	<0.1%	1 (0.1%)	0.10%	<0.1%	0.51 (0.05 - 5.59)	0.579
Fatal Bleeding	6 (0.6%)	0.7%	0.2%	3 (0.3%)	0.3%	0.1%	0.51 (0.13 - 2.02)	0.335
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. Hazard Ratio and p-value were calculated based on 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 subjects 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.								

CHMP comments

The risk of bleeding remains the most important concern with vorapaxar. Bleeding events were more common in patients treated with vorapaxar than placebo across all populations and analyses, with the rates in the *Intended Label Population* very similar to the ones previously reported in post-MI patients only (see table below).

TRA 2ºP-TIMI 50 Bleeding Endpoints with Annualized Event Rates in Subjects with No History of Stroke or TIA Whose Qualifying Condition was CAD: Event Accrual Period Randomization to Last Visit

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
NonCABG-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								
ISTH Major	233 (2.8%)	3.1%	1.1%	347 (4.1%)	4.7%	1.7%	1.49 (1.26 - 1.76)	<0.001
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
Fatal Bleeding	14 (0.2%)	0.2%	0.1%	14 (0.2%)	0.2%	0.1%	0.99 (0.47 - 2.09)	0.989

An interesting finding, when PAD patients are examined alone (in the *PAD stratum*, *Clinical PAD* and *Aspirin-Only PAD* populations), is an overall much higher risk of bleeding (almost double rates in both GUSTO moderate and severe and TIMI major or minor) compared to their CAD counterparts. In PAD patients receiving aspirin alone the overall rates were somewhat lower in both treatment groups but still generally higher than in the CAD population.

The higher rate of bleedings in PAD concerns both vorapaxar and placebo groups suggesting a characteristic independent of treatment. This observation of a general higher bleeding risk in PAD patients is consistent with the results of the CHARISMA trial (see comments in section 2.1 above) which showed that PAD were more prone to bleeding compared to the remaining atherosclerotic populations examined in the trial.

Despite the higher overall rates of bleeding in PAD, the relative risk with vorapaxar versus placebo was similar across strata. Severe bleedings were uncommon with only few reports of ICH and fatal bleeding. For these severe cases the rates were similar between vorapaxar and placebo. Yet GUSTO moderate and TIMI clinical significant bleedings were significantly more common with vorapaxar.

Overall, the above suggests that PAD patients are generally at higher risk of bleeding but the additional risk associated with vorapaxar treatment is consistent to that seen in post-MI patients. Background antiplatelet treatment with aspirin and/or clopidogrel also plays a role (see also subgroups below). In response to previous CHMP request, the MAH has provided further information to clarify this point. Although data about PAD patients receiving vorapaxar on top aspirin alone or clopidogrel alone appear consistent with the overall rates (with the caveat of the small number of reports in patients receiving vorapaxar with clopidogrel), there is a general trend about more bleedings in patients taking vorapaxar concomitantly with both aspirin and clopidogrel. This raised concerns about the safety of long term therapy with vorapaxar as add-on to both aspirin and clopidogrel. It is uncertain whether the expected benefits can outweigh the increased risks in this setting. Therefore, the SmPC has been updated to reflect this point and advise that vorapaxar should be taken only with aspirin *or* clopidogrel alone. This issue is

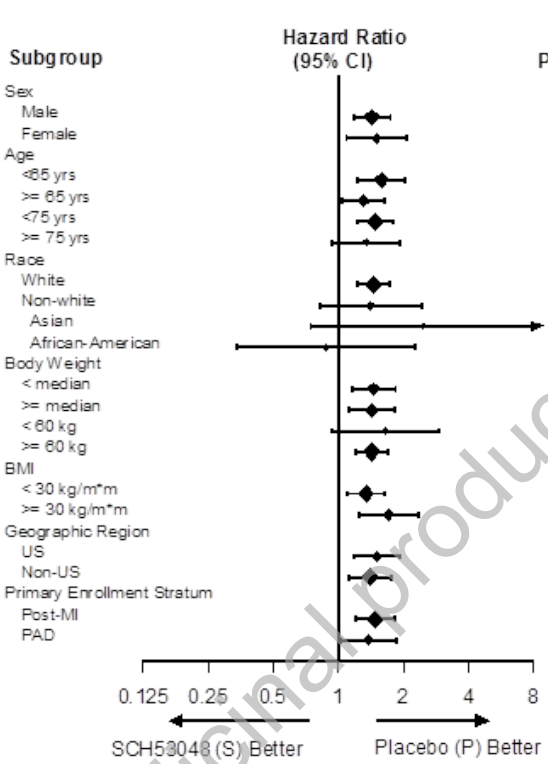
further discussed below.

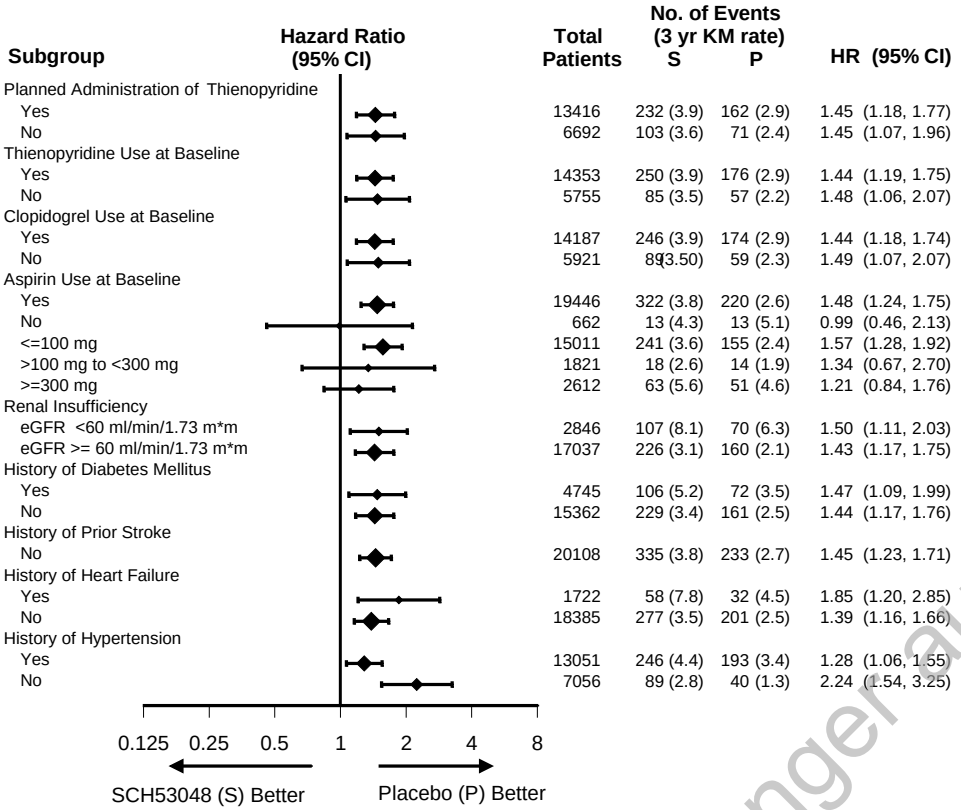
Subgroups

- ***Intended Label Population***

In the *Intended Label Population* there was an increase in bleeding risk associated with vorapaxar treatment compared with placebo treatment across the subgroups examined. The magnitude of the effect of vorapaxar on the bleeding endpoints relative to placebo was consistent across the majority of subgroups. Many of these are shown in Figures S.1a/b. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses.

Figure S.1a/b. TRA 2°P – TIMI 50: Plot of hazard Ratio (95% CI) and Event Rate for GUSTO Severe or Moderate Bleeding by Subgroups in Subjects with No History of Stroke or TIA Whose Qualifying Condition Was CAD or PAD: As-treated Population Event Accrual Period: Randomization to Last Visit





CHMP comments

Generally, subgroup analyses with regard to bleeding risk in the *Intended Label Population* did not show any clear evidence of a clinically significant interaction, including the effect of factors like age, sex, renal status or background therapy. However, in the whole TRA 2ºP-TIMI 50 the risk of bleeding was higher among older patients and those with weight less 60kgr. Relevant warnings (as well as for, patients with renal and hepatic impairment) are included in the SmPC.

In response to CHMP questions, the MAH has also provided similar subgroup analyses for the *PAD stratum*. Generally, the findings appear very consistent with the subgroup analyses in the overall *Intended Label Populatio*n and again there is no clear sign of a significant interaction with a particular demographic or clinical factor where the number of events is large enough to permit comparisons.

The only deviation that was observed was with "Geographic Region" with US patients with PAD not having an overall much higher rate of bleedings than non-US patients but also the risk with vorapaxar was greater compared to their non-US counterparts. The MAH has provided further information to clarify this point. In general, although the possible reason(s) for this discrepancy remain unclear there are no major concerns about the overall results and the validity of the conclusions. .

In terms of concomitant antiplatelets these data do not provide any new information but, as noted above, the concerns of bleeding risk when vorapaxar is given together with aspirin+clopidogrel remain

Other analyses

In addition to the above, the MAH has provided a number of further analyses on bleeding events examining the association with different factors such as bleedings following an ACS event, bleeding associated with CABG or other major surgery as well as information about management of bleeding.

For the *Intended Label Population* comprising mainly post-MI patients the data offer little additional information over and above the evidence assessed during the initial MAA. Therefore, the relevant

tables are not presented again here. In the *PAD stratum* although in general the number of events is small, the results (further data submitted by the MAH in response to CHMP question in the first round) do not suggest an increased risk of major bleeding with vorapaxar in patients undergoing surgery or other invasive procedures. Relevant advice about surgery is already included in the SmPC and no changes are needed.

For the remaining analyses on bleeding events, especially some more information about the management of bleeding which can be a measure of the seriousness of the events is presented (particularly for the *PAD stratum*) below.

In the ***Intended Label Population*****,** there were 338 subjects on vorapaxar and 224 subjects on placebo who experienced a CEC-adjudicated GUSTO moderate or severe bleeding event with 193 vorapaxar subjects and 145 placebo subjects having a procedure to stop the bleeding. Using GUSTO moderate/severe as the threshold, the most frequent bleeding site was gastrointestinal. The most common therapeutic procedure was endoscopy (55 subjects in the vorapaxar group and 32 subjects in the placebo group). The median time from procedure to bleeding resolution was 3.0 days for vorapaxar subjects vs. 3.0 days for placebo treated subjects. Additionally, of those hospitalized for such bleeding, duration of hospitalization were similar (6 days) for both treatment groups.

In the ***PAD stratum*** the findings were generally consistent with the *Intended Label Population.* There were 104 subjects on vorapaxar and 77 subjects on placebo who experienced a GUSTO moderate or severe bleeding event with 36 vorapaxar subjects and 35 placebo subjects having a procedure to stop the bleeding.

Table S.9. TRA 2°P – TIMI 50: Duration, Cause, Action Outcome of GUSTO Severe and GUSTO Moderate Bleeding Events in Subjects No history of Stroke or TIA Whose Qualifying Condition Was PAD: As-Treated Population

Number of Subjects with Any GUSTO Moderate/Severe Bleeding	**Placebo (n= 77)**	**Vorapaxar (n= 104)**
Duration of the First GUSTO Moderate/Severe Bleeding (Days)		
Number of Subjects	73	97
Median (25th to 75th Percentile)	2.0 (1.0 - 5.0)	4.0 (2.0 - 6.0)
Action/Outcome, Number (%) of Subjects[a]		
None	6 (7.8)	7 (6.7)
Additional/Discontinuation/Change in Medications	28 (36.4)	33 (31.7)
Therapeutic Procedures	35 (45.5)	36 (34.6)
Hospitalization	47 (61.0)	64 (61.5)
Study Drug Discontinued	17 (22.1)	22 (21.2)
Study Discontinued	7 (9.1)	6 (5.8)
Study Drug Interrupted	16 (20.8)	24 (23.1)
Death	7 (9.1)	7 (6.7)

a. Subject may have had more than one action/outcome for the bleeding event, and can be counted in multiple rows.

Table S.10. TRA 2°P – TIMI 50: 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 and No History of Stroke or TIA Whose Qualifying Condition Was PAD Number (%) of Subjects Who Received Indicated Transfusate

	Placebo n (%)	**Vorapaxar n (%)**
Number of Subjects with a Bleeding Event	(n= 77)	(n= 104)
Any Transfusion	60 (77.9)	86 (82.7)
Whole Blood Transfusion	13 (16.9)	13 (12.5)
Packed Red Blood Cell Transfusion	44 (57.1)	75 (72.1)
Whole Blood and/or PRBC Transfusion	56 (72.7)	84 (80.8)
<3 Units	30 (39.0)	51 (49.0)

	Placebo n (%)	Vorapaxar n (%)
3-5 Units	17 (22.1)	25 (24.0)
>5 Units	8 (10.4)	6 (5.8)
Missing	1 (1.3)	2 (1.9)
Platelet Transfusion	8 (10.4)	12 (11.5)
Fresh-Frozen Plasma Transfusion	13 (16.9)	10 (9.6)
Cryoprecipitate Transfusion	0	1 (1.0)
Missing	0	1 (1.0)

In general the findings in *PAD stratum* appear consistent with the *Intended Label population.* Regarding need for transfusion for patients with GUSTO moderate/severe bleedings, the rates appear similar with those previously seen in the post-MI patients (see table below).

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: Number (%) of Subjects Who Received the Indicated Transfusate for TRA 2ºP-TIMI 50 overall and Proposed Label Populations

	TRA 2ºP-TIMI 50 Overall		TRA 2ºP-TIMI 50 Proposed Label Population	
	Placebo N (%)	Vorapaxar N (%)	Placebo N (%)	Vorapaxar N (%)
Number of Subjects with a Bleeding Event	**316**	**473**	**157**	**233**
Any Transfusion	221 (69.9)	332 (70.2)	109 (69.4)	178 (76.4)
Whole Blood Transfusion	46 (14.6)	71 (15.0)	26 (16.6)	39 (16.7)
Packed Red Blood Cell Transfusion	170 (53.8)	254 (53.7)	81 (51.6)	135 (57.9)
Whole Blood and/or PRBC Transfusion	213 (67.4)	316 (66.8)	106 (67.5)	170 (73.0)
<3 Units	113 (35.8)	175 (37.0)	57 (36.3)	84 (36.1)
3-5 Units	67 (21.2)	108 (22.8)	34 (21.7)	64 (27.5)
>5 Units	25 (7.9)	26 (5.5)	11 (7.0)	19 (8.2)
Missing	8 (2.5)	7 (1.5)	4 (2.5)	3 (1.3)
Platelet Transfusion	30 (9.5)	44 (9.3)	13 (8.3)	24 (10.3)
Fresh-Frozen Plasma Transfusion	35 (11.1)	44 (9.3)	13 (8.3)	27 (11.6)
Cryoprecipitate Transfusion	1 (0.3)	7 (1.5)	1 (0.6)	6 (2.6)
Missing	0	3 (0.6)	0	1 (0.4)

Note: Units are as entered in the eCRF, and do not imply a predefined standard volume. 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.
PRBC=Packed Red Blood Cells

In summary, in line with what was seen in post MI patients, PAD patients on vorapaxar had a higher frequency of GUSTO moderate and severe bleeding events. However, there was no greater need for a therapeutic procedure or hospitalisations in the vorapaxar group. The percentages of patients requiring a transfusion was slightly greater among vorapaxar patients with the majority not needing more than 3-5 units.

Other bleeding events

The tables below show summaries of bleeding events reported as Treatment Related Treatment Emergent Adverse Events in the *Intended Label Population* and the *PAD stratum*.

- ***Intended Label Population***

Table S.11. TRA 2°P – TIMI 50: Summary of Treatment Related Treatment Emergent Adverse Events (AEs) – Bleeding Events (0.1% Incidence) During Treatment for Subjects With No History of Stroke or TIA Whose Qualifying Condition Was CAD or PAD Intended Label Population

	Placebo (n=10049)		Vorapaxar (n=10059)	
Adverse Events	n	(%)	n	(%)
SUBJECTS REPORTING ANY ADVERSE EVENT	1198	(11.9)	1833	(18.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
HAEMORRHAGIC DIATHESIS	19	(0.2)	36	(0.4)
EAR AND LABYRINTH DISORDERS				
EAR HAEMORRHAGE	6	(0.1)	7	(0.1)
EYE DISORDERS				
CONJUNCTIVAL HAEMORRHAGE	11	(0.1)	40	(0.4)
EYE HAEMORRHAGE	22	(0.2)	18	(0.2)
GASTROINTESTINAL DISORDERS				
GASTROINTESTINAL HAEMORRHAGE	18	(0.2)	44	(0.4)
GINGIVAL BLEEDING	41	(0.4)	85	(0.8)
HAEMATEMESIS	11	(0.1)	14	(0.1)
HAEMATOCHEZIA	20	(0.2)	18	(0.2)
HAEMORRHOIDAL HAEMORRHAGE	36	(0.4)	44	(0.4)
MELAENA	35	(0.3)	62	(0.6)
MOUTH HAEMORRHAGE	0	0	7	(0.1)
RECTAL HAEMORRHAGE	67	(0.7)	87	(0.9)
UPPER GASTROINTESTINAL HAEMORRHAGE	12	(0.1)	5	(<0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
CATHETER SITE HAEMATOMA	11	(0.1)	9	(0.1)
CATHETER SITE HAEMORRHAGE	21	(0.2)	16	(0.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
CONTUSION	180	(1.8)	240	(2.4)
LACERATION	6	(0.1)	12	(0.1)
OPERATIVE HAEMORRHAGE	13	(0.1)	14	(0.1)
POST PROCEDURAL HAEMORRHAGE	19	(0.2)	18	(0.2)
SUBCUTANEOUS HAEMATOMA	4	(<0.1)	6	(0.1)
WOUND HAEMORRHAGE	35	(0.3)	55	(0.5)
INVESTIGATIONS				
BLOOD URINE PRESENT	1	(<.1)	6	(0.1)
OCCULT BLOOD POSITIVE	9	(0.1)	12	(0.1)
NERVOUS SYSTEM DISORDERS				
HAEMORRHAGE INTRACRANIAL	12	(0.1)	17	(0.2)
RENAL AND URINARY DISORDERS				
HAEMATURIA	107	(1.1)	152	(1.5)
HAEMORRHAGE URINARY TRACT	3	(<0.1)	8	(0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
GENITAL HAEMORRHAGE	3	(<0.1)	6	(0.1)
MENORRHAGIA	3	(<0.1)	14	(0.1)
MENSTRUAL DISORDER	4	(<0.1)	6	(0.1)
POSTMENOPAUSAL HAEMORRHAGE	3	(<0.1)	6	(0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
EPISTAXIS	241	(2.4)	544	(5.4)
HAEMOPTYSIS	17	(0.2)	31	(0.3)
PHARYNGEAL HAEMORRHAGE	8	(0.1)	12	(0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
ECCHYMOSIS	33	(0.3)	48	(0.5)
INCREASED TENDENCY TO BRUISE	154	(1.5)	247	(2.5)
PETECHIAE	5	(<0.1)	10	(0.1)
SKIN HAEMORRHAGE	42	(0.4)	76	(0.8)
VASCULAR DISORDERS				
HAEMATOMA	94	(0.9)	146	(1.5)
HAEMORRHAGE	19	(0.2)	47	(0.5)

- ***PAD stratum***

Table S.12. TRA 2°P – TIMI 50: Summary of Treatment Related Treatment Emergent Adverse Events - Bleeding Events (0.1% Incidence) During Treatment for Subjects With No History of Stroke or TIA Whose Qualifying Condition Was PAD As-Treated Number (%) of Subjects

	Placebo (n=1637)		Vorapaxar (n=1615)	
	n (%)		n (%)	
SUBJECTS REPORTING ANY ADVERSE EVENT	177	(10.8)	276	(17.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
ANAEMIA	1	(0.1)	2	(0.1)
HAEMORRHAGIC DIATHESIS	2	(0.1)	8	(0.5)
SPLENIC HAEMORRHAGE	1	(0.1)	0	
SPONTANEOUS HAEMATOMA	0		2	(0.1)
CARDIAC DISORDERS				
PERICARDIAL EFFUSION	1	(0.1)	0	
EAR AND LABYRINTH DISORDERS				
EAR HAEMORRHAGE	2	(0.1)	0	
EYE DISORDERS				
CONJUNCTIVAL HAEMORRHAGE	2	(0.1)	3	(0.2)
EYE HAEMORRHAGE	2	(0.1)	1	(0.1)
OCULAR VASCULAR DISORDER	0		1	(0.1)
RETINAL HAEMORRHAGE	1	(0.1)	2	(0.1)
VITREOUS HAEMORRHAGE	1	(0.1)	1	(0.1)
GASTROINTESTINAL DISORDERS				
ABDOMINAL WALL HAEMORRHAGE	0		1	(0.1)
ANAL HAEMORRHAGE	0		1	(0.1)
DIARRHOEA HAEMORRHAGIC	0		1	(0.1)
DUODENAL ULCER	0		1	(0.1)
EROSIVE OESOPHAGITIS	0		1	(0.1)
FAECES DISCOLOURED	1	(0.1)	0	
GASTRIC DISORDER	1	(0.1)	0	
GASTRIC ULCER HAEMORRHAGE	0		2	(0.1)
GASTROINTESTINAL HAEMORRHAGE	6	(0.4)	16	(1.0)
GASTROINTESTINAL TELANGIECTASIA	0		1	(0.1)
GINGIVAL BLEEDING	3	(0.2)	11	(0.7)
HAEMATEMESIS	2	(0.1)	4	(0.2)
HAEMATOCHEZIA	5	(0.3)	4	(0.2)
HAEMORRHAGIC EROSIVE GASTRITIS	0		1	(0.1)
HAEMORRHOIDAL HAEMORRHAGE	5	(0.3)	3	(0.2)
LARGE INTESTINAL HAEMORRHAGE	0		1	(0.1)
LOWER GASTROINTESTINAL HAEMORRHAGE	1	(0.1)	1	(0.1)
MELAENA	8	(0.5)	11	(0.7)
RECTAL HAEMORRHAGE	12	(0.7)	13	(0.8)
UPPER GASTROINTESTINAL HAEMORRHAGE	0		1	(0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
CATHETER SITE HAEMATOMA	0		2	(0.1)
CATHETER SITE HAEMORRHAGE	2	(0.1)	4	(0.2)
INJECTION SITE HAEMATOMA	1	(0.1)	1	(0.1)
INJECTION SITE HAEMORRHAGE	1	(0.1)	0	
ULCER HAEMORRHAGE	1	(0.1)	1	(0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
ANAEMIA POSTOPERATIVE	1	(0.1)	0	
CONTUSION	22	(1.3)	26	(1.6)
EXCORIATION	0		1	(0.1)
INJURY	0		1	(0.1)
LACERATION	2	(0.1)	0	
OPERATIVE HAEMORRHAGE	3	(0.2)	7	(0.4)
PERIORBITAL HAEMATOMA	1	(0.1)	0	
POST PROCEDURAL COMPLICATION	1	(0.1)	0	
POST PROCEDURAL HAEMATOMA	1	(0.1)	0	
POST PROCEDURAL HAEMORRHAGE	6	(0.4)	2	(0.1)
SUBCUTANEOUS HAEMATOMA	0		1	(0.1)
SUBDURAL HAEMATOMA	0		1	(0.1)
WOUND HAEMORRHAGE	4	(0.2)	7	(0.4)
INVESTIGATIONS				
HAEMOGLOBIN DECREASED	1	(0.1)	1	(0.1)
OCCULT BLOOD	0		3	(0.2)
OCCULT BLOOD POSITIVE	3	(0.2)	6	(0.4)

	Placebo (n=1637)		Vorapaxar (n=1615)	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				
LUNG NEOPLASM MALIGNANT	0		1	(0.1)
NERVOUS SYSTEM DISORDERS				
HAEMORRHAGE INTRACRANIAL	2	(0.1)	3	(0.2)
RENAL AND URINARY DISORDERS				
HAEMATURIA	18	(1.1)	28	(1.7)
HAEMORRHAGE URINARY TRACT	1	(0.1)	0	
RENAL CYST HAEMORRHAGE	0		1	(0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
GENITAL HAEMORRHAGE	0		1	(0.1)
MENORRHAGIA	1	(0.1)	2	(0.1)
OLIGOMENORRHOEA	0		1	(0.1)
PROSTATIC HAEMORRHAGE	0		1	(0.1)
VAGINAL HAEMORRHAGE	1	(0.1)	0	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
EPISTAXIS	24	(1.5)	71	(4.4)
HAEMOPTYSIS	4	(0.2)	5	(0.3)
PHARYNGEAL HAEMORRHAGE	0		2	(0.1)
PULMONARY HAEMORRHAGE	0		1	(0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
ECCHYMOSIS	7	(0.4)	5	(0.3)
HAEMORRHAGE SUBCUTANEOUS	1	(0.1)	0	
INCREASED TENDENCY TO BRUISE	18	(1.1)	31	(1.9)
PETECHIAE	0		1	(0.1)
SKIN HAEMORRHAGE	8	(0.5)	14	(0.9)
SURGICAL AND MEDICAL PROCEDURES				
SURGERY	1	(0.1)	0	
VASCULAR DISORDERS				
AORTIC ANEURYSM RUPTURE	1	(0.1)	0	
HAEMATOMA	10	(0.6)	13	(0.8)
HAEMORRHAGE	6	(0.4)	11	(0.7)

Percentage Cutoff is based on Either Treatment Group Overall

The results in the *PAD stratum* appear again consistent with the *Intended Label population* with vorapaxar patients having an overall higher frequency of bleedings than placebo. The most commonly reported event in both populations was epistaxis with more than double incidence with vorapaxar than controls. The differences between groups for other events, including haematuria and GI bleeding AEs, were smaller but still the rates were higher in patients receiving vorapaxar. These AEs are already included in the SmPC. There is no need for an update.

OTHER ADVERSE EVENTS

- ***Intended Label Population***

In the *Intended Label Population* in TRA 2°P-TIMI 50, most of the reported treatment-emergent non-bleeding AEs occurred at comparable rates in the two treatment groups. The most frequently reported other treatment-related adverse event was anaemia with a higher frequency with vorapaxar than placebo.

Table S.13. TRA 2°P – TIMI 50: Summary of Treatment-Emergent Adverse Events with Annualized

Event Rates – Other Adverse Events (2.0% Incidence) During Treatment for Subjects with No History of Stroke or TIA Whose Qualifying Condition Was CAD or PAD: As-Treated Population Number (%) of Subjects

	Placebo (n=10049)		Vorapaxar (n=10059)	
	Subjects with Events (%)	Event Rate[a]	Subjects with Events (%)	Event Rate[a]
SUBJECTS REPORTING ANY ADVERSE EVENT	7760(77.2)	(89.4)	7696(76.5)	(89.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
ANAEMIA	235 (2.3)	(1.0)	304 (3.0)	(1.4)
CARDIAC DISORDERS				
ANGINA PECTORIS	290 (2.9)	(1.3)	288 (2.9)	(1.3)
ATRIAL FIBRILLATION	219 (2.2)	(1.0)	231 (2.3)	(1.0)
PALPITATIONS	195 (1.9)	(0.9)	197 (2.0)	(0.9)
GASTROINTESTINAL DISORDERS				
DIARRHOEA	301 (3.0)	(1.3)	284 (2.8)	(1.3)
DYSPEPSIA	213 (2.1)	(0.9)	213 (2.1)	(1.0)
NAUSEA	262 (2.6)	(1.2)	235 (2.3)	(1.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
CHEST DISCOMFORT	212 (2.1)	(0.9)	211 (2.1)	(0.9)
CHEST PAIN	632 (6.3)	(2.9)	609 (6.1)	(2.8)
FATIGUE	452 (4.5)	(2.0)	466 (4.6)	(2.1)
NON-CARDIAC CHEST PAIN	733 (7.3)	(3.4)	698 (6.9)	(3.2)
OEDEMA PERIPHERAL	344 (3.4)	(1.5)	331 (3.3)	(1.5)
INFECTIONS AND INFESTATIONS				
BRONCHITIS	300 (3.0)	(1.3)	321 (3.2)	(1.4)
INFLUENZA	279 (2.8)	(1.2)	243 (2.4)	(1.1)
NASOPHARYNGITIS	403 (4.0)	(1.8)	377 (3.7)	(1.7)
PNEUMONIA	201 (2.0)	(0.9)	218 (2.2)	(1.0)
UPPER RESPIRATORY TRACT INFECTION	251 (2.5)	(1.1)	261 (2.6)	(1.2)
URINARY TRACT INFECTION	434 (4.3)	(1.9)	471 (4.7)	(2.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
FALL	296 (2.9)	(1.3)	297 (3.0)	(1.3)
INVESTIGATIONS				
ALANINE AMINOTRANSFERASE INCREASED	172 (1.7)	(0.8)	197 (2.0)	(0.9)
BLOOD CREATINE PHOSPHOKINASE INCREASED	311 (3.1)	(1.4)	301 (3.0)	(1.4)
GAMMA- GLUTAMYLTRANSFERASE INCREASED	218 (2.2)	(1.0)	227 (2.3)	(1.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
ARTHRALGIA	347 (3.5)	(1.6)	340 (3.4)	(1.5)
BACK PAIN	421 (4.2)	(1.9)	383 (3.8)	(1.7)
MUSCLE SPASMS	241 (2.4)	(1.1)	228 (2.3)	(1.0)
MUSCULOSKELETAL PAIN	236 (2.3)	(1.0)	239 (2.4)	(1.1)
MYALGIA	309 (3.1)	(1.4)	326 (3.2)	(1.5)
PAIN IN EXTREMITY	435 (4.3)	(2.0)	400 (4.0)	(1.8)
NERVOUS SYSTEM DISORDERS				
DIZZINESS	546 (5.4)	(2.5)	541 (5.4)	(2.5)
HEADACHE	416 (4.1)	(1.9)	379 (3.8)	(1.7)
PSYCHIATRIC DISORDERS				
DEPRESSION	197 (2.0)	(0.9)	226 (2.2)	(1.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
COUGH	363 (3.6)	(1.6)	385 (3.8)	(1.7)
DYSPNOEA	420 (4.2)	(1.9)	427 (4.2)	(1.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
RASH	187 (1.9)	(0.8)	198 (2.0)	(0.9)
VASCULAR DISORDERS				
HYPERTENSION	547 (5.4)	(2.5)	542 (5.4)	(2.5)
HYPOTENSION	197 (2.0)	(0.9)	181 (1.8)	(0.8)

Note: Percentage cut-off is based on either treatment group overall

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

- ***PAD stratum***

Table S.14. TRA 2°P – TIMI 50: Summary of Treatment-Emergent Adverse Events with Annualized Event Rates –Other Adverse Events (2.0% Incidence) During Treatment for Subjects with No History of Stroke or TIA Whose Qualifying Condition Was PAD: As-Treated Population Number (%) of Subjects

	Placebo (n=1637)		Vorapaxar (n=1615)	
	Subjects with Events (%)	Event Rate[a]	Subjects with Events (%)	Event Rate[a]
SUBJECTS REPORTING ANY ADVERSE EVENT	1295 (79.1)	(85.7)	1268 (78.5)	(89.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
ANAEMIA	77 (4.7)	(2.0)	96 (5.9)	(2.6)
THROMBOCYTOPENIA	22 (1.3)	(0.5)	34 (2.1)	(0.9)
CARDIAC DISORDERS				
ATRIAL FIBRILLATION	50 (3.1)	(1.3)	63 (3.9)	(1.7)
CARDIAC FAILURE	45 (2.7)	(1.1)	36 (2.2)	(0.9)
CARDIAC FAILURE CONGESTIVE	22 (1.3)	(0.5)	37 (2.3)	(1.0)
PALPITATIONS	32 (2.0)	(0.8)	20 (1.2)	(0.5)
GASTROINTESTINAL DISORDERS				
CONSTIPATION	36 (2.2)	(0.9)	46 (2.8)	(1.2)
DIARRHOEA	67 (4.1)	(1.7)	67 (4.1)	(1.8)
NAUSEA	55 (3.4)	(1.4)	46 (2.8)	(1.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
CHEST PAIN	52 (3.2)	(1.3)	44 (2.7)	(1.2)
FATIGUE	57 (3.5)	(1.5)	59 (3.7)	(1.6)
NON-CARDIAC CHEST PAIN	56 (3.4)	(1.4)	61 (3.8)	(1.6)
OEDEMA PERIPHERAL	78 (4.8)	(2.0)	62 (3.8)	(1.6)
INFECTIONS AND INFESTATIONS				
BRONCHITIS	87 (5.3)	(2.3)	67 (4.1)	(1.8)
INFLUENZA	40 (2.4)	(1.0)	30 (1.9)	(0.8)
NASOPHARYNGITIS	65 (4.0)	(1.7)	66 (4.1)	(1.8)
PNEUMONIA	52 (3.2)	(1.3)	62 (3.8)	(1.6)
UPPER RESPIRATORY TRACT INFECTION	44 (2.7)	(1.1)	63 (3.9)	(1.7)
URINARY TRACT INFECTION	93 (5.7)	(2.4)	108 (6.7)	(2.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
FALL	81 (4.9)	(2.1)	72 (4.5)	(1.9)
INVESTIGATIONS				
BLOOD CREATINE PHOSPHOKINASE INCREASED	37 (2.3)	(0.9)	40 (2.5)	(1.1)
GAMMA- GLUTAMYLTRANSFERASE INCREASED	37 (2.3)	(0.9)	38 (2.4)	(1.0)
METABOLISM AND NUTRITION DISORDERS				
DIABETES MELLITUS	31 (1.9)	(0.8)	34 (2.1)	(0.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
ARTHRALGIA	85 (5.2)	(2.2)	61 (3.8)	(1.6)
BACK PAIN	93 (5.7)	(2.4)	72 (4.5)	(1.9)
MUSCLE SPASMS	47 (2.9)	(1.2)	52 (3.2)	(1.4)
MUSCULOSKELETAL PAIN	27 (1.6)	(0.7)	38 (2.4)	(1.0)
OSTEOARTHRITIS	27 (1.6)	(0.7)	34 (2.1)	(0.9)
PAIN IN EXTREMITY	104 (6.4)	(2.7)	91 (5.6)	(2.5)
NERVOUS SYSTEM DISORDERS				
DIZZINESS	82 (5.0)	(2.1)	92 (5.7)	(2.5)
HEADACHE	65 (4.0)	(1.7)	67 (4.1)	(1.8)
SYNCOPE	38 (2.3)	(1.0)	35 (2.2)	(0.9)
PSYCHIATRIC DISORDERS				
DEPRESSION	28 (1.7)	(0.7)	32 (2.0)	(0.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	40 (2.4)	(1.0)	47 (2.9)	(1.2)
COUGH	46 (2.8)	(1.2)	54 (3.3)	(1.4)
DYSPNOEA	58 (3.5)	(1.5)	79 (4.9)	(2.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
RASH	31 (1.9)	(0.8)	36 (2.2)	(0.9)
VASCULAR DISORDERS				
HYPERTENSION	91 (5.6)	(2.3)	105 (6.5)	(2.8)
HYPOTENSION	36 (2.2)	(0.9)	35 (2.2)	(0.9)
INTERMITTENT CLAUDICATION	82 (5.0)	(2.1)	81 (5.0)	(2.2)

Percentage Cutoff is based on Either Treatment Group Overall.
a. Event Rate is expressed as number of patients with events per 100 patient-years of exposure.

The analyses of non-bleeding AEs did not provide any important new information over the data

previously assessed. Anaemia was consistently more frequent with vorapaxar compared to controls and is included in the current SmPC. Otherwise no major differences in the incidence of common AEs were observed between treatment groups across the examined populations. The only exception in the *PAD stratum* was a higher rate of thrombocytopenia with vorapaxar compared to placebo which was not previously observed in post-MI patients. Further clarification, it can be concluded that at this point there is no sufficient evidence to suggest a causal relationship with vorapaxar therapy to justify the inclusion of this AE in the safety information (section 4.8) of the SmPC.

Serious adverse events and deaths

DEATHS

- ***Intended Label Population***

Of the 20,170 subjects in the *Intended Label Population*, 854 (4.2%) died during the study. Of those, 409 (4.1%) were assigned to vorapaxar and 445 (4.4%) to placebo [Table S.15]. Per protocol, deaths were to be reported up to 30 days after the final visit. When spontaneous events, including death, were reported even if they occurred later than required per protocol they were not removed from the database.

There were fewer deaths from any cause in the vorapaxar treatment group than in the placebo group.

Table S.15. TRA 2°P – TIMI 50 All Cause Death During the Study in Subjects With No History of Stroke or TIA Whose Qualifying Condition Was CAD or PAD

	Placebo (n=10090)	**Vorapaxar (n=10080)**
	n (%)	n (%)
Total No. of Deaths	445 (4.4)	409 (4.1)
Total No. Of Deaths On or Before the Last Visit[a,b]	415 (4.1)	382 (3.8)
Total No. of Deaths After the Last Visit	30 (0.3)	27 (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		

- ***PAD stratum***

Similarly, in the *PAD stratum* there were overall fewer deaths among the vorapaxar terated patients.

Table S.16. TRA 2°P – TIMI 50: All Cause Death During the Study in Subjects With No History of Stroke or TIA Whose Qualifying Condition Was PAD

	Placebo (n=1651)	**Vorapaxar (n=1622)**
	n (%)	n (%)
Total No. of Deaths	167(10.1)	156 (9.6)
Total No. Of Deaths On or Before the Last Visit[a,b]	156 (9.4)	144 (8.9)
Total No. of Deaths After the Last Visit	11 (0.7)	12 (0.7)
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		

Across all populations there were fewer deaths among vorapaxar patients than controls. Of interest, the percentage of deaths in the *PAD stratum*, for both vorapaxar and control groups, is almost three times as high (9.6% and 10.1%, respectively) compared to the mortality previously seen in the post-MI patients (3% and 3.3%, respectively) as shown in the table below, which is also reflected in the *Intended Label Population*.

All-Cause Death Recorded During the Study in Overall Population and Post-MI Subjects without a

History of Stroke or TIA: As-Treated Population [a,b]

	Overall Population		Post MI without a History of Stroke or TIA	
	Placebo	Vorapaxar	Placebo	Vorapaxar
	(n=13224)	(n=13225)	(n=8439)	(n=8458)
TOTAL NO. OF DEATHS FROM DEATH or SURVIVAL PAGE	610 (4.6)	580 (4.4)	278 (3.3)	253 (3.0)
TOTAL NO. of DEATHS ON or BEFORE the LAST VISIT	565 (4.3)	540 (4.1)	259 (3.1)	238 (2.8)
TOTAL NO. OF DEATHS AFTER THE LAST VISIT	45 (0.3)	40 (0.3)	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

This further supports the notion of the increased risk and poor prognosis of the PAD population. With regard to specific causes of deaths in the PAD stratum the MAH has provided additional data which do not show any particular pattern that might suggest an unfavourable effect of vorapaxar on specific conditions. However, in most categories the numbers, and the respective differences between groups, are small to permit conclusions. The majority of deaths were due to 'cardiac disorders' and there was a small trend in favour of vorapaxar although overall 'cardiovascular' deaths were slightly more in the active group.

SERIOUS ADVERSE EVENTS

- ***Intended Label Population***

The overall incidence of non-bleeding serious adverse events (SAEs) in TRA 2ºP-TIMI 50 was slightly lower in the vorapaxar group compared to placebo in the *Intended Label Population* (Table S.17). There was a slight imbalance in the incidence of atrial fibrillation and syncope between vorapaxar and placebo but there was no contributable cause for these differences.

Table S.17. TRA 2°P – TIMI 50: Summary of Serious Adverse Events: Other Adverse Events for at Least 20 Subjects During treatment By Descending Frequency For Subjects With No History of Stroke or TIA Whose Qualifying Condition Was CAD or PAD: As-Treated Population Event Accrual Period: Randomization to Last Visit

	Placebo (n=10049)	**Vorapaxar (n=10059)**
SUBJECTS REPORTING ANY ADVERSE EVENT	2256 (22.4)	2190 (21.8)
NON-CARDIAC CHEST PAIN	389 (3.9)	372 (3.7)
CARDIAC FAILURE	116 (1.2)	109 (1.1)
PNEUMONIA	103 (1.0)	107 (1.1)
ATRIAL FIBRILLATION	65 (0.6)	90 (0.9)
CARDIAC FAILURE CONGESTIVE	53 (0.5)	60 (0.6)
SYNCOPE	34 (0.3)	54 (0.5)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	52 (0.5)	49 (0.5)
OSTEOARTHRITIS	60 (0.6)	46 (0.5)
URINARY TRACT INFECTION	23 (0.2)	38 (0.4)
MUSCULOSKELETAL CHEST PAIN	22 (0.2)	33 (0.3)
CHOLELITHIASIS	32 (0.3)	30 (0.3)
INGUINAL HERNIA	23 (0.2)	29 (0.3)
BENIGN PROSTATIC HYPERPLASIA	19 (0.2)	28 (0.3)
CELLULITIS	27 (0.3)	28 (0.3)
PROSTATE CANCER	37 (0.4)	28 (0.3)
VENTRICULAR TACHYCARDIA	26 (0.3)	26 (0.3)
ANAEMIA	7 (0.1)	25 (0.2)
CHOLECYSTITIS	15 (0.1)	25 (0.2)
GASTROENTERITIS	25 (0.2)	25 (0.2)
ATRIAL FLUTTER	14 (0.1)	20 (0.2)
BRONCHITIS	17 (0.2)	20 (0.2)

	Placebo (n=10049)	Vorapaxar (n=10059)
GASTRITIS	16 (0.2)	20 (0.2)
GASTROOESOPHAGEAL REFLUX DISEASE	23 (0.2)	20 (0.2)
RENAL FAILURE ACUTE	22 (0.2)	20 (0.2)
HYPOTENSION	21 (0.2)	19 (0.2)
DEHYDRATION	20 (0.2)	17 (0.2)
INTERVERTEBRAL DISC PROTRUSION	28 (0.3)	16 (0.2)
NEPHROLITHIASIS	22 (0.2)	15 (0.1)
SEPSIS	21 (0.2)	10 (0.1)
PULMONARY EMBOLISM	25 (0.2)	6 (0.1)

Note: Adverse Events are presented in decreasing frequency based upon the treatment group 'vorapaxar'.
Cutoff is based on either treatment group overall.

- ***PAD stratum***

Table S.18. TRA 2°P – TIMI 50: Summary of Serious Adverse Events: Other Adverse Events for at Least 20 Subjects During treatment By Descending Frequency For Subjects With No History of Stroke or TIA Whose Qualifying Condition Was PAD: As-Treated Population Event Accrual Period: Randomization to Last Visit

	Placebo (n=1637)		Vorapaxar n=1615	
Adverse Event	n (%)		n (%)	
SUBJECTS REPORTING ANY ADVERSE EVENT	484	(29.6)	488	(30.2)
NON-CARDIAC CHEST PAIN	24	(1.5)	34	(2.1)
PNEUMONIA	32	(2.0)	33	(2.0)
CARDIAC FAILURE CONGESTIVE	16	(1.0)	24	(1.5)
ATRIAL FIBRILLATION	16	(1.0)	23	(1.4)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	17	(1.0)	23	(1.4)
CARDIAC FAILURE	30	(1.8)	22	(1.4)

Adverse Events are presented in decreasing frequency based upon the treatment group "vorapaxar".
Cutoff is based on Either Treatment Group Overall.

In general, there is little new information over the previously assessed TRA 2ºP-TIMI 50 data. In the *Intended Label Population* the rates of individual SAEs (other than bleeding) was low, with very few events like chest pain (non-cardiac) reaching an incidence >1%. However, it is noted that PAD patients had an overall higher incidence of SAEs across both treatment groups. Still the numbers are small as they are the differences between vorapaxar and placebo.

A finding in the *Intended Label Population,* the previous Proposed Label Population (only post-MI patients) and the *PAD stratum* (where the relative rates are slightly higher) appears to be an slight imbalance in the reports of atrial fibrillation (reported as TEAE and SAE as well as the most frequent non-bleeding cause of discontinuation). Upon CHMP request, the MAH provided more information (on this issue. It is concluded that at this point there is no sufficient evidence to suggest a causal relationship with vorapaxar therapy to justify the inclusion of this AE in the safety information (section 4.8) of the SmPC.

Laboratory findings / Safety in special populations

TRA 2ºP-TIMI 50 laboratory findings and safety in special populations were assessed during the previous review and relevant information, as appropriate, is included in the SmPC.

Safety related to drug-drug interactions and other interactions

There are no significant new data. Safety related to interactions was assessed during the initial MAA

and relevant information on clinical important interactions is included in the SmPC.

Discontinuation due to AES

In the *Intended Label Population*, more subjects in the vorapaxar group (301 [3.0%]) discontinued treatment due to bleeding events compared to subjects in the placebo group (181 [1.8%]).

A large proportion of bleeding events leading to treatment discontinuation were categorized in the gastrointestinal System Organ Class (SOC):100 [1.0%] subjects in the vorapaxar group and vs. 66 [0.7%] subjects in the placebo group. (Subjects who experienced multiple events were only counted once in the respective SOC). The most frequently reported single bleeding event resulting in treatment discontinuation in both treatment groups was epistaxis (47 [0.5%] in the vorapaxar group and 19 [0.2%] in the placebo group). However, gastrointestinal haemorrhage is the most common bleeding event causing discontinuation when relevant bleeding events are combined (melena, rectal haemorrhage, and GI haemorrhage).

For other (non-bleeding) adverse events resulting in treatment discontinuation in the *Intended Label Population*, atrial fibrillation was the most frequently reported event. it should be noted that the protocol stipulated that administration of oral anticoagulation required cessation of study drug. Additionally, a higher observed incidence of anaemia leading to treatment discontinuation was noted in the vorapaxar group compared to placebo (0.3% for vorapaxar and 0.1% for placebo).

CHMP comments

Again there is little significant new information over the previously assessed TRA 2ºP-TIMI 50 data. In the *Intended Label Population* epistaxis was the main bleeding event leading to discontinuation of vorapaxar. It is noted that among non-bleeding events atrial fibrillation was the most common cause of discontinuation for vorapaxar therapy in the *Intended Label Population* (but also the *PAD stratum*). As mentioned above, although the numbers are small this issue needs further investigation.

Post marketing experience

Vorapaxar was approved for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD) by the United States FDA in May 2014. A positive Commission Decision was granted in the European Union on January 19, 2015 for the reduction of atherothrombotic events in patients with a history of MI. Relevant published literature has been cited where applicable to provide context and background around antithrombotic drugs, other treatment options and typical populations which may be particularly useful when considering a new class of antithrombotic drugs.

The MAH has provided additional safety data from post-marketing experience including post-marketing reports of bleeding from PAD patients treated with vorapaxar. However, the numbers are small and the data offer little useful information. It is agreed that in certain serious cases there were factors that increased the general risk of bleeding (such as older age, peptic ulcer, recent surgery) which are already described in the vorapaxar SmPC.

2.6.1. Discussion on clinical safety

The TRA 2ºP-TIMI 50 safety findings were evaluated during the initial MAA. In addition to the post-MI population, data from the *Overall* population of the trial and all strata were also analysed; therefore,

there is little new safety information in this submission over and above what was previously assessed. However, while in the previous review the focus was mainly on post-MI patients, this time safety data for patients with PAD with no history of stroke and TIA have been submitted separately, which allows comparisons between populations.

In this application, as with efficacy, the MAH focuses on safety in the *Intended Label Population*, which comprises the CAD stratum (post-MI patients) enriched with the PAD stratum data. However, the latter group represents a small fraction of the *Intended Label Population*; so it is not surprising that the safety findings are very similar to those in post-MI patients, as reviewed during the initial MAA.

Nevertheless, when PAD patients are examined separately (as *PAD stratum, Clinical PAD* and *Aspirin-only PAD population*) there are some interesting differences and observations. For example, it appears that in general patients with PAD had a higher incidence of bleedings, serious adverse events and deaths compared to their post-MI counterparts. This concerned both vorapaxar and placebo groups, suggesting a population at an overall high risk and poor prognosis. Whether this is a characteristic related to the greater atherosclerotic burden of the disease or other factors it remains unknown.

Clearly, the risk of bleeding is the major concern with vorapaxar and in TRA 2ºP-TIMI 50 this was the principal safety endpoint. Bleeding events were adjudicated by an independent clinical events committee and were graded according to GUSTO as well as TIMI criteria. Patients on vorapaxar were consistently at higher risk of bleedings across all examined populations and subgroups. In the *PAD stratum* the rate of GUSTO moderate or severe accrued event rate in the vorapaxar group was 6.8% compared to placebo at 4.9% (HR 1.38; 95% CI 1.03 to 1.85; p< 0.033) a difference driven mainly by moderate events while GUSTO severe events were similar between groups. GUSTO moderate and TIMI minor/clinical significant bleedings were significantly more common with vorapaxar. There were very few cases of ICH and fatal bleeding, with similar numbers between vorapaxar and placebo. These findings are generally consistent to those previously seen in post-MI patients.

In terms of the impact of concomitant antiplatelet treatment with aspirin and/or clopidogrel, it appears that in general patients receiving aspirin alone had a lower rate of bleeding (according to GUSTO and TIMI) irrespective of whether they were on vorapaxar or placebo. Patients on background clopidogrel alone (although the numbers of events are small) appear to have a similar risk as those on aspirin. However, further data submitted by the MAH showing bleeding events in patients receiving dual therapy with aspirin+clopidogrel raised further concerns. Although there are some limitations which do not permit drawing firm conclusions, the rates of bleeding in patients who received vorapaxar with both aspirin and clopidogrel are not reassuring. It is true that serious and life-threatening events are rare across all groups but the long-term risks of an intense antiplatelet therapy should be carefully considered against the possible expected benefits.

Taking also into account the overall modest efficacy evidence, it is not possible to confirm that the benefit:risk for vorapaxar as part of a triple antiplatelet therapy with aspirin plus clopidogrel remains positive.

In this context and also in the light of the current clinical guidelines, which generally advise against dual antiplatelet therapy in PAD, a recommendation for use of vorapaxar in combination with aspirin plus clopidogrel is not justified. Therefore, the MAH updated the SmPC accordingly (sections 4.1 and 4.2) to indicate that vorapaxar should be “co-administered with acetylsalicylic acid (ASA) ~~and/~~or, where appropriate, clopidogrel…” .

An additional point that deserves further consideration is the cumulative risk of bleeding over long-term therapy. Unlike post-MI patients in whom treatment may be time-limited following the acute event (which applies also to the use of other concomitant antiplatelets like clopidogrel), in PAD, in the absence of an index event, vorapaxar (as well as concomitant aspirin and/or clopidogrel) may be a chronic therapy for

many patients. Therefore, the cumulative risk of bleeding with vorapaxar over time in this group may be higher than in post-MI patients and this needs to be taken into account in the benefit:risk. The currently proposed SmPC (section 4.2) suggests a re-evaluation of the benefits and risks to continue therapy beyond the first 24 months for post-MI patients but not for PAD patients.

With regard to other non-bleeding adverse events in the TRA 2ºP-TIMI 50, there were no particular new findings but a consistency was noted across all populations (although slightly more pronounced in the *PAD stratum*) in the reports of atrial fibrillation with a higher frequency among vorapaxar treated patients and an imbalance in reports of thrombocytopenia. Which do not warrant any SmPC amendment at this time. Total mortality was slightly lower in the vorapaxar group.

2.6.2. Conclusions on clinical safety

There is limited new safety information in this submission over and above the TRA 2ºP-TIMI 50 data assessed during the initial MAA.

Bleeding remains the main safety issue with vorapaxar. In consistence with previous analyses in post-MI patients, the data suggest that risk is also high in PAD patients receiving vorapaxar, although the likelihood of severe bleeding including intracranial haemorrhages and fatal events is much smaller and no significantly different from controls. A point that needs careful consideration is the potential impact of background antiplatelet therapy with the combination of aspirin or clopidogrel. The current data suggest that although vorapaxar may be taken with aspirin or clopidogrel alone, the overall long-term risk of bleeding with vorapaxar as part of a triple antiplatelet therapy may be excessively high.Other than bleeding, there were no major new issues or signals, although there are still outstanding points that the MAH will need to clarify and address to confirm that all safety aspects have been adequately investigated and ensure that all relevant safety information is included in the product information.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.4 is acceptable. The PRAC endorsed PRAC Rapporteur assessment repor> is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

Safety concerns

Important identified risks	• Medically important bleeding, including intracranial hemorrhage • Drug-drug interaction: strong inhibitor of CYP3A4 • Drug-drug interaction: strong inducer of CYP3A4
Important potential risks	• Increased risk of bleeding in patients with body weight < 60 kg • Ocular effects • Phospholipidosis
Missing information	• Pregnant and breastfeeding women • Pediatric population • Patients with severe hepatic dysfunction • Co-administration with oral anticoagulants (e.g. warfarin), prasugrel, or ticagrelor • Severe thrombocytopenia • Coadministration with NSAIDs (other than aspirin)

Pharmacovigilance plan

Study / Activity	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim / Final Reports (target dates)
Category 3: Observational postauthorization safety study (PASS) to characterize normal conditions of use and safety following administration of vorapaxar.	Describe physician prescribing patterns in an outpatient setting during the post-licensure period with regards to key aspects of the product label in terms of appropriate patient selection (medical history, contraindications) and concomitant drug administration, and to estimate rates of hospitalization for bleeding events (e.g. intracranial hemorrhage (ICH), GI hemorrhage) in a real-world clinical setting. Evaluate the effectiveness of the risk minimization measures.	Intracranial haemorrhage, especially among patients with a history of stroke/TIA Medically important bleeding risks, excluding ICH Drug-drug interaction: strong inhibitor of CYP3A4 Patients with severe hepatic dysfunction Co-administration with oral anticoagulants (e.g. warfarin), prasugrel, or ticagrelor Off-label use	Planned	EU PASS: Progress reports will be submitted with each PSUR until completion of the study. Data on prescribing patterns will be submitted 2 years after EMA protocol approval and commercial launch in at least one participating PASS country. Additional reports with prescribing data will be submitted every two years thereafter until completion of the study. The timeline for the interim report with outcomes data and final study report will be included with the full protocol to the EMA at the time of EU commercial launch in at least one EU member state or within 3 months after approval of the indication extension to PAD patients. The final report with outcomes data and baseline data for all patients exposed to vorapaxar will be submitted once the required amount of person years of exposure has been accumulated. The timeline for this report will depend on sample size and the rate of marketing uptake, for which limited information is available at this time. The final report should be submitted no later than December 2020.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Medically important bleeding, including intracranial hemorrhage	SmPC: Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, Section 4.5 Interaction with other medicinal products and other forms of interaction, Section 4.8 Undesirable effects, and Section 5.1 Pharmacodynamic properties	None
Drug-drug interaction: strong inhibitor of CYP3A4	SmPC: Section 4.5 Interaction with other medicinal products and other forms of interaction, and Section 5.2 Pharmacokinetic properties	None
Drug-drug interaction: strong inducer of CYP3A4	SmPC: Section 4.5 Interaction with other medicinal products and other forms of interaction, and Section 5.2 Pharmacokinetic properties	None
Important Potential Risks		
Increased risk of bleeding in patients with body weight < 60 kg	The risk of increased bleeding in patients with low body weight is described in the SmPC in 4.4 Special warnings and precautions for use General risk of bleeding.	None
Ocular effects	Section 5.3 Preclinical safety data.	None
Phospholipidosis	Section 5.3 Preclinical safety data.	None
Missing Information		
Pregnant and Breastfeeding Women	Section 4.6 Fertility, pregnancy and breastfeeding women and Section 5.3 Pre-clinical safety data	None
Pediatric population	Section 4.2 Posology and method of administration and Section 5.1 Pharmacodynamic properties	None
Patients with severe hepatic dysfunction	Section 4.2 Posology and method of administration, Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, and Section 5.2 Pharmacokinetic properties	None
Co-administration with oral anticoagulants (e.g. warfarin), prasugrel, or ticagrelor	Section 4.2 Posology and method of administration, Section 4.4 Special warnings and precautions for use, and Section 4.5 Interaction with other medicinal products	None
Severe thrombocytopenia	No routine risk minimization measure proposed	None
Coadministration with NSAIDs (other than aspirin)	Section 4.4 Special warnings and precautions for use, General risk of bleeding.	None

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the contact details of local representative in Luxembourg in the Package Leaflet. Furthermore, the PI is brought in line with the QRD template version 9.1.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Despite improved management of risk factors and use of antiplatelets, the residual CV risk among patients with PAD remains high, as the TRA 2ºP-TIMI 50 data also confirmed. This suggests a high unmet need for effective therapies that could help prevent future CV events and save lives.

TRA 2ºP-TIMI 50 examined the incremental efficacy and safety of vorapaxar over standard therapy in a wide range of patients with atherosclerotic disease. After the exclusion of patients with history of stroke (and TIA) the results in the remaining patients with a recent history of MI or PAD, i.e. the ***"Intended Label Population"***, showed that vorapaxar could significantly reduce the composite of CV deaths, MIs, stroke and urgent coronary revascularisation and key secondary endpoints by 17% and 20%, respectively relative to placebo. All components of the composite endpoints showed a consistent trend in favour of vorapaxar, although MI was the most frequent event that contributed most to the difference between treatments. The data further suggest that the effect of vorapaxar on the primary and key secondary endpoints was maintained for the duration of the trial. In addition to lowering the risk of the first event within the composite endpoints exploratory analyses indicated that vorapaxar was also associated with a reduction in the incidence of total events.

When the TRA 2ºP-TIMI 50 efficacy was examined separately in the ***PAD stratum,*** the results were generally consistent with the *Intended Label Population* with all components of the composite primary and key secondary endpoints showing a trend in favour of vorapaxar (an overall reduction of 13% and 12%, for the primary and key secondary endpoint respectively relative to placebo). In this case, the component contributing most to the differences between treatment groups was CV mortality (vorapaxar: 47 [2.9%] deaths vs placebo 58 [3.5%]), although again MI was the most common event. However, in the *PAD stratum* the differences between vorapaxar and placebo did not reach statistical significance. Additional analyses in the *Clinical PAD* and *Aspirin-Only PAD* populations were similar to the *PAD stratum*.

Uncertainty in the knowledge about the beneficial effects

As previously discussed, the strength of the efficacy evidence for vorapaxar in this application, depends to a large extent on the examined TRA 2ºP-TIMI 50 population; more specifically, whether the results in the *Intended Label Population* that includes mostly post-MI are adequate to draw conclusions also for PAD patients, or whether this should be based entirely on the findings in the *PAD stratum*.

It is concluded that the results showed a clear consistency across the different populations, with most individual endpoints in the primary and secondary analyses favouring vorapaxar, which suggests that there are patients who are likely to benefit from this treatment. However, in the *PAD stratum* alone the effects were not significantly different between vorapaxar and placebo.

The MAH's view about the primary role of the *Intended Label Population* in this evaluation, based on methodological and clinical arguments (in terms of the study design to maintain the scope and integrity of the trial and, in terms of clinical relevance to examine together patients with a common atherothrombotic background and risk factors) is understood but cannot be fully accepted. As in previous trials (CAPRIE and CHARISMA), TRA 2ºP-TIMI 50 also showed that although patients with various degrees of atherosclerotic disease share clinical features and often a common fate, they also have many important differences that challenge the notion of a uniform and homogeneous population. This, in turn, means that pooling

together data from diverse atherosclerotic patient groups may not be as straightforward as presented. This is even more problematic in the *Intended Label Population* as, due to the relatively small representation of PAD patients, their data are diluted in the much larger pool of patients from the CAD stratum (post-MI).

It can be agreed with the MAH that the number of patients might not be sufficient for a robust analysis as the *PAD stratum* alone was not powered to detect significant differences between treatments (as was also none of the other individual strata in TRA 2ºP-TIMI 50). The results in the larger *Clinical PAD* population which included apart from the PAD stratum also a number of post-MI patients with evidence of PAD, showing a reduction in the primary endpoint with vorapaxar that almost reached statistical significance appear to confort this hypothesis. Whether the failure of the primary analysis to show a significant difference between treatment groups is due to the small number of observations or to the absence of a true effect is however difficult to confirm.

Nevertheless, it is agreed that the TRA 2ºP-TIMI 50 findings show a clear consistency across all populations with the findings in PAD patients showing a positive trend in favour of vorapaxar similar to their post-MI counterparts. The results in PAD stratum look similar to those previously seen in CAD but with wider CIs, suggesting that PAD patients may benefit to a similar degree as post-MI patients but the smaller population does not permit a more robust analysis. A calculation of the treatment-stratum interaction significance levels for the primary and key secondary endpoints has shown no significant heterogeneity.

Further to the above, almost all PAD patients included in TRA 2ºP-TIMI 50 were symptomatic. The clinical guidelines make a distinction in relation to symptoms, recommending antiplatelet therapy primarily to symptomatic patients (higher level of evidence in both ESC and AHA guidelines), based on previous trial data suggesting that symptomatic patients may benefit more than asymptomatic ones. The efficacy of vorapaxar in asymptomatic patients has not been investigated and this is currently reflected in the SmPC which advises that vorapaxar should be used in patients with symptomatic PAD.

Risks

Unfavourable effects

In line with the previous review of TRA 2ºP-TIMI 50 during the initial MAA, the safety findings across all populations showed once again a greater risk of bleeding in subjects receiving vorapaxar than placebo for all pre-specified bleeding endpoints.

In the *Intended Label Population*, the risk of GUSTO severe or moderate bleeding was higher in the vorapaxar group compared to placebo (KM 3-yr rate 3.8% vs. 2.7%; HR 1.45; 95% CI 1.23 - 1.71; p <0.001), but the difference was driven principally by GUSTO moderate bleeding. In the *PAD stratum* the GUSTO severe or moderate rate was generally greater in both groups than in the *Intended Label Population* but the relative differences between vorapaxar and placebo were similar as before (6.8% vs 4.9% respectively; HR 1.38; 95% CI 1.03 to 1.85; p< 0.033). Again the difference was driven mainly by moderate events while GUSTO severe events were similar between groups. There were very few cases of ICH and fatal bleeding, with similar numbers between vorapaxar and placebo. These findings are generally consistent to those previously seen in post-MI patients.

The above suggest that as with their post-MI counterparts, patients with PAD also face an increased risk of bleeding when vorapaxar is added to their standard therapy and this needs to be considered in the benefit:risk; although life-threatening or fatal events are rare. Still PAD patients on vorapaxar will be likely to experience more often less serious bleedings like epistaxis, haematuria, GI haemorrhages and may also require a transfusion but the likelihood of hospitalisation or a procedure to manage the bleeding appears to be similar to controls. Still, anaemia was consistently more common with vorapaxar and

appears to be related to bleeding. Serious events (other than bleeding) were generally rare with no major differences between treatment groups. There were no concerns about overall mortality which actually showed a trend in favour of vorapaxar.

Further to the bleeding risk, there was no indication of any new *major* safety issue in the PAD population over what is already known from the previous review, and most important information is already included in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

An issue that deserves careful consideration is the potential impact of background antiplatelet therapy on bleeding risk in the PAD population. The majority of PAD patients in TRA 2ºP-TIMI 50 were on aspirin but a significant proportion (around 30%) were also receiving concomitantly clopidogrel whereas some patients were on clopidogrel alone. PAD patients receiving vorapaxar as add-on to aspirin alone (approximately 60% of the PAD stratum) appear to have had slightly less bleedings (although in most cases vorapaxar was still worse than placebo), but there are concerns about bleeding events when vorapaxar was given as add-on to both aspirin+clopidogrel as part of triple antiplatelet treatment. This is a critical point as current guidelines do not recommend DAPT in PAD patients. The TRA 2ºP-TIMI 50 data suggest a higher risk of bleeding in patients receiving vorapaxar with both aspirin and clopidogrel and such a combination is not recommended.

An additional point that should also be considered is the cumulative risk of bleeding over long-term therapy. Unlike post-MI patients, in whom treatment may be time-limited following the acute event, vorapaxar therapy in PAD, in the absence of an index event, may be open ended. Taking into account also other possible concomitant antithrombotic therapies, the cumulative risk of bleeding with vorapaxar over time in the PAD group may be greater than in post-MI patients and this needs to be taken into account in the benefit:risk. The currently proposed SmPC (section 4.2) suggests a re-evaluation of the benefits and risks to continue therapy beyond the first 24 months in post-MI but not in PAD.

Effects Table

Effects Table for vorapaxar in the treatment of patients with PAD (TRA 2ºP-TIMI 50; *Intended Label Population* and *PAD stratum with no history of stroke of TIA*)

Effect	Short Description	Unit	Vorapaxar	Placebo	Strength of evidence / Uncertainties	References
Favourable Effects						
Intended Label population *(subjects with no history of stroke or TIA whose qualifying condition was CAD or PAD)*						
CV outcome	Composite of CV death, MI, stroke, UCR	N (%)	896 (8.9%)	1073 (10.6%)	HR 0.83 (95% CI 0.76-0.90). Consistent results across the three individual components	P04737 study report
		3 year KM %	10.1%	11.8%		
	CV death	N (%)	129(1.3%)	154(1.5%)		
	MI	N (%)	450(4.5%)	531(5.3%)		
	Stroke	N (%)	91 (0.9%)	123(1.2%)		
	UCR	N (%)	226(2.2%)	265(2.6%)		
PAD stratum *(subjects with no history of stroke or TIA whose qualifying condition was PAD)*						
CV outcome	Composite of CV death, MI, stroke, UCR	N (%)	177 (10.9%)	206 (12.5%)	HR 0.87 (95% CI 0.71-1.06). Consistent results across the three individual components	P04737 study report
		3 year KM %	11.1%	12.8%		

Effect	Short Description	Unit	Vorapaxar	Placebo	Strength of evidence / Uncertainties	References
	CV death	N (%)	47(2.9%)	58 (3.5%)		
	MI	N (%)	76 (4.7%)	80 (4.8%)		
	Stroke	N (%)	31 (1.9%)	39 (2.4%)		
	UCR	N (%)	23(1.4%)	29 (1.8%)		
Unfavourable Effects						
Intended Label population *(**s**ubjects with no history of stroke or TIA whose qualifying condition was CAD or PAD)*						
Bleedings	GUSTO Severe or Moderate	N (%)	335(3.3%)	233(2.3%)	HR 1.45 (95% CI 1.23 - 1.71).	P04737 study report
		3 year KM %	3.8%	2.7%		
	GUSTO Severe	N (%)	115(1.1%)	105(1.0%)	HR 1.09 (95% CI 0.84 - 1.43).	
		3 year KM %	1.3%	1.3%		
	GUSTO moderate	N (%)	229(2.3%)	138(1.4%)	HR 1.67 (95% CI 1.35 – 2.07).	
		3 year KM %	2.6%	1.6%		
	ICH	N (%)	49 (0.5%)	39 (0.4%)	HR 1.25 (95% CI 0.82 – 1.91)	
		3 year KM %	0.6%	0.5%		
PAD stratum *(subjects with no history of stroke or TIA whose qualifying condition was PAD)*						
Bleedings	GUSTO Severe or Moderate	N (%)	104(6.4%)	77 (4.7%)	HR 1.38 (95% CI 1.03 - 1.85).	P04737 study report
		3 year KM %	4.9%	6.8%		
	GUSTO Severe	N (%)	30 (1.9%)	32 (2.0%)	HR 0.94 (95% CI 0.57 - 1.54).	
		3 year KM %	2.0%	2.1%		
	GUSTO moderate	N (%)	77 (4.8%	50 (3.1%)	HR 1.58 (95% CI 1.11 – 2.25).	
		3 year KM %	5.0%	3.1%		
	ICH	N (%)	11 (0.7%	9 (0.5%)	HR 1.24 (95% CI 0.51 – 2.98)	
		3 year KM %	0.7%	0.6%		

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The earlier review of the pivotal trial established a positive benefit:risk for vorapaxar in the treatment of patients with history of MI (but with no previous stroke or TIA) based on a statistically and clinically relevant reduction in the composite endpoint of CV death, MI, stroke and UCR that outweighed the risk of bleeding. In post-MI patients, compared with placebo, vorapaxar was found (based on calculations after adjustment for exposure) to prevent 80 (95% CI: 41, 120) CV deaths, MIs, strokes and urgent coronary revascularisations per 10,000 patient-years, while causing 6 severe bleeds.

The MAH now seeks to extend the indications to include also patents with PAD, based again on the results of TRA 2ºP-TIMI 50 but, this time, expanded to include also patients from the PAD stratum. In this, so called ***Intended Label Population***, after adjusting for exposure, it was calculated that there were 330 CV death (excluding fatal bleed), MI (excluding CV death), or ischaemic stroke (excluding CV death) events in the placebo-treated group compared to 264 events in the vorapaxar treated group per 10,000 patient-years. The risk difference between the two groups is -66 (95% CI -97, -36) i.e. there were 66 less events among the vorapaxar-treated subjects. This difference was mainly due to MIs (35 out of the

66 events).

Conversely, the risk of irreversible damage from bleeding was slightly increased in vorapaxar treated subjects compared to placebo. There were 45 GUSTO severe bleeding events (including ICH and fatal events) per 10,000 patient-years in the vorapaxar group compared to 41 per 10,000 patient-years in the placebo group (risk difference: +4; 95% CI -8, 15). There was no risk difference between vorapaxar and placebo for fatal bleeding, including fatal ICH (0 [95% CI -5, 5) and for GUSTO severe non-fatal, non-ICH bleeding (0 [95% CI -8, 9]); for non-fatal ICH the risk difference was 2 (95% CI -4, 9). Taken together the above it was calculated that in the *Intended Label Population* the ratio of overall benefit (first event of CV death, MI, or ischemic stroke to overall risk i.e. all GUSTO severe bleeding) is 66:4, when vorapaxar is used on top of standard of care.

The estimation of "net clinical benefit" that included only the most robust endpoints CV death, MI, stroke, and GUSTO severe bleeding showed a significant result for vorapaxar in reducing the rate of the net clinical outcome by 18% (HR 0.82; 95% CI 0.74 – 0.90; Table B-R.1). A similar significant reduction was seen when the net outcome calculation included also UCR and GUSTO moderate bleedings, as per the definition of the 'net benefit' in the protocol (HR 90% ; 95% CI 0.74 – 0.90).

Table B-R. 1 TRA 2°P – TIMI 50 Time-to-Event Analyses of the Net Clinical Outcome in the Intended Label Population: As-Treated Population ~ Event Accrual Period: Randomization to Last Visit

Net Clinical Outcome Endpoints	Subjects With Events (%)				HR (95% CI)[a,b]
	Placebo (n =10049)		Vorapaxar (n =10059)		
CV death / MI / Stroke / UCR / GUSTO Severe / GUSTO Moderate	1226/10049	12.2%	1112/10059	11.1%	0.90 (0.83 - 0.98)
CV death / MI / Stroke / GUSTO Severe	914/10049	9.1%	753/10059	7.5%	0.82 (0.74 - 0.90)
All-Cause Death / MI / Stroke / GUSTO Severe	1052/10049	10.5%	905/10059	9.0%	0.85 (0.78 - 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)

For the ***PAD stratum***, the MAH did not provide any calculations for the adjusted risk difference between groups. However, an estimation of the rate of the net clinical outcome (including CV death/MI/stroke/GUSTO severe) was provided that favours vorapaxar (HR 0.85; 95% CI 0.70 - 1.05) but without reaching statistical significance (Table B-R.2).

The net clinical outcome in *Clinical PAD* (HR 0.84; 95% CI 0.70 - 1.01) and *Aspirin-Only PAD* (HR 0.82; 95% CI 0.62 - 1.07) populations were consistent with the results in the *PAD stratum.*

Table B-R.2 TRA 2°P – TIMI 50 Time-to-Event Analyses of the Net Clinical Outcome (CV death/MI/Stroke/ GUSTO Severe) in PAD: As-Treated Population ~ Event Accrual Period: Randomization to Last Visit

Net Clinical Outcome Endpoints (CV death / MI / Stroke / GUSTO Severe)	Subjects With Events (%)				HR (95% CI) [a,b]
	Placebo		Vorapaxar		
PAD with no history of stroke or TIA	200/1637	12.2%	170/1615	10.5%	0.85 (0.70 - 1.05)
Clinical PAD Population[c]	265/1992	13.3%	218/1931	11.3%	0.84 (0.70 - 1.01)
Aspirin Only PAD Population[d]	119/1044	11.4%	97/1030	9.4%	0.82 (0.62 - 1.07)

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)
c. Subjects With No History of Stroke or TIA Who Were NOT in the CVD Stratum AND Whose Qualifying Condition Was PAD OR (had ABI<= 0.9 with Symptoms~) OR History of Peripheral Arterial Revascularization Symptoms [Fontaine Stage II, III, or IV])
d. Subjects with no history of stroke or TIA whose qualifying condition was PAD who were on aspirin at baseline, and did not plan thienopyridine use during the study.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

Patients with PAD are at high risk of future cardiovascular events. Unlike patients with a recent MI who have benefited from the introduction of newer antiplatelets in recent years, in PAD there has been little progress in this area of CV prevention, with most patients still relying on aspirin alone. Undoubtedly, there is a high unmet need for additional therapies that could help prevent CV events and deaths. TRA 2ºP-TIMI 50 investigated the value of vorapaxar in this role, in practice also testing the concept of dual/triple antiplatelet in PAD. It is reminded that today PAD clinical guidelines do not routinely recommend dual antiplatelet therapy for long-term therapy, mainly due to the negative results of the CHARISMA trial.

Vorapaxar has the potential to contribute to the secondary prevention in patients with atherosclerotic disease and a positive benefit:risk was previously established in post-MI patients. The TRA 2ºP-TIMI 50 data also indicate a positive effect in the high risk symptomatic patients with PAD who were included in the trial. Although the results in the *PAD stratum* alone did not reach statistical significance the clear consistency across endpoints and across populations provides convincing evidence of the incremental benefits of vorapaxar over current therapies in the PAD population.

On the other hand, it is clear that vorapaxar increases the risk of bleeding. Although less severe bleedings are still more common among patients receiving vorapaxar on top of their standard therapy life-threatening events, ICH and fatal cases are rare.

Taken the above together it can be concluded that the expected benefits of vorapaxar co-administered with aspirin *or*, where appropriate, clopidogrel are likely to outweigh the potential risks. Considering also the high unmet need in this population, the overall benefit:risk balance is considered to be positive in patients with symptomatic PAD.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include treatment of patients with symptomatic Peripheral Arterial Disease (PAD) and as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the contact details of local representative in Luxembourg in the Package Leaflet. Furthermore, the PI is brought in line with the QRD template version 9.1. Moreover, revised RMP version 2.4 has been agreed.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).