EUnetHTA WP5 Joint Action 2 Strand A, Rapid assessment of pharmaceuticals

Pilot rapid assessment of pharmaceuticals using the HTA Core Model® for Rapid Relative Effectiveness Assessment

VORAPAXAR FOR THE REDUCTION OF THROMBOTIC CARDIOVASCULAR EVENTS IN PATIENTS WITH A HISTORY OF MYOCARDIAL INFARCTION (MI)

Pilot ID: WP5 - SA-5

Final version, 17 Jun 2015

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description
V1.0	2 April 2015	First draft.
V1.1	4 April 2015	Input from co-author has been processed.
V1.2	28 April 2015	Input from dedicated reviewers has been processed.
V1.3	13 May 2015	Input from medical editor has been processed.
V1.4	17 June 2015	Input from WP5/MAH review has been processed.

Disclaimer

This assessment was produced by experts from the institutions listed below, and was reviewed by members of Work Package 5 (WP5) Joint Action 2 of the EUnetHTA network; the whole process was coordinated by the Zorginstituut Nederland (ZIN).

The assessment represents a consolidated view of the EUnetHTA network members and is in no case the official opinion of the participating institutions or individuals.

EUnetHTA Joint Action 2 is supported by a grant from the European Commission. The sole responsibility for the content of this document lies with the authors and neither the European Commission nor EUnetHTA are responsible for any use that may be made of the information contained therein

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Consultation of the draft Pilot Rapid Assessment

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Conflict of interest

All authors and reviewers involved in the production of this pilot assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA conflicts of interest (COI) statement form.

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SUMMARY OF RELATIVE EFFECTIVENESS OF VORAPAXAR

Scope

Description	Project scope
Population	Adult patients with a history of myocardial infarction (MI) (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10][a] code I21, I22) without history of stroke (ICD-10[a] code I61-64) or transient ischaemic attack (TIA) (ICD-10[a] code G45.8, G45.9). Acute coronary syndrome (ACS) patients are excluded. Secondary prevention treatment.
Intervention	Vorapaxar is prescribed as an add-on therapy to standard of care including acetylsalicylic acid (ASA), with or without (±) clopidogrel, for reduction of atherothrombotic events.
Comparison	Voraxapar is co-administered with ASA ± clopidogrel. The comparator in the study was placebo + ASA ± clopidogrel. This drug evaluation must be understood as a therapeutic strategy comparison.
Outcomes	Cardiovascular (CV) death or ischaemic events (MI, stroke, urgent coronary revascularisation [UCR]). Adverse effects of treatment (haemorrhage).

[a] http://apps.who.int/classifications/icd10/browse/2015/en

Introduction

Description of technology

Vorapaxar (ZONTIVITY™) is a first-in-class selective antagonist of 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. Thrombin-induced platelet activation has been implicated in a variety of cardiovascular (CV) disorders including thrombosis, atherosclerosis, and restenosis following percutaneous coronary intervention (PCI). As an antagonist of PAR-1, vorapaxar blocks thrombin-mediated platelet aggregation and thereby has the potential to reduce the risk of atherothrombotic complications of coronary disease. It is given in combination with acetylsalicylic acid (ASA) and, where appropriate, with a third medicine, clopidogrel, both of which also help prevent atherothrombotic events.

There is limited clinical experience with vorapaxar + prasugrel and no experience with vorapaxar + ticagrelor in the Phase 3 studies. Vorapaxar should not be initiated in patients taking prasugrel or ticagrelor and, in case of need for additional therapy with these agents, vorapaxar should be stopped.

Vorapaxar is the only antiplatelet agent (at the time of this submission) with evidence to improve outcomes in post-MI patients when continued beyond 12 months after an MI. No dose adjustment is necessary in the elderly. No dose adjustment is required in patients with renal impairment. However, reduced renal function is a risk factor for bleeding and should be considered before initiating vorapaxar. There is limited therapeutic experience in patients with severe renal impairment or end-stage renal disease. Therefore, vorapaxar should be used with caution in such patients. Reduced hepatic function is a risk factor for bleeding and should be considered before

initiating vorapaxar. No dose adjustment is required in patients with mild hepatic impairment. Vorapaxar should be used with caution in patients with moderate hepatic impairment. Because of the limited therapeutic experience and the increased inherent risk of bleeding in patients with severe hepatic impairment, vorapaxar is contraindicated in such patients. The safety and efficacy of vorapaxar in children aged less than 18 years have not yet been established. No data are available in paediatrics.

Vorapaxar has received marketing authorisation (MA) for the following indication:

"Vorapaxar, co-administered with acetylsalicylic acid (ASA) and, where appropriate, clopidogrel, is indicated for the reduction of atherothrombotic events in adult patients with a history of myocardial infarction (MI)."

Health problem

Atherosclerosis and ischaemic CV diseases such as coronary artery disease (CAD) are progressive systemic disorders in which clinical events are precipitated by episodes of vascular thrombosis. Patients with an established history of atherothrombotic or athero-ischaemic disease are at particular risk of future cardiac or cerebral events, and vascular death. Antithrombotic therapy options in patients with stable atherosclerosis are not well established. Therefore, long-term therapies are required to modulate effectively the key components responsible for atherothrombosis in the secondary prevention of ischaemic CV disease.

Methods

We performed the assessment using 3 sources of information: the final submission file provided by the marketing authorisation holder (MAH), the assessment report provided by the Committee for Medicinal Products for Human Use (CHMP), and the summary of product characteristics (SmPC).

The MAH sponsored a multinational, randomised (1:1 ratio), double-blind, controlled clinical trial (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events [TRA 2°P-TIMI 50]) to evaluate the safety and efficacy of vorapaxar as an add-on therapy to standard of care (vorapaxar + ASA ± clopidogrel) versus standard of care alone (ASA ± clopidogrel). Subjects enrolled in the original study population were those with a history of atherosclerotic disease, including coronary artery disease (CAD) (indicated by a history of MI), cerebrovascular disease (CVD) (indicated by a history of ischaemic stroke), or peripheral artery disease (PAD).

During an interim analysis in the trial, an independent Data and Safety Monitoring Board (DSMB) observed an increased incidence and relative risk of intracranial haemorrhage (ICH) in subjects with a history of stroke. As a result, the DSMB recommended discontinuation of the study drug in all subjects with previous stroke, including those with a new stroke during the trial, and continuation of the trial in patients without a history of stroke. Subsequently, the European Medicines Agency (EMA) decided against expanding the submission to include subjects from the PAD stratum. Thus, the proposed label population (PLP) included subjects in the CAD stratum of the trial only (history of MI), with no history of stroke or TIA.

N.B.: The rationale for the EMA decision to exclude patients with PAD was described neither in the submission file nor in the Committee for Medicinal Products for Human Use (CHMP) report. Nevertheless the MAH has clarified this point in its comments: "the MAH wished the CHMP to consider the ILP, i.e., include patients qualifying for the TRA-2°P TIMI 50 trial because of PAD. However, the CHMP declined to do so, indicating that the MAH could re-file or file a type II variation after receiving approval of the PLP-based file."

Results

Clinical effectiveness

In the TRA 2°P-TIMI 50 PLP, the primary efficacy composite endpoint (CV death, MI, stroke, or urgent coronary revascularisation [UCR]) was a 3-year Kaplan-Meier event rate of 9.8% in the vorapaxar + ASA ± clopidogrel group compared with 11.4% in the placebo + ASA ± clopidogrel group (hazard ratio [HR]=0.82; 95% confidence interval [CI]: 0.74 to 0.90; p<0.001).

The key secondary efficacy composite endpoint (CV death, MI, or stroke) in the PLP was a 3-year Kaplan-Meier event rate of 7.4% in the vorapaxar + ASA ± clopidogrel group compared with 9.0% in the placebo + ASA ± clopidogrel group (HR=0.78; 95% CI: 0.70 to 0.88; p<0.001).

Safety

In the TRA 2ºP-TIMI 50 PLP, vorapaxar + ASA ± clopidogrel compared with placebo + ASA ± clopidogrel was associated with more bleeding adverse events (AEs):

- A total of 231 subjects (2.7%) experienced “GUSTO severe or moderate bleeding” in the vorapaxar + ASA ± clopidogrel group compared with 156 subjects (1.9%) in the placebo + ASA ± clopidogrel group (HR=1.48; 95% CI: 1.21 to 1.82; p<0.001).

- A total of 1,120 subjects (13.3%) experienced “TIMI clinically significant bleeding” in the vorapaxar + ASA ± clopidogrel group compared with 785 subjects (9.3%) in the placebo + ASA ± clopidogrel group (HR=1.46; 95% CI: 1.34 to 1.60; p<0.001).

- A total of 347 subjects (4.1%) experienced “ISTH major bleeding” in the vorapaxar + ASA ± clopidogrel group compared with 233 subjects (2.8%) in the placebo + ASA ± clopidogrel group (HR=1.49; 95% CI: 1.26 to 1.76; p<0.001).

In different specific populations, an increased bleeding risk was noticed. Older patients (>65 years), patients with a body weight <60 kg, and patients with hepatic or renal failure had an increased risk of bleeding AEs in both treatment groups.

There were no differences in the incidences of other serious adverse events (SAEs) between treatment groups across the TRA 2ºP-TIMI 50 PLP. The most frequently reported other SAEs were non-cardiac chest pain (4.3% in the vorapaxar + ASA ± clopidogrel group compared with 4.0% in the placebo + ASA ± clopidogrel group), cardiac failure, pneumonia, atrial fibrillation, syncope, cardiac failure congestive, and osteoarthritis (all were ≤1.0% in both groups).

Summary table of relative effectiveness of vorapaxar (PLP)

REDUCTION OF THROMBOTIC CARDIOVASCULAR EVENTS TRA 2ºP-TIMI 50 trial										
	Health benefit				Harm					
	Primary composite endpoint (CV death, MI, stroke, UCR) (D0005)		Key secondary composite endpoint (CV death, MI, stroke) (D0005)		GUSTO severe or moderate bleeding		TIMI clinically significant bleeding		ISTH major bleeding	
	KM (%) estimate at 3 years Nb of events	HR (95% CI) p-value	KM (%) estimate at 3 years Nb of events	HR (95% CI) p-value	Nb of events (%)	HR (95% CI) p-value	Nb of events (%)	HR (95% CI) p-value	Nb of events (%)	HR (95% CI) p-value
Vorapaxar + ASA ± clopidogrel	9.8% 719 (N=8,458)	0.82 (0.74 to 0.90) <0.001	7.4% 532 (N=8,458)	0.78 (0.70 to 0.88) <0.001	231 (2.7) (N=8,444)	1.48 (1.21 to 1.82) <0.001	1,120 (13.3) (N=8,444)	1.46 (1.34 to 1.60) <0.001	347 (4.1) (N=8,444)	1.49 (1.26 to 1.76) <0.001
Placebo + ASA ± clopidogrel	11.4% 867 (N=8,439)		9.0% 671 (N=8,439)		156 (1.9) (N=8,412)		785 (9.3) (N=8,412)		233 (2.8) (N=8,412)	
***Quality of body of evidence*[a]**	***Moderate***		***moderate***		***moderate***		***moderate***		***moderate***	

Abbreviations: ASA=acetylsalicylic acid; CI=confidence interval; CV=cardiovascular; GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (trial); HR=hazard ratio; ISTH=International Society on Thrombosis and Haemostasis; KM=Kaplan-Meier; MI=myocardial infarction; n=number of subjects; PLP=proposed label population; TIMI=Thrombolysis in Myocardial Infarction Study Group; UCR=urgent coronary revascularisation

[a] ***High*** **=** We are very confident that the true effect lies close to that of the estimate of the effect; ***Moderate*** **=** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; ***Low*** **=** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Discussion

In terms of effectiveness, a clinical benefit was shown in both the primary and key secondary composite endpoints, which both comprised major adverse cardiovascular events (MACE). MACE are widely used in composite endpoints in numerous clinical trials of antiplatelets and anticoagulants. Nevertheless, a few issues were raised:

- Firstly, as shown in Table 5.4 and Table 5.5, the individual CV events of the composite endpoints didn't occur with the same frequency; the overall result of each endpoint was mainly led by MI. Indeed, MI occurred 5 times more than CV death or stroke in both endpoints and 2 times more than UCR. Each event doesn't have the same weight in the final result.

- Secondly, all-cause deaths should have been one of the first key secondary endpoints. Indeed, the overall interest of the drug is its related efficacy as well as possible harmful effects, in terms of mortality. The study planned to use a hierarchical test sequence to evaluate the endpoints. If the first key secondary criteria showed a significant difference, then the following key secondary endpoint could be considered with the same power, the same robustness and so on, until one of the differences between groups on a criterion was not significant. Considering that, all-cause death should have been one of the first key secondary endpoints, but it was not. Furthermore, the first key secondary endpoint chosen (which includes all of the criteria of the primary endpoint except UCR) didn't provide much more information than the primary endpoint.

In this trial, vorapaxar demonstrated a clinical benefit mainly on morbidity (mainly MI), but no significant difference was shown with regard to CV mortality or overall mortality (all-cause deaths).

A methodological issue has to be raised about the initial statistical analysis plan, which was not modified or redefined after the DSMB and EMA decisions to exclude patients with a history of stroke (following the interim analysis) and then to exclude patients in the PAD stratum, thus reducing the overall population (n= 26,449 patients) to the PLP (n=16,897; 63.9% of the overall population). This exclusion was done without unblinding. The power of the trial, which represents the reproducibility and the ability to conclude robustly, is unknown in the PLP. Furthermore, the initial hypothesis of the trial has been changed by the exclusion of different populations. This reduces the level of evidence of the trial. Considering the absence of a new hypothesis, analysis has to focus first on the overall population and second on the PLP. Here, the PLP analysis remains a post-hoc analysis.

This modification of the trial leads to difficulties in assessing the effectiveness of the drug: the population that needs to be treated in a real-life situation is very different to that of the initial trial population.

Furthermore, in a real-life situation, the use of vorapaxar will need to exclude patients treated by ticagrelor and prasugrel, and patients with a history of stroke or TIA, complicating a patient's care. Ticagrelor and prasugrel are first- or second-line recommendations within the first year of an MI in some guidelines. Because data on vorapaxar as an add-on therapy to these two drugs are lacking, potential clinical interest of vorapaxar associated with ticagrelor or prasugrel can't be assessed. It remains unclear if patients treated with ticagrelor or prasugrel could be switched to vorapaxar schemes and, if this was possible, how the switch could be done.

In terms of safety, bleeding events remain the major concern in the vorapaxar safety profile. Indeed, vorapaxar + ASA ± clopidogrel compared with placebo + ASA ± clopidogrel was associated with more bleeding AEs. Moreover, the number of bleeding events looks higher in more vulnerable populations such as older patients, those with a low weight, and renal and hepatic failure patients. However, in these populations, the number of patients was too low to conclude robustly. Therefore, additional information is needed. Caution should be taken in these special populations, and the use of vorapaxar is contraindicated in patients with severe hepatic failure.

There were no quality-of-life data. Therefore, it is not possible to assess the impact of the addition of vorapaxar to ASA ± clopidogrel in terms of quality of life.

Conclusion

Regarding the primary and key secondary endpoints used in the TRA 2ºP-TIMI 50 trial, vorapaxar 2.5 mg once daily as an add-on therapy to ASA ± clopidogrel seems to improve CV morbidity mainly MI, compared to treatment with placebo + ASA ± clopidogrel alone.

However, CV mortality and overall mortality were not chosen as key secondary criteria nor were they among the first other secondary endpoints in the hierarchical test sequence planned a priori. Thus, these endpoints can't be evaluated and discussed for this trial, because other secondary endpoints, evaluated before these endpoints, were negative. Therefore, data on mortality remains exploratory data without any robustness, and no conclusion can be drawn about vorapaxar's effect on mortality.

From a number needed to treat (NNT) perspective (efficacy expressed as the number of patient years exposure with vorapaxar instead of placebo to prevent 1 additional harmful event), treatment with vorapaxar instead of placebo (as an add-on therapy to ASA ± clopidogrel) would result in 1 fewer non-bleeding CV death, MI, or stroke event per 140 patient-years.

In terms of safety, vorapaxar as an add-on therapy to ASA ± clopidogrel compared with ASA ± clopidogrel alone presents an increased risk of bleeding (GUSTO moderate or severe bleeding rate: 1.1 events per 100 subjects per year) for patients who will be prescribed vorapaxar. Bleeding risk represents the major concern in the vorapaxar safety profile.

According to the MA indication and the population included in the TRA 2 P-TIMI 50 trial, vorapaxar may be used in a very narrow population: subjects with an MI history but without a history of stroke or TIA, and not receiving treatment with ticagrelor or prasugrel. Therefore, it will likely be complicated for physicians to choose patients eligible for this drug. Vorapaxar's place in the therapeutic strategy has to be accurately defined in international guidelines.

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AE	Adverse event
AHA	American Heart Association
ASA	Acetylsalicylic Acid
CAD	Coronary artery disease
CHD	Coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CrCl	Creatinine clearance
CSR	Clinical study report
CV	Cardiovascular
CVD	Cerebrovascular disease
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 isoenzyme 3A4
DSMB	Data and Safety Monitoring Board
EMA	European Medicines Agency
ESC	European Society of Cardiology
EU	European Union
GBD (study)	Global Burden of Disease (study)
GUSTO (trial)	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (trial)
HR	Hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
IHD	Ischaemic heart disease
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-to-treat
KM	Kaplan-Meier
LDL	Low-density lipoprotein
MA	Marketing authorisation
MACE	Major adverse cardiovascular events

MAH	Marketing authorisation holder
MI	Myocardial infarction
MONICA (study)	Monitoring of Trends and Determinants in Cardiovascular Disease (study)
NNH	Number needed to harm
NNT	Number needed to treat
PAD	Peripheral artery disease
PAR-1	Protease-activated receptor 1
PCI	Percutaneous coronary intervention
PK	Pharmacokinetic
PLP	Proposed Label Population
PRAC	Pharmacovigilance Risk Assessment Committee
REACH (registry)	Reduction of Atherothrombosis for Continued Health (registry)
SAE	Serious adverse event
SmPC	Summary of product characteristics
STEMI	ST segment elevation myocardial infarction
TIA	Transient ischaemic attack
TIMI	Thrombolysis in Myocardial Infarction
TRA 2°P-TIMI 50	Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events
TRACER	Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome
UCR	Urgent coronary revascularisation
WHO	World Health Organization

1 SCOPE

Description	Project scope
Population	Adult patients with a history of myocardial infarction (MI) (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10][a] code I21, I22) without history of stroke (ICD-10[a] code I61-64) or transient ischaemic attack (TIA) (ICD-10[a] code G45.8, G45.9). Acute coronary syndrome (ACS) patients are excluded. Secondary prevention treatment.
Intervention	Vorapaxar is prescribed as an add-on therapy to standard of care including acetylsalicylic acid (ASA), with or without (±) clopidogrel, for reduction of atherothrombotic events.
Comparison	Voraxapar is co-administered with ASA ± clopidogrel. The comparator in the study was placebo + ASA ± clopidogrel. This drug evaluation must be understood as a therapeutic strategy comparison.
Outcomes	Cardiovascular (CV) death or ischaemic events (MI, stroke, urgent coronary revascularisation [UCR]). Adverse effects of treatment (haemorrhage).

[a] http://apps.who.int/classifications/icd10/browse/2015/en

2 METHODS AND EVIDENCE INCLUDED

2.1 Pilot team

The Slovak Ministry of Health assessed the Health Problems and Technical domains, while the Haute Autorité de Santé (HAS), France, assessed the Effectiveness and Safety domains.

2.2 Search

A literature search for studies that assessed vorapaxar effectiveness in patients with a history of myocardial infarction (MI) was conducted by the MAH. The search was conducted on 27 October 2014 with no date limits.

The search was conducted in both MEDLINE and EMBASE databases and included the following search terms: (vorapaxar AND (coronary artery disease OR coronary syndrome OR infarction OR angina)). The search was restricted to humans.

Only full original manuscripts meeting the following criteria were retained:

Inclusion criteria

- The study included patients with a history of MI.
- The study included a comparison of vorapaxar with placebo or other antiplatelet agents (acetylsalicylic acid [ASA], clopidogrel, ticagrelor, prasugrel, and their combinations).
- The study assessed efficacy/effectiveness and/or safety of vorapaxar versus placebo or other antiplatelet agents including their combinations.
- The study included a follow up of at least 6 months.

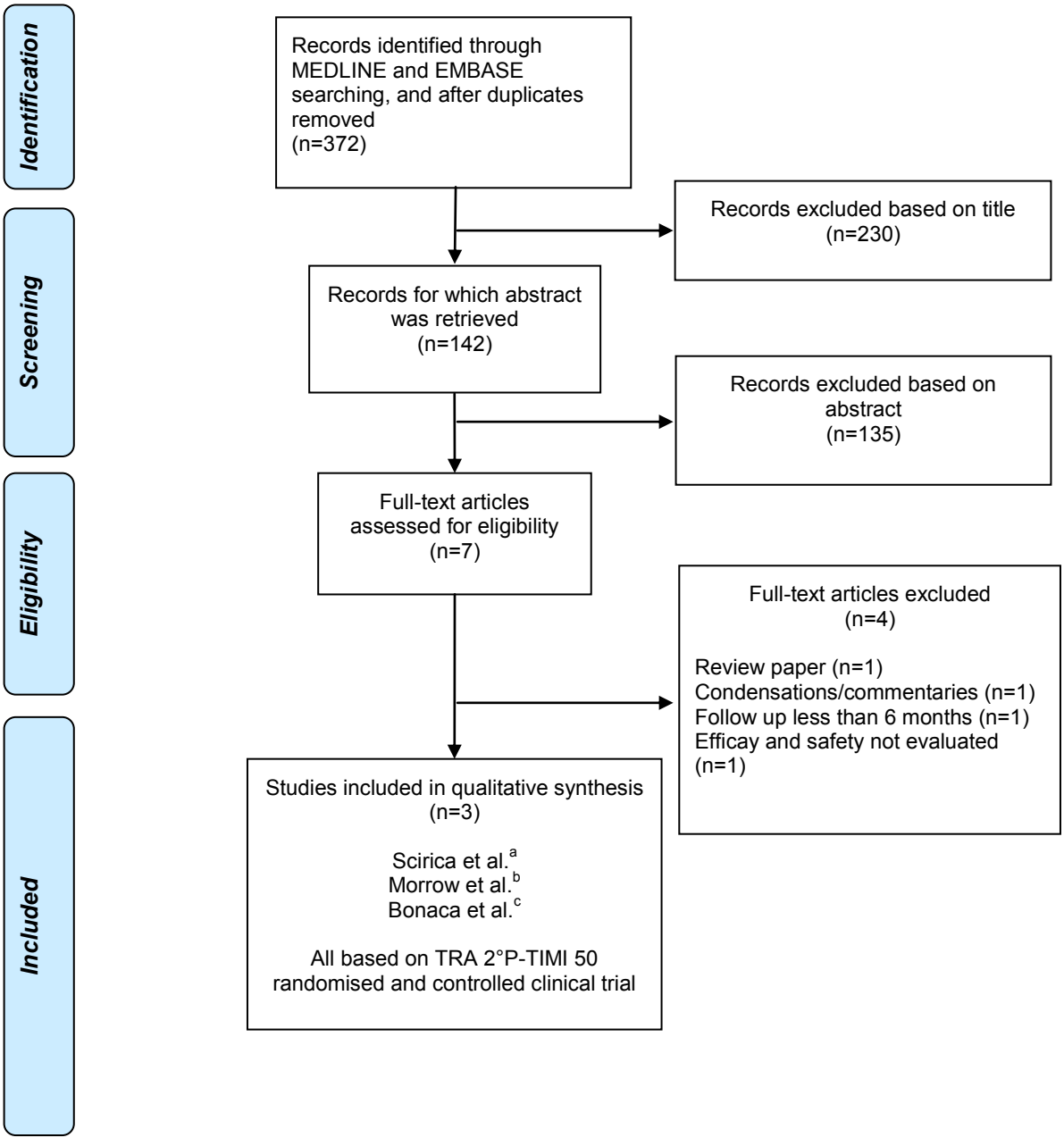
Exclusion criteria

- The study included only acute coronary syndrome (ACS) patients.

2.3 Flow chart of study selection

Figure 2.1 details the results yielded and reasons for final inclusion.

Figure 2.1: Flow chart of literature search



[a] Scirica BM, Bonaca MP, Braunwald E, et al. Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. *Lancet* 2012;380:1317-24.
[b] Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012;366:1404-13.
[c] Bonaca MP, Scirica BM, Creager MA, et al. Vorapaxar in patients with peripheral artery disease: results from TRA 2ºP-TIMI 50. *Circulation* 2013;127:1522-9.

2.4 Description of the evidence used

Table 2.1: Main characteristics of studies included

Study name	Study type	Number of patients	Intervention(s)	Main endpoints	Included in clinical effectiveness and/or safety domain
TRA 2ºP-TIMI 50 trial [1][2]	Multinational, randomised (1:1 ratio), double-blind, controlled clinical trial	Overall population n=26,449 subjects randomised; n=26,352 subjects treated Proposed label population n=16,897	Vorapaxar 2.5 mg once daily as an add-on therapy to standard of care (ASA ± clopidogrel)	- Primary efficacy composite endpoint: CV death, MI, stroke, or UCR - Key secondary composite endpoint: CV death, MI, or stroke	Safety endpoints described in the study objectives: - Composite of moderate and severe bleeding events defined according to GUSTO - Clinically significant bleeding defined according to TIMI

Abbreviations: ASA=acetylsalicylic acid; CV=cardiovascular; GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (trial); MI=myocardial infarction; TIMI=Thrombolysis in Myocardial Infarction (Study Group); UCR=urgent coronary revascularisation
Source: CHMP report and MAH submission file

2.5 Deviations from project plan

During an interim analysis in the trial, an independent Data and Safety Monitoring Board (DSMB) observed an increased incidence and relative risk of intracranial haemorrhage in subjects with a history of stroke, and the study drug was discontinued in all subjects with a history of stroke (including those with a new stroke during the trial). Subsequently, the European Medicines Agency (EMA) decided against expanding the submission to include subjects from the PAD stratum. Thus, the PLP included subjects in the coronary artery disease (CAD) stratum of the trial only, with no history of stroke or transient ischaemic attack (TIA).

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY

3.1 Research questions

Element ID	Research question
B0001	What are vorapaxar and the comparators?
A0020	For which indications has vorapaxar received marketing authorisation?
B0002	Which aspects of the disease are intended to be changed by vorapaxar as an add-on therapy? In the context, which hypotheses were formulated to set up the trials?

3.2 Results

[B0001] What are vorapaxar and the comparators?

Vorapaxar is a first-in-class selective antagonist of 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. Thrombin-induced platelet activation has been implicated in a variety of cardiovascular (CV) disorders including thrombosis, atherosclerosis, and restenosis following percutaneous coronary intervention (PCI). As an antagonist of PAR-1, vorapaxar blocks thrombin-mediated platelet aggregation and thereby has the potential to reduce the risk of atherothrombotic complications of coronary disease. It is given in combination with ASA and, where appropriate, with a third medicine, clopidogrel, both of which also help prevent atherothrombotic events. Once-daily tablets contain 2.08 mg vorapaxar, equivalent to 2.5 mg vorapaxar sulfate [1].

When vorapaxar is considered on its own, the comparator is placebo. Nevertheless, this drug evaluation must be shown as a therapeutic strategy comparison (ASA ± clopidogrel versus vorapaxar + ASA ± clopidogrel in the trial set up by the marketing authorisation holder [MAH]). Thus, comparators are strategies including ASA and clopidogrel or ticagrelor or prasugrel.

In general, with the exception of ASA, current recommendations on the use of oral antiplatelet therapy limit the duration of therapy to up to 12 months following an ACS event. The combination of ASA + clopidogrel can be considered as a comparator for the first 12 months only.

Vorapaxar is indicated to be administered in addition to (not instead of) therapy with ASA alone or ASA + clopidogrel. Therefore, the comparators might be considered as treatment strategies and not as individual drugs. Thus, a placebo is needed to perform a double-blind clinical trial and the two different therapeutic strategies compared are vorapaxar + ASA ± clopidogrel versus ASA ± clopidogrel.

Prasugrel and ticagrelor are newer and more potent than clopidogrel antiplatelet agents.There is limited clinical experience with vorapaxar + prasugrel and no experience with vorapaxar + ticagrelor in the Phase 3 studies. Vorapaxar should not be initiated in patients taking prasugrel or ticagrelor and, in case of need for additional therapy with these agents, vorapaxar should be stopped [2].

ASA inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane A2, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

Clopidogrel is a prodrug, which has a metabolite that inhibits platelet aggregation. Clopidogrel must be metabolised by cytochrome P450 (CYP) enzymes to produce the active metabolite that

inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover.

[A0020] For which indications has vorapaxar received marketing authorisation?

Vorapaxar, co-administered with ASA and, where appropriate, clopidogrel, is indicated for the reduction of atherothrombotic events in adult patients with a history of MI [1].

[B0002] Which aspects of the disease are intended to be changed by vorapaxar as an add-on therapy? In the context, which hypotheses were formulated to set up the trials?

Vorapaxar is indicated for the reduction of atherothrombotic events in adult patients with a history of MI without history of stroke or TIA. Vorapaxar should be initiated at least 2 weeks after an MI and preferably within the first 12 months following the acute events and, as such, would most often be used in an outpatient setting. Vorapaxar should be co-administered with ASA, with or without clopidogrel, according to their indications or standard of care. There are limited data on the use of vorapaxar for periods longer than 2 years. Therefore, after 2 years of treatment, the benefits and risks of vorapaxar should be re-evaluated in individual patients by the treating doctor [1].

Vorapaxar is the only antiplatelet agent (at the time of this submission) with evidence to improve outcomes in post-MI patients when continued beyond 12 months after an MI. No dose adjustment is required in patients with renal impairment. However, reduced renal function is a risk factor for bleeding and should be considered before initiating vorapaxar. There is limited therapeutic experience in patients with severe renal impairment or end-stage renal disease. Therefore, vorapaxar should be used with caution in such patients. Reduced hepatic function is a risk factor for bleeding and should be considered before initiating vorapaxar. No dose adjustment is required in patients with mild hepatic impairment. Vorapaxar should be used with caution in patients with moderate hepatic impairment. Because of the limited therapeutic experience and the increased inherent risk of bleeding in patients with severe hepatic impairment, vorapaxar is contraindicated in such patients. The safety and efficacy of vorapaxar in patients aged less than 18 years have not yet been established. No data are available in paediatrics [2].

The original primary hypothesis was that vorapaxar added to standard of care will reduce the incidence of atherothrombotic ischaemic events relative to standard of care alone, as measured by the composite of CV death, MI, stroke, and urgent coronary revascularisation (UCR) in subjects with a history of CAD (MI), cerebrovascular disease (CVD) (ischaemic stroke), or peripheral artery disease (PAD). However, the target population for vorapaxar in clinical setting now includes only patients with a history of CAD (MI), without a history of stroke or PAD.

3.3 Discussion

Vorapaxar is a selective and reversible inhibitor of PAR-1 receptors on platelets that are activated by thrombin. Vorapaxar, co-administered with ASA and, where appropriate, clopidogrel, is indicated for the reduction of atherothrombotic events in adult patients with a history of MI. Treatment with vorapaxar should start from 2 weeks after and preferably within 1 year of the occurrence of the MI. There are limited data on the use of vorapaxar for periods longer than 2 years. Therefore, after 2 years of treatment, the benefits and risks of vorapaxar should be re-evaluated in individual patients by the treating doctor. No dose adjustment is necessary in the elderly. No dose adjustment is required in patients with renal impairment. However, reduced renal function is a risk factor for bleeding and should be considered before initiating vorapaxar. There is limited therapeutic experience in patients with severe renal impairment or end-stage renal disease. Therefore, vorapaxar should be used with caution in such patients. Reduced hepatic function is a risk factor for bleeding and should be considered before initiating vorapaxar. No dose adjustment is required in patients with mild hepatic impairment. Vorapaxar should be used with caution in patients with moderate hepatic impairment. Because of the limited therapeutic

experience and the increased inherent risk of bleeding in patients with severe hepatic impairment, vorapaxar is contraindicated in such patients. The safety and efficacy of vorapaxar in patients aged less than 18 years have not yet been established. No data are available in paediatrics. The European Commission granted a marketing authorisation (MA) valid throughout the European Union (EU) for ZONTIVITY™ (vorapaxar) on 19 January 2015.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

4.1 Research questions

Element ID	Research question
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for developing thrombotic cardiovascular events?
A0004	What are the risk factors for poor prognosis following an MI? What are the mortality and the ischaemic events rates post-MI in Europe?
A0005	What are the symptoms and the burden of disease or health condition for the patient?
A0006	What is the burden of post-MI atherothrombotic events for society?
A0025	What was the therapeutic strategy chosen among the international guidelines to set up the trials and to define vorapaxar's place in the therapeutic strategy?
A0007	What kinds of patients are targeted by vorapaxar's indication?
A0023	How many patients with a history of MI, without a history of stroke, PAD or TIA, and that are not receiving treatment with by prasugrel or ticagrelor, are there in Europe?

4.2 Results

[A0002] What is the disease or health condition in the scope of this assessment?

There is a need for a reduction of thrombotic CV events in patients with a history of MI. Acute MI occurs when the heart muscle is deprived of blood (and therefore oxygen) for a long enough duration that the heart muscle undergoes irreversible damage and myocardial cell necrosis [3,4].

Acute coronary syndrome refers to a group of clinical symptoms associated with MI and represents a high-risk manifestation of atherosclerosis that blocks or limits the flow of blood to the myocardium. While the patients of interest for this submission have a recent history of MI, and have experienced an acute coronary event, the target population for vorapaxar use includes patients who have been stabilised and will most frequently be treated in an outpatient setting following discharge from the hospital. The transition from an acute phase to the chronic stable phase is not well characterised [5], and there are currently no specific coding criteria to define this patient; rather, identification of this patient relies on an experienced healthcare provider's expertise.

Recurrent MIs, stroke, UCR, and death are all relevant health burdens to this assessment. A recurrent acute MI is generally considered a serious event in survivors of MI, leading to subsequent admissions. It has prognostic implications with regard to patient management and counselling. Stroke can complicate the clinical course of patients in the period following an MI and may manifest in a myriad of health and quality-of-life sequelae depending on aetiology and severity.

[A0003] What are the known risk factors for developing thrombotic cardiovascular events?

The risk of MI, is greater in people of advanced age, men, people with a family history of heart disease, and in people with high blood pressure, high blood cholesterol levels, diabetes, smoking/tobacco use, alcohol use, obesity, physical inactivity, and/or stress. Despite significant medical advances, patients who have had a heart attack continue to be at risk of a further heart attack or stroke, and have an increased risk of death. Atherothrombotic events remain the leading

cause of death worldwide, with approximately 6 in 100 people who experience a heart attack dying within the first year of being discharged from the hospital [2]. Current therapy recommended for patients who have had a heart attack to reduce the risks described above includes ASA, clopidogrel for those intolerant to ASA, or the combination of ASA plus clopidogrel; in addition, patients may need medications for the treatment of other common conditions (e.g. diabetes), and other lifestyle changes (e.g. reduction in cigarette smoking, weight, alcohol use) [1].

Risk factors for experiencing an MI

Smokers aged less than 50 and more than 60 years have 5 and 2 times the relative risk of MI, respectively, compared to non-smokers [6, 7]. Low-density lipoprotein (LDL) cholesterol has also been shown to be linearly related to non-fatal MI as well as CVD mortality (with a 20-25% reduction related to a 1.0 mmol/L reduction) [8].

Risk factors for poor prognosis following an MI

The presence of co-morbidities can impact survival following an acute MI. When comparing long-term mortality rates between those with or without diabetes, it has been observed that diabetes is associated with a significantly increased risk of death following an MI [9, 10, 11]. Likewise, observations suggest other conditions including polyvascular bed involvement [11], dyslipidaemia (specifically LDL cholesterol) [8], and a history of ischaemic event [11], are also significant independent risk factors for future CV events among post-MI patients. Obesity and overweight are both associated with an increased risk of death in CVD [12, 13]. Socioeconomic factors are associated with survival [14] and prognosis [15] following an acute MI.

[A0004] What are the risk factors for poor prognosis following an MI? What are the mortality and the ischaemic event rates post-MI in Europe?

Cardiovascular disease is the main cause of death in Europe, accounting for nearly half (47%) of all deaths (52% in women and 42% in men), and over 4 million deaths each year. Coronary heart disease (CHD) is the single most common cause of death in Europe, accounting for 1.8 million deaths each year [16].

There are differences in the clinical risk profiles of ischaemic and bleeding outcomes between stable CAD and ACS. Proper management of atherosclerotic vascular disease involves recognising the differences at various stages of atherosclerotic disease [5].

Vorapaxar is indicated for the reduction of atherothrombotic events in adult patients with a history of MI and is initiated ideally between 2 weeks and 12 months following the acute event. Studies show that survivors of an MI episode continue to face elevated short- and long-term mortality risks [17-23].

A review of national registry data or large database analyses demonstrated that mortality rates following an acute MI remain elevated. For instance, data from German centres in the World Health Organization (WHO) Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study (a 10-year study that started in 1985 and monitored CHD and acute MI across 27 countries) reported a 28-day case fatality rate of 6.1%, with a long-term mortality rate of 10.6% (median observation time of 4.1 years) [17]. In the Northern Sweden centres in the MONICA study, 45.3% of men and 43.7% of women died during the follow-up period, with a median survival of only 187 and 200 months for men and women, respectively [18]. The 5-year mortality rates were about 24% in younger patients (22-55 years) and about 66% in older patients (56-64 years) [18]. Among patients at high risk of CV events, those with a recent history of an ischaemic event tended to be at greater risk of various events. Four-year follow-up data from the REduction of Atherothrombosis for Continued Health (REACH) registry analysed CV event rates among various categories of patients, including those with a prior ischaemic event (n=21,890), stable atherosclerosis without prior ischaemic events (n=15,264), and those with risk factors only (n=8,073). The occurrence of an ischaemic event within the previous year was independently associated with an increased risk of future ischaemic events (hazard ratio [HR] =1.71; 95% confidence interval [CI]: 1.60 to 1.83) compared to no ischaemic event, even more so than

occurrence of an ischaemic event more than a year before (HR=1.41; 95% CI: 1.32 to 1.51) compared to no ischaemic event before enrolling in the registry. The effects of these factors on event rates were consistent for all geographic regions without significant variation [11].

Patients with a history of ischaemic events (e.g. MI or stroke) are also at higher risk of recurring CV events. Data from the REACH registry demonstrate that, for those patients with an ischaemic event in the past year, there was a 4-year cumulative event rate of ~35% for CV death, MI, stroke, or rehospitalisation [11]. This was similar to, but statistically significantly higher than among those with an ischaemic event over 1 year before baseline, who had a 4-year event rate of approximately 33%. Despite secondary prevention measures, including the use of antiplatelet therapy, the residual risk in post-MI patients is associated with a substantial clinical and economic burden, associated with elevated short- and long-term mortality rates and high rehospitalisation costs. Of the patients who survive an ACS event, it is estimated that up to 50% are rehospitalised for any cause within 1 year [24-27], although reported rates of cardiac-related rehospitalisations are slightly less. Data from the REACH registry revealed a 1-year rehospitalisation rate (for a vascular event other than MI, stroke, or vascular death) of 12.4% among patients with CAD, and a 3-year rehospitalisation rate of 23.0% [28].

Two general approaches are used to reduce the risk of CHD and minimise the potential for ACS: primary prevention and secondary prevention. Primary prevention consists of therapy designed to prevent CHD and includes measures such as lifestyle modifications and, if necessary, pharmacological therapy, to reduce the risk of a coronary event or CHD. Secondary prevention consists of efforts to minimise the progression of diagnosed CHD, with the intention of preventing future CV events. Secondary prevention of CV events in patients with ischaemic heart disease (IHD), including MI, is recognised as an important and achievable goal. Current national and international guidelines recommend the use of a combination of pharmacological agents for secondary prevention of CV events (European Society of Cardiology [ESC]/American Heart Association [AHA]/American College of Cardiology [ACC]) [2]. Studies suggest that the use of a combination of products, including antiplatelet drugs, anticoagulants, statins, and blood pressure-lowering medications (particularly beta-blockers and angiotensin-converting enzyme inhibitors) can reduce the risk of IHD by 75% [29, 30].

However, in post-MI patients receiving standard of care, including antiplatelet therapy, a considerable number of patients continue to experience recurrent thrombotic events. Platelet aggregation plays a critical role in thrombosis leading to acute ischaemic events. Despite both short- and long-term standard of care oral antiplatelet therapy (dual therapy with ASA and clopidogrel or prasugrel or ticagrelor), patients remain at risk for thrombotic events even if guideline-recommended medications other than antiplatelets in post-MI patients are used appropriately. The residual risk can be higher for certain high-risk patient populations, such as older patients and those with diabetes, dyslipidaemia, or polyvascular disease [11].

Further, there is limited evidence for long-term protection from CV events and mortality with current antiplatelet therapies at the time of this submission; despite the use of recommended standard of care following an MI, long-term morbidity and mortality remain elevated [31].

Effects of the disease or health condition

[A0005] What are the symptoms and the burden of disease or health condition for the patient?

Atherosclerosis and ischaemic CV diseases such as CAD are progressive systemic disorders in which clinical events are precipitated by episodes of vascular thrombosis. Patients with an established history of atherothrombotic or athero-ischaemic disease are at particular risk of future cardiac or cerebral events, and vascular death. Antithrombotic therapy options in patients with stable atherosclerosis are not well established. Therefore, long-term therapies are required to modulate effectively the key components responsible for atherothrombosis in the secondary prevention of ischaemic CV disease [1].

While the clinical presentation of an MI can vary, the first symptom is usually chest pain or discomfort that commonly radiates to the anterior neck, lower jaw, upper back, shoulders, or

arms. However, some patients experience no pain and may be subsequently diagnosed with a silent infarction [32].

Studies have also shown that survivors of an MI episode continue to face elevated short- and long-term mortality risks. The WHO MONICA study monitored CHD and acute MI in 27 countries over a 10-year period starting in 1985. Short- and long-term mortality rates have been released from some of the reporting centres that indicate high mortality rates continue to exist in patients following an acute MI [17, 18].

Beyond the clinical presentation and consequences, there is a significant impact on the quality of life of patients following an MI [33]. The impact of an MI can lead to poor sleeping habits, increased anxiety, poor perception of health, and less satisfaction with life when compared to those who have not experienced an MI [25, 33-35]. Among the 22 European countries involved in the EUROASPIRE III study (which included 8,734 CHD patients), lower health-related quality-of-life scores were found in patients with acute MI or ischaemia as the recruiting diagnosis [34].

The large proportion of patients who will be rehospitalised within the first year following an MI will in turn impact patient quality of life, particularly for younger patients who are still employed, resulting in lost work days and potential difficulty in maintaining employment [25, 35].

Several factors can impact quality of life following an MI, including age, gender, education, co-morbidities, social support, and geographic region [35,36]. The impact of an MI on quality of life can persist for years following the event [37]. Depression is highly prevalent among post-MI patients and has been linked with poor clinical outcomes, including higher rates of rehospitalisation and mortality [25, 35]. Compared to post-MI patients without depression, those with either minor or major depression were observed to be hospitalised sooner, with more hospitalisations and emergency department visits, and more days spent in the hospital over time. Only 20.0% of patients without depression were rehospitalised during the follow-up period, compared with 43.0% of patients with major depression [25]. The presence of depression has also been observed to be associated with less likely adoption of secondary prevention measures. In a cohort of post-MI patients aged ≤65 years of age, depressed patients were less likely to stop smoking, be physically active, and participate in cardiac rehabilitation when compared to those without depression [35].

[A0006] What is the burden of post-MI atherothrombotic events for society?

Population studies demonstrate significant reductions in mortality rates due to CV disease over past decades, although CVD remains the main cause of death in Europe, with CHD and stroke accounting for the majority of these deaths (1.8 million and 1.07 million deaths each year in Europe, respectively) [38]. Shifts in CHD prevalence in the various regions of the world is a consequence of several factors [39]. In considering developing regions, as countries progress from agrarian to industrial to post-industrial states, there are a series of environmental, social, and structural changes that occur. Some of these changes lead to increased life expectancy and others expose the population to risk factors for chronic diseases, such as CV disease. Furthermore, an increased level of economic development results in increased risk factor levels (such as obesity, diabetes, dyslipidaemia, and hypertension) in conjunction with improved public health and medical access to a larger proportion of the population [40]. Improved access to healthcare is associated with lower mortality rates from CV events. The result is an overall population that is older and has a higher risk for CV disease, which leads to a higher proportion of the population living following a CV event such as MI [41,42].

Data from the Global Burden of Disease (GBD) 2010 study showed that the absolute global burden of IHD increased by 29 million disability-adjusted life-years (29.0%) between 1990 and 2010. Regions where disability-adjusted life years have trended upwards since 1990 include Eastern Europe, Central Asia, North Africa/Middle East, and South Asia. In most of these regions, the trends appear to have flattened after 2005 [43].

Developed nations tend to show a trend of increasing CHD prevalence through the 1990s and early 2000s followed by a flattening of CHD prevalence by 2005. In Europe, data from the 2012 European Cardiovascular Disease Statistics Report reveal that the number of hospital discharges from CHD in the European Region steadily increased from 1990 to 2004, but has remained generally stabilised up to 2009 [38].

The incidence of MI varies considerably among different regions world-type. In 2010, the GBD study estimated the burden of CV disease using mortality surveillance, verbal autopsy, vital registration data, and systematic review of IHD epidemiology literature published from 1980 to 2008. Overall, the incidence of MI was 2-fold higher in men than in women. Age-standardised MI incidence was highest in Eastern Europe, more than 2-fold higher than Western Europe. Case fatality rates followed similar trends [44]. Approximately 6-14% of ST segment elevation MI (STEMI) (ESC member state) patients die in the hospital [45, 46] and 12.0% die within 6 months [45]. Mortality due to unstable angina/non-STEMI is similar, with 15.0% of patients who die or experience a reinfarction within 30 days of diagnosis [47, 48].

Decreasing mortality rates from MI have been observed in developed countries. While several population-based studies have confirmed a trend towards decreasing mortality rates from acute MI in developed countries [49,50], large studies show that survivors of an MI episode continue to face elevated short- and long-term mortality and morbidity risks. The WHO MONICA study showed that high mortality rates continue to exist in patients following an acute MI [17,18]. Despite robust treatment guidelines and the availability of pharmacological therapies used for secondary prevention, patient morbidity and mortality rates remain elevated following an MI. Survivors of an MI are at an increased risk of recurrent infarctions. In the Cardiovascular Disease in Norway study, a multipurpose research project that analysed all hospitalisations with acute MI in men and women aged ≥25 years during 1994 to 2009, recurrent MIs were identified in 18.3% (11.5% in the 25-64 years and 20.5% in the >65 years age groups) [51]. At the Academic Medical Center, University of Amsterdam, 21.2% of STEMI patients treated with PCI had a recurrent MI during the 2003-2008 period [52]. A large population-based study in England showed that MI survivors remain at high risk of a second MI event (11%). The 7-year cumulative risk of recurrent MI was 13.9% and 16.2% for women and men, respectively [53].

After an episode of MI, stroke is a debilitating complication and its prevention is an important objective of secondary treatment. A meta-analysis of publications between 1978 and 2004 reported a stroke incidence of 1.2% and 2.1% at 30 days and 1 year after acute MI, respectively [54]. The incidence of ischaemic stroke was found to be higher among patients enrolled in the Swedish registry (Register of Information and Knowledge about Swedish Heart Intensive Care Admissions): 2.1% within the first 30 days and 4.1% at 1 year after MI [55,56]. During more than 2 years of follow up of patients with MI who were treated invasively with PCI at an institute in Poland, 2.07% developed stroke, with ischaemic strokes being predominant (80.8%) [57].

Current clinical management of the disease or health condition

[A0025] What was the therapeutic strategy chosen among the international guidelines to set up the trials and to define vorapaxar's place in the therapeutic strategy?

Studies indicate that a substantial proportion of patients discharged from hospital following an ACS episode do not receive recommended antiplatelet therapy or they discontinue therapy within the first year following discharge. Discharge records and prescription patterns were analysed for 7,082 patients hospitalised for ACS in Italy [58]. Of those who were discharged alive, 65.8% were treated with an antiplatelet therapy (21.9% with ASA alone, 33.1% with ASA plus a thienopyridine [mostly clopidogrel], and 10.5% with thienopyridine alone). Dual antiplatelet therapy was prescribed more frequently in patients treated with PCI than in those treated medically (57.3% vs. 19.7%; $p<0.0001$). Prescription continuity of antiplatelet therapy at 6 and 12 months after discharge was 68.0% and 60.3%, respectively.

The Antiplatelet Therapy Observational Registry is a non-interventional, prospective, observational cohort study enrolling patients with ACS undergoing PCI in 14 European countries

[59]. Although 95% of patients were discharged on dual antiplatelet therapy, 71% remained on both treatments at 1 year, with a wide variation among the countries included in the study.

Even among patients who are on antiplatelet therapy, a possible explanation for residual risk is that the use of ASA with a P2Y12 inhibitor (e.g. clopidogrel, ticagrelor, prasugrel) does not fully inhibit the pathways involved in initial platelet recruitment and adhesion during both haemostasis and thrombosis [60]. Other platelet activation pathways remain active in the presence of current antiplatelet agents. The lack of an inhibitory effect by current therapies on multiple platelet activation pathways allows for continued platelet reactivity in the presence of potent agonists, such as thrombin. The presence of additional inhibitory effects would decrease the risk for recurrent thrombotic events, including death. New therapies (such as vorapaxar) that target pathways not affected by ASA or P2Y12 inhibitors could provide complementary and more comprehensive inhibition of platelet activation. When used in combination with current standard of care antiplatelet therapies, these new agents could potentially contribute to greater inhibition of platelet-mediated thrombosis [60]. In Europe, between 2.8 and 5.8 persons per 1000 adults, aged 30 years and older, experience MI [44]. Most of those who are discharged following an acute event and do not have a history of stroke or TIA would be eligible for long-term treatment with vorapaxar for the secondary prevention of major adverse cardiovascular events (MACE). Estimates of those who survive an MI and have a history of stroke/TIA are variable. In Italy, about 89% of those experiencing an MI would be eligible for vorapaxar (93% of patients are discharged following an acute event, and 3.7% of those have a history of stroke) [58]. These estimates of history of stroke are consistent with clinical characteristics of similar trial populations, although regional estimates are sparse and vary by region and country. Vorapaxar is a first-in-class selective antagonist of PAR-1, the primary thrombin receptor on human platelets, which mediates the downstream effects of this critical coagulation factor in haemostasis and thrombosis. Thrombin-induced platelet activation has been implicated in a variety of CV disorders including thrombosis, atherosclerosis, and restenosis following PCI. As an antagonist of PAR-1, vorapaxar blocks thrombin-mediated platelet aggregation and thereby has the potential to reduce the risk of atherothrombotic complications of coronary disease. Vorapaxar is expected to change the long-term management of patients following an MI as an add-on therapy to the current standard of care (ASA with or without clopidogrel) treatment paradigm for the prevention of secondary events. In this way, vorapaxar is also expected to improve the health condition by preventing additional atherothrombotic events over time.

Vorapaxar is indicated to be administered in addition to (not instead of) therapy with ASA alone or ASA plus clopidogrel. It is indicated for the reduction of atherothrombotic events in adult patients with a history of MI and initiated in patients ideally between 2 weeks and 12 months following the acute event. There are limited data on the use of vorapaxar for periods longer than 2 years; therefore, after 2 years of treatment, the benefits and risks of vorapaxar should be re-evaluated in individual patients by the treating doctor [1].

Target population

[A0007] What kinds of patients are targeted by vorapaxar's indication?

Vorapaxar is indicated for the reduction of atherothrombotic events in adult post-MI patients without a history of stroke or TIA, without a history of intracranial haemorrhage, and without any active pathological bleeding or hypersensitivity to the active substance(s) or to any of the excipients. Vorapaxar should be initiated at least 2 weeks after an MI and preferably within the first 12 months following the acute event and, as such, would most often be used in an outpatient setting. Vorapaxar should be co-administered with ASA, with or without clopidogrel, according to their indications or standard of care. There is limited clinical experience with prasugrel and no experience with ticagrelor in the Phase 3 studies. Vorapaxar should not be initiated in patients taking prasugrel or ticagrelor and, in case of need for additional therapy with these agents, vorapaxar should be stopped. No dose adjustment is necessary in the elderly. No dose adjustment is required in patients with renal impairment. Based on the increased inherent risk of bleeding in patients with severe hepatic impairment, vorapaxar is not recommended in such patients. No dose adjustment is required in patients with mild and moderate hepatic impairment.

The safety and efficacy of vorapaxar in patients aged less than 18 years have not yet been established. No data are available in paediatrics [2].

[A0023] How many patients with a history of MI, without a history of stroke, PAD or TIA, and that are not receiving treatment with by prasugrel or ticagrelor, are there in Europe?

Post-MI patients contribute a substantial burden on healthcare systems and societies. Up to 50% of post-MI patients will experience a recurrent CV event and/or will require rehospitalisation within a year of an MI [24]. Although survival in post-MI patients has improved following a CV event [61], short- and long-term mortality rates remain elevated following an MI. This is despite robust treatment guidelines and the availability of pharmacological therapies used for secondary prevention.

Cardiovascular diseases accounted for an estimated 17.8 million deaths in 2008 (representing 30.0% of all global deaths). Of these, 46.0% of CV deaths in men and 38.0% of CV deaths in women were due to IHD, which includes acute MI, stable angina, and ischaemic heart failure [62].

Mortality rates due to IHD vary among different regions of the world [62]. Cardiovascular disease is the main cause of death in Europe, accounting for over 4 million deaths each year. Nearly half (47.0%) of all deaths are from CV disease (52.0% of deaths in women and 42% of deaths in men). Coronary heart disease is the single most common cause of death in Europe, accounting for 1.8 million deaths each year [38].

Population studies demonstrate significant reductions in mortality rates due to CV disease over the past three decades. In the EU, recent CHD rates are now less than half those in the early 1980s. A comparison of CHD mortality rates from 1980 to 2009 showed that all countries in the EU demonstrated very large and significant decreases among both men and women when all ages were considered together. In many countries, age-standardised mortality rates in 2005-2009 were less than half of those in 1980-1984 [63]. The average annual percentage change in CHD mortality rates for all age groups combined between 1980 and 2009 was -2.7% for men and -2.4% for women. Despite the decline in mortality rates due to CV disease, it remains the number one cause of death in the EU, with CHD and stroke accounting for the majority of these deaths [38].

In Europe, data from the 2012 European Cardiovascular Disease Statistics Report reveal that the number of hospital discharges from CHD in the European Region steadily increased from 1990 to 2004, and then generally stabilised up to 2009 [38]. The incidence of MI varies considerably among different regions across the globe. In developed nations, the incidence of MI has shown signs of decline in the past few years [19, 64]. In 2010, the GBD study estimated the burden of CV disease using mortality surveillance, verbal autopsy, vital registration data, and systematic review of IHD epidemiology literature published from 1980 to 2008. Overall, the incidence of MI was 2-fold higher in men than in women [44]. In high-income countries, there is a general and consistent decreasing trend in the incidence of MI (e.g. Denmark [22], Ireland [64], and the United States [19]). However, these trends in Europe and North America have not been consistent with all developed nations [65].

Cardiovascular events and mortality following an MI in patients remain a major concern. Patients with a history of ischaemic events (e.g. MI or stroke) are at higher risk of recurring CV events. Data from the REACH registry demonstrate that, for those patients with an ischaemic event in the past year, there was a 4-year cumulative event rate of ~35% for CV death, MI, stroke, or rehospitalisation [11]. Those patients with an ischaemic event more than 1 year before baseline had a 4-year event rate of approximately 33%.

While the precise number of patients who may use vorapaxar across Europe is difficult to capture and is constantly in flux as incidence rates of MI change over time, one can assume that 90-95% [58, 66-73] of patients surviving an MI would be eligible to benefit from treatment with vorapaxar. More conservatively, based on current treatment practices, many patients are already prescribed other antiplatelet treatment options at the time of their acute event.

4.3 Discussion

It is well known that atherosclerosis and ischaemic CV diseases such as CAD are progressive systemic disorders in which clinical events are precipitated by episodes of vascular thrombosis. There is no doubt that patients with an established history of atherothrombotic or athero-ischaemic disease are at particular risk of future cardiac or cerebral events, and vascular death. Antithrombotic therapy options in patients with stable atherosclerosis are not well established. Therefore, long-term therapies seem to be needed to modulate effectively the key components responsible for atherothrombosis in the secondary prevention of ischaemic CV disease.

5 CLINICAL EFFECTIVENESS

5.1 Research questions

Research questions

The following research questions have been selected and formulated for this domain.

Element ID	Research question
D0001	What is the expected beneficial effect of vorapaxar on post-MI mortality?
D0003	What is the effect of vorapaxar on mortality due to causes other than post-MI atherothrombotic events?
D0005	What is the expected beneficial effect of vorapaxar on post-MI morbidity (MI, stroke and urgent coronary revascularisation)?
D0006	How does vorapaxar affect progression of atherosclerotic coronary lesions?

5.2 Methods and results

The interpretation of the results and quality of evidence assessments represent the authors' view, which may differ from the view expressed by the manufacturer.

Included studies

The MAH sponsored a multinational, randomised (1:1 ratio), double-blind, controlled clinical trial (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events [TRA 2°P-TIMI 50]) to evaluate the safety and efficacy of vorapaxar as an add-on therapy to standard of care (vorapaxar + ASA ± clopidogrel) versus standard of care (ASA ± clopidogrel) in subjects with a history of atherosclerotic disease. The original study population included subjects with coronary artery disease (CAD) (history of MI) (n=17,779 subjects), CVD (history of ischaemic stroke) (n=4,883 subjects), or peripheral artery disease (PAD) (n=3,787 subjects).

The primary study objective was to evaluate the hypothesis that vorapaxar added to ASA ± clopidogrel will reduce the incidence of atherothrombotic events versus placebo + ASA ± clopidogrel alone, in the target population.

A second study was led by the MAH, the P04736 Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) study, which was a multicentre, randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of vorapaxar in addition to standard of care in subjects with ACS. This study was stopped early mainly due to an increased bleeding risk.

TRA 2°P-TIMI 50 study design

Patients were treated with one tablet a day of vorapaxar 2.5 mg + ASA ± clopidogrel or one tablet a day of placebo + ASA ± clopidogrel, according to the randomised treatment group. (ASA ± clopidogrel were given according to local standard of care guidance.)

Treatment was to continue until study completion, i.e. when a given (predefined) number of events of the main efficacy endpoint were observed, and every subject had the opportunity to participate in the study for at least 1 year.

Follow-up visits were at 30 days, 4 months, 8 months, and 12 months during the first year, then every 6 months after the first year of treatment until the end of the study.

Main inclusion criteria

- Subject could be of either sex or any race, and had to be aged at least 18 years.
- Subject had to have evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems:

    a. CAD as indicated by a history of presumed spontaneous MI (hospitalised with final diagnosis of MI, excluding periprocedural or definite secondary MI [e.g. due to profound anaemia or hypertensive emergency, troponin increase in sepsis]) ≥2 weeks but ≤12 months prior, or

    b. Ischaemic (presumed thrombotic) CVD as indicated by a history of ischaemic stroke (hospitalised with final diagnosis of non-haemorrhagic stroke [includes completion of a standard evaluation for stroke in an acute care facility or stroke clinic without hospital admission]) ≥2 weeks but ≤12 months prior, or

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

        - a resting ankle/brachial index of <0.85, or
        - amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischaemia.

Main exclusion criteria

- Any planned coronary revascularisation or peripheral intervention.
- Concurrent or anticipated treatment with warfarin (or derivatives, e.g. phenprocoumon), oral factor Xa inhibitor, or oral direct thrombin inhibitor after enrolment.
- Concurrent or anticipated treatment with a potent inducer (e.g. rifampin) or potent inhibitor (e.g. ketoconazole, erythromycin) of CYP isoenzyme 3A4 (CYP3A4).
- Known platelet count <100,000/mm^3 within 30 days before enrolment.
- History at any time of intracranial haemorrhage (except “microhaemorrhage” [e.g. as detected on T2-weighted magnetic resonance imaging]), intracranial or spinal cord surgery, or a central nervous system tumour or aneurysm.
- Severe valvular heart disease, as defined by the ACC/AHA.

Endpoints

- The primary efficacy endpoint was the time from randomised treatment assignment to the first occurrence of any component of the composite endpoint including CV death, MI, stroke, or UCR.
- The key secondary endpoint was the time from randomised treatment assignment to the first occurrence of any component of the composite secondary endpoint: CV death, MI, or stroke.
- All-cause death was the 7th secondary endpoint.
- The secondary safety endpoints described in the study objectives were:

    - Composite of moderate and severe bleeding events defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) trial

- Clinically significant bleeding defined according to the Thrombolysis in Myocardial Infarction (TIMI) Study Group

These safety endpoints will be detailed in Section 6.

Randomisation

Patients were stratified according to the qualifying diagnosis (CAD, CVD, and PAD) and the physician's intention to use thienopyridine.

Statistical analysis plan

On the basis of primary and key secondary efficacy endpoint incidences in the placebo group, which were expected to be 8% and 4% respectively at 1 year, and a minimum subject participation of 12 months, then a total of 19,500 subjects (9,750 subjects per treatment group) were calculated to be needed to detect a 15% relative risk reduction in the incidence of the primary and key secondary efficacy endpoints with vorapaxar relative to placebo, each added to ASA ± clopidogrel, with at least 85% and 98% power, respectively at a 2-sided significance level of 0.05, and including an adjustment for potential dropouts during the study. It was expected that a minimum of 2,279 primary efficacy endpoint events and 1,322 key secondary efficacy endpoints events would occur during the study. Two blinded sample size re-estimations led to an increase in the recruitment up to 27,000 subjects.

Proposed label population (PLP)

During an interim analysis in the trial, an independent DSMB observed an increased incidence and relative risk of intracranial haemorrhage in subjects with a history of stroke. (The risk was increased for patients randomised in the vorapaxar group, HR=2.55, 95% CI: 1.56 to 4.18; p<0.001). The DSMB recommended discontinuing the study drug in all subjects with a prior history of stroke or a stroke that occurred during the course of the study. This exclusion was done without unblinding. In response to the DSMB recommendation, the Executive and Steering Committees of the trial determined that subjects randomised and stratified to the CVD stratum would discontinue study drug dosing and participation in the trial (n=4,883). The remaining subjects with a history of stroke or stroke endpoint who were randomised and stratified to the CAD (n=882) and PAD (n=514) strata had their study drug discontinued but continued participation in the trial. The DSMB also recommended that the TRA 2°P-TIMI 50 study continue until completion with the remaining subjects without further modification to the study protocol. The MAH and Executive Committee determined that, for the purposes of clinical clarity and patient safety, subjects with a history of TIA would be considered the same way as subjects with a history of stroke because differentiating stroke from TIA could be clinically difficult, especially when based on patient medical history alone. Additionally, the EMA decided against expanding the submission to include subjects from the PAD stratum. Thus, the PLP included patients in the CAD stratum of the trial only, with no history of stroke or TIA (n=16,897) and excluded the PAD stratum (n=3,787) and the CVD (stroke) stratum (n=4,883).

N.B.: The rationale for the EMA decision to exclude patients with PAD was described neither in the CHMP report. Nevertheless the MAH has clarified this point in its comments: "the MAH wished the CHMP to consider the ILP, i.e., include patients qualifying for the TRA-2°P TIMI 50 trial because of PAD. However, the CHMP declined to do so, indicating that the MAH could re-file or file a type II variation after receiving approval of the PLP-based file".

Table 5.1: Baseline characteristics in the PLP

Characteristic	Placebo + ASA ± clopidogrel (n=8,439)	Vorapaxar + ASA ± clopidogrel (n=8,458)
Age (years)		
Mean	58.5	58.7
<65 years n (%)	6,052 (71.7)	5,960 (70.5)
65-75 years n (%)	1,781 (21.1)	1,864 (22.0)
>75 years n (%)	606 (7.2)	634 (7.5)
Weight (kg)		
Mean	84.67	83.99
Race n (%)		
White	7,415 (87.9)	7,481 (88.4)
Asian	340 (4.0)	321 (3.8)
Black/African American	177 (2.1)	172 (2.0)
Region n (%)		
Europe	4,391 (52.0)	4,408 (52.1)
Cardiovascular comorbidities n (%)		
Hypertension	5,211 (61.7)	5,176 (61.2)
Hyperlipidaemia	7,116 (84.3)	7,151 (84.5)
Diabetes	1,814 (21.5)	1,809 (21.4)
Other comorbities n (%)		
Prior renal disease	327 (3.9)	343 (4.1)

Abbreviations: ASA=acetylsalicylic acid; PLP=proposed label population
Source: CSR, CHMP report and MAH submission file

Table 5.2: Baseline antiplatelet medications in the PLP

Antiplatelets	Placebo + ASA ± clopidogrel (n=8,439)	Vorapaxar + ASA ± clopidogrel (n=8,458)
ASA	8,298 (98.3)	8,315 (98.3)
Thienopyridine	6,631 (78.6)	6,604 (78.1)
Clopidogrel	6,572 (77.9)	6,538 (77.3)
Ticlopidine	44 (0.5)	48 (0.6)
Prasugrel	17 (0.2)	21 (0.2)
Aspirin + thienopyridine	6,531 (77.4)	6,482 (76.6)

Abbreviations: ASA=acetylsalicylic acid; PLP=proposed label population
Source: CSR, CHMP report and MAH submission file

Table 5.3.: Prior myocardial infarction – Baseline characteristics in the PLP

Prior myocardial infarction	Placebo + ASA ± clopidogrel (n=8,439)	Vorapaxar + ASA ± clopidogrel (n=8,458)	Total (n=16897)
≤ 1 month	2,419 (28.7)	2,333 (27.6)	4,752 (28.1)
> 1 month to 3 months	2,217 (26.3)	2,222 (26.3)	4,739 (26.3)
> 3 months to 6 months	1,594 (18.9)	1,578 (18.7)	3,172 (18.8)
> 6 months to 12 months	2,153 (25.5)	2,268 (26.8)	4,421 (26.2)
> 12 months	27 (0.3)	32 (0.4)	59 (0.3)
missing	13 (0.2)	6 (0.1)	19 (0.1)
No prior myocardial infarction	16 (0.2)	19 (0.2)	35 (0.2)

Source: CSR

[D0001] What is the expected beneficial effect of vorapaxar on post-MI mortality?

[D0003] What is the effect of vorapaxar on mortality due to causes other than post-MI atherothrombotic events?

[D0005] What is the expected beneficial effect of vorapaxar on post-MI morbidity (MI, stroke, and urgent coronary revascularisation)?

Results (these 3 questions will be answered altogether)

The primary efficacy composite endpoint (CV death, MI, stroke, or urgent coronary revascularisation [UCR]) in the PLP was a 3-year Kaplan-Meier event rate of 9.8% in the vorapaxar + ASA ± clopidogrel group compared with 11.4% in the placebo + ASA ± clopidogrel group (hazard ratio [HR]=0.82; 95% confidence interval [CI]: 0.74 to 0.90; p<0.001).

The key secondary efficacy composite endpoint (CV death, MI, or stroke) in the PLP was a 3-year Kaplan Meier event rate of 7.4% in the vorapaxar + ASA ± clopidogrel group compared with 9.0% in the placebo + ASA ± clopidogrel group (HR=0.78; 95% CI: 0.70 to 0.88; p<0.001).

The primary and key secondary efficacy endpoint results are presented for the overall intent-to-treat (ITT) population and the PLP in Table 5.4 and Table 5.5, respectively.

Table 5.4: Primary and key secondary efficacy endpoints in the overall ITT population

Endpoint	Placebo + ASA ± clopidogrel (n=13,224)		Vorapaxar + ASA ± clopidogrel (n=13,225)		HR (95% CI)	p-value
	No. of patients with event (%)	KM estimate at 3 years (%)	No. of patients with event (%)	KM estimate at 3 years (%)		
Primary endpoint (CV death, MI, stroke, UCR)	1,417 (10.7)	12.4%	1,259 (9.5)	11.2%	0.88 (0.82 to 0.95)	0.001
CV death	199 (1.5)		172 (1.3)			
MI	629 (4.8)		536 (4.1)			
Stroke	297 (2.2)		297 (2.2)			
UCR	292 (2.2)		254 (1.9)			
Key secondary endpoint (CV death, MI, stroke)	1,176 (8.9)	10.5%	1,028 (7.8)	9.3%	0.87 (0.80 to 0.94)	<0.001
CV death	207 (1.6)		175 (1.3)			
MI	665 (5.0)		554 (4.2)			
Stroke	304 (2.3)		299 (2.3)			

Abbreviations: ASA=acetylsalicylic acid; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; ITT=intent-to-treat; KM=Kaplan-Meier; MI=myocardial infarction; UCR=urgent coronary revascularisation
Source: CSR, CHMP report and MAH submission file

Table 5.5: Primary and key secondary efficacy endpoints in the PLP

Endpoint	Placebo + ASA ± clopidogrel (n=8,439)		Vorapaxar + ASA ± clopidogrel (n=8,458)		HR (95% CI)	p-value
	No. of patients with event (%)	KM estimate at 3 years (%)	No. of patients with event (%)	KM estimate at 3 years (%)		
Primary endpoint (CV death, MI, stroke, UCR)	867 (10.3)	11.4%	719 (8.5)	9.8%	0.82 (0.74 to 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)			
UCR	236 (2.8)		203 (2,4)			
Key secondary endpoint (CV death, MI, stroke)	671 (8.0)	9.0%	532 (6.3)	7.4%	0.78 (0.70 to 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)			

Abbreviations: ASA=acetylsalicylic acid; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; KM=Kaplan-Meier; MI=myocardial infarction; PLP=proposed label population; UCR=urgent coronary revascularisation
Source: CSR, CHMP report and MAH submission file

All-cause death data were provided as a non-key secondary endpoint. Moreover, this endpoint can't be evaluated and discussed according to the hierarchical test sequence planned a priori for this trial. This is because other secondary endpoints evaluated before this endpoint were not found to be statistically significant which halted subsequent statistical testing. Therefore, all-cause death results (in the PLP) are only shown as exploratory data: in the vorapaxar + ASA ± clopidogrel group, 238 subjects (KM estimate at 3.4% per 3 years) died compared with 259 subjects (KM estimate at 3.7% per 3 years) in the placebo + ASA ± clopidogrel group (HR=0.91; 95% CI: 0.77 to 1.09; statistical testing is not valid).

From a number needed to treat (NNT) perspective (efficacy expressed as the number of patient-years exposure with vorapaxar instead of placebo to prevent 1 additional harmful event), treatment with vorapaxar instead of placebo (as an add-on therapy to ASA ± clopidogrel) would result in 1 fewer non-bleeding CV death, MI, or stroke event per 140 patient-years.

[D0006] How does vorapaxar affect progression of atherosclerotic coronary lesions?

There is no evidence that vorapaxar modifies the progression of atherosclerotic coronary lesions but, as with any antiplatelet therapy, its mode of action aims to reduce disease progression by reducing platelet thrombus formation.

5.3 Discussion

In the PLP, the primary efficacy composite endpoint (CV death, MI, stroke, or UCR) was a 3-year Kaplan-Meier (KM) event rate of 9.8% in the vorapaxar + ASA ± clopidogrel group compared with 11.4% in the placebo + ASA ± clopidogrel group (HR=0.82; 95% CI: 0.74 to 0.90, p<0.001).

In the PLP, the key secondary efficacy composite endpoint (CV death, MI, stroke) was a 3-year KM event rate of 7.4% in the vorapaxar + ASA ± clopidogrel group compared with 9.0% in the placebo + ASA ± clopidogrel group (HR=0.78; 95% CI: 0.70 to 0.88, p<0.001).

As noted in the CHMP assessment report [1], the event rate increases from 6.0% after 1 year to 11.4% in the next 2-year period. While the rate of events is rising over time, the rate of rise is changing over time, suggesting that the benefit of vorapaxar is varying with time, especially lowering beyond 2 years. This is supported by a potential increase of the effect from year 1 to year 2 and a potential attenuation of the effect from year 2 to year 3 (HR year 1 is 0.85, year 2 is 0.75, year 3 is 0.91).

A clinical benefit was shown in both the primary and key secondary efficacy endpoints, which both comprised MACE. MACE are widely used in composite endpoints in numerous clinical trials of antiplatelets and anticoagulants. Nevertheless, a few issues were raised:

- Firstly, as shown in Table 5.4 and Table 5.5, the individual CV events of the composite endpoints didn't occur with the same frequency; the overall result of each endpoint was mainly led by MI. Indeed, MI occurred 5 times more than CV death or stroke in both endpoints and 2 times more than UCR. Each event didn't have the same weight in the final result. Indeed according to EUnetHTA guidelines on composite endpoints [74]: "The most frequently quoted problem is the risk of misinterpretation when there is heterogeneity of response among components of composite endpoints […] if the effect on a composite endpoint is mostly driven by an effect on one of the components, it is not admissible to conclude that the treatment has an equal or important effect on all the components."

- Secondly, all-cause deaths should have been one of the first key secondary endpoints. Indeed, the overall interest of the drug is its related efficacy as well as possible harmful effects, in terms of mortality. The study planned to use a hierarchical test sequence to evaluate the endpoints. If the first key secondary criteria showed a significant difference, then the following key secondary endpoint could be considered with the same power, the same robustness and so on, until one of the differences between groups on a criterion was not significant. Considering that, all-cause death should have been one of the first key secondary

endpoint. Furthermore, the first key secondary endpoint chosen (which includes all the criteria of the primary endpoint except UCR) did not provide much more information than the primary endpoint.

In this trial, vorapaxar demonstrated a clinical benefit mainly on morbidity (MI), but no significant difference was shown with regard to CV mortality or overall mortality (all-cause deaths).

A methodological issue has to be raised about the initial statistical analysis plan, which was not modified or redefined after the DSMB and EMA decisions to exclude patients with a history of stroke (following an interim analysis) and then to exclude patients from the PAD stratum, thus reducing the overall population (n= 26,449 patients) to the PLP (n=16,897; 63.9% of the overall population). We suppose that this exclusion was done without unblinding although this is not clearly presented in the document. The power of the trial, which represents the reproducibility and the ability to conclude robustly, is unknown in the PLP. Furthermore, the initial hypothesis of the trial has been changed by the exclusion of different populations. This reduces the level of evidence of the trial. Considering the absence of a new hypothesis, analysis has to focus first on the overall population and second on the PLP. Here, the PLP analysis remains a post-hoc analysis.

This modification of the trial resulted in difficulties in assessing the effectiveness of the drug: the population that needs to be treated in a real-life situation is very different to that of the initial trial population. Furthermore, in a real-life situation, the use of vorapaxar will need to exclude patients treated by ticagrelor and prasugrel, and patients with a history of stroke or TIA, complicating a patient's care. Ticagrelor and prasugrel are first- or second-line recommendations within the first year of an MI in some guidelines. Because data on vorapaxar as an add-on therapy to these two drugs are lacking, potential clinical interest of vorapaxar associated with ticagrelor or prasugrel cannot be assessed. It remains unclear if patients treated with ticagrelor or prasugrel could be switched to vorapaxar schemes and, if this was possible, how the switch could be done

The efficacy analysis was made with the clinical study report (CSR), the CHMP assessment report, the summary of product characteristics (SmPC), and the MAH's final submission file.

Note: In the main publication on the trial (Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012; 366:1404-13), the authors referred to a change in the endpoints hierarchy. Before the database was locked and during blinded treatment, the investigators reviewed data from the TRACER trial, On the basis of data from that trial, the steering committee amended the main data analysis plan to re-order the hierarchy of efficacy analyses, defining as the primary endpoint the composite of CV death, MI, or stroke. The composite of CV death, MI, stroke, or UCR became the major secondary endpoint.

The MAH answered in its comments on this point: "academic research organization running the trial (TIMI) elected to make this change prior to database lock. The change in endpoint was only made by the academic research organization, and not by the MAH. The MAH decided that regulatory documents needed to keep the original endpoints despite the change suggested prior to database lock. Only the publication referenced reflects the change made by the academic research organization".

There was no quality-of-life data. Therefore, it is not possible to assess the impact of the addition of vorapaxar to ASA ± clopidogrel in terms of quality of life.

6 SAFETY

6.1 Research questions

Research questions

The following research questions have been selected and formulated for this domain.

Element ID	Research question
C0008	How safe is vorapaxar co-administered with ASA, with or without clopidogrel, in relation to ASA with or without clopidogrel?
C0005	Is there any group of patients excluded from the study for safety reasons? Are some groups of patients more likely to be harmed through the use of vorapaxar as an add-on therapy?
C0002	Is there a relationship between the dose of vorapaxar and the most frequent and serious adverse events in special populations?
C0007	Are vorapaxar and ASA and clopidogrel associated with user-dependent harms? Do their prescriptions need a specific therapeutic management of the patient or a specific education?
C0004	How does the frequency or severity of harms change over time or in different settings?

6.2 Results

The interpretation of the results and quality of evidence assessments represent the authors' view, which may differ from the view expressed by the manufacturer.

In the TRA 2°P-TIMI 50 clinical trial, the patient exposure for the PLP is described in Table 6.1.

Table 6.1: Duration of participation in treatment of all randomised subjects in the PLP

Duration of participation	Placebo + ASA ± clopidogrel (n=8,439) n (%)	Vorapaxar + ASA ± clopidogrel (n=8,458) n (%)
Any participation	8,412 (99.7)	8,444 (99.8)
≥30 days	8,229 (97.5)	8,236 (97.4)
≥90 days	8,031 (95.2)	8,025 (94.9)
≥180 days	7,785 (92.3)	7,787 (92.1)
≥360 days	7,487 (88.7)	7,483 (88.5)
≥540 days	7,218 (85.5)	7,198 (85.1)
≥720 days	5,743 (68.1)	5,675 (67.1)
≥900 days	3,675 (43.5)	3,612 (42.7)
≥1080 days	1,583 (18.8)	1,565 (18.5)
Randomised not treated	27 (0.3)	14 (0.2)
Mean duration in days	818.4	810.5
Median duration in days	869.0	867.0

Abbreviations: ASA=acetylsalicylic acid; n=number of subjects; PLP=proposed label population
Source: CSR, CHMP report and MAH submission file

This table shows that almost 70% of patients were treated for at least 2 years.

[C0008] How safe is vorapaxar co-administered with ASA, with or without clopidogrel, in relation to ASA with or without clopidogrel?

Among subjects treated in the overall population (n=26,352), the main reasons for treatment discontinuation were adverse events (AEs), consent withdrawal, did not meet protocol eligibility, protocol non-compliance, and required prohibited medication. The numbers of subjects in the TRA 2°P-TIMI 50 initial overall ITT population who had a serious adverse event (SAE) or discontinued due to an AE are reported in Table 6.2.

Table 6.2: Frequency of SAEs and discontinuation of study drug treatment due to AEs in the overall ITT population

	Placebo + ASA ± clopidogrel (n=13,166) n (%)	Vorapaxar + ASA ± clopidogrel (n=13,186) n (%)
Any SAE	3,419 (26.0)	3,515 (26.7)
Any AE resulting in treatment discontinuation	1,143 (8.7)	1,273 (9.7)
Any bleeding event resulting in treatment discontinuation	234 (1.8)	401 (3.0)
Any treatment-related AE resulting in death	16 (0.1)	31 (0.2)

Abbreviations: AE=adverse event; ASA=acetylsalicylic acid; ITT=intent-to-treat; n=number of subjects; PLP=proposed label population; SAE=serious adverse event
Source: CSR, CHMP report and MAH submission file

The corresponding SAE and discontinuation due to AE data were not provided for the PLP.

During the study, bleeding events were collected according 3 different bleeding criteria:

- The GUSTO criteria, which provides clinical criteria:
  - Moderate: bleeding requiring transfusion but does not result in haemodynamic compromise.
  - Severe: deadly bleeding, intracranial bleeding, or substantial haemodynamic compromise.
- The TIMI criteria, which are more biological criteria:
  - Major: any intracranial bleeding, or clinically significant overt bleeding associated with a decrease in haemoglobin concentration ≥5 g/dL (or decrease in haematocrit ≥15% if haemoglobin concentration is not available).
  - Minor: overt signs of haemorrhage associated with a decrease in haemoglobin concentration 3 to <5 g/dL (or decrease in haematocrit 9% to <15% if haemoglobin concentration is not available).
  - Clinically significant: TIMI major or minor bleeding, or bleeding that requires unplanned medical or surgical treatment, or unplanned evaluation via laboratory test.
- International Society on Thrombosis and Haemostasis (ISTH) criteria:
  - Major bleeding events: fatal bleeding, and/or symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells.

As a reminder, the secondary safety endpoints described in the study objectives were:

- Composite of moderate and severe bleeding events defined according to the GUSTO criteria.
- Clinically significant bleeding defined according to the TIMI criteria.

A summary of bleeding events in the PLP is provided in Table 6.3.

Table 6.3: Summary of bleeding events in the PLP

	Placebo + ASA ± clopidogrel (n=8,412)[i] n (%)	Vorapaxar + ASA ± clopidogrel (n=8,444)i n (%)	Hazard ratio (95% CI)	p-value
Bleeding AEs: GUSTO criteria				
Severe or moderate	156 (1.9)	231 (2.7)	1.48 (1.21 to 1.82)	<0.001
Severe	73 (0.9)	85 (1.0)	1.16 (0.85 to 1.59)	0.352
Moderate	88 (1.0)	152 (1.8)	1.73 (1.33 to 2.25)	<0.001
Bleeding AEs: TIMI criteria				
Major	133 (1.6)	161 (1.9)	1.21 (0.96 to 1.52)	0.108
Minor	47 (0.6)	105 (1.2)	2.23 (1.58 to 3.15)	<0.001
Clinically significant	785 (9.3)	1,120 (13.3)	1.46 (1.34 to 1.60)	<0.001
Bleeding AEs: Other categories				
ISTH major bleeding	233 (2.8)	347 (4.1)	1.49 (1.26 to 1.76)	<0.001
Intracranial haemorrhage	30 (0.4)	38 (0.5)	1.26 (0.78 to 2.03)	0.348
Fatal intracranial haemorrhage	8 (0.1)	10 (0.1)	1.24 (0.49 to 3.14)	0.649
Fatal bleeding	14 (0.2)	14 (0.2)	0.99 (0.47 to 2.09)	0.989

Abbreviations: AE=adverse event; ASA=acetylsalicylic acid; CI=confidence interval; GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (trial); ISTH=International Society on Thrombosis and Haemostasis; n=number of subjects; PLP=proposed label population; TIMI=Thrombolysis in Myocardial Infarction
Source: CSR, CHMP report and MAH submission file

[i] Safety population (n) is defined by the whole patients who received at least one tablet of vorapaxar, therefore safety population is different to efficacy population which is defined by the whole randomized patients.

The most frequently reported other SAEs in the PLP are shown in Table 6..

Table 6.4: Summary of most frequently reported other SAEs (non-bleeding) in the PLP

SAE	Placebo + ASA ± clopidogrel (n=8,412) n (%)	Vorapaxar + ASA ± clopidogrel (n=8,444) n (%)
Non-cardiac chest pain	365 (4.3)	338 (4.0)
Cardiac failure	86 (1.0)	87 (1.0)
Pneumonia	71 (0.8)	74 (0.9)
Atrial fibrillation	49 (0.6)	67 (0.8)
Syncope	29 (0.3)	41 (0.5)
Cardiac failure congestive	37 (0.4)	36 (0.4)
Osteoarthritis	50 (0.6)	37 (0.4)

Abbreviations: ASA=acetylsalicylic acid; n=number of subjects; PLP=proposed label population; SAE=serious adverse event
Source: CSR, CHMP report and MAH submission file

The number of patients needed to harm (NNH) is the estimation of the number of patient-years treatment with vorapaxar as an add-on therapy instead of placebo, needed to observe 1 additional harmful event. The NNT according to the “GUSTO moderate and severe bleeding” events rate was 1.1 per 100 patient per year with vorapaxar as an add-on therapy instead of placebo. The NNH in terms of additional fatal bleeding events rate was 0.1 per 100 patients per year.

[C0005] Is there any group of patients excluded from the study for safety reasons? Are some groups of patients more likely to be harmed through the use of vorapaxar as add-on therapy?

As a reminder, during an interim analysis, the DSMB observed an increased incidence and relative risk of intracranial haemorrhage in subjects with a history of stroke, and the study drug was discontinued in all subjects with a history of stroke (including those with a new stroke during the trial). Subsequently, the EMA decided against expanding the submission to include subjects from the PAD stratum. Thus, the PLP included patients in the CAD stratum of the trial only, with no history of stroke or TIA.

The pharmacokinetic (PK) data suggest a higher bleeding risk in patients with severe hepatic failure. Moreover, patients with “known active hepatobiliary disease, or known unexplained persistent increase in serum alanine aminotransferase or aspartate aminotransferase activity to 2 times or more the upper limit of the reference range” were excluded from the Phase 3 trials. Therefore, the use of vorapaxar is contraindicated in these patients.

In the TRA 2°P-TIMI 50 PLP, 20% of the patients were older than 65 years, and 7% were older than 75 years. Considering the GUSTO severe/moderate bleeding criteria, the HRs between subgroups were similar but the percentage of patients who experienced a GUSTO severe/moderate bleeding event was higher for older patients in both treatment arms.

Table 6.5: Summary of GUSTO severe/moderate bleeding events in different age subgroups in the PLP

Age (subgroups)	Placebo + ASA ± clopidogrel (n=8,412) n/N (%)	Vorapaxar + ASA ± clopidogrel (n=8,444) n/N (%)	HR (95% CI)
<65 years	79/6033 (1.3)	120/5952 (2.0)	1.54 (1.16 to 2.05)
≥65 years	77/2379 (3.2)	111/2492 (4.5)	1.39 (1.04 to 1.85)
<75 years	132/7809 (0.7)	192/7811 (2.5)	1.46 (1.17 to 1.82)
≥75 years	24/603 (4.0)	39/633 (6.2)	1.57 (0.94 to 2.61)

Abbreviations: ASA=acetylsalicylic acid; CI=confidence interval; GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (trial); HR=hazard ratio; n=number of subjects; PLP=proposed label population
Source: CSR, CHMP report and MAH submission file

According to the European Public Assessment Report, the TIMI major or minor bleeding and other bleeding events analyses revealed similar findings. Older age was found to be a risk factor for bleeding but no dose adjustments were required. Nevertheless, cautions and caveats are needed for vorapaxar use in older patients.

Patients weighing <60 kg seem to be at increased risk for severe bleeding events. The percentage of patients who experienced a GUSTO severe or moderate bleeding event was significantly higher in both treatment arms for patients weighing <60 kg (vorapaxar + ASA ± clopidogrel: 4.4% vs. ASA ± clopidogrel: 2.6%; HR=1.78; 95% CI: 0.85 to 3.74) compared with patients weighing ≥60 kg (2.6% vs. 1.8%; HR=1.46; 95% CI: 1.18 to 1.80). Therefore, vorapaxar should only be prescribed after very careful assessment of individual potential risks and benefits in patients <60 kg.

Patients with renal failure also seem to be at increased risk for bleeding AEs. The percentage of patients who experienced a GUSTO severe or moderate bleeding event was significantly higher in both treatment arms for patients in the subgroup with creatinine clearance (CrCl) <60 mL/min (vorapaxar + ASA ± clopidogrel: 6.6% vs. ASA ± clopidogrel: 4.2%; HR=1.59; 95% CI: 1.01 to 2.48) compared with patients in the subgroup with CrCl ≥60 mL/min (2.3% vs. 1.6%; HR=1.43; 95% CI: 1.14 to 1.80). In patients with renal failure, vorapaxar should also be prescribed after very careful assessment of individual potential risks and benefits. The number of patients and bleeding events was too low in patients with severe renal failure to conclude specifically in this subgroup.

General risk factors for bleeding include older age, low body weight, and reduced renal or hepatic function. Although there was no difference in bleeding risk between the 2 treatment groups, for any subgroup, it should be noted that the number of bleeding events was quite small in the subgroup analysis to allow definitive and robust conclusions.

[C0002] Is there a relationship between the dose of vorapaxar and the most frequent and serious adverse events in special populations?

[C0007] Are vorapaxar and ASA and clopidogrel associated with user-dependent harms? Do their prescriptions need a specific therapeutic management of the patient or a specific education?

These 2 questions will be answered altogether.

Only one dosage is available in the MA, namely 2.5 mg/day. Moreover, the MAH and the CHMP provided further information regarding PK/pharmacodynamic data in case of patient overdose.

Data regarding overdose of vorapaxar are limited, but data from early- and late-stage clinical trials, using loading doses up to 16 times the recommended daily dose of vorapaxar, seem to indicate that vorapaxar would be associated with overdose-related bleeding.

Across the TRACER and TRA 2ºP-TIMI 50 studies, there were 39 subjects who ingested higher doses of vorapaxar than the recommended daily dose and 2 other cases involving family members or acquaintances of participants were also reported. Most of these cases involved subjects who inadvertently took 2 tablets per day instead of one. Five of these subjects had associated AEs, including 3 with bleeding events (bleeding from an existing haemangioma, ecchymosis, and skin haematomas), 1 with diarrhoea, and 1 with an increased creatinine and worsening of renal insufficiency. Four were associated with an intake of 5 mg of vorapaxar per day for ≥28 consecutive days, and 1 was associated with a single dose greater than 120 mg in an intentional overdose (suicide attempt). All subjects recovered after study drug interruption.

An antidote for vorapaxar does not exist and vorapaxar's terminal half-life is long (187 hours), which remains a concern in the case of surgical emergency or to set up surgery. According to the CHMP, in case of emergency, it is possible that platelet transfusion may be helpful, but in the absence of a specific antidote, the effectiveness of any interventions other than standard measures to manage bleeding is uncertain.

[C0004] How does the frequency or severity of harms change over time or in different settings?

No data were provided on this question.

The Pharmacovigilance Risk Assessment Committee (PRAC) and the CHMP endorsed the risk management plan with the following ongoing safety concerns:

Important identified risks	• Medically important bleeding, including intracranial haemorrhage • 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 • Paediatric population • Patients with severe hepatic dysfunction • Co-administration with oral anticoagulants (e.g. warfarin), prasugrel, or ticagrelor • Severe thrombocytopenia • Co-administration with non-steroidal anti-inflammatory drugs (other than aspirin)

6.3 Discussion

In the TRA 2ºP-TIMI 50 PLP, vorapaxar + ASA ± clopidogrel compared with placebo + ASA ± clopidogrel was associated with more bleeding AEs (GUSTO severe or moderate bleeding, TIMI clinically significant bleeding, and ISTH major bleeding). Therefore, bleeding events remain the major concern in the vorapaxar safety profile.

In different special populations, an increased bleeding risk was observed. Older age (>65 years), low body weight (<60 kg), and hepatic or renal failure were risk factors for increased bleeding AEs in both treatment groups. The increase of bleeding AEs in these special populations was no different between the 2 treatment groups. Nevertheless, the number of bleeding events in these subgroups was too low to conclude robustly. Therefore, additional information is needed. Caution should be taken with these special populations, and the use of vorapaxar is contraindicated in patients with severe hepatic failure.

There were no differences in the incidences of other SAEs between treatment groups across the TRA 2ºP-TIMI 50 PLP. The most frequently reported other SAEs were non-cardiac chest pain (4.3% in the vorapaxar + ASA ± clopidogrel group compared with 4.0% in the placebo + ASA ± clopidogrel group), cardiac failure, pneumonia, atrial fibrillation, syncope, cardiac failure congestive, and osteoarthritis (all ≤1.0% in both groups).

Across the TRACER and TRA 2ºP-TIMI 50 studies, there were 41 cases of overdose with only 5 subjects having associated AEs, and most of these cases involved subjects who inadvertently took 2 tablets per day instead of one. However, the lack of an antidote and the long half-life of vorapaxar remain problematic.

A risk management plan has been approved by the PRAC and the CHMP, in which important identified risks are medically important bleeding (including intracranial haemorrhage), drug-drug interaction (strong inhibitor and inducer of CYP3A4), and other important potential risks, including increased risk of bleeding in patients with body weight <60 kg, ocular effects, and phospholipidosis.

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APPENDIX 1. METHODS AND DESCRIPTION OF THE EVIDENCE USED

DESCRIPTION OF THE EVIDENCE USED

Evidence tables of individual studies included for clinical effectiveness and safety

Table A1.1: Characteristics of randomised controlled studies

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 multicentre, international, randomised, double-blind, placebo-controlled, balanced parallel-group, events-driven investigation of orally administered vorapaxar in the secondary prevention of ischaemic 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 (vorapaxar + ASA ± clopidogrel) will reduce the incidence of atherothrombotic ischaemic events relative to standard of care alone (ASA ± clopidogrel), as measured by the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), stroke, and urgent coronary revascularisation (UCR) in subjects with established coronary artery disease (CAD), cerebrovascular disease (CVD), or peripheral artery disease (PAD).
Treatment groups	26,449 patients received randomised treatment: 13,225 vorapaxar and 13,224 placebo (intent-to-treat population [ITT]) Subjects were enrolled in 1 of 3 strata: 17,779 subjects with CAD (history of MI); 4,883 with CVD (history of ischaemic stroke); 3,787 with PAD
	During an interim analysis, the Data and Safety Monitoring Board (DSMB) observed an increased incidence and relative risk of intracranial haemorrhage in subjects with a history of stroke, and the study drug was discontinued in all subjects with a history of stroke (including those with a new stroke during the trial). Subsequently, the European Medicines Agency (EMA) decided to refine the target population and exclude subjects with a history of PAD. Thus, the PLP included subjects in the CAD stratum of the trial only (history of MI), with no history of stroke or transient ischaemic attack (TIA). The proposed label population (PLP) included 16,897 subjects.
Duration of the study	Duration of main phase: median (participation in the study): 906 days for vorapaxar + ASA ± clopidogrel; 905 days for placebo + ASA ± clopidogrel. Duration of run-in phase: not applicable Duration of extension phase: not applicable

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		
Endpoints and definitions	Primary composite 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, UCR, and any revascularisation - The individual components of the composite primary efficacy endpoint: CV death, MI, stroke, and UCR - All-cause death	
Database lock	09 January 2012		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT; randomised to last visit		
Descriptive statistics and estimate variability	Overall ITT population		
		Placebo +ASA ± clopidogrel	Vorapaxar +ASA ± clopidogrel
	Number of subjects	n=13,224	n=13,225
	Primary efficacy endpoint (Events %; KM[a] %)	1417 (10.7%); 12.4%	1259 (9.5%); 11.2%
	CV death	199 (1.5%)	172 (1.3%)
	MI	629 (4.8%)	536 (4.1%)
	Stroke	297 (2.2%)	297 (2.2%)
	UCR	292 (2.2%)	254 (1.9%)
	Key secondary endpoint (Events %; KM[a] %)	1176 (8.9%); 10.5%	1028 (7.8%); 9.3%
	Proposed Label Population		
	Number of subjects	8,439	8,458
	Primary efficacy endpoint (Events %; KM[a] %)	867 (10.3%); 11.4%	719 (8.5%); 9.8%

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		
	CV death	96 (1.1%)	82 (1.0%)
	MI	451 (5.3%)	374 (4.4%)
	Stroke	84 (1.0%)	60 (0.7%)
	UCR	236 (2.8%)	203 (2.4%)
	Key secondary endpoint (Events %; KM[a] %)	671 (8.0%); 9.0%	532 (6.3%); 7.4%

Effect estimate per comparison	Primary endpoint	Overall ITT population	
		Hazard ratio (95% CI)	0.88 (0.82 to 0.95)
		P-value	0.001
		Proposed Label Population	
		Hazard ratio (95% CI)	0.82 (0.74 to 0.90)
		P-value	<0.001
	Key secondary endpoint	Overall ITT population	
		Hazard ratio (95% CI)	0.87 (0.80 to 0.94)
		P-value	<0.001
		Proposed Label Population	
		Hazard ratio (95% CI)	0.78 (0.70 to 0.88)
		P-value	<0.001

Abbreviations: ASA=acetylsalicylic acid; CAD=coronary artery disease; CI=confidence interval; CV=cardiovascular; CVD=cardiovascular disease; DSMB=Data and Safety Monitoring Board; EMA=European Medicines Agency; ITT=intent-to-treat; KM=Kaplan-Meier; MI=myocardial infarction; n=number of subjects; PAD=peripheral artery disease; PLP=proposed label population; TIA=transient ischaemic attack; UCR=urgent coronary revascularisation

[a] 3-year Kaplan-Meier rate.

Source: CHMP report and MAH submission file

Applicability tables

Table A1.2: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	• Adult patients with a history of MI (ICD-10 code I61-64) without history of stroke (ICD-10 code 430-435) or TIA.
Intervention	• Vorapaxar is a selective antagonist of protease-activated receptor 1 (PAR-1), the primary thrombin receptor on human platelets. • Dose of 2.5 mg per day, administered orally.
Comparators	For vorapaxar prescribed as an add-on therapy to standard of care including ASA, with or without clopidogrel (vorapaxar + ASA ± clopidogrel), the comparators are: • A therapeutic strategy: ASA ± clopidogrel
Outcomes	• All-cause death • Cardiovascular death • Cardiovascular morbidity (MI, UCR, stroke)
Setting	• RCTs

Abbreviations: ASA=acetylsalicylic acid; ICD-10=International Statistical Classification of Diseases and Related Health Problems, 10th Revision; MI=myocardial infarction; PAR-1= protease-activated receptor 1; RCT=randomised controlled trial; TIA=triansient ischaemic attack; UCR=urgent coronary revascularisation
Source: CHMP report and MAH submission file

APPENDIX 2. CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

Table A2.1: Checklist for potential ethical, organisational, social and legal aspects

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	**No**
1.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be ethically relevant?	**No**
If you have answered any of this questions with 'yes' please specify/explain your considerations	
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparators require organisational changes?	**No**
2.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be organisationally relevant?	**No**
If you have answered any of this questions with 'yes' please specify/explain your considerations	
3. Social	
3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	**No**
3.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be socially relevant?	**No**
If you have answered any of this questions with 'yes' please specify/explain your considerations	
4. Legal	
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	**No**
4.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be legally relevant?	**No**
If you have answered any of this questions with 'yes' please specify/explain your considerations	

APPENDIX 3: COMMENTS RECEIVED BY DEDICATED REVIEWERS ON THE FIRST ASSESSMENT DRAFT

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Scope				
1. Was there a need to deviate from the Project Plan (protocol) in terms of clinical problem, population, intervention(s), comparison(s) and outcome(s)? If the answer is **NO**, please move directly to the Part II of the reviewer form.	**HVB:** Yes **SNHTA:** Yes	**ZIN:** 'Comparison': further specified: excluding ticagrelor or prasugrel **HVB:** Change of population	**SMC:** No	**AQuAS:** Comparison: from our point of view and, as we expressed in the previous TC, SoC should not be considered the comparator. Vorapaxar is prescribed in add on of standard of care and, therefore, placebo might be the most appropriate comparator. Although, we understand that it is necessary to ensure patients in the comparative assessment are receiving background therapy with ASA and/or clopidogrel **HAS/SK**: We understand and we'll try to be clearer in the 2nd draft, but we prefer showing this evaluation and this trial as a therapeutic strategy comparison: ASA±clopidogrel versus vorapaxar+ASA±clopidogrel. It remains right, that if vorapaxar is considered on its own, the comparator is the placebo.

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
				Nevertheless as vorapaxar is used in add on the appropriate comparison is versus placebo with ASA ± clopidogrel. **AOTMiT:** Population in PICO (as described in REA) is not consistent with the one from pivotal study
2. Was a rationale included for the deviation of the scope that was proposed in the project plan?	**ZIN:** Yes **AQuAS:** -	**SNHTA:** Yes (no specification)	**AOTMiT:** In chapter 2.5 deviation from "project plan" of the included study provided (not from the REA project plan)	**SMC:** N/A
Part II: Methods				
1. If there was a need to deviate from the Project Plan (protocol) in terms of methods used, is it described in the Method's section of the pilot?	**ZIN**: N/A **HVB:** - **SNHTA:** Yes	**AOTMiT:** Search strategy not provided in sufficient details (only general strategy – p. 11 l. 13-14, which is wrong, what was commented at the project plan stage)		**AQuAS:** Not necessary **SMC:** N/A. However section 2.5. in methods section refers to deviation of clinical study protocol and not of the project plan.
2. If there was no manufacturer's submission file available or the received submission file was incomplete, biased or outdated, did the authors conduct a more detailed	**ZIN**: N/A **HVB:** - **SNHTA:** Yes			**SMC:** Manufacturer's submission was available **AOTMiT:** The manufacturer submission was provided but

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
search?	**AQuAS:** Yes			inconsistent with PICO (? not clearly stated)
3. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?	**ZIN:** Yes **HVB:** Yes **SMC:** Yes **AQuAS:** Yes	**SNHTA:** Yes (no specification) **AOTMiT:** Exclusion criteria provided (p. 11 l. 23-24) but inconsistent with "supportive study" TRACER		
4. Are the quality appraisal tools appropriate?	**ZIN:** Yes **HVB:** - **SMC:** Yes	**SNHTA:** Yes (no specification)	**AOTMiT:** Not provided	**AQuAS:** The authors do not specify the quality appraisal tools employed
5. Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE) appropriate for this analysis?	**ZIN:** Yes **HVB:** Yes **SMC:** Yes **SNHTA:** Yes **AQuAS:** Yes	**AOTMiT:** (follow-up time not reported in Tab. 2; median of particip. in the study in tab. 11 vs. tab. 7 are different)		
6. Is the risk of bias sufficiently assessed, both on study level and on an outcome level?	**ZIN:** Yes **HVB:** -	**SNHTA:** Yes (no specification)	**SMC:** No **AOTMiT:** only "Quality of body of evidence	**SMC:** We cannot see any risk of bias assessment **AQuAS:** The authors do not

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
			moderate" in Tab. 1 in Summary Part(I); 3-level risk of bias scale based on personal judgement **HAS**: The pivotal trial does not present major bias: the only methodological problem is the reduction of the overall population to the population with no history of stroke and AOMI, leading to a loss of power but not really a bias.	specify the risk of bias assessment **HAS**: See answer in the previous column
7. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?	**ZIN:** Yes **HVB:** - **SMC:** Yes **AQuAS:** Yes **AOTMiT:** (Study type relevant; study population not relevant)	**SNHTA:** Yes (no specification)		
8. Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs)	**ZIN:** Yes			

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
described?	**HVB:** Yes **SMC:** Yes **SNHTA:** Yes **AQuAS:** yes **AOTMiT:** (Type of studies "to be" included not provided; type of studies included provided in Tab. 2)			
9. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?	**ZIN**: N/A **SNHTA:** Yes **AQuAS:** -	**HVB:** It might have been a possibility to include indirect comparisons (ticagrelor/prasugrel), but this was not done		**SMC:** N/A **AOTMiT:** N/A
10. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?	**ZIN:** Yes **HVB:** - **SMC:** Yes **SNHTA:** Yes **AQuAS:** Yes	**AOTMiT:** (only brief description of e-ps in App. 1 at p. 46)		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
11. Details on sources of information and literature search strategies provided?				

Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
ZIN: Yes **HVB:** Yes **SMC:** Search strategy appeared to be limited **SNHTA:** - **AQuAS:** yes **AOTMiT:** - (inappropriate; not detailed enough)	**ZIN:** Yes **HVB:** Yes **SMC:** PubMed and EMBASE **SNHTA:** - **AQuAS:** yes **AOTMiT:** yes	**ZIN:** Yes **HVB:** - **SMC:** Yes (no limits on time) **SNHTA:** - **AQuAS:** yes (no limits of time) **AOTMiT:** Yes (no limits of time)	**ZIN:** Yes **HVB:** - **SMC:** not detailed **SNHTA:** - **AQuAS:** not specified **AOTMiT:** - (not provided)	**ZIN:** Yes **HVB:** - **SMC:** Yes **SNHTA:** - **AQuAS:** - **AOTMiT:** yes (3 studies)	**ZIN:** Yes **HVB:** - **SMC:** Not detailed **SNHTA:** - **AQuAS:** - **AOTMiT:** yes ("supportive study" TRACER; the rationale for inclusion not provided)

12. Information on basis for the assessment and interpretation of selected data and information?		
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?
ZIN: Yes **HVB:** - **SMC:** Yes (only one study appraised)	**ZIN:** Yes **HVB: -** **SMC:** Yes (GRADE quality assessment) **SNHTA:** -	**ZIN:** Yes **HVB: -** **SMC:** N/A (as only one study appraised)

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
SNHTA: - **AQuAS:** No **AOTMiT:** No	**AQuAS:** No **AOTMiT:** No		**SNHTA:** - **AQuAS:** No **AOTMiT:** No	
13. Do you agree on the selection of the assessment elements and the justification for not including specific elements?	**ZIN:** Yes **SNHTA:** Yes **AQuAS:** yes	**HVB:** It might have been a possibility to include indirect comparisons (ticagrelor/prasugrel), but this was not done **SMC:** Agree in general although suggest that QoL elements should be included D0012&13 **HAS:** No QoL data were assessed by the company in the clinical trial, therefore no QoL data were provided in the final submission book and in the REA report. This comment has been added in the discussion **AOTMiT:** No (It is unclear: 1. Why population in PICO (as described in REA) is not the same as in the pivotal study; 2. Why "supportive study"		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		TRACER was included **HAS:** 1.PICO population is the "proposed label population" that is left at the end of the pivotal clinical trial minus the patients with a history of PAD. After a safety alert in the population with a history of stroke the DSMB decided to exclude these patients. The EMA decision to exclude also patients with PAD was described neither in the company book nor in the CHMP report. The detailed exchanges about this decision stayed between DSMB and EMA. 2. We described only one study in this REA (the TRA 2°P-TIMI50 study). The other study: the TRACER study was stopped early for safety problems, EMA didn't use this study to give the Marketing authorization to the company, but we thought it was providing valuable information to briefly present this trial. It aims to give		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		a better overview of this drug development.		
14. If there was a need to deviate from the Project Plan in terms selection of assessment elements, is the change justified?	**ZIN**: N/A **HVB:** - **SNHTA:** Yes		**AOTMiT:** No (It is unclear: 1. Why population in PICO (as described in REA) is not the same as in the pivotal study; 2. Why "supportive study" TRACER was included **HAS:** See answer to question 13 in the above row.	**SMC:** Not applicable, but see comment above.
Part III: Description of the evidence				
1. Do you agree on the data extracted from the included studies? (See Table [X]. Characteristics of the randomized controlled studies and Table [X]. Relevant non-RCTs identified)	**ZIN:** Yes **HVB:** - **SMC:** Yes **SNHTA:** Yes **AQuAS:** Yes	**AOTMiT:** (safety e-ps, eg. bleeding, not described in app. 1: nor effect, nor methodology of measuring)		
2. Do you agree on the risk of bias tables?	**ZIN:** Yes **HVB:** -		**AOTMiT:** (not provided) **HAS :** Again, see	**SMC:** There are no risk of bias tables

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
	SNHTA: Yes		answer above	**AQuAS:** Not identified **HAS :** See answer above
3. Do you agree on the applicability tables?	**ZIN:** Yes **HVB:** - **SNHTA:** Yes		**AOTMiT:** (Not in line with methodological Guidelines) **AQuAS:** Vorapaxar is labeleded for at add on use therefore, all patients (event those treated with vorapaxar) have to be treated with the SoC (ASA and/or clopidogrel) and thus it would not constitute an alterative, but a background therapy.	**SMC:** It is not clear what the data included in table 12 is for.
Part IV: Results				
Health problem and current use of the technology				
1. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged	**ZIN:** Yes **HVB:** Yes			

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
populations, where it occurs, how it is diagnosed, symptoms and consequences)?	**SMC:** Yes **SNHTA:** Yes **AQuAS:** Yes **AOTMiT:** Yes (very full description)			
2. Are the supporting references current?	**ZIN:** Yes **HVB:** Yes **SMC:** Yes **SNHTA:** Yes **AQuAS:** Yes **AOTMiT:** Yes (mostly)			
3. Do the supporting references provide an international picture of the problem?	**ZIN:** Yes **HVB:** Yes **SNHTA:** Yes **AQuAS**: Yes	**SMC:** No UK data?		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
	AOTMiT: Yes (from answer to A0023 out-of-Europe historical data may be cut out)			
Description and technical characteristics of the technology				
4. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	**ZIN:** Yes **HVB:** Yes **SNHTA:** Yes **AQuAS:** yes **AOTMiT:** yes (Comment: description is chaotic: the answers are not relevant to the questions; A0020 not in line with other part of REA, eg. p. 24 l. 13-14)			**SMC:** Large parts of the text are taken directly from the EPAR and not referenced. Is this acceptable? Suggest that description of the study are removed from this section as covered under clinical effectiveness
5.. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	**ZIN:** Yes **HVB:** Yes **AOTMiT:** Yes (Comment: description is chaotic: the answers are not relevant to the	**SMC:** Suggest noting that existing anti-platelet strategies (duration of clopidogrel treatment post MI) may vary across countries **SNHTA:** Yes (no specification)		**SMC:** Large parts of the text are taken directly from the EPAR and not referenced. Is this acceptable? **AQuAS:** The section describes properly the standard of care

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
	questions; A0020 not in line with other part of REA, eg. p. 24 l. 13-14)			
6. Are the supporting references current and do they provide an international picture of the problem?	**ZIN:** Yes **HVB:** Yes **SMC:** Yes **SNHTA:** Yes **AQuAS:** Yes		**AOTMiT:** No (no references provided, eg. on the use of comparators in European countries)	
Safety and effectiveness				
7. Is the risk of bias clearly reported?	**ZIN:** Yes	**HVB:** Word "bias" not mentioned in report **SMC:** Risk of bias tables are missing **HAS:** Answer provided above. **SNHTA:** Yes (no specification)	**AQuAS:** No **AOTMiT:** No (not reported at all) **HAS :** Same answer than in previous column	
8. Is quality of data sufficiently evaluated?	**ZIN:** Yes **HVB:** Statistical uncertainties are mentioned	**SMC:** Not fully evaluated. Limitations of study not fully explored. **HAS:** In the 2nd draft we criticized the main	**AOTMiT:** No (not at all) **HAS:** Same answer than in previous column	

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
	AQuAS: Yes	methodological issues **SNHTA:** Yes (no specification)		
9. Are both relative and absolute effect measures presented for each dichotomous outcome?	**ZIN:** Yes **SNHTA:** Yes **AQuAS:** Yes	**HVB:** See comment below (add CI etc), p 6 **AOTMiT:** yes (not all outcomes described) **HAS:** In the 2nd draft of the report, all the effectiveness and safety data are provided in detail, including for the subgroup of patients of the PLP population.		**SMC:** NNT may be helpful **HAS:** We added in the 2nd draft
10. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?	**ZIN:** Yes **HVB:** -	**SNHTA:** Yes (no specification)		**SMC:** Not applicable. **AQuAS:** All data were dichotomous outcomes **AOTMiT:** Not applicable
11. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented	**ZIN:** Yes **HVB:** Yes **SMC:** Yes **SNHTA:** Yes		**AQuAS:** No **HAS:** They are presented, so we don't understand why this reviewer says no to this question.	**AOTMiT:** Not applicable

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
12. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported	**ZIN:** Yes **SMC:** Yes **SNHTA:** Yes **AOTMiT:** Yes	**HVB:** Term "precision" not found **HAS:** The term "precision" is not used in the report but for each data presented in the report, other terms have been used such as: robustness… as a description of the precision of the effect estimates	**AQuAS:** No **HAS :** See answer in the previous column	
13. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data	**ZIN:** Yes **SMC:** Yes **AOTMiT:** Yes	**SNHTA:** Yes (no specification) **AQuAS:** NNH is not calculated **HAS:** NNH was added in the 2nd draft version oft he report	**HVB:** NNH not **HAS:** See answer in the previous column	**SMC:** NNH would be helpful **HAS:** See answer in the previous column **AOTMiT:** Comment: question C0004 not answered **HAS:** Clarified in the 2nd version oft he report.
14. In case where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?	**ZIN:** Yes **SNHTA:** Yes **AQuAS:** -		**SMC:** No	**HVB:** Effect on QoI, apparently not addressed **AOTMiT:** Not applicable
15. Do you agree that the results of this REA do not contain any errors or deficiencies?	**ZIN:** Yes **SNHTA:** Yes		**HVB:** See comments below **SMC:** Errors found and	

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
	AQuAS: -		have been noted in further general and specific comments, below **AOTMiT:** No (some statements/data inconsistent with other parts of REA) **HAS:** We modified according to your comments, and when we didn't modify we explained why in our answers to your specific questions below.	
16. If applicable, was the transformation of the surrogate outcomes into patient-relevant final outcomes considered?	**ZIN:** Yes **HVB:** - **SNHTA:** Yes **AQuAS:** -			**SMC:** N/A **AOTMiT:** Not applicable
General				
17. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and	**ZIN:** Yes **HVB:** Yes		**AOTMiT:** No (high internal inconsistency of REA)	

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
synthesised data still answer the question?	**SMC:** Yes **SNHTA:** Yes **AQuAS:** Yes			
18. Can the results be applied to the intended population?	**ZIN:** Yes **SMC:** Yes **SNHTA:** Yes **AQuAS:** Although it has to be noted that results come from subgroups and post-hoc analysis	**SMC:** Reassurance that duration of clopidogrel used in the study reflects current practice would be helpful. **HAS:** This information was not provided by the company and isn't in the CHMP report. We added a sentence in the 2nd version of the report on the fact that we don't have any data on that point.	**AOTMiT:** No (not clear what is intended population: PICO? PLP?)	**HVB:** Patients with MI longer than 12 Months ago? **HAS**: This point is described in the report: "vorapaxar should be initiated at least 2 weeks after a MI and preferably within the first 12 months from the acute event". As far as we know there is no antiplatelet therapy initiated more than 12 months after an ACS.
19. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	**ZIN:** Yes **HVB:** Yes **SNHTA:** Yes **AQuAS:** Yes			**SMC:** Would benefit from more discussion on the limitations of the evidence **AOTMiT:** The REA is chaotic so hard to evaluate **HAS**: Constructive remarks would be appreciated. It is not possible for us to answer such

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
				comment.
Part V: Summary of Relative Effectiveness				
1. Does the summary present a balanced representation of the content of the report?	**ZIN:** Yes **HVB:** Yes **SNHTA:** Yes **AQuAS:** Yes		**AOTMiT:** (not all fields filled; methods not fully described) **HAS:** We filled the missing fields in the 2nd draft's summary	**SMC:** Description of technology and health problem still to be completed. **HAS:** See the answer in the previous column.
2. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	**ZIN:** Yes **HVB:** Summary / conclusions should be specified (See comments below) **SNHTA:** Yes **AOTMiT:** (in the discussion some potential biases and shortages are properly addressed; are they all - hard to say as the rest of REA does not provide any)	**SMC:** Gaps in relation to duration of clopidogrel treatment (as above). **AQuAS:** Yes **HAS:** See the answer in part IV, the line 18 of this table		**ZIN:** Add introduction to Discussion (p. 8): background technology, assessment scope and results **SK:** We filled the missing fields in the 2nd draft summary

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part VI: Other Considerations				
1. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)	**ZIN:** Yes **HVB:** Yes **SMC:** Yes **SNHTA:** - **AQuAS:** yes **AOTMiT:** (Appendix 2)			

GENERAL AND SPECIFIC COMMENTS FOR THE AUTHORS

Page	Line	Comments	Comments from the author
General		**AOTMiT:** According to the methodology of REA the report should consist of elements which may be used separately - eg. all text should be provided as the collection of answers to basic questions. In this report there are big parts of "free" text, not comprising the answer to any question.	Little information, which do not directly answer the REA report's basic questions, remains relevant for final evaluation, discussion and conclusion. An evaluation remains an overview of the drug.
General		**AOTMiT:** It would be useful for reader to give the list of abbreviations at the beginning of the report as they are not explained in the plain text when they come for a first time.	We agree and modified in the plain text when they come for a first time
General		**AOTMiT:** As commented in the comments to protocol, "ASA (acetylsalicylic acid)" should be used rather than "aspirin"	We agree and modified

Page	Line	Comments	Comments from the author
General		**AOTMiT:** There is no consistent definition of population assessed. The population in the study was: subjects with the history of CAD, CVD, PAD further restricted to the one with no history of stroke and TIA (and at p. 24, lines 13-15 even wider population is excluded). So why the population in the assessment is “patients with the history of MI …”? (and no patients with the history of CAD, CVD and PAD incidents?). These differences result in lowering the body of evidence as phase III study was not designed to assess “after MI” population. If any information in the study data is present to justify the choice of “after MI” population (eg. data on subgroup), it should be provided.	The main inclusion criteria were : a. CAD as indicated by a history of presumed spontaneous MI (hospitalized with final diagnosis of MI, excluding periprocedural or definite secondary MI [e.g., due to profound anaemia or hypertensive emergency, troponin increase in sepsis]) ≥ 2 weeks but ≤ 12 months prior, or b. ischemic (presumed thrombotic) CVD as indicated by a history of ischemic stroke (hospitalized with final diagnosis of nonhemorrhagic stroke [includes completion of a standard evaluation for stroke in an acute care facility or stroke clinic without hospital admission]) ≥ 2 weeks but ≤ 12 months prior, or c. 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 But as detailed in different parts of the report (summary, effectiveness and safety), CVD and PAD population were excluded during the study. Therefore only CAD population (without history of stroke) were evaluated, which means as described in the inclusion criteria: “subjects with history of presumed spontaneous MI.” Moreover, we criticized this point in the summary (chapter discussion) on that way:” The power of the trial, which represents the reproducibility and the ability to conclude robustly, is unknown in the PLP. Furthermore, the initial hypothesis of the trial has been changed by the exclusion of different populations. This reduces the level of

Page	Line	Comments	Comments from the author
			evidence of the trial. Considering the absence of a new hypothesis, analysis has to focus first on the overall population and second on the PLP."
General		**ZIN:** Spelling mistakes should be checked (verb conjugations, singular/plural)	We corrected
General		**AOTMiT:** The whole review should be read and edited by somebody in consistent manner	The 2nd version is edited by a medical editor
General	All Tables	**ZIN:** Please name all tables indicating in which domain/chapter they belong e.g. the first Table in Chapter two would be Table 2.1.	We modified
General		**ZIN:** For the upcoming versions the explanations parts we use in the template as support should be deleted e.g. page 5 Line 11-14	We modified
General		**SNHTA:** The whole review should be read and edited by somebody in consistent manner	The 2nd version is edited by a medical editor
General		**SNHTA:** It would be useful for reader to give the list of abbreviations at the beginning of the report as they are not explained in the plain text when they come for a first time.	We agree and modified in the plain text when they come for a first time
General		**SNHTA:** As commented in the comments to protocol, "ASA (acetylsalicylic acid)" should be used rather than "aspirin"	We agree and modified
General		**SNHTA:** There is no consistent definition of population assessed. The population in the study was: subjects with the history of CAD, CVD, PAD further restricted to the one with no history of stroke and TIA (and at p. 24, lines 13-15 even wider population is excluded). So why the population in the assessment is "patients with the history of MI …"? (and no patients with the history of CAD, CVD and PAD incidents?). These differences result in lowering the body of	The main inclusion criteria were : a. CAD as indicated by a history of presumed spontaneous MI (hospitalized with final diagnosis of MI, excluding periprocedural or definite secondary MI [e.g., due to profound anemia or hypertensive emergency, troponin increase in sepsis]) ≥ 2 weeks but ≤ 12 months prior, or

Page	Line	Comments	Comments from the author
		evidence as phase III study was not designed to assess “after MI” population. If any information in the study data is present to justify the choice of “after MI” population (eg. data on subgroup), it should be provided.	b. ischemic (presumed thrombotic) CVD as indicated by a history of ischemic stroke (hospitalized with final diagnosis of nonhemorrhagic stroke [includes completion of a standard evaluation for stroke in an acute care facility or stroke clinic without hospital admission]) ≥ 2 weeks but ≤ 12 months prior, or c. 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 But as detailed in different parts of the report (summary, effectiveness and safety), CVD and PAD population were excluded during the study. Therefore only CAD population (without history of stroke) was evaluated, which means as described in the inclusion criteria: “subjects with history of presumed spontaneous MI.” Moreover we criticized this point in the summary (chapter discussion) on that way:”The power of the trial, which represents the reproducibility and the ability to conclude robustly, is unknown in the PLP. Furthermore, the initial hypothesis of the trial has been changed by the exclusion of different populations. This reduces the level of evidence of the trial. Considering the absence of a new hypothesis, analysis has to focus first on the overall population and second on the PLP.”
General		**AQuAS:** Some abbreviations lack description first time they are used in the text. Because use of abbreviations in this document is frequent it would be useful to include a list of	We modified.

Page	Line	Comments	Comments from the author
		abbreviations.	
Footnote		**ZIN:** Update the Footnote with the different version details	We updated
All even		**AOTMiT:** Problem with EunetHTA logo	This has been solved in final layouting.
2	11	**SNHTA:** Instead of HCUGE - please use the abbreviation FOPH standing for Federal Office of Public Health	We modified
2	11+	**AOTMiT:** Please use the new abbreviation of Polish Agency for Health Technology Assessment and Tariff System – AOTMiT: Reviewer(s) AOTMiT (Poland)	We modified
2	Version Table	**ZIN:** Add the versions for the input from the Co-Author and the DR's	We modified
4	Table of Content	**ZIN:** Take out the last item in the Table of Content → A separate appendix ….	We modified
5	Scope Box	**ZIN:** Make this box fit in layouting to the other boxes →Colouring grey	We modified
5	3	**AQuAS:** Comparison: from our point of view and, as we expressed in the previous TC, standard of care should not be considered the comparator. Vorapaxar is prescribed in add on of standard of care and, therefore, placebo might be the most appropriate comparator.	See answer above. The comparator of vorapaxar is the placebo both in association with ASA +/- clopidogrel. Another way to say the same thing is to consider the following strategies as compartors: vorapaxar + ASA +/- clopidogrel and ASA +/- clopidogrel only. The issues are the same. We understand and we'll try to be clearer in the 2nd draft, but we prefer showing this evaluation and this trial as therapeutic strategy

Page	Line	Comments	Comments from the author
			comparison: ASA±clopidogrel versus vorapaxar+ASA±clopidogrel. It remains too simple to compare a drug versus placebo, moreover in this case we are not comparing vorapaxar versus placebo in the effectiveness chapter or the safety chapter, indeed the effects came from the use of ASA±clopidogrel in the treatment group using placebo as add-on to.
5	3	**HVB:** Intervention: As add on to ?	We corrected
5 11 14	3 1 21-22	**AOTMiT:** These information are not consistent: Standard of care included antiplatelet treatment with aspirin alone or aspirin with clopidogrel, and excluded ticagrelor and prasugrel Standard of care including antiplatelet treatment with aspirin alone or aspirin with clopidogrel Comparators are strategies including Aspirin (acetylsalicylic acid : ASA) and clopidogrel or ticagrelor or prasugrel.	In our opinion, vorapaxar is indicated to be administered in addition to (not instead of) therapy with ASA alone or ASA plus clopidogrel. Therefore the comparators might be considered as treatment strategies and not as individual drugs, thus a placebo is needed to realize a double blind clinical trial and the two different therapeutic strategies compared are vorapaxar + ASA ± clopidogrel versus ASA ± clopidogrel.
5 11	3+ 1+	**AOTMiT:** Details of ICD classification used needed to be reported together with the link to website. To be changed to: **ICD-9** code 410; **ICD-9** code 430-435; or TIA In Poland ICD-10 classification is used by public payer (http://apps.who.int/classifications/icd10/browse/2015/en or - in the reality – http://apps.who.int/classifications/icd10/browse/2010/en, but let's say, it is a technical problem) where these diseases are classified as (to be confirmed by clinician): **ICD-10**: myocardial infarction (ICD-10 I21, I22); stroke (ICD-10: (I60?), I61(?), I64(?)); or TIA (ICD-10 G45; G45.9(?))	The company exchanged with us on ICD-9 but ICD-10 must be used. We modified these points.

Page	Line	Comments	Comments from the author
5 11	3 and 1	**SNHTA:** Please, do not use ICD-9 (in the 1990s), but ICD-10 because nobody use this obsolete classification any more	The company exchanged with us on ICD-9 but ICD-10 must be used. We modified these points
5	6-9	**AOTMiT:** Description of technology is not filled in	We corrected
5	11-14	**AOTMiT:** Health problem is not filled in	We corrected
5	16-28	**AOTMiT:** In this section all methodological issues should be put in – like search methods, analysis methods, etc. additionally to what was provided by drug manufacturer, study results are not methods.	We changed the chapter's heading in "methods and results", but we want to present both methods and results in the same chapter for effectiveness and follow EUnetHTA's REA template.
5	27	**SMC:** Sentence should read; *This was the proposed...*	We modified.
5-6		**SNHTA:** Use PICO to standardize the population type – **ACS** (Acute Coronary Syndrome) **definition?**	We modified.
5-6		**AOTMIT:** We would suggest that in plain text summary the plain text (and not pico table etc) is used in the way it can be read separately (now one have to study all the review to understand the summary).	See answer 4 and 5 lines above (chapters were added to the summary to get a complete overview oft he assessment)
5-6	Bullet Points	**ZIN:** Make sure that the usage of bullet points is consistent throughout the whole report → Now stripes and points are used	We modified.
6	4-23	**AOTMiT:** This section should be more clear for the recipients. Therefore, this section should be edited to provide explicit information eg. all abbreviation should be expand, "proposed label population" should be defined and specified , etc.	A lot of abbreviations have been expanded but few were detailed at first and then used in rest of the summary as TRA2°P-TIMI50, CAD, CVD, PAD. Moreover PLP is already well defined, even if the reasons which lead to reduce the trial overall population to PLP are more detailed in the chapter "effectiveness", but a summary must remain a summary.

Page	Line	Comments	Comments from the author
6	7	**SMC:** 95% CI not CI95% (this is applicable throughout document).	We modified
6	14	**HVB:** more bleeding: recommend adding %, CI / p values given, like for effectiveness above on this page	We agree, we added the %, nb CI and p-value.
6	21	**SMC:** Why are proportions of patients with chest pain reported but proportions of other adverse events not reported?	Only one “other AEs“ occurred in more than 1% of subjects in each treatment group and this chapter of the document is the summary, therefore providing an exhaustive list of others AEs was not considered as relevant (all the main other AEs are described in the safety chapter).
7	1	**SMC:** Table 1: the population that these data refer to needs to be made clear. It is the proposed licensed population (PLP).	We clarified that by a table heading modification.
7	2	**HVB:** Health benefit columns: why not add numbers, like in Harm columns of this table where no. and % are shown	Kaplan-Meier rate at 3-year represents the data used to calculate the Hazard ratio between the 2 treatment groups. Therefore it is the main result observed to assess the effectiveness. The other results are detailed in the chapter “effectiveness“
8	3	**HVB:** specify „both criteria“	We modified this sentence to be clearer. In the first draft we meant “primary and key secondary criteria“
8	7	**AQuAS:** Although this statement is true, the use of composite variables is common in cardiovascular studies and the represent a suitable tool to reduce sample size and to increase feasibily of the study.	We agree and we clarified our thought and our critics on this point. A hierarchical test sequence was planned therefore we preferred to get all-cause death at least as a key secondary end-point because key secondary endpoint didn’t provide more information than the primary endpoint.
8	11	**HVB / SMC:** doesn’t	We corrected

Page	Line	Comments	Comments from the author
8	15	**SMC:** Sentence should read; *It does not look consistent to consider CV deaths in the composite end-point, and not all cause deaths.*	Here we modified all the paragraph content
8	15/16	**HVB:** wording of sentence more directly	Rewording done
8	16	**AQuAS:** In our opinion, the use of CV deaths as part of the composite end point could be acceptable.	We agree
8	16+	**HVB:** I would add a paragraph on benefit risk ratio in Discussion. Vorapaxar reduces MI by 1-2% but increases ISTH bleedings. Weighing out these risks, is this a net benefit.	We agree with you but we prefer to leave the benefit/risk ratio to EMA assessment. We prefer to present separately the effectiveness and safety results. Therefore, each country is able to draw its own conclusions about this ratio.
8	21	**SMC:** CSR needs to be defined (clinical study report)	We modified
8	26	**HVB:** leads	We corrected
8	29	**HVB:** patients	We corrected
8	30+	**HVB:** I would add a paragraph: However, ticagrelor/prasugrel are first line recommendations within first year of MI in some guidelines. As data are lacking it is not fully clear how potential benefits/risks of vorapaxar-containing treatments can be compared/related to those of ticagrelor/prasugrel-containing regimes.	We agree and we added the following sentence: ”Ticagrelor and prasugrel are first or second line recommendations within first year of MI in some guidelines. As data on vorapaxar in add on to these two drugs are lacking, potential clinical interest of vorapaxar associated to ticagrelor or prasugrel can’t be assessed.”

Page	Line	Comments	Comments from the author
8	30+	**HVB:** In addition I would add a sentence on decision making: On that is unclear how/if/when patients treated with ticagrelor/prasugrel should be switched to vorapaxar schemes.	We agree and we added the following sentence: "It remains unclear if patients treated with ticagrelor/prasugrel could be switched to voraxapar schemes and if it is the case, how this switch can be done."
8	31	**AQuAS:** We strongly agree with the author about the special populations in which data regarding the use of vorapaxar is scarce and in which safety concerns might arise.	
8	35	**SMC:** Sentence should read; *Therefore additional data are needed.*	We corrected
8	38	**SMC:** Sentence should read; *The clinical study report (CSR)...*	We modified
8	41	**SMC:** The key study is published (Morrow 2012 etc); was the publication used for the analysis of efficacy?	Yes this publication was partly used, but the two main documents used were the CHMP report and the company's final submission book.
9	1	**HVB:** I would rework the conclusions, including a safety comment and benefit/risk ratio	We modified the conclusion's content and the wording.
9	3/4	**HVB:** 1. conclusion rather weak 2. wording?	We modified the conclusion's content and the wording.
9	5	**SMC:** Sentence should read; *However no [not any] conclusion can ....*	We modified
9	5-6	**AOTMiT** : Not clear what this sentence means	We clarified by changing the wording

Page	Line	Comments	Comments from the author
9	5/6	**HVB:** What does this mean? More specific.	We clarified by changing the wording
9	7	**AQuAS:** We do not identify which is the population that might benefit of Vorapaxar's use**.** Patients with increased risk of events and low bleeding risk might require treatment with prasugrel or ticagrelor. If in those patients use of potent antiagregants is not recommended because higher risk of bleeding, use of Vorapaxar should be discouraged as well according to available safety data.	See lines 34 to 40 page 8
9	7	**HVB:** can be used? /should be used only in/is suitable only for a defined population/i.e. …	We modified the conclusion's content and the wording.
9	7	**SMC:** I do not understand what this means; Vorapaxar can be used in a very specific population...	We modified to be clearer. We mean that Vorapaxar can only be used in a very specific population (subjects with a MI history but without history of stroke and without any treatment prescribed involving ticagrelor or prasugrel)
9	9+	**HVB:** suggest to add comment to population: vorapaxar tested only when MI was within <12 months ago.	This point is described in the REA report: "vorapaxar should be initiated at least 2 weeks after a MI and preferably within the first 12 months from the acute event" (moreover an antiplatelet therapy is not initiated more than 12 months after an ACS.
10	Table	**SNHTA:** http://apps.who.int/classifications/icd10/browse/2015/en	We added below the table.
10	1	**HVB:** check if all abbreviations are here: ISTH, GUSTO, ASA … just to name some	We added the missing abbreviations.
10	Table of abbreviations	**AOTMiT:** ICD-9 International Classification of Diseases, Ninth Revision (plus link to the website) ICD-10 International Statistical Classification of Diseases and Related Health Problems, 10th Revision	We added to the table of abbreviations.

Page	Line	Comments	Comments from the author
		http://apps.who.int/classifications/icd10/browse/2015/en	
10	Table of abbreviations	**AOTMiT:** The abbreviation ACS (acute coronary syndromes) should be included The abbreviation IHD should be explained And other, eg. ABI, ...	We modified and we added the missing abbreviations to the table of abbreviations.
11	Scope Box	**ZIN:** Adjust the colours to all other grey boxes	We modified
11	Table	**AOTMiT:** It should be the same as in the table as at the page 11 line 18-19 and page 14 line 21-22	Page 11 lines 18-19: The study protocol words were quoted to detail the inclusion criteria which is the company point of view about comparison, nevertheless and in the table p 11, and p14 line 21-22 it is our point of view which is written, therefore it could be different.
11	9-15	**AOTMiT:** The information about methodology of systematic review is not sufficient. e.g.: research question (PICO form), details of search strategy (precise queries, methods of the formulation of the queries, filters), number of reviewers, selection methods of included studies etc.	No more information was provided by the company about methodology of the systematic review.
11	1	**ZIN:** Chapter 1: Update Project Scope (Comparison) (see [B0001])	We modified
11	1	**AQuAS:** Standard of care should not be considered the comparator. Vorapaxar is prescribed in add on of standard of care and, therefore, placebo should be the most appropriate comparator.	We understand and we'll try to be clearer in the 2nd draft, but we prefer to showing in this evaluation that the comparator is a therapeutic strategy associating ASA±clopidogrel versus vorapaxar+ASA±clopidogrel.
11	11	**SMC:** Sentence should read; *The search was conducted....*	We corrected
11	12	**AOTMiT:** Medline and EMBASE databases should be written (PubMed is not a database)	We modified
11	12-14	**SNHTA:** e.g. **ACS** (Acute Coronary Syndrome) / unstable Angina / ressucitation after cardiac arrest	As the numbering of pages has changed between the version we have and the version you have, we did not find to what this comment

Page	Line	Comments	Comments from the author
			refers to.
11	13-14	**AOTMiT:** As provided in the previous comments: search terms: (vorapaxar AND **(**coronary artery disease OR coronary syndrome OR infarction OR angina**)**)	We modified
11	14	**AOTMiT:** It should be written how restriction to humans was made, by default filter or in different way (in general – search strategy should be provided)	No more information was provided by the company about methodology of the systematic review
13		**ZIN:** Paragraph 2.5: Project Plan v3 included this deviation already.	We don't see which conclusion we have to draw? What change do you want to see? We don't understand your point because a deviation to a protocol has to be presented.
13		**ZIN:** According to the assessment template, paragraph 2.4 concerns the quality rating of the studie(s). 2.5 is the description of the evidence.	We did not have comments on 2.4, therefore we delete this sub-title. And 2.5 became 2.4
13	3	**AOTMiT:** The table contains one trial: TRA 2ºP-TIMI 50 trial. However, the description of results (p. 16, l.3) indicate also Study P04736- TRACER study as supportive study. These information are not consistent.	Already answered above. We described only one study in this REA (the TRA 2°P-TIMI50 study), so it is logical that in this table we describe also only one study: theTRA2°P-TIMI50. The other study: the TRACER study was stopped early for safety problems, EMA didn't use this study to give the Marketing authorization to the company, but we thought it was interesting to tell few words about this study. Again, it was to get a better overview of this drug development.
13	4	**SMC:** Overall population should be 26,449 (randomised) and 26,352 (treated)	We added these details
13	4	**SMC:** Table 2: I do not think final column has been completed correctly; primary efficacy and key secondary	The final column aims to describe the other endpoints of interest

Page	Line	Comments	Comments from the author
		efficacy endpoints were also included in clinical effectiveness section as well as the safety endpoints noted.	included or not in both clinical effectiveness and safety domains. Here the objective is not to detail once again the main effectiveness endpoints (described in the previous column), but relevant endpoints included in the study objectives.
13	6	**SMC:** Project plan; what is this referring to? I think the information relates to the deviation from protocol of the clinical study but is this what is meant by deviations from the project plan?	Exactly this is a real and huge deviation to the protocol.
14	11	**SMC:** Description of vorapaxar is taken directly (i.e verbatim) from EPAR	We corrected, the citation was included.
14	21	**AQuAS:** Comparison: from our point of view, standard of care should not be considered the comparator. Vorapaxar is prescribed in add on of standard of care and, therefore, placebo maybe the most appropriate comparator.Ticagrelor or prasugrel could be considered as comparator but it should be noted that they do not share the same licensed indication that vorapaxar and that their use, in contrast to vorapaxar, is intented for the initial phase of an acute coronay syndrome.	See answer above.
14	21	**HVB:** replace „Aspirin“ throughout manuscript by „ASA“	We modified
14	21/22	**HVB:** That is true! But isn't this a discrepancy with beginning ticagrelor/prasugrel are no alternatives?	In our opinion, Vorapaxar is indicated to be administered in addition to (not instead of) therapy with ASA alone or ASA plus clopidogrel. Therefore the comparators might be considered as treatment strategies and not as individual drugs, thus a placebo is needed to realize a double blind clinical trial and the two different therapeutic strategies compared are vorapaxar + ASA ± clopidogrel versus ASA ± clopidogrel. There is limited clinical experience with vorapaxar + prasugrel and no experience with vorapaxar + ticagrelor in the Phase 3 studies.

Page	Line	Comments	Comments from the author
			Vorapaxar should not be initiated in patients taking prasugrel or ticagrelor and in case of need for additional therapy with these agents, vorapaxar should be stopped.
14	28	**AQuAS:** We don't fully understand the following statement „Therefore the comparators might be considered as treatment strategies and not as individual drugs"	In our opinion, Vorapaxar is indicated to be administered in addition to (not instead of) therapy with ASA alone or ASA plus clopidogrel. Therefore the comparators might be considered as treatment strategies and not as individual drugs, thus a placebo is needed to realize a double blind clinical trial and the two different therapeutic strategies compared are vorapaxar + ASA ± clopidogrel versus ASA ± clopidogrel.
14	28-31	**AOTMiT:** It is not an answer for the question B0001 and should be deleted	We modified
14	33	**HVB:** ..limited clinical experience with vorapaxar + prasugrel and no experience with vorapaxar + ticagrelor in …	We corrected
14	34-35	**AOTMiT:** It is not an answer for the question B0001 and should be deleted. Mechanisms of action should be descripted.	We modified
14	37	**SMC:** Change acetylsalicylic acid to ASA as this appears to be used as standard abbreviation throughout the document	We corrected
14 15	10-39 1-8	**AOTMiT:** There is lack of the information about source of data. Search strategy for comparators or for clinical guidelines may be provided for the statement "there is limited clinical experience with prasugrel"	We modified
15	23	**SMC:** Sentence should read; *There is limited clinical experience* ***of use of vorapaxar*** *with prasugrel and no experience with ticagrelor in the Phase 3 studies.*	We corrected
15	28/29	**HVB:** You mean versus clopidogrel/prasugrel/ticagrelor. But isn't there such evidence for ASA, which is also an antiplatelet agent? As it is recommended for a life time as	We corrected. In general, with the exception of ASA, current recommendations on the use of oral antiplatelet therapy (clopidogrel, prasugrel, ticagrelor) limit the duration of therapy to 12 months

Page	Line	Comments	Comments from the author
		standard?	following an ACS event.
15	30	**SMC:** Use in renal and hepatic impairment needs to be expanded (from summary of product characteristics)	We expanded based on summary of product characteristics.
15	40	**ZIN:** Are data known regarding the distribution of patients over the different background antiplatelet regimens in study TRA2P-TIMI?	We modified
15	41	**SMC:** Spelling - should read; events	We corrected
15 16	36-49 1-13	**AOTMIT:** It is not an answer for the question B0002 and should be deleted	We modified
16	18	**SMC:** Why use the terms heart attacks (rather than MI) in discussion section?	We corrected
16	17	**ZIN:** Move in Space at beginning of sentence	We modified
16	22	**AQuAS:** Data on the use of vorapaxar for periods longer than 2 years is limited. This is remarkable for a drug that is intended to be used in a chronic manner.	We agree
16	32	**ZIN:** Delete ; at the very end of the sentence	We modified
16	17-32	**AOTMiT:** The paragraph is written with non-medical wording (“heart attack”, “special cells in the blood called platelets” ...)	We modified.
17-26		**SMC:** Health problem and current use of technology: this section is far too detailed and lengthy and needs to be summarised.	We modified

Page	Line	Comments	Comments from the author
17	15	**AQuAS:** Acute coronary syndrome also includes unstable angina.	We agree
17	18	**HVB:** only recent MI <12 months? be aware: EPAR/text above, formally suggesting any MI (also longer ago).	We fully agree. Although the TRA 2°P - TIMI 50 trial was not designed to evaluate the relative benefit of Zontivity in individual patient subgroups, the benefit was most apparent in patients who were enrolled on the basis of a recent MI as indicated by a history of spontaneous MI ≥2 weeks but □12 months prior (post-MI patient population) with no history of stroke or TIA.
19	29	**ZIN:** Missing word: "ischemic event more than a year **before**.."	We modified
34	1	**SMC:** Table 7: these data are in the PLP and this should be included in table heading.	We clarified.
24	30	**AQuAS:** Stroke or PAD? Or Stroke or TIA?	We clarified. Vorapaxar is indicated for the reduction of atherothrombotic events in adult post-MI patients without history of stroke or TIA,
24	30	**AQuAS:** Regarding question [A0023] an extensive review of epidemiolgical data is offered. However, the review is focuss in CHD incidence and mortality and the number of patients candidates to receive treatment according the labeled indication (this is, excluding the estimate number of patients with history of stroke or AIT) is not offered.	We modified
25	8-22	**AOTMiT:** These paragraphs are not relevant to the assessment made for Europe; the suggestion to omit them.	We modified.
25	44	**ZIN:** Words missing: "…about 2,5 – 2,7 **????** and 5,2 - 5,5 MI patients..	We corrected.

Page	Line	Comments	Comments from the author
27	10	**SMC:** Study TRA2°P-TIMI50 was also company sponsored.	Yes.
27	14	**ZIN:** The number of patients in each of the three strata could be added (table 11 in Appendix 1, p. 45 mentions the numbers).	We added these data.
27	24	**SMC:** Sentence should read; *Patients were treated with one tablet a day of vorapaxar 2.5 mg + ASA ± clopidogrel or one tablet a day of placebo + ASA ± clopidogrel.*	We modified.
27	25	**SMC:** The following information should be included: **ASA±clopidogrel were given according to local standard of care guidance.**	We added this information.
27	26	**SMC:** The following information on randomisation should be included. **Patients were stratified according to qualifying diagnosis and physician's intention to use thioenopyridine.**	We added p29 l.1 in the 2nd draft oft he REA report.
27 33	"Clinical effectiveness" chapter "Safety" chapter	**AOTMiT:** The idea if "European collection" rather than European Report lays in having all information divided into small basic pieces of information easy to be incorporated in national reports. Thus the report consists of questions (eg. D0001, D0003, D0005, D0006 for clin. eff.) and answers. Here these two chapters include information (p. 27-30, p.33-34) not enclosed in such a structure – I wonder if this breaks methodological rules? Does this information need a question to be asked?	This structure is also used in previous pilots.
27	7-8	**AOTMiT:** The statement is obvious. Nobody expects that	It is useful to clarify upon which point of view the assessment has

Page	Line	Comments	Comments from the author
33	7-8	public HTA is made from manufacturer perspective.	been done. Furthermore, it is a regulatory sentence, which you can find in each EUnetHTA REA published, but if the EUnetHTA WP5 pilot team ask us to remove this sentence it will be ok for us.
28	3-42	**SNHTA:** Exclusion criteria not specified + which statistic software has been used?	We added the main exclusion criteria. Statistic software information was not provided by the company.
28	3	**AOTMiT:** There is lack of the information about exclusion criteria.	We added the main exclusion criteria.
28	39	**SMC:** Sentence should read; ... *and included an adjustment for potential dropouts during the study*.	We corrected.
28	42	**SMC:** 25,000 noted in protocol published with Morrow 2012 publication (and not 27,000).	At first a sample size re-estimation led to increase the recruitment up to 25,000 subjects but then they decided to include 2 000 subjects more to reach a number of 27 000 subjects included: 26,449 patients have been randomized.
29	15	**SMC:** EPAR notes that it was the sponsor and executive committee (not the Executive and Steering Committees) who predefined populations of interest, and went on to exclude history of TIA in the PLP.	The company gave us the information whereby it was **the sponsor** and **the Executive and Steering Committees** who predefined the population of interest, and excluded patients with a history of TIA of the PLP.
29	20	**SMC:** Need to note that the analysis in PLP was post hoc.	We added a sentence to p.8 and p.33
30	Question A0023	**AOTMiT:** On what a base PAD is excluded here? (not in other places of the report)	EMA decided to exclude patients with PAD, but the aim of this decision was described neither in the company book nor in the CHMP report. The detailed exchanges about these safety points stayed between DSMB and EMA. We suggest to add the fact that we don't know why this population has been excluded in the report (p6 and p29)

Page	Line	Comments	Comments from the author
30	1	**SMC:** Table 4: for consistency should aspirin be changed to ASA?	We modified.
30	1	**SMC:** Table 4: The proportion of patients who receieved ASA + thienopyridine was around 77%.Standard practice in UK is to use ASA + thienopyridine for 12 months and then to continue with ASA alone At what stage were patients recruited to the study; soon after MI or close to 12 months after MI? Are there any data on the length of time since MI, before patients were recruited to study. This will effect baseline medication as patients will not be treated with clopidigrel long-term but will be treated with aspirin long-term.	Indeed, this standard of care is quite common in Europe and this is an interesting question but unfortunately this information was not provided/noticed by the company. We suggest adding a sentence on the fact that we don't have any data on that point in p.33 l.15. of the report.
30	3/4	**ZIN:** If D0001 and D0003 are answered together with D0005 this should be mentioned in the text.	We clarified this point by adding a sentence.
30	9	**SMC:** Table 5: error in voraxapar group patients with key secondary endpoint should be **1028 (7.8%)** and not 532 (7.8%)	We modified.
30	9	**HVB:** Key secondary endpoint/Vorapaxar+ASA±clopidogrel/Patients with event: 532 doesn't seem to be correct? Cannot be 7,8%.	We corrected.
31	3	**SMC:** It is not clear whether the all cause death data are for overall population in PLP. I have been unable to confirm from	The company gave us these data, they are PLP data. They are

Page	Line	Comments	Comments from the author
		EPAR.	different from the publication data which are on the overall population.
31	7	**SMC:** Sentence is unfinished.	We modified.
31	7-8	**ZIN:** Meaning of wording not clear: "..that vorapaxar modifies the progression of atherosclerotic coronary lesions **but as?** an antiplatelet therapy."	We modified, it was a punctuation mistake.
31	19-21	**ZIN:** The meaning of this sentence is not clear to me: "a clear benefit was shown in both criteria and MACE as primary and key secondary composite endpoints are widely used in trials."	Ok we modified the wording to be clearer.
31	15	**ZIN:** Add in Discussion (paragraph 5.3) after line 15: The event rate increases from 6% after one year to 11.4 % in the next two years period. While the rate of events is rising over time, the rate of rise is decreasing over time, suggesting that the benefit of vorapaxar is lowering with time, especially beyond 2 years. This is supported by an attenuation of the effect from year 2 to year 3 (HR year 1 is 0.85, year 2 is 0.75, year 3 is 0.91). *This also could be added to paragraph 3.3 Discussion (p. 16, line 24).*	We added this paragraph with the precision that this comment came from the CHMP assessment report.
31	19	**AQuAS:** Although this statement is true, the use of composite variables is common in cardiovascular studies and the represent a suitable tool to reduce sample size and to increase feasibily of the study	Indeed, it is common in cardiovascular trial, but at present and with the current use of a hierarchical test sequence in the study set up, we thought that a key secondary as a composite endpoint doesn't bring any additional data of interest fort the drug evaluation. But we modified the way we wrote our thought to be clearer.
31	24	**SMC:** Spelling	We modified.

Page	Line	Comments	Comments from the author
		Sentence should read; ... is **mainly** led by MI, indeed MI occurred	
31	24	**SMC:** The definition of MI/size was highlighted in the EPAR given that it is a key driver for the primary endpoint. Suggest that this be added to the assessment document.	We already explained that the overall result of the main criteria is mainly led by MI because MI occurred 5 times more than CV death or stroke in both criteria. We have presented it as a key driver.
32	1	**SMC:** Note that there is consistency between the overall population and PLP in terms of breakdown of primary efficacy endpoint results, which provides reassurance given that data for PLP are from a post hoc analysis.	We are not sure whether the consistency between the overall population and the PLP results allows to conclude with confidence on the data in the PLP.
32	3	**AQuAS:** In our opinion, the use of CV deaths as part of the composite end point is, indeed, adequate.	We agree and we modified our comment on that point.
32	3-7	**ZIN:** A drawback of 'all-cause death' as criterion of the composite endpoint is that death related to comorbidities contributes to this endpoint. The standard treatment of comorbidities however is not included into the study protocol and thus can introduce differences between study arms.	In a real-life situation we are strongly interested in "all-cause deaths". These criteria bring information on the global benefit of the treatment, especially with antiplatelet drug that can provide haemorrhage as well as avoid events. If a trial is correctly randomised, all cause death does not introduce difference between study arms.
32	8	**SMC:** Analysis in PLP was post hoc. This needs to be noted. But there are two issues here: 1) the change to the protocol following the DSMB recommendation to discontinue all patients with a history of stroke; was this decision made before the study was unblinded? 2) EMA's decision to focus on patients with CAD without	This was noted (cf few lines above in this table) 1) Discussed in the report (cf p33 l.1 to 10) 2) We did not understood the aim of this part of the comment

Page	Line	Comments	Comments from the author
		history of stroke or TIA (PLP). The PLP was defined post-hoc considering that the diagnosis of stroke versus TIA can be difficult based on subject history alone	
33	Research questions table	**AOTMiT:** The suggestion that the order of questions in the table (C0008, C0002, ...) is the same as in the text below. Question C0004 not answered in the text	We modified this point.
33	9	**ZIN:** Change sentence: "Reminder that the DSMB **decided the study TRACER to be discontinued** earlier due to…. etc."	We agree and we modified the safety chapter to gain clarity.
34	5	**SMC:** This sentence lists all reasons for treatment discontinuation (and not the main reasons). Suggest changing the sentence to as follows; Among subjects treated in the overall population (n=26,352), the main reasons for treatment discontinuation were AEs, consent withdrawal, and protocol non-compliance.	We don't agree, because this is an exhaustive list which has its place in this chapter. Moreover, we don't have the data/the percentages for each treatment discontinuation reason, therefore, we don't know the main reasons.
35	3-6	**SMC:** Error in definitions of GUSTO criteria The GUSTO criteria should read: **Moderate: bleeding requiring transfusion, but does not result in haemodynamic compromise** **Severe: deadly bleeding, intracranial bleeding, or substantial haemodynamic compromise**	We corrected.
36	5	**SMC:** Table 10 title suggest changing to;	We don't agree because some of these SAEs occurred in < 0,5% of

Page	Line	Comments	Comments from the author
		Table 10 : Summary of other serious adverse events in TRA 2°P-TIMI 50 Proposed Label Population (Post-MI subjects without history of stroke or TIA) in >0.5% of patients in either group	patients in either groups.
37	9	**SMC:** Error Result is **not** significantly higher for <60kg subgroup, as 95% CI includes 1 (HR=1.78, CI95 = [0.85-3.74])	There is no error. Here we are not comparing the treatment arms. "The percentage of patients who experienced a GUSTO severe/moderate bleeding event was significantly higher **in both treatment arms** for patients weighting < 60 kg" but we are comparing patients subgroups bleeding risks in general (with or without vorapaxar)
37	16	**SMC:** Error: a mixture of KM rates and proportions have been used. The sentence should read: The percentage of patients who experienced a GUSTO severe/moderate bleeding event was significantly higher in both treatment arms for patients in subgroup with Clcr < 60 ml/min (ASA±clopidogrel=4.2% versus vorapaxar+ASA±clopidogrel=6.6%, HR= 1.59, CI95 = [1.01-2.48]) compared with patients in subgroup with Clcr ≥ 60 ml/min (1.6% versus 2.3%, HR=1.43, CI95 = [1.14-1.80]).	We modified.
37	26	**ZIN:** If C0002 is answered together with C0007 it should be mentioned in the text (or using a + sign for example).	We clarified this point by adding a sentence.
37	44	**SMC:** Suggested change to sentence: An antidote for voraxapar does not exist....	We modified.
37		**SMC: General comments: these include more focus on potential limitations of the study particularly when**	See previous column

Page	Line	Comments	Comments from the author
		translating the results to practice. • Is it worth commenting on length of treatment with aspirin (median duration 902 days) and clopidogrel (median duration 517 days). Does this reflect usual clinical practice? • The correct comparator 12 months post MI would be aspirin monotherapy. Is it reasonable to assume that the risk/benefit of adding vorapaxar to this strategy would be the same as shown in the study? • What was length of time after MI before patients were recruited to the study? HAS/SK answer : : Not provided • Is the event rate in the placebo arm what would be expected in a population at this level of risk? HAS/SK answer : Depends on the country • In practice are patients likely to be commenced on vorapaxar soon after the MI? HAS/SK answer : NO national/international guideline already published • Has the clinical study provided data on the optimal duration of therapy with vorapaxar? In the clinical study the median duration of treatment was 2.5 years and >76% of patients were on treatment for at least 2 years. 1 A key issue is balancing the benefits in terms of reduced cardiovsacular events against the increased risk of bleeding. It may be helpful to present as NNT and NNH and to discuss the net clinical outcome (covered in one of the published papers).	
45	table	**AOTMiT/ SNHTA:** Data on median duration of the study are	It is not the same duration taken into account : table 7 present data

Page	Line	Comments	Comments from the author
		different than in table 7 p. 34	on Duration of participation in treatment, whereas table 11 page 45/46/47/48 presents data on Duration of participation in the study, which is not the same thing and explained the small difference between the two median durations
45	Appendix	**ZIN:** Name all the Tables as A.1.;A2. …	We named all the tables in the appendix according to your request
46		**AQuAS:** In the publication of TRA2ªP-TIMI 50 study (N Engl J Med 2012;366:1404-13.), the authors refered a change in the endpoints hierachy. Before the database was locked the authors explain that „On the basis of data from that trial [TRACER], the steering committee amended the main data-analysis plan to reorder the hierarchy of efficacy analyses, defining as the primary end point the composite of cardiovascular death, myocardial infarction, or stroke	We will address this point/question in the 2nd draft document (p.33l.21). We didn't address this point because neither EMA through CHMP report, nor does the company provide any information about that. We didn't expound upon this point in the document because the two mains endpoints were positive for vorapaxar. And as we explained above, this trial was set up according to a hierarchical test sequence; therefore these two criteria have the same power in the results analysis. This point could be a real problem only if the primary endpoint didn't show any difference between the two therapeutic strategies, in this case the key secondary endpoint's results couldn't be analysed.
47		**AOTMiT:** There is no list of ongoing studies nor information that they have been seek and not found There is no "Risk of bias" table/information	Firstly, there is no on-going study planned except the risk management plan. Secondly, this trial does not present major bias : the only methodological problematic released was the reduction of the overall population which no represent those described in the statistical analysis plan, leading to a loss of power but not to a bias, therefore the risk of bias table was not detailed.
47		**SNHTA:** Detail on whether there are some ongoing studies and intention to treat outcomes to minimize bias	There is no on-going study planned except the risk management

Page	Line	Comments	Comments from the author
48	Table 12	**ZIN:** This summary of Table 12 does not mention the correct outcomes: all cause death was a non-key secondary endpoint. Update Population: treated with ASA± clopidogrel excluding patients treated with ticragelor or prasugrel.	This has been corrected.

APPENDIX 4. INPUT FROM THE MARKETING AUTHORIZATION HOLDER AND THE WP5 MEMBERS ON THE EDITORIAL DRAFT ASSESSMENT

Input from the Marketing Authorization Holder on the Editorial Draft Assessment

GENERAL AND SPECIFIC COMMENTS FOR THE AUTHOR

Page	Line	Comments	Comments from the author
7 (10) (30) (34)	39-45 (25-26) (34-40) (28-29)	The reviewer's comment here is not an accurate statement. The EMA did not decide to limit the population, but rather the MAH, in filing for European regulatory approval only initially filed among patients in the CAD stratum with no history of stroke or TIA. During review of the submission, the MAH wished the CHMP to consider the ILP, i.e., include patients qualifying for the TRA-2˚P TIMI 50 trial because of PAD. However, the CHMP declined to do so, indicating that the MAH could re-file or file a type II variation after receiving approval of the PLP-based file.	We adapted what is written in the report in details : - First: "the DSMB recommended discontinuation of the study drug in all subjects with previous stroke", - and then: "the European Medicines Agency (EMA) decided against expanding the submission to include subjects from the PAD stratum.. We added this clarification about the PLP in the "n.b." pages 7 and 30.
9	1, 6-7	It is unclear why the reviewers rate the quality of body of evidence for both efficacy and safety as only "moderate," and the MAH struggles to understand why there would be a "possibility that [the true effect] is substantially different" than the effect estimate. The MAH can only assume this rating was driven by other critiques that are described in the remaining assessment and we have addressed those specifically in the table herein.	The answers hereunder help to understand why the assessors cannot grant a high level of evidence to the results obtained.

		The MAH is confident that the true effect lies close to that of the estimate of effect and would consider the body of evidence provided to be of "high" quality. Our submission cites robust evidence that vorapaxar provides significant incremental clinical benefits and reduces the occurence of major CV events when co-administered with standard of care regardless of timing of vorapaxar initiation, regardless of background treatments, and among various high risk patients. As described in detail below, we object to the reviewers' criticisms around the composite endpoints, hierarchical testing of endpoints, the power of the trial, the consistency of drug effect over time, and the rationale for focusing on the PLP. Bleeding is vorapaxar's only serious side-effect, and fatal bleeding is not increased with vorapaxar. The MAH arrived at the PLP after excluding patients in whom there was a safety risk which outweighed the benefit. We have shown consistency of effect and demonstrated statistical significance for the primary and key secondary endpoints in the Overall pre-specified population, in the PLP (and in the ILP populations).	
10 (33) (34)	2-21 (6-12) (9-24)	The assessor's objections with regard to the trial endpoints, if valid, would apply to all anti-platelet trials. The TRA2°P TIMI 50 trial is no different from PLATO (ticagrelor) or TRITON TIMI 38 (prasugrel) with regard to using a composite endpoint. No directive or precedent specifies that components of a composite endpoint must contribute equally. Thus, the MAH views the assessor's comment as an observation rather than a valid criticism. The MAH is not aware of any antiplatelet trial with a primary composite endpoint that has shown equally occurring components, and wonders why a desireable composite would need its components to do so. Likewise, the number of MI events in PLATO and TRITON also outnumbered strokes and CV	On these points, the assessors only listed facts. Indeed composite endpoints artificially increase the power of the results, we didn't criticize the value of the final result of the composite endpoints because of that, but we deleted this issue which can be misunderstood by readers. Then, vorapaxar is a new antiplatelet therapy, and is used as an add-on therapy, therefore, we may not compare to previous antiplatelets trials' design. Moreover a common trial design is not expected to be the gold standard for years and can evolve. When a composite endpoint is chosen it is expected not to see

		deaths: in PLATO there were 1097 MIs, 231 strokes, and 795 CV deaths; in TRITON there were 1095 MIs, 121 strokes, and 283 CV deaths. Moreover, the individual components of the composites in TRA2°P have directionally consistent results – a feature not common to pivotal trials of other antiplatelets: for the overall population in TRA2°P, MI, stroke, and CV death endpoints had individual HR point estimates of 0.83, 0.97, and 0.89 respectively – all less than 1.0; for the PLP in TRA2°P, 0.80, 0.62, and 0.82 – again, all less than 1.0. Contrast with PLATO (ticagrelor): these values were 0.84, 1.17, and 0.79; in TRITON,(prasugrel) 0.76, 1.02, 0.89.	only one of the criteria driving the overall result. In the vorapaxar trial, the results of the composite end point is driven by one of the criteria (here MI occurred 5 times more than CV death or stroke). This does not allow robustly assessing the drug based on the other criteria. In this trial, vorapaxar demonstrated a clinical benefit mainly on morbidity (mainly MI), but no significant difference was shown with regard to CV mortality (or overall mortality). According to EUnetHTA guidelines, ***Endpoints used for relative effectiveness assessment of pharmaceuticals - Composite endpoints***: "The most frequently quoted problem is the risk of misinterpretation when there is heterogeneity of response among components of composite endpoints […]if the effect on a composite endpoint is mostly driven by an effect on one of the components, it is not admissible to conclude that the treatment has an equal or important effect on all the components. This has been demonstrated by several systematic reviews of studies using composite endpoints endpoints" Here again it is a fact, MI occurred 5 times more than CV death or stroke, and show a real difference between arms, therefore we have concluded with this sentence in the report p10: vorapaxar demonstrated a clinical benefit mainly on morbidity (mainly MI), but no significant difference was shown with regard to CV mortality"

		The assessor describes hierarchical testing accurately. However, there does not exist a directive or precedent regarding ordering the tests by importance. Indeed, in PLATO (ticagrelor), all-cause mortality was the last listed test in its specified hierarchy. No safety signal exists for vorapaxar that would suggest a harmful effect in terms of mortality. Fatal bleeding is not increased with vorapaxar, and bleeding is vorapaxar's only serious side-effect. The key secondary endpoint is of critical importance: it contains the objective components of the primary composite and corresponds to the endpoint of other major antiplatelet trials. The assessor's objection to the traditional MACE endpoint appearing as the first secondary is puzzling to the MAH: in hierarchical testing, a similar composite has no impact on the success of tests occurring after it (although if it fails, all those after it fail as well). Thus placing a composite largely similar to primary as the first secondary does not inflate the likelihood to succeed of those that follow. Hierarchical testing is a way of conducting valid statistical multiple testing, and may or may not reflect in its ordering the relative clinical importance of the items in its list.	There doesn't exist a directive for choosing a specific hierarchical testing, however, it is commonly done in trials since a few years ago, mainly in the cardiologic area. This is the only way to conclude robustly about all the secondary endpoints. We don't agree: the key secondary endpoint chosen didn't provide much more information than the primary endpoint. Therefore it is important to think strategically on the endpoints order when a trial is designed.
10	27-29	Yes, the supposition by the reviewer with regard to the exclusion is correct. Patients with a history of stroke or TIA were excluded without unblinding. This is described in Table 3.2.2, which	We modified this sentence.

		references CSR section 9.8 where this exclusion is described in detail. The CSR was provided to all reviewers along with all references in the final submission file.	
10 (34)	29-37 (27-37)	The power of a trial is its ability to detect a difference in treatment effect. Since the trial had positive results and did demonstrate such a difference, the power is moot. As both populations achieved statistical significance, the MAH struggles to understand why the reviewer is criticizing power. The trial was powered based on the wider original population. As the PLP is a smaller sample, at the same relative efficacy, a smaller population will reduce the power to show differences in treatment effect. Since efficacy was observed even in this smaller population, the results observed may certainly be interpreted as robust. As noted in Table 3.2.2, study population, "***The decision to submit for this limited population was made for the purpose of safety/benefit/risk, and not to reach statistical significance.***" The PLP analysis is not "post hoc" in the negative sense of a selection to show statistical significance that was not previously present: the overall population demonstrated statistical significance; and, a safety-issue drove definition of the label population to exclude prior stroke/TIA. Surely, the regulatory authority would want to know the results in the population that it would ultimately designate to receive drug.	The reviewers are not discussing the power of the trial and the validity of the results. Vorapaxar was evaluated in the MA indication meaning in the PLP. However we needed information or arguments about the statistical analysis plan changes; we would have liked to see a new calculation of the power in the PLP. It is true that the statistical analysis was planned for the overall population, not for the PLP. The results and the effect obtained in the PLP are not as precise as the one obtained in the overall population. Indeed the confidence interval is wider; therefore the quantity of effect is less precise. In addition to the internal validity, the estimation of the external validity is also part of the HTA assessment. The external validity of the results obtained in the vorapaxar trial is not guaranteed. Therefore the reviewers cannot grant a high level of evidence to the results obtained.

		Details (provided in Table 3.2.2 of the final submission) as below: *‡Note: Important to note is that the PLP was a subset of the overall population that was defined in response to the DSMB recommendation to exclude stroke patients, which was done after randomization and prior to database lock, and to exclude TIA patients, which was done after database lock for the purpose of clinical clarity and patient safety as described above, and as per EU decision to include only subjects whose qualifying condition was CAD.* ***The decision to submit for this limited population was made for the purpose of safety/benefit/risk, and not to obtain statistical significance, which had already been achieved with the overall study population.*** *Efficacy was demonstrated in the Overall population* *MAH did what would be expected that Regulators would do, to exclude patients for which there is a safety risk which outweighs the benefit.* *- This excludes patients with a history of stroke or TIA, and leaves the Intended Label Population (ILP)§.* *We achieved significance in our pre-specified population, i.e. Overall and arrived at PLP (or ILP§) for the purpose of safety/Benefit-Risk by excluding patients with a history of stroke or TIA.* *- We have shown consistency of effect.* *- We demonstrated statistical significance for the primary and key secondary in the Overall, in the PLP, and in the ILP populations.*	
10	43-44	No clinical data exist on switching. Unlike clinically relevant issues when switching among drugs that all target the same $P2Y_{12}$ receptor, starting or stopping vorapaxar, which targets the PAR-1 receptor, does not raise the possibility of ineffective	We understand this argument , however, physicians need information to know how a switch from prasugrel or ticagrelor must be done.

(34)	(38-46)	activity at the $P2Y_{12}$ receptor. Thus, we anticipate no such pharmacodynamic issues when giving vorapaxar before, during, or after a $P2Y_{12}$ inhibitor, and did not experience any with clopidogrel.	
11 (34)	6-7 (13-14)	It is not clear what the reviewer's criticism is based on the comment as written. We are assuming the comment is with regard to a comparison of vorapaxar+ASA+clopidogrel compared to ticagrelor+ASA and compared to prasugrel+ASA. As described in detail, in Module 3.1, due to the heterogeneity of patient populations treated by vorapaxar and ticagrelor and prasugrel, an indirect comparison would not be scientifically appropriate. Results of such analyses would not be informative in comparing these treatment options as they would be both scientifically invalid, uninterpretable and insufficiently powered.	We agree. The statement has therefore been deleted from the final report.
11 (35)	14-19	The MAH does not accept the assessor's logic leading to a conclusion that CV mortality cannot be evaluated. See prior comment (second row) regarding the irrelevancy of placement of mortality in the hierarchy. CV mortality is a component of the primary and the key secondary endpoints, contrary to the assessor's claim. The MAH challenges the assessor's statement that data on mortality are exploratory: CV mortality and all-cause mortality were each pre-specified, adjudicated, and underwent formal statistical testing both in the composite endpoints and as	Yes it is a component of the primary and key secondary endpoints but it didn't show any difference between treatment arms. (1,1% versus 1,0% in the primary endpoint and 1,2% versus 1,0% in the secondary endpoint) moreover the total frequency of these events remains low. All-cause deaths criteria remains exploratory outcomes: it is the 7th secondary endpoint…the alpha risk is really too high to conclude that results are not due to chance (basic statistical

		secondary endpoints. Such treatment does not describe exploratory outcomes. They deserve evaluation each in their respective contexts.	law)
11	24-29 (35-36)	This comment is not accurate with regard to the indication for vorapaxar. The assessor is inappropriately assuming that the patient qualifying strata indicated the presence or absence of disease. Patients who qualified in the PAD stratum may have coronary arterial disease, and those in the CAD stratum may also have PAD. Vorapaxar is indicated in patients with a history of MI and without a history of stroke or TIA. According to the EU SPC, PAD patients do not currently have an independent indication for vorapaxar based on PAD alone. It is NOT accurate that patients with history of PAD are ineligible among the indicated label population. In addition, while patients taking ticagrelor or prasugrel should not be additionally treated with vorapaxar, patients not receiving either are eligible even if treated prior. Physicians make decisions with regard to disease management including prescribing medications taking into account the risks and benefits for individual patients. We don't foresee the prescribing of vorapaxar to be inconsistent with the challenges of individual patient care. ACS is a serious life-threatening illness	We modified this sentence about PAD stratum. According to the MA indication, it remains complicated for physicians to decide how and when its patients really need this "add-on drug". Guidelines are needed

		and patients deserve treatment by physicians in a thoughtful way. This is true for any disease management strategy, and certainly true for other antiplatelet therapies. In fact, in many ways, it's much easier for a physician to decide to prescribe vorapaxar compared to other antiplatelet strategies. For instance prasugrel use is limited to patients with ACS managed with PCI; vorapaxar is more simply indicated for patients with history of an MI (with or without PAD), as long as not otherwise contraindicated. Vorapaxar was approved by EMA in January 2015; we do anticipate that it will be better defined in the international guidelines in the near future.	
11 (18)	11	This is an inaccurate statement; the EMA did not decide to further refine the population. The PLP does not exclude patients with PAD. As clarified above, while we did not include additional patients who had a history of PAD (and did not have a recent MI), we did not exclude PAD patients among those patients who had a recent MI.	As we answered previously, we modified this sentence into : "the EMA decided against expanding the submission to include subjects from the PAD stratum.." We understood your point of view and to be clearer we modified the sentence into: the EMA decided against expanding the submission to include subjects from the PAD stratum..
16	20-24	This statement describing the TRACER study is not entirely accurate. The TRACER study was conducted in parallel with the TRA°2P TIMI 50 study, on a distinct patient population. Efficacy evidence only includes data from the TRA°2P TIMI 50 study, though all patients exposed to vorapaxar, including TRACER participants were used for safety evidence.	The fact is that TRACER could not be helpful for efficacy assessment.

		TRACER was not stopped early. TRACER was an event-driven trial and had accrued its requisite number of events.	"The DSMB concluded this study earlier due to the higher number of intracranial haemorrhage on the vorapaxar arm" (CHMP report – 20/11/2014 - page 35/116)
28	17-21	The reviewer's critique seems unfounded. As noted in Table 3.2.1, there were specific procedures in place to both maintain blinding and ensure patient safety. As described in the blinding procedure section of the table, and detailed in the CSR as referenced (the CSR was provided along with all references in the final submission file), as is typical of a blinded randomized controlled clinical trial: *The Data Safety Monitoring Board (DSMB) was allowed to inspect unblinded results only in defined circumstances if it were felt necessary to make decisions about the safety or continued participation of subjects. Thus, an independent statistician within Duke Clinical Research Institute* *(DCRI) was given a copy of the randomization schemes to support* *requests by the DSMB; these schemes were protected by the standard operating procedures of DCRI. (CSR section 9.4.6)*	We modified (cf answer already done previously)
30	1-5	The reviewer's comment with regard to the change in benefit of vorapaxar over time is unfounded. The rate of rise of the event rate (the hazard – not the hazard	You are right we have ignored the HR decrease from year 1 to year 2, therefore we added a sentence about it. However, this global remark came from the CHMP report and many European HTA agencies requested to add this point to the final assessment report.

		ratio) denotes the risk to patients and depends on the disease, not on the effect of vorapaxar. This becomes clear by noting that the phenomenon mentioned by the assessor occurs in the placebo arm alone, and thus could not be due to an effect of vorapaxar. The HR denotes the drug effect. The assessor notes the HRs in years 1, 2, and 3 as 0.85, 0.75, and 0.91, focusing on 0.91 and ignoring the decrease from 0.85 to 0.75. These variations in HR provide no inference on time-varying drug effect because the confidence intervals all overlap, i.e., these represent random variation of a consistent drug effect from randomization to the trial's end. The proportional hazard assumption was tested and found to hold throughout the trial, i.e., the data do not support a significant change in the HR over time.	
34	1-3	The reviewer mentions a lack of data on trial patients with regard to time since MI. This was described in the submission. Patients included in the trial at time of randomization would be equally likely to be on clopidogrel as all patients had a history of MI within 2-52 weeks (guidelines recommend clopidogrel no more than one year following an MI), though the continuation of clopidogrel would vary over follow-up.	We deleted this sentence and we added a new table in the final REA report (table 5.3 page 32). However these data were found in the CSR (table 21 p166) but in table 1.2.2 of the submission file.

		Data on the distribution of patients' time since MI is described in the submission and shown in Table 1.2.2, which illustrates consistency of effects among patients regardless of duration since MI (~44% <3 months; ~29% 3-6 months; ~27% 6-12 months).	
35	11-12	Reviewers mention a change in the endpoints of the TRA°2P TIMI 50 study. The academic research organization running the trial (TIMI) elected to make this change prior to database lock. The change in endpoint was only made by the academic research organization, and not by the MAH. The MAH decided that regulatory documents needed to keep the original endpoints despite the change suggested prior to database lock. Only the publicaton referenced reflects the change made by the academic research organization, no analyses that impact regulatory submission filings. In fact, what the reviewers describe as a criticism on the part of the MAH is in fact a conservative action. This change was described on page 125 of the final submission file in Table 3.2.2 as described in the "Main outcome measure" row: *"The primary efficacy endpoint†‡ was the first occurrence of any component of the composite of CV death, MI, stroke, and urgent coronary revascularization. (CSR section 9.5.1.1)*	We added your justification/answer on this point to the final assessment report

		*†**Note**: This is the major secondary end point in Morrow 2012 publication. TIMI reversed the primary and key secondary end points as reported in the CSR prior to database lock in the statistical analysis plan* *‡All suspected efficacy endpoint events were adjudicated, except as follows:* …"	
35	17-18	The following statement is incorrect: "Subsequently, the EMA decided to further refine the target population and exclude subjects with a history of PAD." These patients were never excluded by the EMA, CHMP, or the MAH. As clarified previously, this comment is not entirely accurate as described with regard to safety concerns. Vorapaxar is indicated in patients with a history of MI and without a history of stroke or TIA. According to the EU SPC, PAD patients do not currently have an independent indication for vorapaxar based on PAD alone. It is NOT accurate that patients with history of PAD are ineligible among the indicated label population. Important to note, while the exclusion of patients with a history of stroke/TIA was done as a result of DSMB observations and safety concerns, the PAD population's absence from regulatory	As we answered previously, we modified this sentence into : "the EMA decided against expanding the submission to include subjects from the PAD stratum.."

		filings had nothing to do with safety concerns; in fact, approximately 5% of the PLP had concomitant PAD.	

Input from the WP5 Members on the Editorial Draft Assessment

GENERAL AND SPECIFIC COMMENTS FOR THE AUTHOR

Page	Line	Comments	Comments from the author
FIMEA			
		General comment: Overall the report is very well written and compact. The summary section highlights some important results and limitations. Furthermore, the domains are clearly and explicitly written. Secondly, the main limitations which complicates patient's care and leads to difficulties in assessing effectiveness are clearly stated which can be helpful in national adaptation of the report. It seems that the report may provide added value for national decision making. A few detailed comments are below.	
10	6-11	These are important issues. EUnetHTA guideline on composite endpoints may provide even further insight into interpretation of composite endpoints and this could be referred in this context.	We agree and we quoted this guideline in chapter 5 (discussion), page 35 of the final report. We also quoted this guideline to answer to MAH comments/questions.
33	9-12	Regardless of the fact that the all-cause death results are only descriptive, I feel it could be important to mention these results in the summary section (page 8) and also the fact that there is no QoL-data available. This is because all-cause deaths and QoL are key issues in terms of relative effectiveness and it seems that the conclusive evidence on both of these variables is missing.	In this part we preferred providing only the main results on which a conclusion and a robust evaluation are possible. Therefore we only précised the lack of overall mortality data and QoL data. However, it remains important to avoid criticize too strongly this trial on QoL data, indeed these data are complicated to set up in this therapeutic area.
51		The applicability table could provide further details on the applicability of the evidence. Applicability assessment could be further extended.	We needed more clarification about what is expected to add on this point to modify the final report.

MoH Czech Republic			
7	10	SmPC Zontivity: at least 2 weeks after an MI and continued 12 months	Included in [B0002]
17	22	SmPC Zontivity: at least 2 weeks after an MI and continued 12 months	Included in [B0002]
AIFA			
7	9-21	The text doesn't seem not pertinent with the health problem.	We modified
14	13-15	We suggest to search also the Cochrane Library databases in order to have a more comprehensive systematic review of the literature.	We are sorry but it is not our scope, we have to evaluate mainly the source data and give our conclusion. We should not go too far.
9		The quality of evidence is usually assessed when several studies are available. Anyway, the methods should be described in the specific section.	All the critics about methodological bias leading to "moderate" were described in the different chapters in the part "discussion", no specific table is needed here for only one study.
14	9-16	It is not clear if the search was conducted by the Manufacturer and then checked by the Authors team or only by the Authors.	The search was done by the MAH, we added this clarification on page 14. The authors read the different articles provided on vorapaxar by the MAH. No other search or checking was provided by the authors mainly focus on the source data (CSR).
14	9-16	It is not reported if clinical trial registers were in order to identify pertinent planned or ongoing studies and/or completed studies that have not been published yet?	We wrote a short summary about the other study TRACER, but clinical registers were not checked by the authors.
15	7	To better detail the flow chart of the literature search, we suggest to report:	This information was not provided by the MAH and it is not the authors' mission scope.

		- the number of the records identified through databases (and/or additional sources) searching, - the reasons for the exclusion of the studies based on title/abstract as you did for the full-text articles assessment.	
15	9-14	The references for the included studies should be added to the list of total references (pp 43-47).	Here they are integrated in this figure.
15		The assessement of risk of bias is missing, Even if only one study is available for the assessement the risk of bias assessment is needed. We suggest to describe the tool in the methods section and report the relative risk of bias tables in the Appendix 1.	The pivotal trial does not present major bias: the only methodological problem is the reduction of the overall population to the population with no history of stroke and AOMI, without a new statistical analysis plan but not really a major bias. All the other critics were provided through the report.
17	7-39	More features on vorapaxar should be reported in order to better characterize the technology, for example, which are the galenic form, route of administration and dosing of voraxapar?	Modified.
24	46	Did you search for relevant clinical guidelines for diagnosis and management of the disease or health condition (adult patients with a history of myocardial infarction with or without history of stroke) for which varaxapar is indicated? A summary of recommendations and the relative level of evidence could be useful in this section of the assessment report.	Thank you, there are different clinical guidelines.
51	Table A1.2	The assessment of the applicability of the evidence needs some discussion.	We do not agree, see previous responses to comments from reviewers.
MoH Malta			

Reviewed the assessment report, well researched and written, no further comments			
SNHTA			
42	27	I would add that Drug-drug interaction profile with proton-inhibitor should be assessed as with clopidogrel (with reduction in aggregation effect because it is a frequent constellation by patient with coronary disease.	This is more PK/PD issues belonging to EMA scope
ZIN			
General	Comparator	Since no final version of the project plan is created, it would be good to reflect on comments from the dedicated reviewers on the choice of comparator in the discussion.	We agree, although not described in the discussion, the comments from the dedicated reviewers are taken into account.
General	Outcomes / endpoints	We suggest to reflect on which endpoints are the most important in the discussion. It would be very important to refer in the discussion on the composite endpoints on the EUnetHTA guideline (e.g. like in the Zostavax report). In the discussion it would be good to reflect on comments from the dedicated reviewers on this choice of the relevant outcome measures.	We already wrote our point of view on which endpoints are important/relevant and which endpoints are missing, in the whole. We quoted the EUnetHTA guideline in chapter 5 discussion and for answering to MAH comments.
General	Health domain	It looks like quite a lot of information is actually taken from the manufacturers file and sometimes it sounds like an advertisement for vorapaxar.	We have adapted the report accordingly.
4		There are several abbreviations in the summary. Is it an option to put the list of abbreviations before the summary?	We agree that it is a good option; you could modify as you want this table in the final report.
9	TIMI clinically significant bleeding	What was the rational for selecting the 3 different outcomes to assess the harm? In the scope (PICO) haemorrhage was selected as an important outcome. Maybe this information can be included in a footnote?	These outcomes were quoted in the trial's protocol as the relevant safety endpoints for 2 of them and the other one was added as a major safety endpoint by the authors. No need to define more precisely in the PICO, because hemorrhages remain the most relevant safety endpoint. However

			different scales exist to assess hemorrhage and these scales are described more precisely in the chapter “safety”.
9	Table	Health benefits are based on Kaplan-Meier (KM)-estimates, harms on N. Why are harms and benefits not both based on KM?	This information was not provided by the MAH in the protocol, but KM estimates is not usually used to compare side effects between treatment arms. Estimation is not well received to evaluate the drugs’ safety.
9 General		I miss the table(s) which show how the authors came to the conclusion the quality of the evidence was moderate (i.e. the risk of bias tables).	In this Summary table of relative effectiveness of the drug it is asked by the EUnetHTA REA template to fulfill the table’s line “quality of body evidence” without any other request or justification. According to all our critics and comments on this trial all along the report, we have decided to qualify this trial on this point as “moderate”. Our reasoning is explained in the body of the report. Therefore no other table will be provided to discuss this point of view.
10	12	In the r*ep*ort was stated that all-cause death was the most important outcome. If this is true, why was the data on all-cause death not included in table S.1.?	Because we didn’t get relevant data from the trial on this point. So we only described in this table the robust data provided which helped us to evaluate this drug.
10	35	I am not sure I understand this comment. Is it always a problem that patients included in a trial do not reflect the real-world population of patients. Why did the modification made it worse?	No, we meant that the indication’s population will complicate patient’s care in real-life. According to the MA indication and the population included in the TRA 2 P-TIMI 50 trial, vorapaxar can be used in a very narrow population: subjects with an MI history but without a history of stroke or TIA, without a PAD history, and not receiving treatment with ticagrelor or prasugrel. **Thus, it will likely be complicated for physicians to choose patients eligible for this drug**. Vorapaxar’s place in the therapeutic strategy has to be accurately defined in international guidelines.
10	47	‘More bleeding AEs’ → The effect was however not always statistically significant. Is “more bleeding AE” not an overstatement?	We don’t agree. “More bleeding AE’s” is a global remark which took place in the global discussion part. There was more bleeding AE’s in the vorapaxar+ASA±clopidogrel treatment group in the 3 main

			safety endpoints *GUSTO severe or moderate bleeding, TIMI clinically significant bleeding ISTH major bleeding.* So yes we can wrote that there was more bleeding AE's in the vorapaxar+ASA±clopidogrel treatment group.
11	7	Suggestion: Delete 'or'	We don't understand why.
11	13	Suggestion: Delete 'on'	We modified
11	25	Suggestion: Vorapaxar can → Vorapaxar may. 'Can' might be too strong in relation to all possible doubts and questions.	We modified
11	27	Suggestion: Thus → Therefore	We modified
14	Scope – comparison	Why are prasugrel and ticagrelor missing in this list?	Because the trial and therefore in the report no data were provided on these drugs versus vorapaxar.
14	Scope - outcomes	What are the most important outcomes? The text in the report and the project plan do not seem to match.	The most important outcomes are described in the report.
17	20	Ticagrelor or prasugrel: These are not mentioned in the scope. If these agents were comparators (as stated in the text of the report): why did the authors not search for studies that evaluated the effect of prasugrel or ticagrelor?	Vorapaxar is not an add-on therapy to prasugrel or ticagrelor but only to ASA±clopidogrel (MA indication). So we evaluated vorapaxar in this indication. We don't have to evaluate this drug for an off-label use. Moreover we don't have to realize indirect comparisons by our own.
18	34	subjects with a history of CAD (MI)→ Is this correct? Or is it history of MI.	Modified
24	44	2.07% → Probably somewhat too exact?	It is a citation.
27	6	Who is 'we'?	Text removed.

27	6	Market research → Very speculative, are there no better data? We recommend not reporting this data.	Text removed.
27	11	Suggestion: Does → May	Text removed.
27	19	Suggestion: Are needed → Seem to be needed	Modified
28	28	Is it possible to add information on the dosage of ASA? This might be important information for HTA agency. In the article (Scirica 2012) was stated: 17 448 patients (98%) were treated with aspirin (<100 mg: 6988 [39%], 100–162 mg: 7704 [43%], >162 mg: 2755 [15%]) and 13 894 (78%) with a thienopyridine	According to the randomization, the ASA dosage didn't impact the final results.
29	39/40 TIMI	And ISTH major bleeding?	Not described as the 2 others in the protocol but for the authors it represents a major safety endpoint.
31	Table 5.1	Section race: percentages do not add up to 100%. What were the other categories?	Describe the others categories won't bring any important information for this drug evaluation. The other categories were only minorities with a small number of patients
31	Table 5.1	Region: I can not find this information in the EPAR; also not the other data. Can you provide the source?	The CSR (we received it later) and the Company submission file
31	3	Was the source the CHMP report or MAH submission file? I can not find all the information in this table in the EPAR. . Is the sentence "CHMP report and MAH submission file" correct? Or should it be CHMP report or MAH submission file?	We added The CSR as a source. We kept "and" because for each table we quoted an exhaustive list of the sources used to make the table. Some of these tables were made by the authors and some were copy from the different source files.
31	Table 5.2	Is this data reported in the EPAR?	No you are right and we deleted "CHMP report as a source", be careful we used the CHMP report not the EPAR.

32	Table 5.3	Was the source the CHMP report or MAH submission file? I can not find all the information in this table in the EPAR.	In the last REA version you will receive this table become table 5.4 and you could find all these data on page 49 in the CHMP report from 21 November (not in the EPAR).
33	11/12	Where can we find this information?	The CSR (we received it later) and the final submission file
33	Section 5.3	Would it be possible to add information on the subgroup-analysis in the results and discussion? See page 48 or 112 of EPAR	Which subgroups are you talking about? we won't provide efficacy data on subgroups, these results are not relevant (alpha risk too high) but we described safety data in subgroups (Chapter 6)
34	7	Firstly, composite endpoints artificially increase the power of the results → Please refer to the EUnetHTA GUIDELINES on Composite endpoints.	We did. We deleted this sentence in the final REA report. This sentence appeared as a major criticism but it was not the case, it was just a fact described.
34	12	Please refer to EUnetHTA guidelines on composite endpoints.	We referred in chapter 5 section 5.3
34	36-38	Please explain, this sentence is not fully clear to me.	We needed information or arguments about the statistical analysis plan changes; we would have liked to see a new calculation of the power in the PLP. It is true that the statistical analysis was planned for the overall population, not for the PLP. The results and the effect obtained in the PLP are not as precise as the one obtained in the overall population. Indeed the confidence interval is wider; therefore the quantity of effect is less precise. In addition to the internal validity, the estimation of the external validity is also part of the HTA assessment. The external validity of the results obtained in the vorapaxar trial is not guaranteed.
37	12	Was the source the CHMP report or MAH submission file? I can not find all the information in this table in the EPAR.	In both documents and in the CSR. (CHMP report page 61)

38	Table 6.3	In the rest of the document the KM% have been reported. Maybe this should also be reported in this table?	We don't feel comfortable with estimation for safety data, even if KM is a validated statistical method. But this is mainly used for efficacy data.
40	26	Subgroup → Why was the data of history of hypertension not included (data might suggest a potential difference in effect) HR = 1.29 (1.02-1.63) for patients with history of hypertension and HR=2.22 (1.47-3.37) for patients with no history. EPAR page 77.	We did not find this subgroup relevant as compared to the others subgroups and we could not be exhaustive.
HVB			
2		Second table: reviewer: move HVB to line with Austria	We don't understand this comment it is already the case in the document we had (v1.3)
6		Table/comparison: This eval. must be "shown" ..? or better ".. be read/interpreted/understood as…"	We modified
7	40-45	Study population restricted, excluding stroke AND PAD patients. However, PLP only excludes stroke/TIA patients, but not PAD patients? Isn't this an unacceptable discrepancy between study population and label? If so , this should be criticized! However, on page 11, line 26 it says the label is also restricted regarding PAD history – what is true? I suggest, mentioning here how much of the original study population was lost by this stroke/TIA/PAD restriction (in % + absolute numbers)	You are right, this was not clear. We clarified this point in the final report: The fact is that EMA decided to exclude patients from the PAD stratum, and not patients with PAD history in the CAD stratum. No the label is not restricted regarding PAD, we modified. We added these data.
9		Numbers in Table: In Harm columns three kinds of numbers are given:	We added these data.

		Number of events (% of events) and total number (N=) In health benefit columns only two kinds of numbers are given: (%) and (N=) I recommend also adding the no. of events in these columns.	
10	31	I suggest mentioning also here how much of the original study population was lost by this stroke/TIA/PAD restriction (in % + absolute numbers)	We added these data.
10	42	“potential clinical interest of voraxapar associated with tic. and pras. . can’t be assessed: Isn’t it more appropriate : .. lacking , the potential clinical benefit of a therapeutic strategy including voraxapar cannot be assessed in comparison to therapeutic strategies including ticagrelor and prasugrel	Thank you for this suggestion, we kept the original sentence
	43	..” ..could or should be switched to voraxapar. “	Could in our point of view
11	22	In conclusion only one value: 1.1 for bleeding without comparison. For efficacy no numbers. Suggest Either , all the essential parameters with value, or only discussion, without one single uncompared value.	Thank you for this suggestion, we kept the original text
11		Conclusion: For me, there remains an uncertainty on the benefit risk ratio of this drug: +1-2% benefit in CV events: -1-2% in major bleedings. No benefit in OS. So is the benefit risk ratio positive?	We didn’t have any discussion with EMA on this point. Indeed the benefit risk/ratio remains EMA scope. We were factual on our evaluation, presenting on one hand the drug added value on CV morbidity and on the other hand the negative safety profile of this drug. We should stay factual and then each country, each European HTA agency will draw its own conclusion on this drug.

		Questioning this would mean questioning the approval? Was this discussed by EMA? Or is there a common perception, that CV event is clinically more severe than severe bleeding, justifying the approval? Was this concern discussed with specialists?	
33	16	WouldNt the NNT value of 140 be good for the summaries on p. 11 and 42? And add also NNH (number needed to harm)?	You are right we added this data on p11.
35	1	- Length of time since MI: no data. - I thought this was known: it was within <12 months since MI, see p. 29, line 7-8 (which is not reflected in label?)	Yes but it is not precise. In the final report we added a new table (table 5.3) with accurate data from the CSR.
	General	The review is quite good already!! Good work	
SMC			
6	2	scope table: suggest rewording of *comparison* box. I am not sure if this is referring to comparison in study or comparators in clinical practice. If it is comparison in study then suggest rewording as follows: Voraxapar is co-administered with ASA ± clopidogrel. The comparator in the study was placebo + ASA ± clopidogrel.	We modified
7	39	Use of *subjects* and *patients*; suggest consistency and use one term only throughout the document.	We modified
8	11	Suggest addition of *placebo* as follows (in red font): In the TRA 2ºP-TIMI 50 PLP, vorapaxar + ASA ± clopidogrel	We modified

		compared with placebo + ASA ± clopidogrel was associated with more bleeding adverse events (AEs):	
8	28	Suggest addition of *placebo* as follows (in red font): The most frequently reported other SAEs were non-cardiac chest pain (4.3% in the vorapaxar + ASA ± clopidogrel group compared with 4.0% in the placebo + ASA ± clopidogrel group), cardiac failure, pneumonia, atrial fibrillation, syncope, cardiac failure congestive, and osteoarthritis (all were ≤1.0% in both groups).	We modified
10	10	Suggest removal of following sentence and addition of sentence (in red font) as follows; ~~Each event doesn't have the same weight in the final result.~~ Events contributing to the composite endpoint occurred in differing proportions.	We modified
10	46	Suggest addition of *placebo* as follows (in red font): In terms of safety, bleeding events remain the major concern in the vorapaxar safety profile. Indeed, vorapaxar + ASA ± clopidogrel compared with placebo + ASA ± clopidogrel was associated with more bleeding AEs.	We modified
11	3	There are a number of publications related to the pivotal study; were these not used for the efficacy analysis?	No we only read it to avoid any misunderstanding of the trial's story.
11	6	Given that vorapaxar is not licensed for use with prasugrel or ticagrelor I am not sure why this statement has been included. However comparative evidence of vorapaxar + ASA ± clopidogrel versus prasugrel + ASA or versus ticagrelor + ASA would be useful given that prasugrel + ASA or versus ticagrelor + ASA are relevant	Thank you for this remark, we agree. The statement therefore has been deleted from the final report.

		comparators.	
11	13	Suggest addition of *placebo* as follows (in red font): Regarding the primary and key secondary endpoints used in the TRA 2ºP-TIMI 50 trial, vorapaxar 2.5 mg once daily as an add-on therapy to ASA ± clopidogrel seems to improve CV morbidity mainly on MI, compared to treatment with placebo + ASA ± clopidogrel alone.	We modified
14	1	scope table: see previous comment in page 6, line 2.	We modified
17	17	This paragraph needs to be reworded. Suggestion as follows: ~~When vorapaxar is considered on its own, the comparator is placebo. Nevertheless,~~ Voraxapar is used with aspirin ± clopidogrel. ~~this drug evaluation must be shown as a therapeutic strategy comparison (ASA ± clopidogrel versus vorapaxar + ASA ± clopidogrel in the trial set up by the marketing authorisation holder [MAH]).~~ Thus, comparators are strategies including ASA and clopidogrel or ticagrelor or prasugrel.	We did not modify
17	34	Suggest changing acetylsalicyclic acid to ASA (as used in rest of the document).	Modified
19	1	Suggest change as follows (in red font): The safety and efficacy of vorapaxar in patients ~~children~~ aged less than 18 years have not yet been established.	Modified
20	8	Remove; *commonly called a heart attack*	Removed
20	27	Remove; *commonly called a heart attack*	Removed

23	3	This paragraph is repetition of previous paragraph on page 22, line 5.	Removed
24	13	Suggest change as follows (in red font): The incidence of MI varies considerably among different regions world-wide ~~across the globe~~.	Modified
25	22	Suggest change as follows: Most of those who are discharged ~~alive~~ following an acute event and do not have a history of stroke or TIA would be eligible for long-term treatment with vorapaxar for the secondary prevention of major adverse cardiovascular events (MACE).	Modified
25	27	Suggest change as follows: In Italy, about 89% of those experiencing an MI would be eligible for vorapaxar (93% of patients are discharged ~~alive~~ following an acute event, and 3.7% of those have a history of stroke) [58].	Modified
26	2	Due to repetition suggest removal of whole sentence; ~~Therefore, vorapaxar...~~	Removed
26	9	Suggest change as follows (in red font): The safety and efficacy of vorapaxar in patients ~~children~~ aged less than 18 years have not yet been established.	Modified
27		I still think section 4 is very lengthy.	Modified
28	13	Suggest addition of *placebo* as follows (in red font): The MAH sponsored a multinational, randomised (1:1 ratio),	We don't agree on this sentence because the standard of care is ASA ± clopidogrel and not placebo + ASA ± clopidogrel.

		double-blind, controlled clinical trial (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events [TRA 2°P-TIMI 50]) to evaluate the safety and efficacy of vorapaxar as an add-on therapy to standard of care (vorapaxar + ASA ± clopidogrel) versus standard of care (placebo + ASA ± clopidogrel) in subjects with a history of atherosclerotic disease.	
28	18	Suggest addition of *placebo* as follows (in red font): The primary study objective was to evaluate the hypothesis that vorapaxar added to ASA ± clopidogrel will reduce the incidence of atherothrombotic events versus placebo + ASA ± clopidogrel alone, in the target population.	We modified
32	8	Suggest change as follows (in red font): The primary efficacy composite endpoint (CV death, MI, stroke, or urgent coronary revascularisation [UCR]) in the PLP was a 3-year Kaplan-Meier event rate of 9.8% in the vorapaxar + ASA ± clopidogrel group compared with 11.4% in the placebo + ASA ± clopidogrel group (hazard ratio [HR]=0.82; 95% confidence interval [CI]: 0.74 to 0.90; p<0.001).	We modified
33	9	Suggest change as follows (in red font): This is because other secondary endpoints evaluated before this endpoint were not found to be statistically significant which halted subsequent statistical testing ~~negative~~.	We modified, it is really clearer.
33	12	Suggest change as follows as statistical testing is not valid. Therefore, all-cause death results (in the PLP) are only shown as exploratory data: in the vorapaxar + ASA ± clopidogrel group, 238	We modified

		subjects (3.4% per 3 years) died compared with 259 subjects (3.7% per 3 years) in the placebo + ASA ± clopidogrel group (HR=0.91; 95% CI: 0.77 to 1.09; ~~not statistically significant~~).	
34	13	Suggest removal of following sentence and addition of sentence (in red font) as follows; ~~Each event doesn't have the same weight in the final result.~~ Events contributing to the composite endpoint occurred in differing proportions.	It is not exactly the same meaning, because we meant that this fact impacts the result (has a real consequence).
34	22	Suggest change as follows Considering that, all-cause death should have been one of the first key secondary endpoints~~, but it was not~~.	We modified
34	23	Suggest change as follows (in red font): Furthermore, the first key secondary endpoint chosen (which includes all the criteria of the primary endpoint except UCR) did not ~~didn't~~ provide much more information than the primary endpoint.	We modified
34	45	Suggest change as follows Because data on vorapaxar as an add-on therapy to these two drugs are lacking, potential clinical interest of vorapaxar associated with ticagrelor or prasugrel cannot ~~can't~~ be assessed.	We modified
34	45	But a comparison of vorapaxar + ASA ± clopidogrel versus ASA + ticagrelor or prasgurel may be warranted as they may be relevant comparators?	No, a comparison may not be warranted because when the trial was designed: - Patients treated by ticagrelor couldn't be included in this trial, as this drug was not launched on the market when inclusions of the pivotal trial started.

			- The number of patients treated with prasugrel was very low (30 of 13000 patients) therefore it was difficult to get a sufficient sample of patients to make statistical analysis. At time of inclusions, this number of patients represented real life data about therapeutic strategies chosen by physicians. It is emphasized that in the planning of the trial, patients with prasugrel could have been included, but this was not emphasized due to the design of the trial (standard of care)
34	47	There are a number of publications related to the pivotal study; were these not used for the efficacy analysis?	We only read them. They are quite different from the trial CSR.
35	1	Also need to note whether the patients in the study are similar to those in clinical practice in terms of timing of initiation of vorapaxar. In the study patients could commence vorapaxar if they had an event 2 weeks or 12 months previously. In clinical practice would patients be commenced on vorapaxar much sooner after the event?	We don't have the answer on that point. But vorapaxar should be used according to its MA indication.
42	2	Suggest addition of *placebo* as follows (in red font): In the TRA 2ºP-TIMI 50 PLP, vorapaxar + ASA ± clopidogrel compared with placebo + ASA ± clopidogrel was associated with more bleeding AEs (GUSTO severe or moderate bleeding, TIMI clinically significant bleeding, and ISTH major bleeding).	We modified
42	15	Suggest addition of *placebo* as follows (in red font): The most frequently reported other SAEs were non-cardiac chest pain (4.3% in the vorapaxar + ASA ± clopidogrel group compared with 4.0% in the placebo + ASA ± clopidogrel group), cardiac failure, pneumonia, atrial fibrillation, syncope, cardiac failure congestive, and osteoarthritis (all ≤1.0% in both groups).	We modified