20 November 2014
EMA/CHMP/85159/2015
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Zontivity

### International non-proprietary name: VORAPAXAR

### Procedure No. EMEA/H/C/002814/0000

## Note

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



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# List of abbreviations

| Abbreviation / Term | Definition |
|---|---|
| ABI | ankle/brachial index |
| ACE | angiotensin converting enzyme |
| ACS | acute coronary syndromes |
| ACT | activated clotting time |
| ADP | adenosine diphosphate |
| AE | adverse event |
| ACC | American College of Cardiology |
| AHA | American Heart Association |
| AMI | acute myocardial infarction |
| aPTT | accelerated partial thromboplastin time |
| ARB | angiotensin II receptor blocker |
| ASA | aspirin |
| AUC | area under the curve |
| BB | beta blockers |
| BCS | Biopharmaceutics Classification System |
| BMI | body mass index |
| B/R | Benefit-risk |
| CABG | coronary artery bypass grafting |
| CAD | coronary artery disease |
| CAPRIE | acronym for a clinical study in secondary prevention of ischemic events: Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events |
| CEC | Clinical Events Committee |
| CHARISMA | acronym for a clinical study in primary and secondary prevention of ischemic events: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance |
| CI | confidence interval |
| CrCl | creatinine clearance |
| CSR | clinical study report |
| CV | cardiovascular |
| CVD | cerebrovascular disease |
| CYP | refers to cytochrome P450 isoenzymes |
| DAP | data analysis plan |
| DAPT | dual anti-platelet therapy |
| DDI | drug-drug Interactions |
| DSMB | data and safety monitoring board |
| ECG | electrocardiogram |
| eCRF | electronic case report form |

| Abbreviation / Term | Definition |
|---|---|
| ECT | ecarin clotting time |
| EDC | electronic data capture |
| eGFR | estimated glomerular filtration rate |
| ESC | European Society of Cardiology |
| EU | European Union |
| F | female |
| GCP | good clinical practice |
| GMR | geometric mean ratio |
| GUSTO | **G**lobal **U**tilization of **S**treptokinase and **T**issue Plasminogen Activator for **O**ccluded Arteries cooperative group; a classification system for degree of bleeding |
| HR | hazard ratio |
| HC | Health Canada |
| ICH | intracranial hemorrhage |
| INR | international normalized ratio |
| ITT | intent to treat- refers to a study data set for statistical analysis |
| KM, K-M | Kaplan-Meier |
| LDL-C | low-density-lipoprotein cholesterol |
| M | male |
| MI | myocardial infarction |
| N/A | not applicable |
| NSTE-ACS | non-ST segment elevation acute coronary syndrome |
| NSTEMI | non ST segment elevation myocardial infarction |
| NNH | number needed to harm (BR analysis) |
| NNT | number needed to treat (BR analysis) |
| NSH | no stroke history |
| P | Placebo (used as abbrev in many of the statistical figures) |
| PAD | peripheral artery(arterial) disease |
| PAR-1 | protease-activated receptor 1 (the "thrombin receptor") |
| PCI | percutaneous coronary intervention |
| PD | pharmacodynamics |
| PH | proportional hazard |
| PK | pharmacokinetics |
| PMF | Preliminary Marketing Formulation |
| PT | prothrombin time |
| RAAS | renin-angiotensin aldosterone system |
| RIR | recurrent ischemia with rehospitalization |
| RRR | relative risk reduction |
| RR | risk reduction |
| Revasc | revascularization |
| S | SCH 530348 (used in many of the statistical figures) |

| Abbreviation / Term | Definition |
|---|---|
| SAE | serious adverse event |
| STEMI | ST segment elevation myocardial infarction |
| TIA | transient ischemic attack |
| TIMI | Thrombolysis in Myocardial Infarction Study Group |
| TRA | thrombin-receptor antagonist; specifically SCH 530348, as used in this study |
| TRAP | thrombin receptor agonist peptide |
| TRA 2°P – TIMI 50 | Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events; the present study |
| TRACER | acronym for study under Protocol P04736 (A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard of Care in Subjects With Acute Coronary Syndrome: **T**hrombin **R**eceptor **A**ntagonist for **C**linical **E**vent **R**eduction in Acute Coronary Syndrome) |
| TT | thrombin time |
| TQT | thorough QT |
| UA | unstable angina |
| UCR | urgent coronary revascularization |
| US | United States |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Merck Sharp & Dohme Limited submitted on 28 November 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zontivity, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2012.

The applicant applied for the following indication

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

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Vorapaxar was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

***Information on Paediatric requirements***

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0222/2013 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0222/2013 was not yet completed as some measures were deferred.

***Information relating to orphan market exclusivity***

***Similarity***

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

**Applicant's request(s) for consideration**

**New active Substance status**

The applicant requested the active substance Vorapavar contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

***Scientific Advice***

The applicant received Scientific Advice from the CHMP on 13 October 2005 and 21 October 2006. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

***Licensing status***

A new application was filed in the following countries: United States.

The product was not licensed in any country at the time of submission of the application.

## *1.2. Manufacturers*

**Manufacturer responsible for batch release**

Schering-Plough Labo N.V.
Industriepark 30
BE-2220 Heist-op-den-Berg
Belgium

## *1.3. Steps taken for the assessment of the product*

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

Rapporteur: Greg Markey

Co-Rapporteur: Alar Irs

CHMP Peer reviewer: Juris Pokrotnieks

- The application was received by the EMA on 28 November 2013.
- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 March 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 10 April 2014.
- During the meeting on 25 April 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 2 5 April 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 01 September 2014.
- Adoption of PRAC overview and advice on 11 September 2014.
- During the CHMP meeting on 25 September 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 October 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 October 2014.
- During a meeting of a SAG on 4 November 2014, experts were convened to address questions raised by the CHMP.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 6 November.

- The Rapporteurs circulated the Updated Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 11 November 2014.
- During the meeting on 20 November 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zontivity .

# 2. Scientific discussion

## 2.1. Introduction

Atherosclerosis and ischemic cardiovascular (CV) diseases like 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-ischemic disease are at particular risk of future cardiac or cerebral events, and vascular death. Anti-thrombotic therapy options in patients with stable atherosclerosis are not well-established. Long-term therapies to effectively modulate the key components responsible for atherothrombosis in secondary prevention of ischemic CV disease are therefore required.

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

The applicant has investigated whether a new class of antiplatelet agents, PAR-1 antagonists, can further decrease the risk of cardiovascular events in a population of established atherothrombosis when added to standard of care, in secondary prevention of ischemic diseases.

The following therapeutic indication has been submitted for vorapaxar:

*Vorapaxar is indicated for the reduction of atherothrombotic events in patients with a history of MI. Vorapaxar has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization.*

*Vorapaxar will be contraindicated in patients with a history of stroke or TIA.*

The indication sought in the current application is supported by the efficacy results of the TRA 2P-TIMI, which is considered the pivotal trial for this indication.

During the procedure, the applicant requested the possibility of extending the indication initially sought for, to extend it to the population of PAD patients. This request was discussed at the CHMP and not accepted by the Committee.

## 2.2 About the product

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

The Application concerns a single strength 2.08 mg film-coated tablet (as 2.5 mg vorapaxar sulfate) recommended to be taken once daily irrespective of food.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as immediate release film-coated tablets containing 2.5 mg of vorapaxar sulfate as active substance per tablet, corresponding to 2.08 mg vorapaxar.

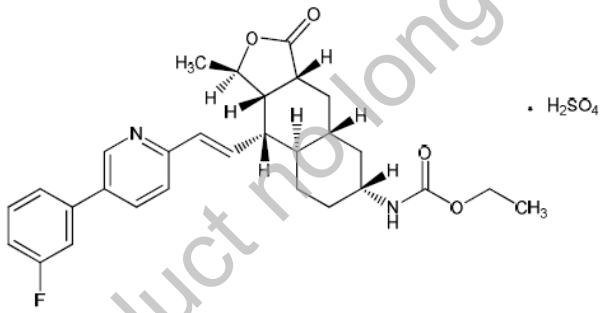
Other ingredients are: lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium (E468), povidone (E1201) , magnesium stearate (E572), hypromellose (E464), titanium dioxide (E171), triacetin (glycerol triacetate) (E1518), iron oxide yellow (E172), as described in section 6.1 of the SmPC.

The product is available in Aluminium–Aluminium blisters (Alu-Alu) as described in section 6.5 of the SmPC.

### 2.2.2. Active Substance

***General information***

The chemical name of the active substance vorapaxar sulfate is ethyl[(1R,3aR,4aR,6R,8aR,9S,9aS)--9-{(1*E*)-2-[5-(3-fluorophenyl)pyridin-2-yl]ethen-1-yl}-1-methyl-3-oxododecahydronaphtho[2,3-c]furan-6-yl]carbamate sulfate, corresponding to the molecular formula $C_{29}H_{33}FN_2O_4 \bullet H_2SO_4$ and has a relative molecular mass 590.7. It has the following structure:




The structure of the active substance has been confirmed by mass spectrometry, infrared spectroscopy, 1H- and 13C-NMR spectroscopy and X-ray crystallography, all of which support the chemical structure elemental analysis.

It appears as a white to off-white, slightly hygroscopic, crystalline powder. It is freely soluble in methanol and slightly soluble in ethanol and acetone but insoluble to practically insoluble in aqueous solutions at pH above 3.0. The highest solubility in aqueous solution can be achieved at pH 1.0 or in simulated gastric fluids at pH 1.4. The dissociation constant of vorapaxar sulfate was determined to be pKa = 4.7 and its partition coefficient LogP was determined to be 5.1.

Vorapaxar sulfate contains seven chiral centers and a *trans* double bond. The seven chiral centres are defined by the manufacturing process of one of the intermediates in the vorapaxar synthesis and potential enantiomers are controlled by appropriate specifications. The *cis*-isomer of the double bond is controlled by a highly stereo-specific process reaction resulting in non-detectable levels of cis-isomer impurity. The *cis*-isomer impurity is controlled in one of the intermediates as an unspecified impurity.

A single crystalline stable anhydrous form has been observed.

***Manufacture, characterisation and process controls***

Vorapaxar sulfate is manufactured in seven synthetic steps from three well-defined commercially available and appropriately controlled starting materials. Process intermediate products are also

defined. Reworking is foreseen and clearly described. The synthesis has been described in sufficient detail and critical process parameters (CPPs) and in-process controls (IPCs) have been reported and are considered satisfactory. The potential carry-over of reagents and solvents used during the synthesis of currently defined starting materials has been adequately discussed. The characterisation of the active substance and its impurities, including potential genotoxic ones, are in accordance with the EU guideline on chemistry of new active substances. A satisfactory risk assessment of potential genotoxic impurities that might arise from the starting materials or the process has been carried out. Potential and actual impurities and degradation products have been characterised and toxicologically qualified as appropriate. The active substance is packaged in double low density polyethylene bags with desiccant pouches and stored in a container. The polyethylene bags comply with the applicable EU Food Packaging requirements as per EU Regulation No 1282/2011 and Ph. Eur. requirements.

***Specification***

The active substance specification includes appropriate tests and limits for: appearance (visual), identity (vorapaxar: IR; sulfate: Ph. Eur.), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (Ph. Eur.), particle size (laser diffraction) and heavy metals (Ph. Eur.).

Studies were conducted to assess the potential for microbial growth. Based on ICH Q6A, a microbiological quality specification is not considered necessary.

Out of all the potential stereoisomers those 15 which are possible from an energy perspective are sufficiently controlled by discriminating analytical methodology and appropriate specifications are applied on the relevant intermediate. Therefore the absence of a chiral identity test based on the chiral control of the intermediate has been justified in line with decision tree #5 of ICH Q6A and supported by data. The *cis*-isomer of the double bond is controlled in the vorapaxar free base intermediate as an unspecified impurity. Thus, a test for the enantiomer of vorapaxar is not included in the vorapaxar sulfate active substance specification. The particle size specification has also been satisfactorily justified.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines.

Batch analysis data for three primary stability batches, three process validation batches and 14 commercial batches of vorapaxar sulfate manufactured with the proposed process were provided. In addition results from other batches used for development and clinical purposes have also been presented. The submitted batch analysis data confirm that the manufacture is sufficiently robust and provide reassurance that the process yields active substance of consistent quality, complying with the designated specification.

***Stability***

Stability data on four commercial scale batches of active substance manufactured at the intended manufacturing site stored in the intended commercial packaging for 60 months under long term conditions at 25°C/60% RH and for six months under accelerated conditions at 40°C/75% RH according to the ICH guidelines were provided.

The following parameters were tested: description, polymorph, specific rotation, assay, impurities, water content, particle size and microbial limits. The analytical methods used were the same as for release and were stability indicating.

No significant changes or trends were observed in the formal stability batches under long term conditions or accelerated conditions. Based on the collected data and statistical analyses the retest period has been set.

A photostability study was conducted as part of the formal stability study on batch as per ICH Q1B guidance. No significant change was observed after the light exposure.

In addition, forced degradation studies were conducted on substance from one batch in solution and solid state under acidic, basic, oxidative and light stress conditions. The intended commercial method for the related compounds testing was able to monitor the key degradation products.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable and justify the proposed retest period in the proposed container.

## 2.2.3. Finished Medicinal Product

***Description of the product and pharmaceutical development***

The objective of the pharmaceutical development was to develop a product with a quality target product profile (QTPP) defined as follows: a small size immediate-release tablet for once daily administration of a dose between 0.5 and 2.5 mg of vorapaxar sulfate, that meets the ICH guidelines on impurities and degradation products.

Based on the active substance physicochemical properties and Caco-2 permeability data, vorapaxar sulfate is considered to be a BCS Class 2 compound (high permeability, low solubility). A sulfate salt of vorapaxar was chosen early in development based on comparison of the physico-chemical characteristics of the free base and available salts. However later it was discovered that vorapaxar sulfate converts to the free base during the finished product manufacture. A risk assessment was conducted to identify potential links between the formulation components and the extent of amorphous free base formation during manufacture and subsequent product storage. The assessment also considered the potential for the amorphous free base to convert to crystalline free base during the finished product manufacturing process and subsequent storage. Hence several development studies were conducted to investigate free base formation in the vorapaxar sulfate tablet. According to the studies it was concluded that the extent of free base growth during manufacture was related to granulation temperature and the drug substance particle size.. The data also showed a relationship between the water activity of the finished product and the development of free base during storage.. On this basis, an effective control strategy was designed for the manufacturing process such that the free base content of the tablets following manufacture and over the course of the shelf life is equivalent to the free base content of the clinical batches.

An overview of the formulation development has been provided and the different formulations used during the early phases were presented. A tablet formulation based on a standard wet granulation process was selected for Phase II, Phase III clinical studies and commercialisation. The impact of different coating levels on the product quality attributes of Zontivity tablets, especially description and dissolution was assessed and a suitable coating was selected.

Two dissolution methods were used during development. Details about dissolution media, volume and apparatus of both methods have been presented. The first method was optimised with a view to improve discrimination of formulation (including free base content) and manufacturing changes. The proposed dissolution method showed adequate sensitivity to changes in excipient levels and variations in the manufacturing process inputs. However sufficient discrimination was not achieved with respect to levels of free base, therefore the free base in the tablets is controlled by an FT-Raman test.

Dissolution profiles comparison of formulations used in the Phase III Clinical studies and Commercial Formulation was presented and showed that in all three dissolution media (pH 1, pH 4.5 and pH 6.8) the Phase III and the commercial formulations exhibit similar dissolution release rates.

The direct compression manufacturing process was changed early to a wet granulation process upon content uniformity considerations. A risk based approach was used to identify process inputs to be evaluated during commercial manufacturing process development. This led to the identification of potential linkages between process inputs for each of the process steps to in-process material

attributes and finished product quality attributes. Process development studies were conducted with different shape and colour tablets. The formulation and process have not changed from Phase II to the product proposed for marketing with the exception of the film-coating and the shape. Both of these factors have been adequately evaluated and the majority of the process knowledge developed is considered to be applicable to the commercial tablet. Process development also focused on the free base formation in the product. A detailed analysis was performed to understand free base levels in the drug product. The manufacturing process has been thoroughly assessed and a process and control strategy were developed which ensure that the levels of free base in the finished product are properly controlled.

The packaging material of Zontivity is Alu–Alu blister that complies with the relevant EU regulations. The pack ensures that the low water activity of the product following manufacture is maintained throughout the shelf life.

***Manufacture of the product and process controls***

The manufacturing process includes standard unit operations and equipment for tablet production via high-shear wet granulation and comprises the following steps: wet granulation, screening, fluid-bed drying, blending, tableting, film-coating and packaging. The manufacturing process of the finished product is considered a standard process. Process intermediates are defined and controlled by appropriate specifications; holding times have been qualified for these intermediates. The critical process parameters and in-process controls have been presented and are justified in relation to how the product quality attributes are affected.

A satisfactory process validation protocol has been provided. The manufacturing process for Zontivity tablets will be validated at the intended commercial production site prior to commercialisation.

Overall it is considered that the manufacture is sufficiently robust to provide assurance that the process produces the finished product Zontivity film-coated immediate release tablets of consistent quality, complying with the designated specification.

***Product specification***

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), identification (IR-at release only), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.- HPLC), free base content (FT-Raman) and microbiological quality (Ph. Eur.- not routinely).

The limits for impurities are set as per the thresholds in ICH Q3 B (R2) guideline. The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. In addition, the absence of chiral conversion of vorapaxar during manufacture and storage in the product has been demonstrated therefore the omission of a chiral ID test in the specification is justified in accordance with ICH guidance Q6A decision tree #5. The free base content limits has been set based on the Phase III clinical experience and are supported by biopharmaceutics studies evaluating the effect of varying amounts of free base on vorapaxar bioavailability and bioequivalence.

Batch analysis data on four commercial scale batches at the commercial site were provided. In addition, results from one Phase II trial small batch, seven batches of the commercial formulation used for stability and development and 25 other batches up to commercial scale - some of them manufactured at a different site - have been presented. The tablets in these batches differed only in shape and colour while the core tablet was unchanged. The presented data are considered sufficient to confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

***Stability of the product***

Stability data on three full scale batches from the proposed manufacturer stored in the intended commercial package for 18 months under long term conditions at 30 °C / 75 % RH and for six months under accelerated conditions at 40 °C / 75 % RH according to ICH guidelines were also provided.
In addition stability data on three pilot scale batches from a different manufacturer stored in the intended commercial package for 36 months under long term conditions at 30 °C / 75 % RH and for six months under accelerated conditions at 40 °C / 75 % RH according to ICH guidelines were provided.
All batches were manufactured using drug substance manufactured by the commercial route at the intended commercial site.

The following tests were carried out: description, assay, degradation products, water activity, moisture, free base content, dissolution and microbial limits. The effectiveness of the free base control durin manufacture and storage was confirmed during the stability studies. The analytical methods were shown to be stability indicating.
No significant changes in any of the tested parameters were observed over the storage period and all results were within the proposed specification with the exception of free base content for the three pilot stability batches because the control strategy for free base content had not yet been implemented. Linear regression was applied to evaluate the product shelf life, following the principles in ICH guideline Q1E.

A photostability study was also carried out in accordance with ICH Q1B. Zontivity tablets have been shown to be stable after exposure to visible and UV light.

Based on the presented data the proposed shelf life at the proposed storage conditions, as stated in the SmPC, are supported.

***Adventitious agents***

Lactose monohydrate is used as an excipient and in the coating originates from bovine sources. It is confirmed that lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The active substance chirality and its potential conversion into the free base that could affect the product quality and performance have been sufficiently investigated. An adequate control strategy in this respect has been set throughout both the active substance and the finished product manufacture. The clinical trials formulations have been properly bridged with the commercial formulation as appropriate. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Information has been presented to give reassurance on viral/TSE safety.

### 2.2.6. Recommendation(s) for future quality development

Not applicable.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

The MAH submitted a comprehensive nonclinical dossier supporting the initial application.

The pivotal safety pharmacology studies (CV in monkey, respiratory, CNS and hemostasis) were performed in compliance with the appropriate Good Laboratory Practices.Generally the ADME studies were not performed under Good Laboratory Practice (GLP) guidelines while toxicity/TK studies were performed under GLP guidelines.

All pivotal toxicity studies were conducted in compliance with the appropriate Good Laboratory Practice with the exception of polymerase chain reaction analysis used in Study ref. SN 04056 to detect simian retrovirus Type D. It was considered that this exception did not affect the outcome or interpretation of the study results.

### 2.3.2. Pharmacology

***Primary pharmacodynamic studies***

Vorapaxar is a potent, selective and orally active antagonist of PAR-1. Vorapaxar binds reversibly to PAR-1 with high affinity and displayed slow on and off rate. Vorapaxar inhibits TRAP-induced platelet aggregation in human PRP. When administered at a single oral dose of 0.1 mg/kg, vorapaxar achieved a rapid and complete inhibition of ex-vivo platelet aggregation in cynomolgus monkeys for 24h with moderate inhibition observed as late as 48h.

Investigation of pharmacodynamic properties in animals revealed no evidence of an untoward effect of vorapaxar. In monkeys, hemostsis and cardiovascular endpoints were not affected at the highest doses of 1 or 20 mg/kg, respectively. In addition, in a surgical blood loss model, monkeys were administered a 1 mg/kg single oral dose of vorapaxar alone or in combination with aspirin and clopidogrel. The results demonstrated that there was no increase in bleeding time in animals administered vorapaxar alone and no exacerbation of increased bleeding observed with aspirin when they were co-administered with vorapaxar, these results confirmed by a separate study assessing the potential bleeding liability in anesthetised monkeys. In rats, safety pharmacology endpoints were unaffected at oral doses up to 3 mg/kg (gastrointestinal, renal and hemostasis) or 100 mg/kg (respiratory and CNS). The 20 mg/kg dose in monkeys in the 12 month general toxicity study represented an exposure of approx. 71-fold the maximum exposure (Cmax) achieved at the recommended clinical dose of 2.5 mg/day, while the 100 mg/kg dose in rats represents an exposure multiple of approx. 39- (males) and 59-fold (females) the maximum exposure (Cmax) at the recommended human dose (RHD).

Vorapaxar decreased the hERG current with an IC50 of 341 nM (nominal concentration) in mouse L-929 cells stably transfected with the human *hERG* (encodes the pore-forming subunit of the IKr in the heart). Up to a concentration of 200 nM, vorapaxar did not affect in vitro ventricular repolarisation measures of resting membrane potential, maximum rate of depolarisation, upstroke amplitude or action potential duration (APD) at 60 and 90% repolarisation in dog Purkinje fibres. In addition no effects on QT interval were noted in a cardiovascular safety pharmacology study in monkeys or in ECG measurements conducted during repeat dose toxicology studies in monkeys at doses up to 20 mg/kg/day for up to 1 year (Cmax exposures of 71-fold relative to maximum human exposure at the recommended human dose). Overall, these data suggest no effect on QT interval in animals and data from a thorough QT study demonstrated that a supratherapeutic dose of 120 mg vorapaxar

administered to healthy volunteers did not cause QTc prolongation. While some studies were not conducted in compliance with GLP, with consideration to available clinical data and GLP toxicity data, it is considered that effects on vital systems has been adequately covered.

In conclusion, the results of the pharmacology studies support the proposed indication in patients. Although unwanted adverse effects were not seen in the preclinical studies increased bleeding related to the pharmacological action was identified and reflected in the available clinical data.

### 2.3.3. Pharmacokinetics

The pharmacokinetic and metabolism data demonstrate that the dose of vorapaxar used in the toxicity and carcinogenicity studies provided adequate exposure to vorapaxar, and its active metabolite M20, and characterised human metabolites to permit an evaluation the safety of vorapaxar from the non-clinical study results.

Exposure values for vorapaxar and M20 were greater than the exposure seen in humans at the recommended human dose of 2.5 mg/day vorapaxar sulfate in mice, rats (vorapaxar only), rabbits and monkeys.

Vorapaxar and M20 are highly bound to plasma proteins (≥98%) in all species. In plasma, the unbound fraction of M20 is 5-fold greater than the unbound fraction of vorapaxar. The estimated human blood to plasma ratio for vorapaxar was 0.59, suggesting little distribution of vorapaxar into blood cells. The volume of distribution for male rats and monkeys were 4.6 L/kg and 2.2 L/kg, respectively. A tissue distribution study with 14C-vorapaxar in pigmented and albino rats showed extensive distribution of radiocarbon to the tissues. Longer retention of radiocarbon was seen in the melanin-containing tissues (eye and skin) of pigmented rats, in the pituitary gland, and in the epididymis of both rat species than other tissues. Vorapaxar and/or its metabolites crossed the placenta from maternal blood to developing fetuses and were secreted in milk of lactating female rats resulting in exposure to nursing pups. Vorapaxar is eliminated via metabolism with metabolites eliminated in the faeces.

Vorapaxar is metabolised extensively across species and the metabolic pathways involve mainly oxidative cleavage of the carbamate group or hydroxylation of vorapaxar. The major metabolite in excreta from all species (including humans) except monkey was the amine, M19. In monkeys, the major metabolite in excreta was the acid, M16, formed from oxidation of M20. The major circulating metabolite in rodents was M19 and M20 in monkeys and humans. Approximately 50% of an administered dose of vorapaxar is metabolised by CYP3A4 and CYP2J2 to M19, M20, and M16. The CYPs responsible for the metabolism of vorapaxar via other pathways is not known. The pharmacokinetics of vorapaxar and M20 could be affected when dosed with CYP3A4 and CYP2J2 inducer/inhibitors in humans.

Vorapaxar is highly permeable with nearly complete oral bioavailability and is extensively metabolised with little excreted unchanged, and therefore the potential for DDIs mediated by drug transporters seems low. In vitro CYP induction and in vitro and/or in vivo CYP/transporter inhibition studies indicated that vorapaxar has low potential to induce CYPs or inhibit any CYP450s or the transporters PGP, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 after administration of vorapaxar sulfate at the 2.5 mg clinical dose.

The human safety margin was determined by comparing steady-state AUC0-24h values for vorapaxar and SCH 2046273 observed at the no-adverse-effect level (NOAEL) in repeated-dose toxicity/TK studies to human exposure (AUC0-24h) following repeated maintenance doses of 2.5 mg vorapaxar sulfate in tablet form. All nonclinical species included in toxicology studies at the NOAEL doses or highest carcinogenicity doses had greater exposure to vorapaxar than did humans. Mice, pregnant rabbits, and monkeys at the same doses had greater exposure to M20 than did humans.

## 2.3.4. Toxicology

A complete programme of toxicity studies has been conducted. All pivotal toxicology studies were conducted with the partially amorphous free base of vorapaxar and the sulphate salt was used for clinical development. The species selected for toxicity studies were justified based upon pharmacological and metabolic profiles.

The potential for acute toxicity appears to be low. Repeated dose studies in mice (up to 3 months), rats (up to 6 months) and monkeys (up to 12 months) were associated with findings that generally occurred at high animal-to-human exposures and with the exception of phospholipodosis (all species), seem to be species specific (rat retinal vacuolation) and reversible. The main histopathology findings include urinary bladder and ureter hyperplasia in mice, hepatic vascular thrombi, lymphoid necrosis and retinal vacuolation in rats and phospholipidosis in all species. The phospholipidosis was observed in mice and monkeys at exposures up to 398-times and 214-times the human steady-state exposure at 2.5 mg/day. The NOAEL for this finding in rats, a species documented in the literature as particularly sensitive to this finding, was 30 mg/kg/day equating to an exposure multiple of 10-fold and 29-fold in males and females, respectively. Up to this dose level, the finding was fully reversible after a 1-month treatment-free period, did not appear to be progressive in incidence or severity, was minimal in nature and not associated with any detectable functional changes. Phospholipidosis is not uncommon in preclinical species treated with cationic amphiphilic drugs or drugs which are metabolised to give a cationic amphiphilic structure. Phospholipidosis occurred at acceptable human to animal safety margins was reversible and there was no signal in the most commonly affected organs (liver, kidney and CNS) in the clinical studies up to 2.5 years. The clinical significance of this finding is currently unknown as stated in the SmPC.

The low incidence of vacuolation in the inner nuclear layer of the retina was present in rats only and did not appear to be associated with phospholipidosis. This finding was not seen in the other species used for toxicity testing. There was no obvious increase in incidence or severity with increased length of dosing across studies. The vacuolation was considered to be minimal in severity and was fully reversible after a 1-month vorapaxar-free period. In addition, a further investigative study in rats showed no visual changes as assessed by electroretinography (ERG) after 6 weeks of dosing. Similar findings (1 or 2 unilateral vacuoles) were observed in controls but at a lower incidence. In Sprague Dawley rats that received structurally dissimilar PAR-1 antagonists, no retinal vacuolation was noted, suggesting that the finding may not be mechanism driven. In investigative studies conducted with a close structural analog of vorapaxar, retinal vacuolation was seen in the strain used in the general toxicity studies but not in Han Wistar rats, suggesting that the finding may be specific to the latter strain of rat. Therefore based on an overall weight of evidence approach, the retinal vacuolation seems to have unlikely relevance to humans at the therapeutic dose of 2.5 mg/day. In addition, a clinical substudy was carried out to investigate these findings and did not show any ocular safety signals in man when compared to placebo although the study was small and the effect rare. Exposure in male and female rats at the lowest dose of 3 mg/kg/day, equates to approximately 1 to 2 times the human steady state exposure at a dose of 2.5 mg/day.

Vorapaxar was negative for genotoxicity, carcinogenicity, phototoxicity and adverse effects on fertility. No teratogenicity was seen in the embryo-fetal development study in rabbits. The data from an initial PPND study suggested treatment-related effects on survival and body weights (decreases when dams were administered ≥ 25 mg/kg/day) in offspring of both F1 and F2 generations. A repeat PPND study was conducted with a different study design to that used in the initial study (cross-over study design and increased statistical power) to address these treatment-related findings. Although the majority of changes noted in the first PPND study were not repeated, a decrease in body weight for F1 pups nursing from vorapaxar-treated dams was seen. The change in study design may partially explain any absence of effects in the repeat PPND study. In light of this, all treatment-related findings in both PPND studies have been considered to the SmPC. The NOEL for these findings is thus

considered to be 5 mg/kg/day (6.8-times [female animals] the human steady-state exposure at 2.5 mg/day.

Vorapaxar was well-absorbed and showed good systemic exposure. Exposure to vorapaxar and a major circulating active metabolite, M20, and other characterised human metabolites permitted the safety evaluation of varapaxar from the non-clinical studies. Exposure to M20 was assessed in a 2-week toxicokinetics study in mice, rats, monkeys, pregnant rats and rabbits. Mice, pregnant rats and monkeys had greater exposure to M20 (at least 5-fold) than humans and thus the toxicity of this metabolite was considered to be adequately assessed.

The lack of juvenile studies is acceptable since the intended patient population for vorapaxar is an adult population. Dedicated local tolerance studies have not been conducted and none are required since the drug is for oral administration. No formal immunotoxicity studies have been performed and the repeat dose toxicity studies did not elicit any treatment-related immunological effects. Preclinical phototoxicity studies were conducted given the radiocarbon labelled distribution to eye and skin. There were no treatment-related findings.

Impurities (desfluoro and imide) were qualified by use in the 6-month chronic toxicity study in rats and genotoxicity studies.

## 2.3.5. Ecotoxicity / environmental risk assessment

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, the environmental risk assessment report was submitted in support of the Marketing Authorization Application for vorapaxar. A Phase I and Phase II Tier A and Tier B environmental risk assessment for vorapaxar were included. The recommended daily oral dose of vorapaxar is 2.5 mg as salt taken once daily.

The Phase I screening for persistence, bioaccumulation and toxicity (PBT) indicates indicated that further evaluation of vorapaxar was warranted due to a log Pow > 4.5. Based on the outcome of the Phase I environmental assessment, the predicted environmental concentration in surface water (PECsurfacewater) for the active ingredient, vorapaxar (MK-5348), is 0.013 µg/L, indicating that vorapaxar may represent a risk to the environment following its prescribed usage in patients. Therefore, a Phase II Tier A environmental effect assessment and concomitant risk assessment was required.

The outcome of the Phase II Tier A Assessment comparing the Predicted No Effect Concentration (PNEC) and PEC ratios concluded that vorapaxar does not present a risk to surface water, ground water, micro-organisms or to sediment-dwelling organisms.

However; because the sludge and soil Koc values are greater 10,000 L/kg and the Kd values were greater than 3700 L/kg, a Phase II Tier B environmental effect assessment and concomitant risk assessment was required.

The outcome of the Phase II Tier B Assessment evaluating the fate and effects of vorapaxar in the terrestrial environment concludes that vorapaxar does not present a risk to the soil ecosystem. Vorapaxar is unlikely to represent a risk to surface water, ground water, micro-organisms or sediment dwelling organisms. Vorapaxar will not bioconcentrate in aquatic organisms and is not a PBT compound (BCF < 2000), indicating little risk to aquatic and sediment environments. Additionally, vorapaxar will not bioconcentrate and thus does not meet the criterion to be defined as a persistent, bioaccumulative and toxic (PBT) compound. Vorapaxar is not expected to pose a significant risk to the environment due to normal patient use. Thus, no further action is necessary in this case.

**Summary of main study results**

| **Substance (INN / Invented Name): Vorapaxar** |
|---|

| **CAS-number (if available):** 705260-08-8 | | | | | |
|---|---|---|---|---|---|
| ***PBT screening*** | | Result | | | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | *OECD 107 + OECD 123 slow-stir method* | pH<br>5<br>7<br>9 | Log $P_{ow}$<br>5.03<br>5.11<br>5.10 | | Potential PBT: **Yes** |
| ***PBT-assessment*** | | | | | |
| **Parameter** | **Result relevant for conclusion** | | | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | - | | | - |
| | BCF | 776 – 858 (< 2 000) | | | **not B** |
| Persistence | DT50 or ready biodegradability | 408 days in soil (> 120 in freshwater sediment or soil) | | | P |
| Toxicity | NOEC or CMR | 27 µg/L, no CMR (chronic NOEC < 10 µg/L, should be CMR) | | | not T |
| **PBT-statement :** | The compound is not considered as PBT nor vPvB | | | | |
| ***Phase I*** | | | | | |
| ***Calculation*** | **Value** | **Unit** | | | **Conclusion** |
| $PEC_{surfacewater}$ , default or refined (e.g. prevalence, literature) | 0,0125 ≈ 0,013 | µg/L | | | > 0.01 threshold **Yes** |
| Other concerns (e.g. chemical class) | - | - | | | No |
| ***Phase II Physical-chemical properties and fate*** | | | | | |
| **Study type** | **Test protocol** | **Results** | | | **Remarks** |
| Adsorption-Desorption | OECD 106 | *Soils Log* $K_{oc}$ =4.69 – 5.15<br>Individual $K_{OC}$ values<br>1 48 681<br>2 148 703<br>3 104 779<br>4 141 647<br>Sludges: Log $K_{oc}$=4.13-4.15<br>Individual $K_{OC}$ values<br>1 14 195<br>2 13 630 | | | Performed in 4 soils, 2 sludges<br><br>Additional studies for terrestrial environment triggered |
| Ready Biodegradability Test | OECD 301B | -6.1 % | | | Not readily biodegradable |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | $DT_{50, water}$ = 3.2-3.5<br>$DT_{50, sediment}$ = *no data*<br>$DT_{50, whole\ system}$ = 231-347<br>% shifting to sediment = | | | Results not properly reported in EIA main report |
| ***Phase IIa Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata* | OECD 201 | NOEC | 130 | µg/L | Both for growth rate and yield |
| *Daphnia* sp. Reproduction Test | OECD 211 | NOEC | 55 | µg/L | For reproduction and growth (220 µg/L for survival) |
| Fish, Early Life Stage Toxicity Test / *Pimephales promelas* | OECD 210 | NOEC | 27 | µg/L | The most sensiti-ve endpoint was larval growth |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | EC | > $10^6$ | µg/L | The value is greater than the water solubility of vorapaxar: no effects on respi-ration in WWTPs |
| ***Phase IIb Studies*** | | | | | |
| Bioaccumulation / *Lepomis macrochirus* | OECD 305 | BCF | 776-858<br><br>163-169 | L/kg<br><br>L/kg | For whole body fish tissue.<br><br>Normalised 4,77 – 5,08 %lipids |
| Aerobic and anaerobic transformation in soil | OECD 307 | DT50<br>%$CO_2$ | 408<br>408<br><br>533<br>770 | days | Cumulative % of $^{14}CO_2$ was 0,2 %<br><br>Cumulative % of $^{14}CO_2$ was 0,1 % |
| Soil Micro-organisms: Nitrogen Transformation Test | OECD 216 | %effect | 10 | mg/kg | At 10 * PEC devi-ation from |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | control at day 7 was 95% and 19 % at D14, 12 % at D28: vorapaxar has no lasting adverse effects on nitrifi-cation processes in soil at tested concentrations |
| Terrestrial Plants, Growth Test / *Species: 1)* Common bean (*Phaseolus vulgaris*) 2) Oats (*Avena sativa*) 3) Peren-nial ryegrass (*Lolium perenne*) 4) Soybean (*Glycine max*), 5) Tomato (*Lycopersicon esculentum*) 6) Wheat (*Triticum aestivum*). | OECD 208 | NOEC | 10 | mg/kg | Exposure at a nominal applicat-ion rate of 10 mg/kg did not cause inhibition of % emergence or fresh shoot weight exceeding 25% |
| Earthworm, Acute Toxicity Tests | OECD 207 | NOEC | 1000 | mg/kg | No additional testing needed to further define the $LC_{50}$ value |
| Collembola, Reproduction Test | OECD 232 ISO 11267 | NOEC | 1000 | mg/kg | MATC for % sur-vival and repro-duction: > 1000 mg/kg |
| Sediment dwelling organism / *Chironomus riparius* | OECD 218 | NOEC | 13 | mg/kg | $EC_{50}$ for emer-gence was deter-mined by linear interpolation to be 21 mg/kg |

***PNECand PEC/PNEC calculation***

| Media | PNEC | PEC/PNEC | Remarks |
|---|---|---|---|
| Surface water $PEC_{SW}$ = 0.0125 µg/L | 2.7 µg/L (NOEC = 27 µg/L) | $4.6 * 10^{-3}$ | OECD 210 (AF = 10) |
| Ground water $PEC_{GW}$ = 0,25 $PEC_{SW}$ = 0,003125 | 5.5 µg/L (NOEC = 55 µg/L) | $5.7 * 10^{-4}$ | OECD 211 (AF = 10) |
| Micro-organisms $PEC_{SW}$ = 0.0125 µg/L | 100 000 µg/L (NOEC = 1 000 mg/L) | $1.3 * 10^{-7}$ | OECD 209 (AF = 10) |
| Sediment organisms $PEC_{SED}$ = ~~27,8~~ µg/kg = 40,4 µg/kg (formula in guideline) | 130 µg/kg (NOEC = 13 mg/kg) | ~~0.214 ≈ 0.2~~ 0,31 | OECD 218 (AF = 100) Highest measured $K_{oc}$ was reported to be 102329.3, but actually is 148 703 L/kg |
| Soil $PEC_{SOIL}$=0,0475 µg/kg (calculated with SimpleTreat v. 3.1) | 200 µg/kg (NOEC = 10 mg/kg) | $2,4 * 10^{-4}$ | OECD 208 (AF = 50 as chronic terrestrial data on two trophic levels were available) |

To conclude, vorapaxar has a high affinity to soils and sediments and is very persistent in these environmental compartments.

## 2.3.6. Discussion on non-clinical aspects

There was no obvious increase in incidence or severity with increased length of dosing.
The vacuolation was considered to be minimal in severity and was fully reversible after 1-month.
An investigative study in rats showed no visual changes by electroretinography (ERG) after 6 weeks of dosing. Other investigative studies showed no retinal vacuolation in a different strain of rat (Han Wistar) when compared to the strain (Sprague Dawley) used in the general toxicology studies and the presence of this finding decreased when several different fixatives were tested during histological processing. Thus there is evidence that the strain of rat used for toxicology studies and the post-mortem fixative is likely to be involved in the development of this finding in this species of rat. Therefore based on an overall weight of evidence approach, the retinal vacuolation seems to have unlikely relevance to humans at the therapeutic dose of 2.5 mg/day. . In addition, a clinical substudy

was carried out to investigate these findings and did not show any ocular safety signals in man when compared to placebo although the study was small and the effect rare. Exposure in male and female rats at the lowest dose of 3 mg/kg/day, equates to approximately 1 to 2 times the human steady state exposure at a dose of 2.5 mg/day. These findings were not present in the other preclinical species up to >300x human exposure in mice and >200x in monkeys.

Phospholipidosis was seen in all preclinical species used in the general toxicology studies (rats, mice and moneys). Vacuolated macrophages and other cells with transmission electron microscopy findings suggestive of phospholipid accumulation were observed in liver and small intestine in the most relevant species that express PAR-1 on platelets. The phospholipidosis was also observed in mice and monkeys at exposures nearly 400-times and >200-times the human steady-state exposure at 2.5 mg/day. The exposure multiple in rats at the NOAEL for this finding was 10x and 29x human exposure in males and females, respectively. Up to this dose level, the finding was fully reversible after a 1-month treatment-free period, did not appear to be progressive in incidence or severity and was minimal in nature. Phospholipidosis is not uncommon in preclinical species treated with cationic amphiphilic drugs or drugs, which are metabolised to give a cationic amphiphilic structure. There was no similar finding in the most commonly affected organs (liver, kidney and CNS) in the clinical studies up to 2.5 years although the relevance to humans is currently unknown. The SmPC has been updated to include that the clinical significance of these findings is currently unknown but occurred at acceptable human to animal safety margins and was reversible.

Reproductive parameters, mating and fertility indices in rats were not affected by administration of vorapaxar at doses up to and including 50 mg/kg/day. There was a decrease in maternal body weight gain, food consumption and mean fetal body weight at 75 mg/kg/day. There were no vorapaxar-related fetal external, visceral or skeletal findings. There were no vorapaxar-related effects on the numbers of corpora lutea, implantation sites, fetuses or resorptions. In rabbits, vorapaxar was not teratogenic or maternotoxic. . The SmPC has been updated to include a statement that all findings occurred at exposures sufficiently in excess of human exposure at the RHD.

Treatment-related effects were seen in the pre-and post-natal development studies in rats. The effects on peri-natal survival and body weight in pups at maternal exposures 38 times those expected at the recommended human dose and neurological effects (impaired memory and startle reflex) in males and/or females from 19x the human daily dose. These findings were studied in a second PPND study with different outcomes. Due to a change in the study design (introduction of cross-fostering), it is not entirely agreed that the effects to gravid and nursing rat dams in the original study can be discarded as incidental even if the repeat study was more robustly powered, especially since vorapaxar was shown to transfer to milk. . The SmPC was updated to include the overall NOEL for these effects i.e. 5 mg/kg/day (6.8-times [female animals] the human steady-state exposure at 2.5 mg/day).

There appeared to be no evidence for carcinogenic potential in mice and rats since all findings were either not dose-related or were within historic control values for the test facilities.

Conclusion on the non-clinical aspects

Overall Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential, and fertility.

In repeat dose oral toxicity studies in rodents and monkeys, the principal treatment-related findings were urinary bladder and ureter hyperplasia in mice, hepatic vascular thrombi, lymphoid necrosis and retinal vacuolation in rats and phospholipidosis in all species. Phospholipidosis occurs at acceptable human to animal safety margins and was reversible. The clinical significance of this finding is currently unknown.

No defects were observed in embryo-fetal developmental studies in rats and rabbits at exposures sufficiently in excess of human exposure at the recommended human dose (RHD). Pre and postnatal studies in rats only showed some inconsistent developmental effects at exposures sufficiently in excess of human exposure at the RHD of 2.08 mg vorapaxar. The overall no effect level for the pre- and postnatal development effects was 5 mg/kg/day (6.8-times [female animals] the human steady-state exposure at 2.5 mg/day).

Vorapaxar had no effects on fertility of male and female rats at exposures sufficiently in excess of human exposure at the RHD.

Vorapaxar was not mutagenic or genotoxic in a battery of in vitro and in vivo studies.

Vorapaxar did not increase bleeding time in non-human primates when administered alone at 1 mg/kg. Bleeding time was prolonged slightly with administration of acetylsalicylic acid alone or in combination with vorapaxar. Acetylsalicylic acid, vorapaxar, and clopidogrel in combination produced significant prolongation of bleeding time. Transfusion of human platelet rich plasma normalised bleeding times with partial recovery of ex vivo platelet aggregation induced with arachidonic acid, but not induced with ADP or TRAP. Platelet poor plasma had no effect on bleeding times or platelet aggregation. (See section 4.4.)

No vorapaxar-related tumours were observed in 2-year rat and mouse studies at oral doses up to 30 mg/kg/day in rats and 15 mg/kg/day in mice (8.9 and 30 times the recommended therapeutic exposures in humans based on plasma exposure to vorapaxar for rats and mice, respectively).

The above information has been included in section 5.3 of the SmPC.

### 2.3.7. Conclusion on non-clinical aspects

The non clinical data have been adequately investigated and support the use of Vorapaxar in humans.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

***GCP***

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

### 2.4.2. Pharmacokinetics

***Absorption***

Vorapaxar shows high in vitro permeability and low solubility thus BCS class 2. Vorapaxar is rapidly absorbed following oral administration with a median Tmax of 1 hour. The estimated absolute bioavailability is approximately 100%. Bioequivalence has been demonstrated between vorapaxar sulfate capsules used in early clinical development and vorapaxar sulfate tablets. Vorapaxar exposure, AUC and Cmax was similar across increasing free base levels with only slight deviations from the interval of 0.80–1.25. Food decreases the rate but not extent of absorption at the clinically relevant dose. Drug that affect gastric pH do not affect the absorption of vorapaxar.

***Distribution***

Vorapaxar is 99.8% bound to human plasma proteins. The mean blood/plasma concentration ratio was 0.59. Protein binding was determined to compare the free fraction ratio of the major plasma metabolite M20 to vorapaxar, the free fraction of M20 was approximately 5-fold that of parent. Protein binding of vorapaxar is high (≥99%) from in vitro assessments approximating hypoalbuminemic conditions consistent with severe hepatic impairment, renal disease or burns. Vorapaxar is widely distributed with a volume of distribution of 424 L. Vorapaxar is not a substrate of Pgp.

***Elimination***

Vorapaxar is extensively metabolized with no parent drug excreted in urine and only a small percentage of vorapaxar excreted in bile (≤3.4%). The excretion is predominantly in the faeces (91.6%). The major route of metabolism was oxidative cleavage of the carbamate group to the amine, M19. Additional metabolites were hydroxylated metabolites (30%), and glucuronides or sulfates of hydroxylated metabolites. M20 is an active metabolite that contributes to pharmacological activity of vorapaxar and has similar potency in vitro. The mean metabolite/parent AUC ratio is ~20%, demonstrating that vorapaxar is present at much higher concentrations compared to its major active metabolite under steady state conditions. However that free fraction of the metabolite is 5 fold higher therefore they would be expected to contribute similarly to the potency. M20 exhibits formation-rate limited pharmacokinetics such that the terminal phase of plasma concentration-time profiles largely parallel those of vorapaxar; the M20:parent AUC ratio is generally conserved across a broad range of vorapaxar exposures, doses and subpopulations. Following administration of vorapaxar, the M20 concentration-time profile generally parallels that of vorapaxar with a median Tmax of ~3 hours, with a wide individual range of 1-24 hours), and an apparent terminal t1/2 (187 hours) comparable to that of vorapaxar, consistent with formation rate-limited disposition. CYP3A4 and CYP2J2 are the predominant enzymes involved in forming M19 and M20. Since vorapaxar is cleared by hepatic metabolism and the contribution of the metabolite M20 to the efficacy of Zontivity is estimated to about 50%, and its elimination is mainly governed by metabolism, the applicant was asked to determine if vorapaxar and M20 is a substrate for OATP1B1 and 1B3 in vitro. The submitted data showed no significant uptake of vorapaxar or M20 metabolite by OATP1B1 or OATP1B3.

***Dose proportionality and time dependencies***

There was a slightly less than dose-proportionality between 1 to 40 mg. Steady-state of vorapaxar is achieved by 21 days of once-daily dosing. Estimates of vorapaxar AUC accumulation, based upon the increase from single- to multiple-dose, approximates 6-fold and is comparable for M20 (~8-fold) this is largely consistent with that expected based on the elimination half-life.

***Special populations***

The pharmacokinetics of vorapaxar were essentially similar between patients with ESRD and matched healthy controls. Based on the population PK model and the covariate distributions represented in the patients in the population PK dataset, exposures were predicted to be higher in patients with mild (17%) and moderate (34%) renal impairment compared to those with normal renal function. Subgroup analyses of patients with renal insufficiency (CrCl <60 ml/min or eGFR < 60 ml/min/1.73 m*m) showed no increased risk for bleeding events or other adverse events compared to reference groups with CrCl ≥60 ml/min or eGFR ≥ 60 ml/min/1.73 m*m, consistent with no clinically important increased risk for bleeding events or other adverse events due to renal insufficiency. Thus the 30 – 40% increase in vorapaxar exposure in moderate renal impairment is not considered to be clinically important and no special labelling guidance with respect to dosage and administration is needed for

mild-to-moderate renal impairment. Although exposure data in severe renal impairment is limited to only 4 patients, it is suggested that the impact of varying degrees of renal impairment fall on a gradual continuous relationship, such that the exposure and safety experience in moderate renal impairment supports no need for specific label guidance around severe impairment this could not be agreed based solely on this data. However as no effect was seen in patients on dialysis this can be agreed. Still, very few patients with severe renal disease/ESRD were included in the pivotal trial and the safety of vorapaxar in this group has not been established; therefore, vorapaxar should be used with caution in these patients (see Safety section below)

In subjects with mild or moderate hepatic impairment, no clinically relevant differences in vorapaxar or M20 metabolite exposure compared to matched healthy subjects was observed, however subject numbers were small (n=6). Although exposure to vorapaxar and M20 is lower in patients with severe hepatic impairment compared to matched healthy subjects; due to a potential decrease in plasma protein binding free drug concentrations may be slightly increased. Considering the inherently increased tendency towards bleeding in these patients and the fact that patients with evidence of clinically significant hepatobiliary disease or an ALT/AST > 3 times the upper limit of normal were excluded from participation in Phase 2/3 trials, vorapaxar should be used with caution in patients with moderate disease; in those with severe hepatic impairment should be contraindicated (see Safety section below).

Evaluation of the covariates selected from the PK models requires further justification, in particular in terms of the analysis of correlation of the covariates. In addition there are a number of covariates on the pharmacokinetics, namely gender, race, weight and age, but it is suggested that none of these are clinically significant. Further analysis of the effect of a combination of covariates on efficacy and safety is required.

At concentrations achieved clinically following the clinical dose of 2.5 mg, and based on in vitro studies, vorapaxar has the potential to inhibit only intestinal P-gp. Vorapaxar is unlikely to result in clinically significant inhibition of human CYP2A6, 2B6, 2C9, 2C19, 3A4 and CYP2D6. M20 did not show potent in vitro reversible inhibition for any of the CYPs (CYP2C19, 3A, 2B6 and 2D6). No clinically meaningful inhibition of OATP1B1, OATP1B3, OAT1, OAT3, OCT2 and BCRP by vorapaxar or M20 is anticipated. Vorapaxar does not exhibit an induction potential for major CYPs (CYP3A4, 1A2, 2B6, 2C8, 2C9 and 2C19).

Ketoconazole increases systemic exposure, 1.96-times higher than corresponding values for vorapaxar administered alone. Rifampin decrease vorapaxar AUC (54%). M20 was not directly assessed but it is suggested that as M20 is both formed and metabolized by CYP3A4/CYP2J2, the effects on M20 are anticipated to mimic those of vorapaxar pharmacokinetics. This is not fully agreed but considering the supporting safety data it is considered that this data is not needed. It is proposed that the concomitant use of vorapaxar should be avoided in patients taking strong inhibitors or strong inducers of CYP3A. The effect of moderate and mild CYP 3A4 inhibitors has not been provided. The ketoconazole dose however is not considered to represent the worst case as vorapaxar has a long half-life, therefore PBPK modelling is suggested to model the effect of ketoconazole 200 mg bid. In addition the impact of moderate inhibitors should be explored. The role of CYP2J2 in the elimination has not been fully explored and a cautionary statement is included for the SmPC.

***Pharmacokinetic interaction studies***

Vorapaxar had no significant effect on digoxin AUC but increased the Cmax by 54%.. Vorapaxar concentrations required to achieve P-gp inhibition are not expected following the recommended clinical dose of 2.5 mg, however appropriate monitoring of digoxin is recommended as clinically indicated.

No clinically significant pharmacokinetic interaction was observed following co-administration of rosiglitazone and vorapaxar or with warfarin or prasugrel and vorapaxar.

## 2.4.3. Pharmacodynamics

***Primary and Secondary pharmacology***

Vorapaxar is a selective PAR-1 antagonist with a Kd of 1.5 nM. Vorapaxar shows slow on and off binding rates at the receptor. The significance of the slow offset for the pharmacodynamics of the drug is not clear. Vorapaxar shows in vitro effects on platelets at concentrations between 15 and 76 nM. Vorapaxar inhibits thrombin receptor agonist (or activating) peptide (TRAP)-induced *ex vivo* platelet aggregation without affecting ADP or collagen-induced platelet aggregation, has no effect on commonly used coagulation tests (PT, aPTT, ACT, TT, ECT) and does not increase bleeding time in healthy volunteer studies. In a coronary artery disease population, vorapaxar on a background of aspirin and clopidogrel (in the majority of patients) has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (P04737). Furthermore, in these patients vorapaxar reduced the rate of hard endpoints, including cardiovascular death, MI and stroke.

The *ex vivo* TRAP-induced platelet aggregation assay was used as a PD end point. On an individual basis, vorapaxar exhibits a steep exposure-response relationship characterized by a rapid transition from minimal inhibition to TRAP-induced platelet aggregation to high levels of inhibition over a narrow vorapaxar concentration range. Consistent with the steep exposure response, the vast majority of the PD data obtained in the 7 Phase 1 and 2 studies and TRACER sub-study are either at high levels or low levels of inhibition with very little data reflecting intermediate levels of inhibition. An intermediate mean inhibition does not generally reflect that most subjects/patients exhibit intermediate levels of response, but rather that there are a mix of subjects/patients with high and low inhibition responses. For this reason an alternate measure (% of subjects/patients achieving 80% inhibition) is used as a more informative summary measure of target engagement. These data suggests 2.5 mg is required to achieve consistent efficacy in the majority of patients. However there is a difference in response between healthy subjects and patients with 1 mg appearing sufficient in the patient studies.

The population PK/PD modelling integrated the exposure-response data across all 8 studies with TRAP-induced platelet aggregation data. The concentration range for the step change to high inhibition varies between individuals, such that on a population basis a broader exposure-response relationship is seen. There is a slight time-lag between plasma concentrations and platelet aggregation biomarker response, which is accounted for in the modeling by a link model to an effect compartment.

Achievement of ≥80% inhibition in most patients by end of the first week of dosing (Day 7 trough) was selected as an appropriate engagement. Overall, the model supports that 2.5 mg daily represents lowest dose likely to provide complete response in most patients within one week of treatment.

There are aspects of the PKPD modelling that limit confidence in the model. For example there is large variability in the data only partially accounted for by the covariates investigated and the final VPC's show huge variability in the predictions. Particularly of importance is the difference in the $EC_{50}$ calculated for patients and HV which is not explained, if the lower values is correct then a dose of 1 mg would appear acceptable. In addition there appears to be a lack of a mechanistic understanding of a number of aspects of the model: with the delay being modelled as an indirect effect, slow offset at the receptor not being incorporated in the model, and a very steep dose response curve. As a result this modelling is seen as useful to identify covariates but is not considered highly supportive of the dose of 2.5 mg for efficacy and strong clinical efficacy data is required.

There is only limited further linkage of exposure to clinical endpoints such as efficacy event rate or bleeding rate has been possible. The available exposure-response data do not suggest a strong association with exposure for target engagement, efficacy or bleeding within the PK variation seen at 2.5 mg daily and therefore PK comparability bounds are not rigorous enough to use as a sole assessment of clinical significance of intrinsic and extrinsic factor effects. As a result, direct assessments of efficacy and safety in the large Phase 3 dataset inform the clinical relevance of PK differences and appropriate recommendations for intrinsic and extrinsic factors.

The long duration of action could be a concern for patients intending to undergo surgery. In certain cases treating physicians may consider necessary for their patients to temporarily discontinue vorapaxar therapy before major surgery. Therefore, taking into account the long-half life and the pharmacodynamic effects on platelets, the SmPC includes relevant recommendations as to how long before surgery the treatment should be stopped.

Resistance to aspirin has been documented as a polymorphism. However, based on the mechanism of action of vorapaxar, and of aspirin, the polymorphisms known for aspirin are not expected to impact on the pharmacodynamics response to vorapaxar.

### 2.4.4. Discussion on clinical pharmacology

The MAH provided an adequate clinical pharmacology documentation investigating PK/PD of Vorapaxar. The data can be summarised as follows:

After oral administration of a single vorapaxar sulfate 2.5 mg dose, vorapaxar is rapidly absorbed and peak concentrations occur at a median tmax of 1 hour (range: 1 to 2) under fasted conditions. The mean absolute bioavailability of vorapaxar from the 2.5 mg dose of vorapaxar sulfate is 100%.

Ingestion of vorapaxar with a high-fat meal resulted in no meaningful change in AUC with a small (21%) decrease in Cmax and delayed tmax (45 minutes). Zontivity may be taken with or without food. Co-administration of an aluminium hydroxide/magnesium carbonate antacid or proton pump inhibitor (pantoprazole) did not affect vorapaxar AUC with only small decreases in Cmax. Therefore, Zontivity may be administered without regard to co-administration of agents that increase gastric pH (antacid or proton pump inhibitor).

The mean volume of distribution of vorapaxar is approximately 424 litres. Vorapaxar and the major circulating active metabolite, M20, are extensively bound (≥99%) to human plasma proteins. Vorapaxar is highly bound to human serum albumin and does not preferentially distribute into red blood cells.

Vorapaxar is eliminated by metabolism, with CYP3A4 and CYP2J2 responsible for formation of M20, its major active circulating metabolite, and M19, the predominant metabolite identified in excreta. The systemic exposure of M20 is ~20% of the exposure to vorapaxar.

The primary route of elimination is through the faeces, with approximately 91.5% of radiolabeled dose predicted to be recovered in the faeces compared to 8.5% in the urine. Vorapaxar is eliminated primarily in the form of metabolites, with no vorapaxar detected in urine. The apparent terminal half-life for vorapaxar is 187 hours (range 115-317 hours) and is similar for the active metabolite.

Vorapaxar exposure increases in an approximately dose-proportional manner following single doses of 1 to 40 mg and multiple doses of 0.5 to 2.5 mg of vorapaxar sulfate. The systemic pharmacokinetics of vorapaxar are linear with accumulation (6-fold) predictable from single- to multiple-dose data. Steady-state is achieved by 21 days following once-daily dosing.

The effects of renal (end-stage renal disease undergoing haemodialysis) and hepatic impairment on the pharmacokinetics of vorapaxar were evaluated in specific pharmacokinetic studies and are summarized below:

Pharmacokinetics of vorapaxar are similar between patients with end-stage renal disease (ESRD) undergoing haemodialysis and healthy subjects. Based on population pharmacokinetic analysis using data from healthy subjects and patients with atherosclerotic disease, vorapaxar mean AUC is estimated to be higher in patients with mild (17%) and moderate (34%) renal impairment compared to those with normal renal function; these differences are not considered to be clinically relevant. No dose adjustment is necessary for patients with renal impairment, including subjects with ESRD. There is limited therapeutic experience in patients with severe renal impairment or end stage renal disease. Therefore, Zontivity should be used with caution in such patients.

Pharmacokinetics of vorapaxar are similar between patients with mild (Child Pugh, 5 to 6 points) to moderate (Child Pugh, 7 to 9 points) hepatic impairment and healthy patients. Reduced hepatic function is a risk factor for bleeding and should be considered before initiating Zontivity. No dose adjustment is required for patients with mild hepatic impairment. Zontivity should be used with caution in patients with moderate hepatic impairment. Zontivity is contraindicated in patients with severe hepatic impairment (Child Pugh, 10 to 15 points) (see sections 4.3 and 4.4).

Pharmacokinetics of vorapaxar are similar between elderly, including those ≥75 years of age, and younger patients. No dose adjustment is necessary (see section 4.4).

The mean estimated vorapaxar Cmax and AUC were 30% and 32% higher, respectively, in females compared to males. These differences are not considered to be clinically relevant and no dose adjustment is necessary.

The mean estimated vorapaxar Cmax and AUC were 35% and 33% higher, respectively, in patients with a body weight of <60 kg compared to those weighing 60-100 kg. By comparison, vorapaxar exposure (AUC and Cmax) is estimated to be 19-21% lower in patients with a body weight of >100 kg compared to those weighing 60-100 kg. In general, a body weight <60 kg is a risk factor for bleeding. Zontivity should be used with caution in patients with a body weight <60 kg.

The mean estimated vorapaxar Cmax and AUC were 24% and 22% higher in Asian patients compared to that of Caucasians. Vorapaxar exposure (AUC and Cmax) in patients of African descent is estimated to be 17-19% lower compared to that of Caucasians. These differences are not considered to be clinically relevant and no dose adjustment is necessary.

In vitro metabolism studies demonstrate that vorapaxar is unlikely to cause clinically significant inhibition of human CYP1A2, CYP2B6, CYP3A, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. No clinically meaningful inhibition of CYP2B6, CYP3A, CYP2C19, or CYP2D6 by M20 is expected. In addition, no clinically meaningful inhibition of OATP1B1, OATP1B3, BCRP, OAT1, OAT3, and OCT2 by vorapaxar or M20 is anticipated. Based upon in vitro data, chronic administration of vorapaxar is unlikely to induce the metabolism of drugs metabolized by major CYP isoforms.

The above information is included in the SmPC in section 5.2.

Vorapaxar is contraindicated in severe hepatic impairment. The delayed onset of action (at least 7 days) and the related long half-life is mentioned adequately in the SmPC.

The CHMP discussed extensively the data available in lower body weight, elderly >75 years of age and took into account the SAG Expert view in these populations at risk. Further information is provided later in the efficacy and safety part of the report. In summary no dose adjustment is necessary in these patients and caution is advised for the patients with low body weight and elderly patients due to the increased risk of bleeding.

## 2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology data have been adequately discussed. The SmPC adequately reflects the current data and limitations in populations at risk of bleeding (elderly, low weight <60kg patients, hepatic and renal impairment), taking also into account the efficacy and safety data (as discussed further below).

# *2.5. Clinical efficacy*

## 2.5.1. Introduction

The clinical development program consisted of twenty-one (21) Phase 1 clinical studies that included 1215 subjects, of which 1060 received vorapaxar. Most subjects were healthy men or women, but one study included 8 subjects with end-stage renal disease requiring hemodialysis and another included 16 subjects with mild to severe hepatic impairment. In addition, there were 19 subjects with documented atherosclerotic disease in the Phase 1 ocular safety study. The range of doses evaluated were 0.25 mg to 120 mg administered as single doses. Multiple-dose regimens of up to 7.5 mg/day for 6 days (with loading doses of up to 40 mg), 5 mg/day for 28 days, or 2.5 mg/day for 3 months (after a 40 mg loading dose) were also evaluated. Vorapaxar was reported to be generally safe and well tolerated in the Phase I program.

Three Phase 2, randomized, double-blind, placebo-controlled studies of safety and efficacy were conducted. The first was a multicenter study in 1030 subjects eligible for non-emergent PCI (TRA-PCI); 573 subjects received vorapaxar at an initial loading dose of 10, 20, or 40 mg followed by treatment with 0.5, 1, or 2.5 mg/day for 59 additional days (60 days total), then no-treatment follow-up for 60 days. Two smaller phase 2 studies were conducted in Japan to gain experience in a Japanese subject population. One was a study involving 117 subjects with ACS with a design similar to TRA-PCI. The second was a study in 90 subjects with a history of ischemic stroke that included treatment with placebo or vorapaxar in doses of 1 or 2.5 mg for 60 days, then no-treatment follow-up for 60 days.

Phase 3 Dose Selection:

Based on the Phase 1 and 2 studies, a dose of vorapaxar 2.5 mg daily was selected for chronic administration in Phase 3. With complete inhibition defined as >80% inhibition of TRAP induced platelet aggregation in ≥80% of the patients, vorapaxar at a dose of 2.5 mg daily consistently achieved complete inhibition of TRAP-induced platelet aggregation within one week of initiation of treatment. For one Phase 3 study in ACS (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER); see below), a 40-mg loading dose of vorapaxar, started during the acute phase in the hospital and followed by a 2.5-mg daily maintenance dose, was studied. The choice of a 40-mg loading dose was based on achieving a complete inhibition in ≥80% of subjects within 1-2 hours post-dose on the first day of treatment. In the second Phase 3 study, a chronic daily dose of 2.5 vorapaxar without a loading dose was studied in secondary prevention (Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P - TIMI 50 trial; see below).

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

The following therapeutic indication has been proposed for Vorapaxar:

*Vorapaxar is indicated for the reduction of atherothrombotic events in patients with a history of MI. Vorapaxar has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization.*

*Vorapaxar will be contraindicated in patients with a history of stroke or TIA.*

## 2.5.2. Dose response studies

### Dose response studies

**Table E.1** Phase 2 trials

| Study No., Phase –center(s) –start date –status/date | Design, Objective(s), Test Product and Control, Regimen, and Duration of Treatment | Total Number of Subjects, by Sex, Age Range (y), Diagnosis and Criteria for Inclusion | Treatment[a] | Number of Subjects per Treatment |
|---|---|---|---|---|
| P03573, TRA-PCI, Phase 2 Multicenter (international) Started AUG 2005 Completed JAN 2007 | Randomized, double-blind, placebo-controlled, sequential-parallel-groups trial of the safety of TRA vs. placebo in subjects who had symptoms of CAD and were scheduled for non-emergent PCI; separate randomization for oral loading dose and oral maintenance dose; single loading dose at enrollment; maintenance dose QD for 59d in subjects with PCI; loading dose only in subjects with no PCI.<br>Follow-up for 60d after last dose.<br>Endpoints: safety, clinical activity (death, MACE, stroke); substudy assessed PK/PD, biomarkers. | 749 men/281 women (total, 1030) aged 29-94y with history of CAD signs and/or symptoms, scheduled for non-emergent catheterization with intent to perform PCI.<br>Cohort 1: PCI performed.<br>Cohort 2: no PCI performed. | COHORT 1<br>Placebo x 60d<br>Vorapaxar 10 mg x 1d +<br>0.5 mg x 59d<br>1 mg x 59d<br>2.5 mg x 59d<br>Vorapaxar 20 mg x 1d +<br>0.5 mg x 59d<br>1 mg x 59d<br>2.5 mg x 59d<br>Vorapaxar 40 mg x 1d +<br>0.5 mg x 59d<br>1 mg x 59d<br>2.5 mg x 59d<br>COHORT 2<br>Placebo x 1d<br>Vorapaxar x 1d<br>10 mg<br>20 mg<br>40 mg | Randomized<br>151<br>129<br><br>42<br>43<br>41<br>120<br><br>41<br>37<br>39<br>173<br><br>53<br>59<br>58<br><br>106<br><br>93<br>118<br>140 |
| P04772, Phase 2 Multicenter (Japan) Started NOV 2006 Completed OCT 2007 | Randomized, double-blind, placebo-controlled, sequential-parallel-groups trial of the safety of TRA vs. placebo in subjects with ACS who were scheduled to undergo PCI; single randomization for oral loading dose and oral maintenance dose; single loading dose at enrollment, maintenance dose QD for 59d in subjects with PCI; loading dose only in subjects with no PCI.<br>Follow-up for 60d after last dose.<br>Endpoints: safety, clinical activity (death, MACE including stroke); substudy assessed PK/PD, biomarkers. | 88 men/29 women (total, 117) aged 35-87y with signs/symptoms of ACS, scheduled for catheterization with intent to perform PCI.<br>Cohort 1: PCI performed.<br>Cohort 2: no PCI performed. | COHORT 1<br>Placebo x 60d<br>Vorapaxar<br>20 mg x 1d +<br>1 mg x 59d<br>20 mg x 1d +<br>2.5 mg x 59d<br>40 mg x 1d +<br>1 mg x 59d<br>40 mg x 1d +<br>2.5 mg x 59d<br>COHORT 2<br>Placebo x 1d<br>Vorapaxar x 1d<br>20 mg<br>40 mg | Treated<br>21<br><br><br>21<br><br>19<br><br>16<br><br>15<br><br>2<br><br>6<br>17 |
| P05005, Phase 2 Multicenter (Japan) Started DEC 2006 Completed NOV 2007 | Randomized, double-blind, placebo-controlled, parallel-group trial of the safety of TRA vs. placebo in subjects with symptomatic cerebral infarction; oral maintenance dose QD for 60d.<br>Follow-up for 60d after last dose.<br>Endpoints: safety, clinical activity (death, MACE including stroke); substudy assessed PK/PD, biomarkers. | 69 men/21 women (total, 90) aged 30-83y with confirmed thrombotic cerebral infarction ≥2w to <1y previous. | Placebo x 60d<br>Vorapaxar<br>1 mg x 60d<br>2.5 mg x 60d | Treated<br>28<br><br>33<br>29 |

**Abbreviations:** ACS = acute coronary syndrome; CAD = coronary artery disease; CVD = cerebrovascular disease; F (Sex) = female; M (Sex) = male; MACE = P03573–major adverse cardiac event, P04772 and P05005–major adverse cardiovascular event; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation ACS; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; vs. = versus

[a] Randomized treatment assignment



### Study P03573:

"A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety of SCH 530348 in Subjects Undergoing Non-Emergent Percutaneous Coronary Intervention (Thrombin Receptor Antagonist in PCI [TRA-PCI]) " (P03573) was a Phase 2 study conducted to determine whether the clinical development program would proceed to Phase 3, and if so, the appropriate dosing regimen. The primary objective was to evaluate the safety of multiple dose levels of vorapaxar with respect to the incidence of TIMI (Thrombolysis in Myocardial Infarction Study Group) major and minor bleeding in subjects undergoing non-emergent PCI, and as maintenance therapy after the procedure. Clinical events and inhibition of TRAPinduced platelet aggregation were assessed to facilitate selection of a dosing regimen for Phase 3. This was a randomized, double-blind, placebo-controlled study

conducted in 1030 subjects 45 years of age or older with atherosclerosis and symptoms of CAD who were scheduled to undergo non-emergent PCI (PCI cohort; n=573) or non-emergent cardiac catheterization with intent to undergo PCI (non-PCI cohort; n=457). Investigational treatment was administered in addition to standard of care (aspirin and clopidogrel). Subjects were enrolled in 3 sequential groups based on the vorapaxar loading dose level: Group 1, 10 mg; Group 2, 20 mg; and Group 3, 40 mg. Within each group, on the day of the procedure, subjects were randomized to a loading dose of vorapaxar or placebo. Subjects who did not undergo PCI (non-PCI cohort) received only the loading dose of placebo (total of 106 subjects across the 3 groups), vorapaxar 10 mg (n=93), vorapaxar 20 mg (n=118), or vorapaxar 40 mg (n=140). After initiation of PCI (i.e., guidewire crossing the lesion), subjects given a vorapaxar loading dose were assigned to a maintenance dose of 0.5 mg, 1 mg, or 2.5 mg/day in a 1:1:1 ratio in a double-blinded manner, and subjects given a placebo loading dose continued taking placebo. Subjects in the PCI cohort began maintenance dosing on the day after PCI and received study drug for a total of 60 days.

The vorapaxar loading dose caused a dose-dependent inhibition of TRAP-induced platelet aggregation. At 1.5 hours after the loading dose, only the 40 mg dose achieved a complete response, defined as ≥80% inhibition of TRAP-induced platelet aggregation. At 2 hours after the loading dose, 96% of the subjects who received 40 mg had a complete response compared with 53% and 43% of the subjects who received 20 mg or 10 mg, respectively.

At 30 days and 60 days of maintenance dosing, a complete response (see above) was achieved in 91% of subjects receiving 0.5 mg/day vorapaxar and 100% of subjects receiving 1 or 2.5 mg/day vorapaxar. In comparison, 9% of placebo subjects achieved complete inhibition on Day 30 and 11% on Day 60. Thus, maintenance dosing preserved inhibition of platelet aggregation.

A 40 mg loading dose was selected for use in the acute setting in the TRACER trial based on 40 mg achieving complete response in at least 80% of subjects within 1- 2 hours post-dose on the first day of treatment in the TRA-PCI study. A maintenance dose of 2.5 mg/day was selected for the Phase 3 trials based on (1) comparable safety profiles between 1 mg and 2.5 mg in the TRA-PCI study, (2) 100% of subjects maintaining complete response at 30 and 60 days in the TRA-PCI study, and (3) dose-pharmacodynamic response (i.e., inhibition of platelet aggregation) projections which supported that doses much lower than 2.5 mg (e.g., 1.0 mg) would be expected to demonstrate less response in TRAP-induced platelet aggregation and as such suggested that efficacy could be reduced at these lower doses.

Based on the main phase II study P03573, a 40 mg loading dose was selected for use in the acute setting in the TRACER trial and a maintenance dose of 2.5 mg/day was selected for the Phase 3 trials. Studies **P04772** and **p05005** in a small number of Japanesse patients showed supportive results to the main phase II study in terms of dose selection. In addition , study p05005 demonstrated that short-term co-administration of vorapaxar with aspirin was not associated with an increase in overall adverse events nor with any other indicator of a lack of safety in a small number of Japanese subjects with a history of cerebral infarction.

## 2.5.3. Main study(ies)

The vorapaxar Phase 3 clinical program included two major placebo-controlled clinical outcome studies designed to evaluate the hypothesis that vorapaxar added to standard of care would reduce the incidence of atherothrombotic events compared to placebo with standard of care in two distinct populations.

**Study P04736 TRACER** and **study P04736 TRA 2°P - TIMI 50** trials were independent, long-term, large-scale outcome studies designed to independently support different indications of ACS and secondary prevention of post MI, post stroke or PAD respectively. Study P04736 TRACER in patients with ACS was stopped early mainly due to an increased bleeding risk. The indication sought

in the current application “reduction of atherothrombotic events in patients with a history of myocardial infarction” is supported by the efficacy results of study P04736 TRA 2°P - TIMI 50 , which is considered the pivotal trial for the currently sought indication.

**Table E.2** Phase 3 trials

| Study No., Phase –center(s) –start date –status/date | Design, Objective(s), Test Product and Control, Regimen, and Duration of Treatment | Total Number of Subjects, by Sex, Age Range (y), Diagnosis and Criteria for Inclusion | Treatment[a] | Number of Subjects per Treatment |
|---|---|---|---|---|
| P04737, TRA 2°P – TIMI 50, Phase 3 Multicenter (international) Started SEP 2007 Completed DEC 2011 | Randomized, double-blind, placebo-controlled trial of the long-term (≥1y) safety and efficacy of standard of care plus once-daily oral maintenance dose vorapaxar or placebo (1:1 ratio) for secondary prevention of atherothrombotic ischemic events in subjects who had evidence or a history of atherosclerosis (post MI, CVD, or PAD). Randomization was stratified by planned use of thienopyridine and by qualifying disease (post MI:CVD:PAD in a ratio of 70:15:15). Follow-up (telephone contact) until study completion. Endpoints: safety, efficacy, biomarkers. | 20,123 men/6326 women (total, 26,449) ages 21-95 y with a history of MI, ischemic stroke, or PAD. | Standard of care (i.e., aspirin, thieno-pyridine) + Vorapaxar 2.5 mg QD x ≥1y<br>Placebo QD x ≥1y | 13,225<br>13,224 |
| P04736, TRACER, Phase 3 Multicenter (international) Started DEC 2007 Completed JUL 2011 | Randomized, double-blind, placebo-controlled trial to evaluate the long-term (≥1y) safety and efficacy of a single oral loading dose plus once-daily oral maintenance dose of vorapaxar vs. placebo (1:1 ratio) in addition to standard of care in subjects with documented atherosclerotic disease and symptoms of non-ST-segment elevation ACS (NSTE-ACS). Randomization was stratified by (1) planned use of a GP IIb/IIIa inhibitor, and (2) type of antithrombin used or anticipated to be used (heparin vs. direct thrombin inhibitor). Follow-up (telephone contact) until study completion. Endpoints: safety, efficacy, biomarkers. | 9312 men/3632 women (total, 12,944) ages 29-94 y with NSTE-ACS and at moderate-risk to high-risk | Standard of care (i.e., aspirin, thieno-pyridine) + Vorapaxar 40 mg x 1d + 2.5 mg QD x ≥1y<br>Placebo QD x ≥1y | 6473<br>6471 |

### *2.5.3.1. Study P04736- TRACER study (supportive study)*

As mentioned, TRA 2°P - TIMI 50 is the pivotal trial for the proposed indication and TRACER is only considered as supporting study considering the applied indication. Therefore this study is described but further efficacy assessment is limited as it was considered not directly relevant to the indication applied for.

Title of study

Study P04736: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of vorapaxar in Addition to Standard of Care in Subjects With Acute Coronary Syndrome: Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER).

***Study participants***

The study included patients with moderate-risk to high-risk subjects with NSTEACS. Men and women at least 18 years old with clinical manifestation and objective evidence of non-ST-segment-elevation acute coronary syndrome (NSTEACS) were the target population. Subjects were to be enrolled into the study after the index event (which was the ACS event that qualified the subject for inclusion into the study) and before discharge from acute care for the index event.

***Treatments***

A loading dose of vorapaxar 40 mg or matching placebo was to be administered at the time of randomized treatment assignment, followed by daily maintenance dosing with 2.5 mg or matching placebo beginning the next calendar day after administration of the loading dose. Additional therapy was to be administered according to current standard of care.

***Objectives***

The primary objective was to evaluate the hypothesis that vorapaxar added to standard of care will reduce the incidence of atherothrombotic ischemic events relative to standard of care alone, as measured by the composite of cardiovascular (CV) death, myocardial infarction (MI), stroke, recurrent ischemia with rehospitalization, and urgent coronary revascularization. The key secondary

objective was to evaluate clinical benefit with respect to the composite of cardiovascular death, MI, and stroke.

***Sample size/Randomisation***

In total, 89.3% (11512/12944) of the study subjects initially randomised completed the study with similar overall discontinuation rate on both groups (28.2% vs 26.8% discontinuation in Vorapaxar vs Placebo); however discontinuation due to adverse events was most common in the Vorapaxar group. [649 (10%) vs 489 (7.6%) Vorapaxar vs Placebo]. The Data Safety Monitoring Board (DSMB) concluded the study earlier due to the high bleeding findings particularly due to the higher number of intracranial haemorrhage on the vorapaxar arm.

**Results**

**Table E.3** TRACER Primary and Key Secondary Endpoints and Contributing Components With Stroke Sub-Categories Included: ITT Population (Event Accrual Period: Randomization to Last Visit)

| Endpoints | Placebo (n=6471) Subjects With Events (%) | KM%[c] | Vorapaxar (n=6473) Subjects With Events (%) | KM%[c] | Hazard Ratio[a,b] (95% Confidence Interval) | P Value[b] |
|---|---|---|---|---|---|---|
| **Primary Efficacy Endpoint** | 1102 (17.0%) | 19.9% | 1031 (15.9%) | 18.5% | 0.92 (0.85-1.01) | 0.072 |
| CV Death | 122 (1.9%) | - | 115 (1.8%) | - | - | - |
| MI | 668 (10.3%) | - | 596 (9.2%) | - | - | - |
| Stroke | 89 (1.4%) | - | 83 (1.3%) | - | - | - |
| Ischemic (Non-Hemorrhagic Cerebral Infarction) | 82 (1.3%) | | 63 (1.0%) | | | |
| Hemorrhagic Stroke[d] | 6 (0.1%) | | 19 (0.3%) | | | |
| Uncertain | 1 (0.0%) | | 1 (0.0%) | | | |
| RIR | 53 (0.8%) | - | 60 (0.9%) | - | - | - |
| UCR | 170 (2.6%) | - | 177 (2.7%) | - | - | - |
| **Key Secondary Efficacy Endpoint** | 910 (14.1%) | 16.4% | 822 (12.7%) | 14.7% | 0.89 (0.81-0.98) | 0.018 |
| CV Death | 127 (2.0%) | - | 122 (1.9%) | - | - | - |
| MI | 692 (10.7%) | - | 614 (9.5%) | - | - | - |
| Stroke | 91 (1.4%) | - | 86 (1.3%) | - | - | - |
| Ischemic (Non-Hemorrhagic Cerebral Infarction) | 84 (1.3%) | | 66 (1.0%) | | | |
| Hemorrhagic Stroke[d] | 6 (0.1%) | | 19 (0.3%) | | | |
| Uncertain | 1 (0.0%) | | 1 (0.0%) | | | |

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

**Figure E.1** Kaplan-Meier Estimate of Time to the First Occurrence of Primary Efficacy Endpoint for All Subjects in the Intent to Treat Population (Event Accrual Period: Randomization to Last Visit)

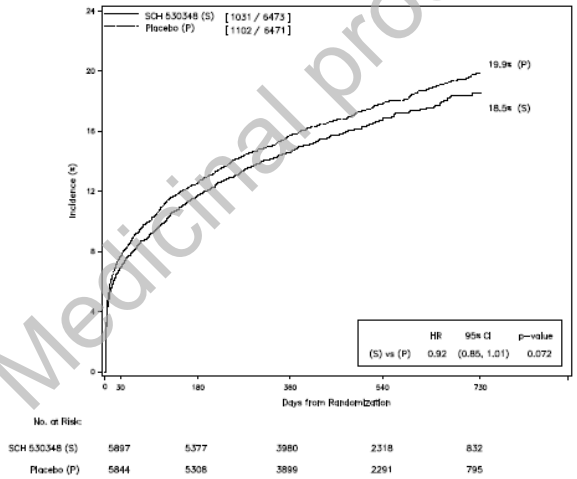
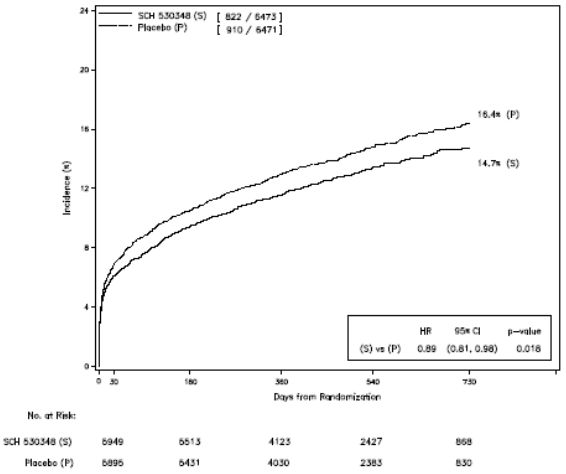



**Figure E.2.** Kaplan-Meier Estimate of Time to the First Occurrence of Key Secondary Efficacy Endpoint for All Subjects in the Intent to Treat Population (Event Accrual Period: Randomization to Last Visit)




The findings for the primary efficacy composite endpoint (first occurrence of CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) show 2- year Kaplan-Meier event rates of 18.5% in the vorapaxar group compared with that of 19.9% in the placebo group. These results were not statistically significant (hazard ratio [HR], 0.92; 95% CI, 0.85 to 1.01; P = 0.072). For the key secondary efficacy composite endpoint (first occurrence of CV death, MI, or stroke), 2-year Kaplan- Meier event rates of 14.7% in the vorapaxar group versus 16.4% in the placebo group were observed (HR, 0.89; 95% CI, 0.81 to 0.98; P = 0.018). While the observed p-value was 0.018, these results are not statistically significant after adjustment under the pre-specified multiplicity strategy.

As a result of the outcome of the TRACER trial, the indication for Vorapaxar in NSTE-ACS at dose of40 mg loading dose and 2.5 mg daily maintenance dose was not pursued by the applicant. The study was terminated earlier mainly due to the higher bleeding rate on the vorapaxar arm, particularly due to higher incidence of intracranial bleeding (see section safety).

#### *2.5.3.2. Study P04737- TRA2P-TIMI 50*

- ***Study title***

**Study P04737 (TRA 2P – TIMI 50):** Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Vorapaxar in Addition to Standard of Care in Subjects With a History of Atherosclerotic Disease: Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events.

- ***Study population***

The population selected in this study were patients with evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems as follows:

a. CAD as indicated by a history of presumed spontaneous MI (hospitalized with final diagnosis of MI, excluding periprocedural or definite secondary MI [eg, due to profound anemia 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
    i. a resting ankle/brachial index (ABI) of <0.85, or
    ii. amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia.

- ***Treatments***

Subjects were to receive randomized allocation of treatment with vorapaxar 2.5 mg or matching placebo in a 1:1 ratio. All doses were to be taken by the subject orally, once daily, with or without food, as follows:

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

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

- ***Study objective***

The primary objective was to evaluate the hypothesis that vorapaxar added to standard of care will reduce the incidence of atherothrombotic ischemic events relative to standard of care alone, as measured by the composite of cardiovascular (CV) death, myocardial infarction (MI), stroke, and urgent coronary revascularization (UCR) in subjects with established coronary artery disease (CAD), cerebrovascular disease (CVD), or peripheral artery disease (PAD). The key secondary objective was to evaluate clinical benefit with respect to the composite of cardiovascular death, MI, and stroke.

- **Outcomes/endpoints**

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

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

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

- **Sample size**

The initial plan was to recruit 19500 subjects, but following a blinded sample size re estimation in March 2009, up to 25,000 subjects were to be recruited at approximately 1000 centres in North America, Latin America, Eastern and Western Europe, Israel, South Africa, Asia/Pacific, and Australia/New Zealand; 1032 study sites in 32 countries. This sample size was required to provide adequate power to test the hypothesis of a 15% relative risk reduction with vorapaxar relative to placebo, each added to the existing standard of care, for occurrence of the primary and key secondary composite efficacy endpoints, plus adjust for potential dropouts during the study.

- **Randomisation**

Randomized treatment assignment was stratified by qualifying condition at entry –CAD, CVD, or PAD – and planned use of a thienopyridine (none versus already being taken or to be added).

- **Blinding (masking)**

Treatment assignment was blinded for subjects, investigators and staff who evaluated subjects and their responses or made decisions about subject care, and Sponsor personnel who had direct contact

with subject records or were involved with study contact or data review. Unblinding during the study was to occur only in the event of an emergency or adverse event for which it was necessary to know the study treatment to determine an appropriate course of therapy for the subject.

- **Statistical methods**

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

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

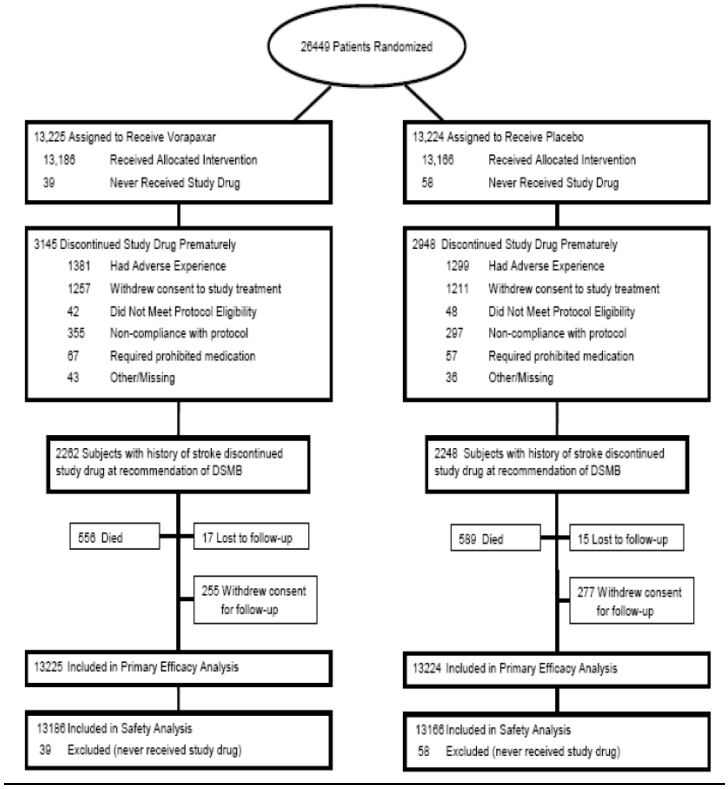
The following analyses were pre-specified in the study Data Analysis Plan (DAP), and were covered under a multiplicity adjustment procedure. The primary efficacy endpoint: composite of CV death, MI, stroke or UCR, The key secondary efficacy endpoint: the composite of CV death, MI or stroke.

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

**Results**

- ***Patients disposition***

**Table E.4.** Subject Disposition




- **Baseline data / numbers analysed**

In total, 26,352 subjects were treated (13186 vorapaxar vs 13166 placebo) of which 23% overall discontinued treatment (2984 placebo and 3145 vorapaxar) from which discontinuation due to adverse events was slightly more common in the Vorapaxar group. (1381 subjects in vorapaxar vs 1299 in placebo). Additionally, the Data Safety Monitoring Board (DSMB) recommendation to discontinue all patients with a history of stroke which involved discontinuation of 4510 subjects of both groups (2262 vorapaxar and 2248 placebo). Twenty five (25) subjects in the CVD stratum were incorrectly classified as they had no history of stroke. The Applicant has clarified this point. The data suggest that these misclassifications are unlikely to have had a significant impact on the analyses and conclusions.

The treatment groups were comparable with respect to demographic, baseline characteristics and concomitant medication in the proposed label population (patients without history of stroke or TIA).

A total of 16,897 subjects were finally included in the proposed label population that mainly included white (88.2%) males (79.9%) who were < 65 years old (71.1%) and ≥ 60kg (94.85%) with cardiovascular comorbidities: high prevalence of hypertension (61.5%) and hyperlipidaemia (84.4%) and low prevalence of diabetes (21.4%). Concomitant medications were also well balanced with 98.3% of the subjects taking aspirin, 78% taking a thienopyridine (clopidogrel in the vast majority of subjects), and 77% were receiving dual antiplatelet therapy.

- **DSMB recommendation**

A communication from the DSMB in January 2011 recommended that all subjects with a stroke either prior to or during the study should discontinue study medication and that all other subjects continue the study drug as planned (see also Safety section n below). This was due to an increased number of cases with intracranial haemorrhage (ICH) reported in subjects with a prior history of stroke. A communication was sent to all study sites to inform them to discontinue subjects with a prior history of stroke from treatment, conduct follow-up visit and communicate new risk information to subjects.

Subjects with MI and PAD who also had a stroke were to discontinue treatment but continue their follow-up visits. Subjects were enrolled in one of three strata based on their qualifying atherosclerotic disease presentation and the data from these three strata in their entirety was the basis for the primary efficacy analysis in the overall population.

Following the recommendation of the DSMB and prior to database lock, the Executive Committee and Sponsor pre-specified populations that excluded the population identified by the DSMB. The observation that subjects with a history of stroke did not display a positive benefit/risk ratio, prior to database lock, the Sponsor along with the Executive Committee examined the remaining strata and pre-defined populations of interest:

Overall population – subjects, regardless of the qualifying condition, who received randomized treatment assignment

NSH population – subjects with no stroke history (NSH) – regardless of the qualifying condition, who received randomized treatment assignment

CAD (Post MI) and no history of stroke – subjects whose qualifying condition was CAD and did not have a documented history of stroke prior to randomization.

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

Proposed Label Population – This is the target population for the "proposed" indication. It corresponds to subjects whose qualifying condition was CAD (post MI) who did not have documented history of stroke or TIA prior to randomization. This population was defined post-hoc considering that the diagnosis of stroke versus TIA can be difficult based on subject history alone.

**Results**

In the Overall population, the results for the primary efficacy composite endpoint (first occurrence of CV death, MI, stroke, or UCR) was a 3-year Kaplan-Meier event rate of 11.2% in the vorapaxar group compared to 12.4% in the placebo group. These results were statistically significant (hazard ratio [HR], 0.88; 95% Confidence Interval {CI}, 0.82 to 0.95; P=0.001). The results for the key secondary composite efficacy endpoints (first occurrence of CV death, MI, or stroke) show 3-year KM event rate of 9.3% in the vorapaxar group compared to 10.5% in the placebo group. These results were statistically significant ([HR] 0.87; 95% CI, 0.80 to 0.94; P<0.001). Thus, the primary objective of the study based on the overall population (which includes all three qualifying atherosclerotic condition strata) was met.

Results for the pre-specified efficacy analysis of subjects with no stroke history (NSH) demonstrated a 3-yr KM event rate of 10.6% in vorapaxar and 11.8% in the placebo group (HR; 0.86 95% CI, 0.79-0.94; P<0.001).

The efficacy results for the primary efficacy endpoint in CAD subjects with no history of stroke comprised 17191 subjects; 8583 in placebo, and 8608 in vorapaxar, a large well-balanced population. The results were a 3-yr KM rate for primary efficacy endpoint of 10.1% in the vorapaxar group compared to 11.5% in the placebo group; HR, 0.84; 95% CI 0.76-0.93, P<0.001). A 16% treatment effect, and key secondary efficacy endpoints hazard reduction of 19% (HR; 0.81; 95% CI, 0.73 to 0.91; P ≤ 0.001). The individual component of the composite endpoints that most contributed to the difference between vorapaxar and placebo was the reduction of the rate of MI, 4.5% vs 5.4% as component of the primary endpoint and 4.7% vs 5.7% as component of the secondary endpoint.

The Proposed Label Population (CAD subjects without a history of stroke or TIA; 64% of subjects enrolled in this study) had efficacy results that favored vorapaxar (18% relative risk reduction on top

of standard care). In this population, the primary efficacy composite endpoint was a 3-year KM event rate of 9.8% in the vorapaxar group compared to 11.4% in the placebo group (HR; 0.82; 95% CI 0.74-0.90, P<0.001). Consistent with the results in the overall population, the individual component of the composite endpoints that most contributed to the difference between vorapaxar and placebo was the reduction of the rate of MI. MI was reported in 374 vorapaxar subjects (4.4%) vs. 451 placebo subjects (5.3%) as a component of the primary endpoint, and in 387 vorapaxar subjects (4.6%) vs. 481 placebo subjects (5.7%) as a component of the secondary endpoint.

The efficacy results in all the analysed populations (including the proposed label population) are consistent and in favour of vorapaxar. The results showed that vorapaxar is more efficacious (greater clinical benefit and more statistically significant) in the proposed label population than in the overall population.

Duration of treatment was for at least a year and the median participation was more than 2.5 years.

The following tables and figures summarise the key results in the different populations with further details in the Proposed Label population.

**Table E.5.** Primary and Key Secondary Efficacy Endpoints- Event Accrual Period: Randomization to Last Visit-ITT Population

| Populations<br>Endpoint | Placebo | | Vorapaxar | | Hazard Ratio (95% CI)[b,c] P-value | |
|---|---|---|---|---|---|---|
| | Subjects With Events[d](%) | KM %[a] | Subjects With Events[a] (%) | KM %[a] | | |
| **Overall** | (n=13224) | | (n=13225) | | | |
| Primary Efficacy | 1417 (10.7%) | 12.4% | 1259 (9.5%) | 11.2% | 0.88 (0.82 – 0.95) | 0.001 |
| Key Secondary Efficacy | 1176 (8.9%) | 10.5% | 1028 (7.8%) | 9.3% | 0.87 (0.80 – 0.94) | <0.001 |
| **NSH** | (n=10344) | | (n=10355) | | | |
| Primary Efficacy | 1104 (10.7%) | 11.8% | 959 ( 9.3% ) | 10.6% | 0.86 (0.79 - 0.94) | <0.001 |
| Key Secondary Efficacy | 878 ( 8.5% ) | 9.6% | 742 ( 7.2% ) | 8.3% | 0.84 (0.76 - 0.93) | <0.001 |
| **CAD Subjects No History of Stroke** | (n=8583) | | (n=8608) | | | |
| Primary Efficacy[e] | 887 (10.3% ) | 11.5% | 757 (8.8% ) | 10.1% | 0.84 (0.76 - 0.93) | <.001 |
| Key Secondary Efficacy | 687 (8.0% ) | 9.1% | 564 (6.5% ) | 7.7% | 0.81(0.73 - 0.91) | <0.001 |
| **Proposed Label** | (n = 8439) | | (n=8458) | | | |
| Primary Efficacy | 867 (10.3%) | 11.4 % | 719 (8.5%) | 9.8% | 0.82 (0.74-0.90) | <0.001 |
| Key Secondary Efficacy | 671 (8.0%) | 9.0% | 532 (6.3%) | 7.4% | 0.78 (0.70-0.88) | <0.001 |

Note: Primary Efficacy Endpoint: CV Death / MI / Stroke / UCR Key Secondary Efficacy Endpoint: CV Death / MI / Stroke
a: Kaplan-Meier estimate at 1080 days
b: Hazard Ratio is vorapaxar group versus placebo group.
c: Hazard Ratio and P-value were calculated based on Cox Proportional Hazard (PH) model with covariates treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use).
d: Each patient was counted only once (first component event) in the component summary that contributed to the primary or key secondary efficacy endpoint.

***Proposed Label Population Results***

**Figure E.3.** TRA 2oP – TIMI 50 Kaplan-Meier Estimate of Time to the First Occurrence of Primary Efficacy Endpoint in Subjects With No History of Stroke or TIA Whose Qualifying Condition was CAD (Event Accrual Period: Randomization to Last Visit)

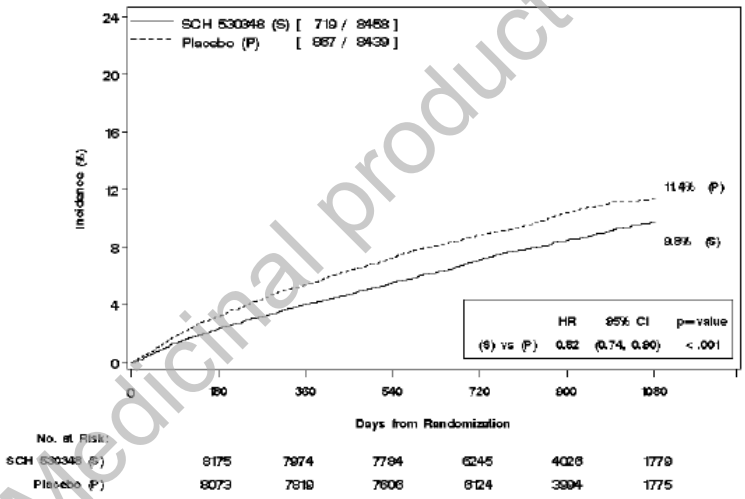


**Figure E.4.** TRA 2oP – TIMI 50 Kaplan-Meier Estimate of Time to the First Occurrence of Key Secondary Efficacy Endpoint in Subjects With No History of Stroke or TIA Whose Qualifying Condition was CAD (Event Accrual Period: Randomization to Last Visit)

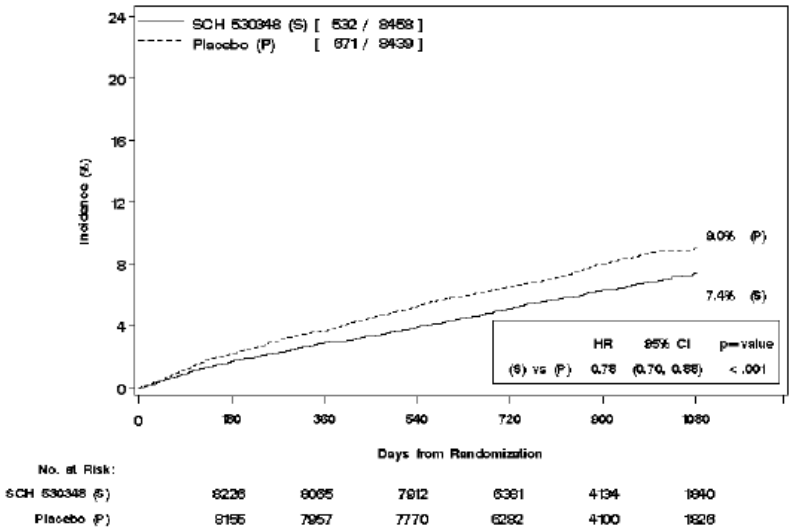



**Table E.6.** TRA 2oP – TIMI 50 Primary and Key Secondary Efficacy Endpoints and Contributing Components With Stroke Sub-Categories Included, in Subjects With No History of Stroke or TIA Whose Qualifying Condition was CAD (Event Accrual Period: Randomization to Last Visit)

| | Placebo (n = 8439) | | Vorapaxar (n = 8458) | | | |
|---|---|---|---|---|---|---|
| Endpoint and Contributing Component | Subjects With Events (%) | KM%[c] | Subjects With Events (%) | KM%[c] | Hazard Ratio[a,b] (95% Confidence Interval) | P Value[b] |
| **Primary Efficacy Endpoint** | 867 (10.3%) | 11.4% | 719 (8.5%) | 9.8% | 0.82 (0.74-0.90) | <0.001 |
| CV Death | 96 (1.1%) | | 82 (1.0%) | | | |
| MI | 451 (5.3%) | | 374 (4.4%) | | | |
| Stroke | 84 (1.0%) | | 60 (0.7%) | | | |
| Ischemic (Non-Hemorrhagic Cerebral Infarction) | 69 (0.8%) | | 38 (0.4%) | | | |
| Hemorrhagic Stroke | 11 (0.1%) | | 16 (0.2%) | | | |
| Uncertain | 4 (0.0%) | | 6 (0.1%) | | | |
| UCR | 236 (2.8%) | | 203 (2.4%) | | | |
| **Key Secondary Efficacy Endpoint** | 671 (8.0%) | 9.0% | 532 (6.3%) | 7.4% | 0.78 (0.70-0.88) | <0.001 |
| CV Death | 101 (1.2%) | | 84 (1.0%) | | | |
| MI | 481 (5.7%) | | 387 (4.6%) | | | |
| Stroke | 89 (1.1%) | | 61 (0.7%) | | | |
| Ischemic (Non-Hemorrhagic Cerebral Infarction) | 72 (0.9%) | | 39 (0.5%) | | | |
| Hemorrhagic Stroke | 12 (0.1%) | | 16 (0.2%) | | | |
| Uncertain | 5 (0.1%) | | 6 (0.1%) | | | |

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

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

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

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

[c] Kaplan-Meier estimate at 1080 days



- ***Clinical studies/results by subgroups***

The following graphs present the key efficacy results by the main subgroups examined, including both intrinsic and extrinsic factors.

**Figure E.5.** TRA 2°P – TIMI 50 Plot of Hazard Ratio (95% CI) for Primary Efficacy Endpoint in Subjects With No History of Stroke or TIA Whose Qualifying Condition was CAD (Event Accrual Period: Randomization to Last Visit)

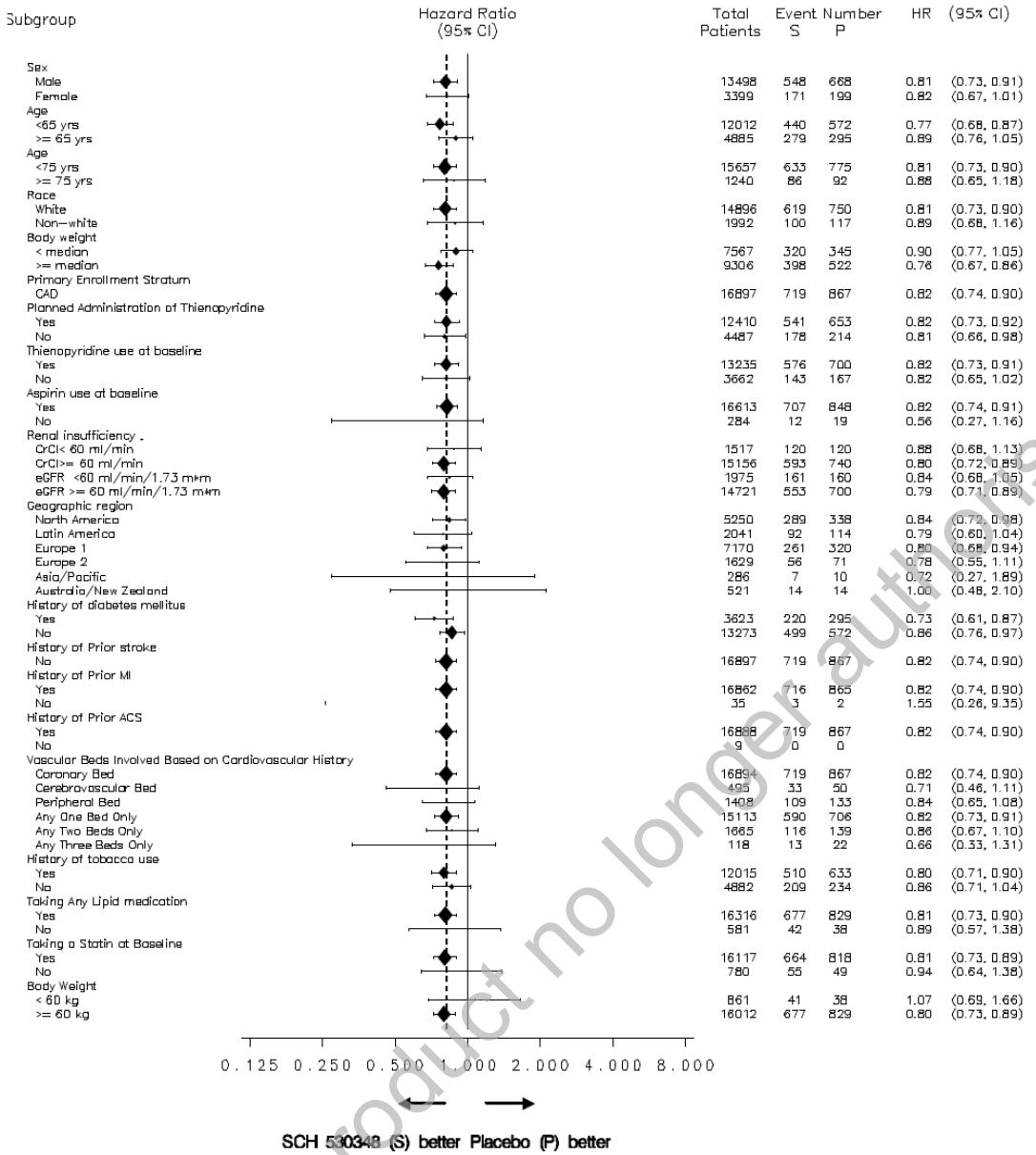



**Figure E.6.** TRA 2oP – TIMI 50 Plot of Hazard Ratio (95% CI) for Key Secondary Efficacy Endpoint in Subjects With No History of Stroke or TIA Whose Qualifying Condition was CAD (Event Accrual Period: Randomization to Last Visit)

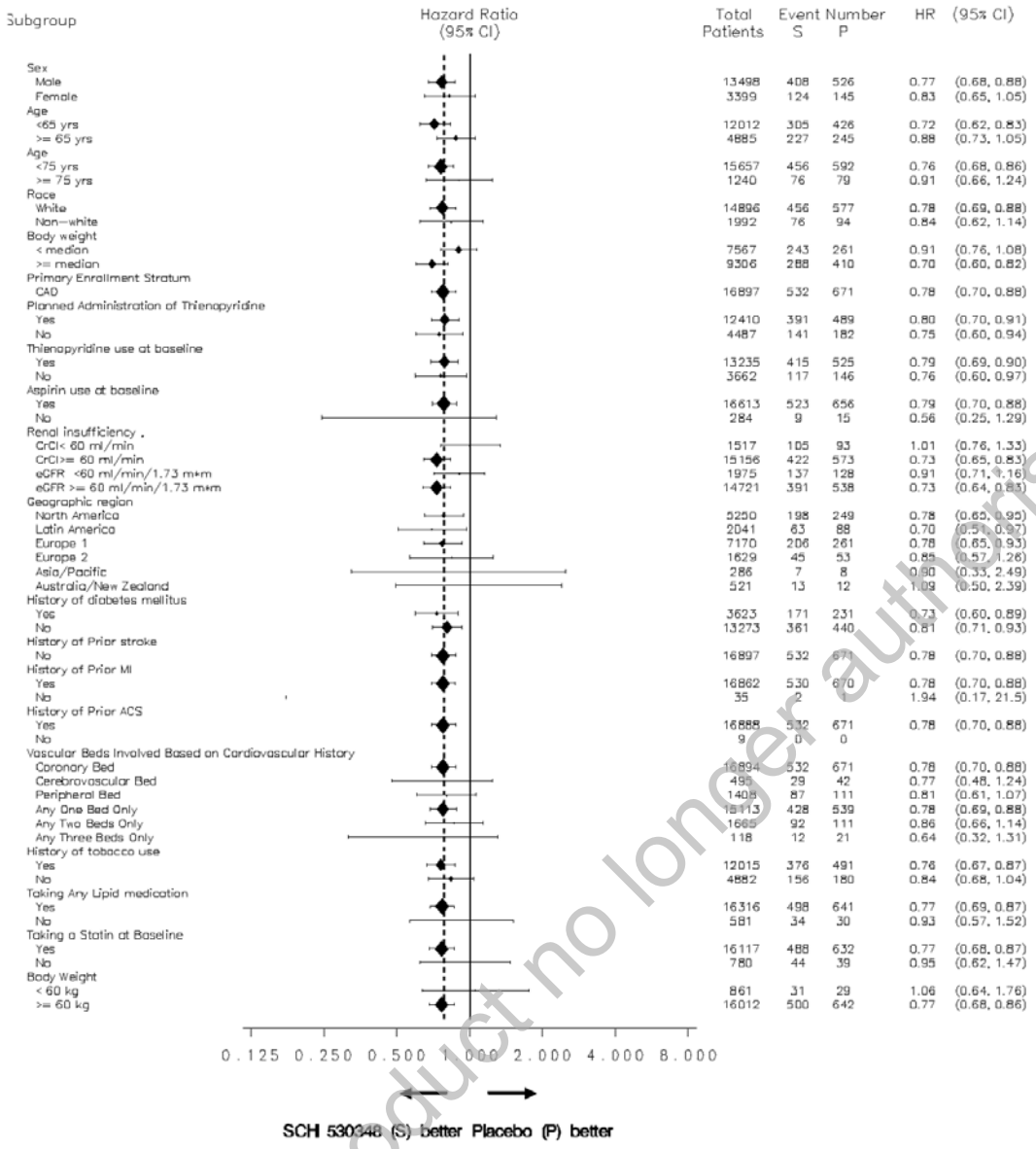



**Table E.7**. [Supplementary Secondary Analysis] Primary and Key Secondary Composite Efficacy Endpoints in Subjects with Weight Less Than 60 kg: ITT Population (Event Accrual Period: Randomization to Last Visit)

| Endpoint & Contributing Component | Placebo (n =921) Subjects With Events (%) | KM%[c] | Vorapaxar (n =931) Subjects With Events (%) | KM%[c] | Hazard Ratio[a,b] (95% CI) |
|---|---|---|---|---|---|
| **Primary Efficacy Endpoint** | 75 (8.1%) | 9.6% | 96 (10.3%) | 13.6% | 1.28 (0.95 – 1.73) |
| CV Death | 16 (1.7%) | | 16 (1.7%) | | |
| MI | 24 (2.6%) | | 35 (3.8%) | | |
| Stroke | 25 (2.7%) | | 29 (3.1%) | | |
| Ischemic (Non-hemorrhagic CI) | 23 (2.5%) | | 16 (1.7%) | | |
| Hemorrhagic Stroke | 1 (0.11%) | | 10 (1.1%) | | |
| UCR | 10 (1.1%) | | 16 (1.7%) | | |
| **Key Secondary Efficacy Endpoint** | 65 (7.1%) | 8.4% | 80 (8.6%) | 11.5% | 1.22 (0.88 – 1.69) |
| CV Death | 16 (1.7%) | | 16 (1.7%) | | |
| MI | 24 (2.6%) | | 35 (3.8%) | | |
| Stroke | 25 (2.7%) | | 29 (3.1%) | | |
| Ischemic (Non-hemorrhagic CI) | 23 (2.5%) | | 16 (1.7%) | | |
| Hemorrhagic Stroke | 1 (0.1%) | | 10 (1.1%) | | |
| Uncertain | 1 (0.1%) | | 3 (0.3%) | | |

a: Kaplan-Meier estimate at 1080 days.
b: Hazard Ratio (HR) is vorapaxar group versus placebo group.
c: HR was calculated based on Cox PH model with covariates treatment and stratification factors (planned thienopyridine use).
d: Each subject was counted only once (first event) in the summary that contributed to primary or key secondary efficacy endpoint.
e: Hemorrhagic stroke includes primary intracerebral hemorrhage, non-hemorrhagic infarction with hemorrhagic conversion and subarachnoid hemorrhage.

**Table E.8.** TRA 2oP – TIMI 50 Primary and Key Secondary Efficacy Endpoints and Contributing Components With Stroke Sub-Categories Included, in Subjects With No History of Stroke or TIA Whose Qualifying Condition was CAD and Weight <60 kg (Event Accrual Period: Randomization to Last Visit)

| Endpoint and Contributing Component | Placebo (n=429) Subjects With Events (%) | KM%[c] | Vorapaxar (n=432) Subjects With Events (%) | KM%[c] | Hazard Ratio[a,b] (95% Confidence Interval) |
|---|---|---|---|---|---|
| **Primary Efficacy Endpoint** | 38 (8.9) | 10.0 | 41 (9.5) | 11.5 | 1.07 (0.69-1.66) |
| CV Death | 4 (0.9) | | 7 (1.6) | | |
| MI | 20 (4.7) | | 20 (4.6) | | |
| Stroke | 5 (1.2) | | 4 (0.9) | | |
| Ischemic (Non-Hemorrhagic Cerebral Infarction) | 5 (1.2) | | 2 (0.5) | | |
| Hemorrhagic Stroke[d] | 0 | | 2 (0.5) | | |
| Uncertain | 0 | | 0 | | |
| UCR | 9 (2.1) | | 10 (2.3) | | |
| **Key Secondary Efficacy Endpoint** | 29 (6.8) | 7.9 | 31 (7.2) | 8.9 | 1.06 (0.64-1.76) |
| CV Death | 4 (0.9) | | 7 (1.6) | | |
| MI | 20 (4.7) | | 20 (4.6) | | |
| Stroke | 5 (1.2) | | 4 (0.9) | | |
| Ischemic (Non-Hemorrhagic Cerebral Infarction) | 5 (1.2) | | 2 (0.5) | | |
| Hemorrhagic Stroke[d] | 0 | | 2 (0.5) | | |
| Uncertain | 0 | | 0 | | |

**Note:** The primary composite efficacy endpoint is the first occurrence of any component: cardiovascular death, myocardial infarction, stroke, or urgent coronary revascularization. The key secondary composite efficacy endpoint is the first occurrence of any component: cardiovascular death, myocardial infarction, or stroke.
**Abbreviations:** CAD = coronary artery disease; CV=cardiovascular; KM = Kaplan-Meier; MI=myocardial infarction; PH = proportional hazards; TIA = transient ischemic attack; UCR=urgent coronary revascularization.
[a] Hazard ratio is vorapaxar group versus placebo group.
[b] Hazard ratio was calculated based on Cox PH model with covariates treatment and stratification factors (planned thienopyridine use).
[c] Kaplan-Meier estimate at 1080 days
[d] Hemorrhagic stroke includes primary intracerebral hemorrhage, non-hemorrhagic infarction with hemorrhagic conversion, and subarachnoid hemorrhage.



In subjects who took aspirin and no baseline thienopyridine, the 3-year KM estimate was 10.3% in the vorapaxar group compared to 11.4% in the placebo group for the primary endpoint (HR; 0.88; 95% CI, 0.77 to 1.00) (Table below). In subjects with no prior history of stroke who took aspirin and no baseline thienopyridine, the event rates were reduced; the 3-year KM estimate was 6.6% in the vorapaxar group compared to 7.1% in the placebo group for the primary endpoint. Vorapaxar demonstrated efficacy whether or not subjects had taken a thienopyridine at baseline.

**Table E.9.** Primary and Key Secondary Composite Efficacy Endpoints in Subjects Who Took Aspirin But No Thienopyridine at Randomization: ITT Population (Event Accrual Period: Randomization to Last Visit)

| Endpoints | Placebo | | Vorapaxar | | Hazard Ratio[a,b] (95% Confidence Interval) | P Value[b] |
|---|---|---|---|---|---|---|
| | Subjects With Events (%) | KM%[c] | Subjects With Events (%) | KM%[c] | | |
| **All Subjects who had Baseline Aspirin but no Baseline Thienopyridine** | | | | | | |
| n | 4794 | | 4867 | | | |
| CV Death/MI/Stroke/UCR | 455 (9.5%) | 11.4% | 409 (8.4%) | 10.3% | 0.88 (0.77 - 1.00) | 0.052 |
| CV Death/MI/Stroke | 420 (8.8%) | 10.6% | 368 (7.6%) | 9.4% | 0.85 (0.74 - 0.98) | 0.028 |
| **All Subjects without History of Stroke who had Baseline Aspirin but no Baseline Thienopyridine** | | | | | | |
| n | 2863 | | 2926 | | | |
| CV Death/MI/Stroke/UCR | 279 ( 9.7% ) | 7.1% | 247 (8.4%) | 6.6% | 0.85 (0.72 - 1.01) | 0.072 |
| CV Death/MI/Stroke | 248 ( 8.7% ) | 6.4% | 211 (7.2%) | 5.7% | 0.82 (0.68 - 0.98) | 0.035 |

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

**Abbreviations:** CEC = Clinical Endpoints Committee.

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

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

[c] Kaplan-Meier estimate at 1080 days

In the Proposed Label Population, the effect of vorapaxar relative to placebo was shown to be consistent across the majority of subgroups for the primary and key endpoints, including subgroups defined by gender, age, race, diabetes mellitus, and thienopyridine use at baseline.

A post hoc exploratory analysis was conducted on the effect of body weight <60 kg vs. ≥60 kg because patients weighing <60 kg may be at increased risk for severe bleeding events. In the overall population, 7% of subjects weighed <60 kg at baseline, the 3-year KM rate for the primary endpoint was 13.6% in the vorapaxar group vs. 9.6% in the placebo group. Subjects who weighed <60 kg had more haemorrhagic strokes in the vorapaxar group (10 subjects, 1.1%) vs. the placebo group (1 subject, 0.1%).

In the Proposed Label Population, 861/16897 subjects (5.1%) weighed < 60 kg at baseline, the imbalance between treatment groups in haemorrhagic strokes was not as evident as in the overall population, haemorrhagic strokes occurred in 2 subjects in the vorapaxar group vs. no subjects in the placebo group. The removal of subjects with no history of stroke or TIA that resulted in the Proposed Label Population seemed to mitigate the risk of excess haemorrhagic strokes. Nevertheless, based on the overall data in patients weighting less than 60kg there is little evidence of benefit while the possibility of an increased risk of bleeding cannot be excluded (see also Safety section below). Therefore, positive recommendations for this patient group are not possible and use with caution is advised in these patients.

An additional analysis was performed in patients who took aspirin but no thienopyridine, vorapaxar demonstrated efficacy whether or not subjects had taken a thienopyridine at baseline.

As mentioned in the description of the baseline data, 98.3% of patients were taking aspirin and therefore the efficacy of vorapaxar seems to be highly related to the effect of aspirin. The SmPC (including section 4.1) should better reflect the importance of the co-administration of vorapaxar with aspirin. .

**Summary of Efficacy for pivotal trial TRA 2°P-TIMI 50**

| | | |
|---|---|---|
| **Title**: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Vorapaxar (SCH 530348) in Addition to Standard of Care in Subjects With a History of Atherosclerotic Disease: Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P-TIMI 50) | | |
| Study identifier | Protocol No. P04737 | |
| Design | A multicenter, international, randomized, double-blind, placebo-controlled, balanced-parallel-groups, events-driven investigation of orally administered vorapaxar in the secondary prevention of ischemic events in patients with a history of atherosclerotic disease | |
| Hypothesis | Superiority | |
| Primary objective | The primary objective was to evaluate the hypothesis that vorapaxar added to standard of care will reduce the incidence of atherothrombotic ischemic events relative to standard of care alone, as measured by the composite of cardiovascular (CV) death, myocardial infarction (MI), stroke, and urgent coronary revascularization (UCR) in subjects with established coronary artery disease (CAD), cerebrovascular disease (CVD), or peripheral artery disease (PAD) | |
| Treatments groups | 26,449 patients received randomized treatment:<br>13,224 placebo and 13,225 vorapaxar (Intent to Treat population; ITT)<br>Subjects were enrolled in one of three strata:<br>17,779 subjects with CAD; 4,883 with CVD; 3,787 with PAD | |
| | Following DSMB advice all subjects with a stroke either prior to or during the study discontinued study medication (due to an increased number of intracranial haemorrhages (ICH) reported in subjects with a prior history of stroke). Subjects with MI and PAD who had a stroke also discontinued treatment but continued their follow-up visits. Data from subjects in the remaining two strata were reviewed in the following populations of interest:<br>• Overall population (n=26,449) – subjects, regardless of the qualifying condition, who received randomized treatment.<br>• NSH population (n=20,699) – subjects with no stroke history (NSH) – regardless of the qualifying condition, who received randomized treatment assignment<br>• CAD (Post MI) and no history of stroke (n=17,191) – subjects with CAD and did not have a documented history of stroke prior to randomization.<br>• *Proposed Label Population (n=16,897)* – subjects with CAD (post MI) who did not have documented history of stroke or TIA prior to randomization. This population was defined *post-hoc*.<br><br>Note: results below are presented for the 'Overall' and 'Proposed Label population' only | |
| Duration of the study | Duration of main phase:<br><br>Duration of Run-in phase:<br>Duration of Extension phase: | Median (participation in the study): 905 days for placebo; 906 days for vorapaxar<br>not applicable<br>not applicable |
| Endpoints and definitions | Primary endpoint | Composite of CV death, MI, stroke or UCR |
| | Key Secondary endpoint | Composite of CV death, MI or stroke |
| | Other Secondary endpoints | - Different composite endpoints with combinations of all-cause death, MI, stroke, and urgent coronary revascularization, any revascularization.<br>- The individual components of the composite primary efficacy endpoint: a. cardiovascular death, b. MI, c. stroke, d. UCR,<br>- All-cause death |
| Database lock | 09 January 2012 | |
| **Results and Analysis** | | |
| **Analysis description** | **Primary Analysis** | |

| | | | |
|---|---|---|---|
| Analysis population and time point description | Intent to treat; Randomization to Last Visit | | |
| Descriptive statistics and estimate variability | *Overall* Population | | |
| | | Placebo | Vorapaxar |
| | Number of subject | (n =13224) | (n =13225) |
| | Primary Efficacy Endpoint (Events %; KM%*) | 1417 (10.7%); 12.4% | 1259 (9.5%) 11.2% |
| | CV Death<br>MI<br>Stroke<br>UCR | 199 (1.5%)<br>629 (4.8%)<br>297 (2.2%)<br>292 (2.2%) | 172 (1.3%)<br>536 (4.1%)<br>297 (2.2%)<br>254 (1.9%) |
| | Key Secondary Endpoint (Events %; KM%*) | 1176 (8.9%); 10.5% | 1028 (7.8%) 9.3% |
| | *Proposed Label* Population | | |
| | Number of subject | (n =8439) | (n =8458)) |
| | Primary Efficacy Endpoint (Events %; KM%*) | 867 (10.3%); 11.4% | 719 (8.5%); 9.8% |
| | CV Death<br>MI<br>Stroke<br>UCR | 96 (1.1%)<br>451 (5.3%)<br>84 (1.0%)<br>236 (2.8%) | 82 (1.0%)<br>374 (4.4%)<br>60 (0.7%)<br>203 (2.4%) |
| | Key Secondary Endpoint (Events %; KM%*) | 671 (8.0%); 9.0% | 532 (6.3%); 7.4% |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint | *Overall* Population | |
| | | Hazard Ratio (95% CI) | 0.88 (0.82 – 0.95) |
| | | P-value | 0.001 |
| | | *Proposed Label* Population | |
| | | Hazard Ratio (95% CI) | 0.82 (0.74-0.90) |
| | | P-value | <0.001 |
| | Key Secondary Endpoint | *Overall* Population | |
| | | Hazard Ratio (95% CI) | 0.87 (0.80 – 0.94) |
| | | P-value | <0.001 |
| | | *Proposed Label* Population | |
| | | Hazard Ratio (95% CI) | 0.78 (0.70-0.88) |
| | | P-value | <0.001 |
| *3-year Kaplan-Meier event rate | | | |



## 2.5.4. Discussion on clinical efficacy

Atherosclerosis and ischaemic cardiovascular (CV) diseases like 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-ischemic disease are at particular risk of future cardiac or cerebral events, and vascular death. Anti-thrombotic therapy options in patients with stable atherosclerosis are not well-established. Long-term therapies to effectively modulate the key components responsible for atherothrombosis in secondary prevention of ischemic CV disease are therefore required. The applicant has investigated whether a new class of antiplatelet agents, PAR-1 antagonists, can further decrease the risk of cardiovascular events with an appropriate balance of efficacy and bleeding risk in a population of established atherothrombosis when added to standard of care by studying vorapaxar, a first-in-class PAR-1 receptor antagonist, in secondary prevention of ischemic diseases.

**Design and conduct of clinical studies**

- *Tracer study*

In the current application, the Applicant presented the results from two Phase III studies TRACER and TRA 2P-TIMI. TRACER study in patients with ACS was stopped early due to an increased bleeding risk.

The indication sought in the current application "reduction of atherothrombotic events in patients with a history of myocardial infarction" was supported by the efficacy results of the TRA 2P-TIMI study.

TRACER (p04736), which has only a supporting role in this application, included patients with moderate- to high-risk subjects with NSTEACS. A loading dose of vorapaxar 40 mg or matching placebo was to be administered at the time of randomized treatment assignment, followed by daily maintenance dosing with 2.5 mg or matching placebo. Additional therapy was to be administered according to current standard of care. In total, 89.3% (11512/12944) of the study subjects initially randomised completed the study with similar overall discontinuation rate on both groups (28.2% vs 26.8% discontinuation in vorapaxar vs placebo); however, discontinuation due to adverse events was most common in the vorapaxar group. Following the DSMB advice the study was terminated early mainly due to the high bleeding findings particularly the higher number of intracranial haemorrhage on the vorapaxar arm, but also because of lack of clear evidence of benefit with vorapaxar.

The findings for the primary efficacy composite endpoint (first occurrence of CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) showed 2- year Kaplan-Meier event rates of 18.5% in the vorapaxar group compared with that of 19.9% in the placebo group. These results were not statistically significant (hazard ratio [HR], 0.92; 95% CI, 0.85 to 1.01; P = 0.072). For the key secondary efficacy composite endpoint (first occurrence of CV death, MI, or stroke), 2-year Kaplan- Meier event rates of 14.7% in the vorapaxar group versus 16.4% in the placebo group were observed (HR, 0.89; 95% CI, 0.81 to 0.98; P = 0.018). While the observed p-value was 0.018, these results are not statistically significant after adjustment under the pre-specified multiplicity strategy. As a result of the outcome of the TRACER trial, the indication for NSTE-ACS at dose of40mg loading dose and 2.5 mg daily maintenance dose was not pursued.

- *TRA2P-TIMI 50*

**TRA 2P – TIMI 50 (P04737)** is the pivotal trial for the current indication. It included patients with a history of atherosclerosis (ATC) from 3 different categories: cerebral, coronary or peripheral ATC, examined as three separate strata. Patients were administered 2.5 mg/d of vorapaxar without loading dose or matching placebo.Treatment duration was for at least 1 year. Additional therapy was to be administered according to current standard of care.

The primary objective was to evaluate the hypothesis that vorapaxar added to standard of care will reduce the incidence of atherothrombotic ischemic events relative to standard of care alone, as measured by the composite of cardiovascular (CV) death, myocardial infarction (MI), stroke, and urgent coronary revascularization (UCR) in subjects with i. established coronary artery disease (CAD), ii. cerebrovascular disease (CVD), or iii. peripheral artery disease (PAD).

In total, 26,352 subjects were treated (13186 vorapaxar vs 13166 placebo) of which 23% overall discontinued treatment (2984 placebo and 3145 vorapaxar) from which discontinuation due to adverse events was slightly more common in the Vorapaxar group (1381 subjects in vorapaxar vs 1299 in placebo). In consistent with TRACER, the DSMB recommended the discontinuation of all patients with a history of stroke, in 4510 subjects from both groups (2262 vorapaxar and 2248 placebo). The treatment groups were comparable with respect to demographic, baseline characteristics and concomitant medication in the proposed label population (patients without history of stroke or TIA).

Following a refining of the initial population and based on the bleeding risks, a group was isolated i.e. the Proposed Label Population from the CAD stratum and no history of stroke or TIA with a total of 16,897 subjects including mainly white (88.2%) males (79.9%) who were < 65 years old (71.1%) and ≥ 60kg (94.85%) with cardiovascular comorbidities: high prevalence of hypertension (61.5%) and hyperlipidaemia (84.4%) and low prevalence of diabetes (21.4%). Concomitant medications

were well balanced between groups with 98.3% of the subjects taking aspirin, 78% taking a thienopyridine (clopidogrel in the vast majority of subjects), and 77% receiving dual antiplatelet therapy.

**Efficacy data and additional analyses**

In the **Overall population**, the results for the primary efficacy composite endpoint (first occurrence of CV death, MI, stroke, or UCR) was a 3-year Kaplan-Meier event rate of 11.2% in the vorapaxar group compared to 12.4% in the placebo group. These results were statistically significant (hazard ratio [HR], 0.88; 95% Confidence Interval {CI}, 0.82 to 0.95; P=0.001). The results for the key secondary composite efficacy endpoints (first occurrence of CV death, MI, or stroke) show 3-year KM event rate of 9.3% in the vorapaxar group compared to 10.5% in the placebo group. These results were also statistically significant ([HR] 0.87; 95% CI, 0.80 to 0.94; P<0.001). Thus, the primary objective of the study based on the overall population (which includes all three qualifying atherosclerotic condition strata) was met.

In the **Proposed Label Population** (**CAD subjects without a history of stroke or TIA**; 64% of the subjects enrolled in this study) had efficacy results that favoured vorapaxar (18% relative risk reduction on top of standard care). In this population, the primary efficacy composite endpoint was a 3-year KM event rate of 9.8% in the vorapaxar group compared to 11.4% in the placebo group (HR; 0.82; 95% CI 0.74-0.90, P<0.001). All components of the composite endpoints were reduced by vorapaxar compared with placebo. Consistent with the results in the overall population, the individual component of the composite endpoint that most contributed to the difference between vorapaxar and placebo was the reduction of the rate of MI. MI was reported in 374 vorapaxar subjects (4.4%) vs. 451 placebo subjects (5.3%) as a component of the primary endpoint, and in 387 vorapaxar subjects (4.6%) vs. 481 placebo subjects (5.7%) as a component of the secondary endpoint. In general, the efficacy results in the various analysed subpopulations including the proposed label population were consistent and in favour of vorapaxar. A greater effect (greater clinical benefit and with higher statistical significance) was seen in the proposed label population than the overall population.

In the Proposed Label Population, the effect of vorapaxar relative to placebo was shown to be consistent across the majority of subgroups for the primary and key endpoints, including parameters such as gender, age, race, history of diabetes mellitus, and thienopyridine use at baseline. A post hoc exploratory analysis was conducted on the effect of body weight <60 kg vs. ≥60 kg because patients weighing <60 kg may be at increased risk for severe bleeding events. The analyses provided little evidence of benefit with vorapaxar in patients <60kgr compared to placebo; while instead there is a possibility of an increase in the risk of severe bleeding. The numbers are very small and patients with low body weight are a heterogeneous group but the overall evidence is very limited thus a general question with regarding to high risk patients was raised and the CHMP considered necessary to seek expert advice.

An additional analysis was performed in patients who took aspirin but no thienopyridine, vorapaxar demonstrated efficacy whether or not subjects had taken a thienopyridine at baseline. The vast majority (98.3%) of patients were taking aspirin and therefore the efficacy of vorapaxar seems to be highly related to the effect of aspirin. This is appropriately reflected in the SmPC and the indication. Further discussion occurred with regards to clopidogrel and combination with tigatrelor and prasugrel. (see below)

Patients in the pivotal trial mostly had a history of a recent (12 months or less) myocardial infarction. Relevant recommendations about the time of initiation of treatment after an MI are included in the SmPC.

Treatment duration in TRA 2P-TIMI study was at least 1 year for all patients; and the median participation in the study was more than 2.5 years. The optimal duration of therapy and if there is

scope for specific recommendations as to how long patients should receive Vorapaxar was a point of concern and thus a SAG view was requested (see below). In response to a CHMP request the applicant provided additional data showing the net benefit (CV death, MI, and stroke against serious bleeding) of vorapaxar therapy over time in TRA 2ºP-TIMI 50 trial. Overall, there was no clear evidence of a diminishing net benefit during the study.

More generally the CHMP was concerned about the place of vorapaxar in the treatment of these patients, considering the current standard of care and agreed to convey the Scientific Advisory Group Cardiovascular to address the following issues:

*1) - the combined use with other antithrombotic agents, in particular the combination with ASA and clopidogrel and with newer agents such as ticagrelor and prasugrel.*
*2) - the unlimited duration of treatment of treatment taking into account the time trends in the risk of repeated events and the absolute benefit achieved at later time-points (long-term treatment duration over that used in the trial) versus the risk of bleeding.*
*3) - the risk of bleeding, taking into consideration duration of treatment and clopidogrel co-administration during the study.*

**Additional expert consultation**

The minutes of the SAG discussion are detailed below :
Taking into account the indication of Zontivity for the reduction of atherothrombotic events in adult patients with a history of myocardial infarction (MI) the view of the SAG is asked regarding

1) - the combined use with other antithrombotic agents, in particular the combination with ASA and clopidogrel and with newer agents such as ticagrelor and prasugrel.

Vorapaxar is an antagonist of the protease-activated receptor 1, a new class of antiplatelet drugs. The SAG Experts considered the observed benefit as to the reduction in the combined primary efficacy endpoint of CV death, MI, stroke or UCR, (9.8% Kaplan Meier 3 years estimated event rate in Vorapaxar group in comparison to 11.4% in the placebo group) as small and clinically only marginally relevant. Vorapaxar leads on the other hand to a small increased bleeding rate. The benefit risk ratio was considered slightly positive, though some experts doubted the overall usefulness of the drug.

The subgroups of patients with PAD and with prior stroke or TIA were not part of the discussion albeit some experts felt that exclusion of subgroups might have impacted the overall positive risk benefit ratio. It was clarified that the PAD subgroup was excluded for procedural reasons in relation to the application initially applied for by the Company. The subgroup of patients with history of stroke or TIA was excluded following the decision of the DSMB.

There was a clear consensus among SAG experts that co administration of vorapaxar with new antiplatelet drugs like prasugrel or ticagrelor should be avoided due to a potential increased risk of bleeding and uncertainty about benefit, considering the lack of scientific data available. The extrapolation of results with clopidogrel co administration in ultra metabolisers was considered not adequate to substitute clinical data on co-medication with these agents.

The SAG unanimously agreed that for patients currently treated with prasugrel or ticagrelor, therapy should not be initiated and in case of need for additional therapy with these agents, vorapaxar should be stopped.

The combination with anticoagulants eg warfarin, heparin, LMWH and NOACs was considered potentially harmful and should be avoided considering the TRACER study results where anticoagulants were co- administered and much higher bleeding rates were described.

The patient representative raised also concerns about bleeding risks especially when considering cumulative effect of multiple therapies leading to an increased bleeding risk and pointed out the need of patient safety together with thorough evaluation of the need for combination therapy.

2) - the unlimited duration of treatment of treatment taking into account the time trends in the risk of repeated events and the absolute benefit achieved at later time-points (long-term treatment duration over that used in the trial) versus the risk of bleeding.

The treatment effect over time was discussed in the context of the TRA2 P- TIMI 50 trial where the median duration of treatment was 2.5 years and more than 76% of patients were on treatment for at least 2 years.
The SAG Experts noted that the event rate is about 6 % after one year and increases to 11.4 % in the next two years period. Thus, they considered that while the rate of events is rising over time, the rate of rise is decreasing over time, suggesting that the benefit is lowering with time, especially beyond 2 years. This is supported by an attenuation of the effect from year 2 to year 3 (hazard ratio first year 0.85, second year 0.75, third year 0.91). On the other hand, the bleeding risk remains and will increase over time with age and co morbidities. Also the SAG judged a 2.5 years experience as not sufficient to support in principle life-long therapy with voraxapar.

The reduction of MI are driving the positive results observed, thus the definition of MI in the study was discussed.
*Definition used in TRA2 P-TIMI 50 study*
*Myocardial infarction was defined by symptoms suggestive of ischemia or infarction in association with electrocardiographic, cardiac biomarker, or pathologic evidence of infarction using criteria adapted from the definition developed by the Universal Definition of MI.*

The SAG pointed out that the sizes of MI's in the primary endpoint have to be further clarified in order to properly judge the clinical importance of the reduction of MI frequency, considering also that the reduction of MI is mainly driving the positive results observed. The company should clarify the size of the MIs that were found.

The SAG commented that the reduction in MI frequency should in principle be reflected by a similar reduction in the Urgent Coronary Revascularisation endpoint. However the same magnitude of effect was not observed in the UCR.

The definition of bleeding (GUSTO moderate and severe bleeding) used in the TRA2P trial was discussed compared to the TIMI clinically significant bleeding definition, which was used in previous studies by the same investigators and considered more relevant in this setting by some experts. Though the hazard ratios for both bleeding definitions are similar, the Group noted that the absolute rate of bleeding increases when using the TIMI definition (14.6% in Vorapaxar group compared to 10.2% in placebo) and 3.1% vorapaxar versus 2.2% placebo (Gusto definition). This naturally affects the risk benefit analysis. Using the TIMI classification the risk numerically exceeds the benefit.

In conclusion, there was consensus among the SAG experts to recommend limiting treatment duration and modify the SmPC accordingly.

After discussing possible options of 2, 2.5 or 3 years, the majority of the SAG favoured a recommendation to stop treatment after 2 years, especially in view of the limited observed benefit, while other experts considered 2.5 years as acceptable.

3) - the risk of bleeding, taking into consideration duration of treatment and clopidogrel co-administration during the study.

The Group view that the bleeding risks were primarily judged by Gusto severe bleedings which in the opinion of the SAG do not entirely reflect clinically important bleedings. There was a consensus that using TIMI clinically important bleedings definition is more appropriate to reflect the bleeding risk. (see above comments).

The specific subgroups of patients with low body weight less than 60 kgs, patients above 75 years of age and as well as patients undergoing CABG were discussed as a point of concern.

In patients above and below 75 years of age, it was noted that although the relative risk of bleeding in these patients is the same, the absolute risk of bleeding increases with age. (using the Gusto moderate and severe bleeding definition, the Hazard Ratio is similar around 1.7% in both groups of patients (above and below 75 years of age) but the risk of bleeding is higher 8.4 (patients above 75) versus 3.7 (patients below 75). In the relative small subgroup of patients with body weight below 60 kg, there was no benefit and the bleeding risk is increased. No data are available to the SAG on a lower dose regimen for these subgroups.

The SAG debated the best recommendations for patients <60 kg; some experts were in favour of more stringent exclusion of patients <60 kg while others thought that an advice as to thorough weighting risk and benefit is sufficient.
Nevertheless, the SAG overall agreed, that in these subgroups Vorapaxar should only be prescribed after very careful assessment of individual likely risk and benefit.

In patients undergoing CABG surgery, the Group expressed concerns about the small benefit observed compared to the bleeding risk (patients with bleeding events 4.5% versus 5.3% in vorapaxar). If clinically feasible, the drug should be stopped before elective surgery.

In conclusion, the majority of the SAG recommended that for the specific subgroup of patients (less than 60kgs, above 75 years of age and patients undergoing CABG surgery), a careful assessment of the individual potential benefit and individual bleeding risks as well as need for co-medications was considered mandatory.

***Further discussion following the SAG recommendations***

The SAG confirmed the CHMP view that prasugrel and ticagrelor should not be co-administered with vorapaxar in view of the limited experience with these agents. 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. This is reflected in the SmPC.

The potential implications of recommending stopping the drug after patients have been on therapy possibly for 2-3 years vs continuing the treatment are equally uncertain and will also depend on the characteristics of the individual patient. Generally, defining a specific duration of treatment and recommending discontinuation of therapy after a certain time is not currently justified by the available evidence. However, the limited data about the efficacy and safety of vorapaxar treatment beyond 24 months are agreed upon and treating physicians may decide the best course of action for their patients long term management. It is concluded that continued therapy after 24 months must be

based on the re-evaluation of the individual benefits and risk, taking into account their patient's characteristics and clinical evidence. This is appropriately reflected in the SmPC.

Further to the above, a point that was raised during the initial review, especially when considering the negative results of TRACER and the continuum of the CAD disease and atherosclerotic plaque pathophysiology following an acute event, was which patient group would most likely benefit and should receive vorapaxar following an acute MI. Taking further into account the relevant recommendations of the latest Clinical Guidelines and the newer antiplatelet agents (such as prasugrel and ticagrelor) the place of vorapaxar in the modern management of patients with a recent MI was questioned. However, it is agreed that not all patients with an acute MI will be able or suitable to start therapy with one of the newer antiplatelets prasugrel or ticagrelor. After discharge some patients will be treated with aspirin or clopidogrel alone and many will be prescribed dual (ASA+clopidogrel) antiplatelet therapy. Those patients can receive vorapaxar. Also not all patients who will start therapy with either prasugrel or ticagrelor during the acute phase will be able to remain on them during the post-MI phase because of tolerability, safety or compliance issues. A switch to vorapaxar may be an option for such patients. Finally, those patients who will be treated with prasugrel or ticagrelor will normally receive therapy for up to a year (their SmPC recommends treatment for up to 12 months as experience beyond that period is limited). In contrast, vorapaxar has demonstrated a favourable benefit:risk beyond the first year post MI.

The above suggest that a proportion of MI patients will be treated with aspirin with or without clopidogrel in the post MI phase and there is sufficient evidence from the large pivotal trial that they could benefit from vorapaxar addition to their treatment.

The indication sought initially in the current application "reduction of atherothrombotic events in patients with a history of myocardial infarction" is supported by the efficacy results of the TRA 2P-TIMI study which, particularly in the Proposed Label Population, are consistently in favour of vorapaxar. The effect of vorapaxar relative to placebo was also shown to be consistent across the majority of subgroups for the primary and key endpoints, including subgroups defined by gender, age, race, diabetes mellitus, and thienopyridine use at baseline. However, this was not entirely the case for the group of patients with weight <60kg and this is reflected in the product information.

The vast majority of patients were taking aspirin and most of them clopidogrel and therefore the efficacy of vorapaxar seems to be highly related to the effect of aspirin. The indication was therefore revised to reflect this point as follows *: Zontivity, 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).*

The patients at risk are further discussed in the safety discussion part of this report.

### 2.5.5. Conclusions on the clinical efficacy

In conclusion, all issues raised had been addressed. The CHMP considered that the efficacy data adequately supported the revised indication *Zontivity, 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).*

## *2.6. Clinical safety*

The safety review includes data from across the whole vorapaxar clinical program with twenty one (21) phase 1 studies, three Phase 2 studies and the two large Phase 3 trials TRACER and TRA 2ºP-TIMI 50, including an ocular sub-study of the latter.

Because of the difference in the populations enrolled in the two main trials the focus is on TRA 2°P-TIMI 50, which is considered the pivotal study for this application, with TRACER findings having a

supporting role. The safety results of the TRA 2ºP-TIMI 50 trial are presented for i. the *Overall* study population ii. *Proposed label population*. This is followed by the results of the TRACER trial.

As specified in the original TRACER and TRA 2ºP-TIMI 50 protocols, there were two populations for the analyses in each study: the 'Intent to Treat (ITT)' which includes all subjects who received randomization assignment and the 'As-Treated' population which includes all subjects who were randomized and received at least one dose of study treatment. The safety analyses were performed in the '*As-Treated'* population.

For analyses concerning bleeding events, the *Chronic Pool* is also presented which includes all bleeding events that occurred ≥ 30 days in TRACER and all bleeding events that occurred in TRA 2ºP-TIMI 50. This is further discussed in detail in the relevant subsection on 'Bleeding' below.

For analyses concerning other adverse events, vital signs, laboratories or ECGs, data for the *Overall Pool* was presented which includes all non-bleeding safety events from randomization to last visit combined from both TRACER and TRA 2ºP-TIMI 50. Phase 2 and 1 safety data were also summarized and presented.

### Patient exposure

In 21 Phase 1 studies, 1060 subjects received at least one dose of vorapaxar. In the three Phase 2 studies (P03573, P04772, P05005), 1237 subjects received at least one dose of vorapaxar. In the Phase 3 program for the overall pool, 19,632 subjects (13,186 subjects in TRA 2°P-TIMI 50 and 6446 in TRACER) received at least one dose of vorapaxar with an estimated compliance greater than 90% in 17,276 (88%) of subjects

The extent of exposure in the studies estimated by duration of participation on treatment calculated from randomization through the last dose of study treatment for each subject without regard to intervening days or intervals when a dose was not taken is shown in Table S.1.

**Table S.1.** Phase 3 All Randomized Subjects Duration of Participation in Treatment

| | TRA 2°P-TIMI 50 Overall Population | | TRA 2°P-TIMI 50 All Randomized Subjects for Proposed Label Population | | TRACER Overall Population | |
|---|---|---|---|---|---|---|
| | Placebo n=13224(%) | Vorapaxar n=13225(%) | Placebo n=8439(%) | Vorapaxar n=8458(%) | Placebo n=6471(%) | Vorapaxar n=6473(%) |
| Any Participation | 13166(99.6) | 13186(99.7) | 8412(99.7) | 8444(99.8) | 6441(99.5) | 6446(99.6) |
| >= 30 Days | 12831(97.0) | 12818(96.9) | 8229(97.5) | 8236(97.4) | 5648(87.3) | 5659(87.4) |
| >= 90 Days | 12503(94.5) | 12459(94.2) | 8031(95.2) | 8025(94.9) | 5374(83.0) | 5362(82.8) |
| >= 180 Days | 12076(91.3) | 12032(91.0) | 7785(92.3) | 7787(92.1) | 5042(77.9) | 5021(77.6) |
| >= 360 Days | 11551(87.3) | 11521(87.1) | 7487(88.7) | 7483(88.5) | 3560(55.0) | 3460(53.5) |
| >= 540 Days | 10931(82.7) | 10877(82.2) | 7218(85.5) | 7198(85.1) | 2019(31.2) | 1939(30.0) |
| >= 720 Days | 8290(62.7) | 8185(61.9) | 5743(68.1) | 5675(67.1) | 726(11.2) | 704(10.9) |
| >= 900 Days | 5284(40.0) | 5225(39.5) | 3675(43.5) | 3612(42.7) | 110 (1.7) | 87 (1.3) |
| >= 1080 Days | 2224(16.8) | 2187(16.5) | 1583(18.8) | 1565(18.5) | 3 (<.1) | 3 (<.1) |
| Randomized Not Treated | 58 (0.4) | 39 (0.3) | 27 (0.3) | 14 (0.2) | 30 (0.5) | 27 (0.4) |
| Summary Statistics (Duration in days)[a] | | | | | | |
| Number of Subjects | 13166 | 13186 | 8412 | 8444 | 6441 | 6446 |
| Mean | 786.8 | 779.1 | 818.4 | 810.5 | 398.6 | 393.4 |
| Standard Deviation | 320.10 | 323.09 | 311.72 | 315.09 | 251.68 | 250.82 |
| Median | 826.0 | 823.0 | 869.0 | 867.0 | 393.0 | 379.0 |
| 25th to 75th Percentile | 655.0 – 1022.0 | 645.0 – 1016.0 | 699.0 – 1050.0 | 694.0 – 1043.0 | 236.0 – 588.0 | 231.0 – 585.0 |
| Minimum | 1 | 1 | 1 | 1 | 1 | 1 |
| Maximum | 1461 | 1461 | 1461 | 1461 | 1122 | 1103 |

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

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

In the *Proposed Label Population*, 8444 subjects received at least one dose of active treatment which accounts for 64% of the overall TRA 2ºP-TIMI 50 population exposed to vorapaxar. Compliance was greater than 90% in 7496 (88.8%) of the subjects. More than half of the subjects in the Proposed Label Population participated 'in the Study' for at least 900 days. Two thirds of this Population participated 'in Treatment' for at least 720 days. The median duration of treatment was 2.5 years (867 days for vorapaxar and 869 for placebo).

The median duration of participation in the study was longer in the TRA 2ºP-TIMI 50 study (906 days for vorapaxar and 905 days for placebo) than for the TRACER study (482 days for vorapaxar and 481 days for placebo).

Overall, the exposure to vorapaxar, in terms of number of patients included in the clinical program and duration of treatment, is considered sufficient to establish the key aspects of its safety profile. Moreover, the TRA 2ºP-TIMI 50 trial alone is large enough, even if considering the 'Proposed Label Population' alone, to provide sufficient data to evaluate safety in the target population. Additional pooled analyses across the two Phase 3 trials and the whole program are useful to further examine safety under certain conditions and explore the possibility of rare adverse effects.

## Characteristics of Study Population

*Demographics*

Table S.2 shows the demographic and other baseline characteristics of the Phase 3 populations of TRA 2ºP-TIMI 50 overall and Proposed Label Population, TRACER and chronic pooled population.

**Table S.2.** Demographic and Other Baseline Personal Characteristics in Phase 3 Studies

| | TRACER | | TRA 2ºP-TIMI 50 | | TRA 2ºP-TIMI 50 Proposed Label Population | | Pooled Chronic Experience[b] | |
|---|---|---|---|---|---|---|---|---|
| | Placebo n=6441 | Vorapaxar n=6446 | Placebo n=13166 | Vorapaxar n=13186 | Placebo n=8439 | SCH 530348 n=8458 | Placebo n=19393 | Vorapaxar n=19434 |
| **Age (years)** | (n=6441) | (n=6446) | (n=13166) | (n=13186) | (n=8439) | (n=8458) | (n=19393) | (n=19434) |
| Mean (SD) | 64.4 (9.97) | 64.4 (9.95) | 60.9 (10.83) | 61.0 (10.90) | 58.5 (10.46) | 58.7 (10.58) | 62.0 (10.65) | 62.0 (10.70) |
| Median | 64.0 | 64.0 | 61.0 | 61.0 | 58.0 | 59.0 | 62.0 | 62.0 |
| 25th to 75th Percentile | 58 - 72 | 58 - 71 | 53 - 69 | 53 – 69 | 51 - 66 | 51 - 66 | 55 - 70 | 55 - 70 |
| Min-Max | 29 - 94 | 31 - 92 | 21 - 93 | 24 – 95 | 22 - 92 | 24 - 92 | 21 - 94 | 24 - 95 |
| **Age (n(%))** | | | | | | | | |
| <65 | 3352(52.0) | 3373(52.3) | 8236(62.6) | 8170(62.0) | 6052(71.7) | 5960(70.5) | 11509(59.3) | 11472(59.0) |
| 65 - <75 | 2001(31.1) | 1967(30.5) | 3434(26.1) | 3510(26.6) | 1781(21.1) | 1864(22.0) | 5372(27.7) | 5419(27.9) |
| >=75 | 1088(16.9) | 1106(17.2) | 1496(11.4) | 1506(11.4) | 606 (7.2) | 634 (7.5) | 2512(13.0) | 2543(13.1) |
| **Race (n(%))** | | | | | | | | |
| White | 5483(85.1) | 5505(85.4) | 11470(87.1) | 11529(87.4) | 7415(87.9) | 7481(88.4) | 16780(86.5) | 16878(86.8) |
| Non-White | 940(14.6) | 926(14.4) | 1693(12.9) | 1650(12.5) | 1021(12.1) | 971(11.5) | 2593(13.4) | 2534(13.0) |
| **Weight (kg)** | (n=6417) | (n=6421) | (n=13141) | (n=13167) | (n=8425) | (n=8448) | (n=19345) | (n=19390) |
| Mean (SD) | 82.25(17.640) | 82.69(18.139) | 82.76(17.255) | 82.29(16.881) | 84.67(17.299) | 83.99(16.800) | 82.64(17.383) | 82.47(17.292) |
| Median | 80.00 | 80.50 | 81.00 | 81.00 | 83.00 | 82.50 | 81.00 | 81.00 |
| < 60 kg | 489 (7.6) | 493 (7.6) | 916 (7.0) | 928 (7.0) | 429 (5.1) | 432 (5.1) | 1382 (7.1) | 1391 (7.2) |
| >=60 kg | 5928(92.0) | 5928(92.0) | 12225(92.9) | 12239(92.8) | 7996(94.8) | 8016(94.8) | 17963(92.6) | 17999(92.6) |
| Missing | 24 (0.4) | 25 (0.4) | 25 (0.2) | 19 (0.1) | 14 (0.2) | 10 (0.1) | 48 (0.2) | 44 (0.2) |

| Calculated Body Mass Index (kg/m²) [a] | (n=6402) | (n=6403) | (n=13133) | (n=13152) | (n=8419) | (n=8441) | (n=19325) | (n=19357) |
|---|---|---|---|---|---|---|---|---|
| Mean (SD) | 28.45(5.160) | 28.58(5.347) | 28.32 (4.988) | 28.19 (4.836) | 28.62 (4.981) | 28.47 (4.847) | 28.37 (5.044) | 28.32 (5.008) |
| Median | 27.70 | 27.80 | 27.70 | 27.60 | 27.90 | 27.80 | 27.70 | 27.70 |

| Systolic Blood Pressure (mm Hg) | (n=6408) | (n=6397) | (n=13133) | (n=13157) | (n=8415) | (n=8440) | (n=19329) | (n=19359) |
|---|---|---|---|---|---|---|---|---|
| Mean (SD) | 131.8(20.83) | 132.0(20.67) | 133.4(19.42) | 133.5(19.52) | 130.2(18.63) | 130.3(18.76) | 132.9(19.89) | 133.0(19.89) |
| Median | 130.0 | 130.0 | 131.0 | 131.0 | 129.0 | 130.0 | 130.0 | 130.0 |
| **Diastolic Blood Pressure (mm Hg)** | (n=6408) | (n=6397) | (n=13133) | (n=13153) | (n=8415) | (n=8439) | (n=19329) | (n=19355) |
| Mean (SD) | 75.0 (12.48) | 74.8 (12.43) | 78.1 (10.81) | 78.0 (10.87) | 77.8 (10.72) | 77.6 (10.66) | 77.1 (11.44) | 77.0 (11.49) |
| Median | 75.0 | 75.0 | 79.0 | 79.0 | 78.0 | 78.0 | 78.0 | 78.0 |

In TRA 2ºP-TIMI 50, a total of 26,449 subjects were randomly assigned to treatment based on the following three strata: 17,779 (67%) CAD stratum (post MI population), 4883 (18.5%) CVD stratum, and 3787 (14.3%) PAD stratum; 58% of subjects were assigned to the 'planned thienopyridine administration during the study' stratum. In the study, the qualifying and stratifying conditions were well balanced between the treatment groups at entry.

Subjects were predominantly white (87%), male (approximately 76%), and a median of 61 years. Additionally, 11% were over 75 years old. In the TRA 2ºP-TIMI 50 Proposed Label Population, (i.e., post MI with no history of stroke or TIA) the two treatment groups were well balanced in terms of demographic characteristics at baseline, with no apparent differences. Compared to the overall population, Proposed Label Population subjects were younger and of a greater body weight and body mass index (BMI). Median age was 59 years. Additionally, 7.5% were over 75 years old.

The TRACER population was older and with lower body weight than the Proposed Label Population of TRA 2ºP-TIMI 50. TRACER enrolled subjects in the midst of an acute episode during hospitalization that resulted in parenteral use of anti-coagulants and loading dose regimens of both anti-coagulants and anti-platelet agents. In an emergency setting these agents are aggressively and often concomitantly initiated in subjects whose susceptibility to bleeding is unknown. Hence it is a setting with a high incidence of bleeding events.

The overall pool and the chronic pool were similar in terms of demographic characteristics at baseline, with no apparent differences.

*Cardiovascular and Other Relevant Baseline Characteristics*

In the TRA 2ºP-TIMI 50 overall population the characteristics were similar between the two treatment groups. Approximately 69% of subjects had a history of hypertension and approximately 83% had a history of hyperlipidaemia. Approximately 70% of the subjects reported an MI within the past year, 22% of subjects had a prior history of stroke, approximately 4% of subjects had a prior TIA, and 19% of subjects had a history of PAD. 25% of subjects had a history of diabetes. More than 57% of subjects had a prior PCI procedure and 13% of subjects had a prior CABG procedure.

In the Proposed Label Population, 61.2% of subjects in the vorapaxar group had a history of hypertension and 84.5% had a history of hyperlipidaemia. Approximately 28% of subjects had a prior history of MI less than one month prior to randomization (overall 99.8%) and 5% of subjects had prior PAD. Approximately 79% of subjects had a prior PCI procedure and 13% of subjects had a prior CABG. Approximately 21% of subjects in the vorapaxar group had a history of diabetes. In subjects with impaired renal function i.e. <60 mL/min based on creatinine clearance (CrCl) at baseline and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m$^2$ at baseline, those on vorapaxar treatment were 9.5% and 12.4%, respectively.

In TRACER, only approximately 29% of subjects had a prior history of MI or coronary revascularization (prior PCI approximately 24% or prior CABG approximately 12%). Only, 7.2% of

the subjects had a prior history of PAD, with 2.9% of subjects having undergone prior peripheral arterial revascularization. Overall, 4.3% of subjects had a prior history of stroke and 2.5% had a prior history of TIA. Approximately 31% of subjects had diabetes and included subjects with impaired renal function defined as <60 mL/min based on CrCl at baseline (12.9%) or eGFR at baseline of <60 mL/min/1.73m² (13.7%). Additionally, 70.5% of subjects had a history of hypertension and 62.3% had a history of hyperlipidaemia.

### Concomitant medication

Table S.3 presents the baseline concomitant medications.

**Table S.3.** Concomitant Medications During Index Hospitalization: Number (%) of Subjects:

| | TRA 2ºP TIMI-50 Intent to Treat Population | | | TRACER Intent to Treat Population During the Index Hospitalization | | |
|---|---|---|---|---|---|---|
| | Placebo | Vorapaxar | Total | Placebo | Vorapaxar | Total |
| Variable | (n = 13224) | (n = 13225) | (n = 26449) | (n = 6471) | (n = 6473) | (n = 12944) |
| Any Aspirin | 12363 (93.5) | 12371 (93.5) | 24734 (93.5) | 6415 (99.1) | 6410 (99.0) | 12825 (99.1) |
| Any Clopidogrel | 8124 (61.4) | 8076 (61.1) | 16200 (61.2) | 5933 (91.7) | 5950 (91.9) | 11883 (91.8) |
| Loading Dose[a] | N/A | N/A | N/A | 3942 (60.9) | 3908 (60.4) | 7850 (60.6) |
| Maintenance Dose[b] | N/A | N/A | N/A | 5644 (87.2) | 5691 (87.9) | 11335 (87.6) |
| Aspirin Only | 4121 (31.2) | 4197 (31.7) | 8318 (31.4) | 387 (6.0) | 355 (5.5) | 742 (5.7) |
| Aspirin Plus Any Thienopyridine[c] | 7569 (57.2) | 7504 (56.7) | 15073 (57.0) | 5961 (92.1) | 5971 (92.2) | 11932 (92.2) |
| Aspirin Plus Any Other Antiplatelet Agent(s)[d] | 8242 (62.3) | 8174 (61.8) | 16416 (62.1) | 6028 (93.2) | 6055 (93.5) | 12083 (93.3) |
| Any Oral Anticoagulant[e] | 12 (0.1) | 16 (0.1) | 28 (0.1) | 127 (2.0) | 115 (1.8) | 242 (1.9) |
| Any Fibrinolytic | 0 | 0 | 0 | 20 (0.3) | 13 (0.2) | 33 (0.3) |
| Any Glycoprotein IIb/IIIa inhibitor | N/A | N/A | N/A | 1349 (20.8) | 1352 (20.9) | 2701 (20.9) |
| Any Antithrombin Agent | 58 (0.4) | 47 (0.4) | 105 (0.4) | 5777 (89.3) | 5747 (88.8) | 11524 (89.0) |
| Any Statin | 11927 (90.2) | 11810 (89.3) | 23737 (89.7) | 5991 (92.6) | 5983 (92.4) | 11974 (92.5) |
| Any Proton Pump Inhibitor | 3241 (24.5) | 3245 (24.5) | 6486 (24.5) | 2917 (45.1) | 2887 (44.6) | 5804 (44.8) |
| Any H2-Receptor Antagonist | 664 (5.0) | 635 (4.8) | 1299 (4.9) | 1266 (19.6) | 1295 (20.0) | 2561 (19.8) |

**Note**: Index Hospitalization was the time from acute presentation/initial hospitalization through discharge from acute care.
a Clopidogrel loading dose is defined as the highest non-continuous dose given on a single day during the interval.
b Clopidogrel maintenance dose is defined as the highest continuous dose given during the interval.
c Includes clopidogrel, ticlopidine, prasugrel, and ticagrelor.
d Includes any thienopyridine, dipyridamole, cilostazole, or a glycoprotein IIb/IIIa inhibitor.
e Includes warfarin, phenprocoumon, acenocoumarol, and fluindione

In TRA 2ºP-TIMI 50, the use of concomitant medications was similar between the two treatment groups and reflected subjects' individual baseline disease state and stratum. At baseline, approximately 94% of the subjects were taking aspirin, while approximately 61% of the subjects were taking clopidogrel. For the *Proposed Label Population*, the baseline history of CAD resulted in a near universal administration of aspirin (98.3%) with the vast majority of the subjects (77.6%) taking clopidogrel. Approximately 77% of subjects were taking aspirin in addition to a thienopyridine (DAPT).

In TRACER study because of patients' NSTE-ACS presentation at the time of hospitalization, approximately 97% of the subjects were taking aspirin, with approximately 74% taking aspirin at doses 100 mg or higher. During the early follow-up period, principally during initial hospitalization, aggressive antiplatelet and anticoagulant therapies were utilized. The vast majority of subjects received clopidogrel in addition to aspirin (85%) and nearly one-quarter of subjects received loading doses of clopidogrel of 600 mg or higher and approximately 86% of the subjects were treated with an

antithrombin agent, most commonly unfractionated heparin and/or a low molecular weight heparin. Finally, approximately 18% of subjects received a glycoprotein IIb/IIIa antagonist.

The above data indicate the key differences in the characteristics between the study populations of TRACER and TRA 2ºP-TIMI 50 highlighting the rather limited value of TRACER in the evaluation of vorapaxar safety in the currently proposed target population.

With regard to TRA 2ºP-TIMI 50, the overall patient characteristics are consistent with what is expected in a secondary prevention population while the Proposed Label Population reflects a more selected post-MI group with a range of background risk factors and co-morbidities. Patients in this group were younger with the percentage of those older than 75ys much smaller than the overall population; still the numbers are sufficient to allow assessment of safety in these older patients.

It is noted that the vast majority of patients in TRA 2ºP-TIMI 50 (especially the Proposed Label Population) were on aspirin and most of them were also receiving clopidogrel (i.e. DAPT) but there were very few patients on other antiplatelet agents like prasugrel or ticagrelor. This is a limitation especially for the assessment of any incremental bleeding risks with those agents, which which needs to be adequately reflected in the product information and be taken into account in the benefit:risk evaluation. Furthermore there were very few patients on oral anticoagulants (n=28)/warfarin (n=18). In fact among the exclusion criteria was “concurrent or anticipated treatment with warfarin (or derivatives, eg, phenprocoumon), oral factor Xa inhibitor, or oral direct thrombin inhibitor after enrolment”.

The SmPC includes relevant information in sections 4.2 and 4.5. Still due to the lack of relevant experience, the SmPC also advise that the use of vorapaxar with prasugrel and ticagrelor is not recommended.

### Adverse events

- Common adverse events

Bleeding risk was considered the major potential safety concern for vorapaxar and the Phase 3 studies were designed to examine bleeding as the main safety endpoint. Hence, the largest part of the safety review is devoted to bleeding events. These are discussed in detail in the ‘Bleeding’ subsection below.

A high-level summary of bleeding and other AEs for both studies is shown in Table S.4 below.

**Table S.4**. Phase 3 Number (%) of Subjects With the Indicated Type of Adverse Event Reported During the Study

| | TRA 2ºP-TIMI 50 | | TRACER | |
|---|---|---|---|---|
| Event | Placebo (n =13166) | Vorapaxar (n =13186) | Placebo (n = 6441) | Vorapaxar (n = 6446) |
| **Any Bleeding or Other Adverse Event** | | | | |
| Any Treatment-Emergent Adverse Event | 10425(79.2) | 10489(79.5) | 4848 (75.3) | 5056 (78.4) |
| Any Treatment-Related Treatment Emergent Adverse Event | 3135(23.8) | 3727(28.3) | 1408 (21.9) | 1801 (27.9) |
| Any Serious Adverse Event | 3419(26.0) | 3515(26.7) | 1718 (26.7) | 1866 (28.9) |
| Any Treatment-Related Serious Adverse Event | 299 (2.3) | 465 (3.5) | 275 (4.3) | 380 (5.9) |
| Any Adverse Event Resulting in Treatment Discontinuation[a] | 1143 (8.7) | 1273 (9.7) | 456 (7.1) | 626 (9.7) |
| Any Treatment-Related Adverse Event Resulting in Treatment Discontinuation[a] | 483 (3.7) | 632 (4.8) | 192 (3.0) | 323 (5.0) |

| | | | | |
|---|---|---|---|---|
| Any Treatment-Related Adverse Event Resulting in Treatment Discontinuation[a] | 483 (3.7) | 632 (4.8) | 192 (3.0) | 323 (5.0) |
| Any Adverse Event Resulting in Study Discontinuation | 1186 (9.0) | 1323(10.0) | 467 (7.3) | 647(10.0) |
| Any Treatment-Related Adverse Event Resulting in Discontinuation | 485 (3.7) | 638 (4.8) | 194 (3.0) | 324 (5.0) |
| Any Adverse Event Resulting in Death | 342 (2.6) | 339 (2.6) | 191 (3.0) | 197 (3.1) |
| Any Treatment-Related Adverse Event Resulting in Death | 16 (0.1) | 31 (0.2) | 12 (0.2) | 25 (0.4) |
| **Any Bleeding Event** | | | | |
| Any Treatment-Emergent Bleeding Event | 2420(18.4) | 3358(25.5) | 1555 (24.1) | 2058 (31.9) |
| Any Treatment-Related Treatment Emergent Bleeding Event | 1450(11.0) | 2251(17.1) | 949 (14.7) | 1364 (21.2) |
| Any Serious Bleeding Event | 475 (3.6) | 692 (5.2) | 365 (5.7) | 518 (8.0) |
| Any Treatment-Related Serious Bleeding Event | 221 (1.7) | 395 (3.0) | 216 (3.4) | 330 (5.1) |
| Any Bleeding Event Resulting in Treatment Discontinuation[a] | 234 (1.8) | 401 (3.0) | 125 (1.9) | 255 (4.0) |
| Any Treatment-Related Bleeding Event Resulting in Death | 11 (0.1) | 24 (0.2) | 9 (0.1) | 22 (0.3) |
| **Any Other Adverse Event** | | | | |
| Any Treatment-Emergent Other Adverse Event | 10227(77.7) | 10208(77.4) | 4651 (72.2) | 4795 (74.4) |
| Any Treatment-Related Treatment Emergent Other Adverse Event | 2070(15.7) | 2124(16.1) | 643 (10.0) | 733 (11.4) |
| Any Serious Other Adverse Event | 3255(24.7) | 3250(24.6) | 1561 (24.2) | 1638 (25.4) |
| Any Treatment-Related Serious Other Adverse Event | 93 (0.7) | 83 (0.6) | 75 (1.2) | 63 (1.0) |
| Any Other Adverse Event Resulting in Treatment Discontinuation[a] | 960 (7.3) | 926 (7.0) | 348 (5.4) | 407 (6.3) |
| Any Treatment-Related Other Adverse Event Resulting in Treatment Discontinuation[a] | 314 (2.4) | 327 (2.5) | 95 (1.5) | 122 (1.9) |
| Any Other Adverse Event Resulting in Study Discontinuation | 1007 (7.6) | 981 (7.4) | 361 (5.6) | 429 (6.7) |
| Any Treatment-Related Other Adverse Event Resulting in Discontinuation | 316 (2.4) | 330 (2.5) | 96 (1.5) | 122 (1.9) |
| Any Other Adverse Event Resulting in Death | 319 (2.4) | 306 (2.3) | 177 (2.7) | 175 (2.7) |
| Any Treatment-Related Other Adverse Event Resulting in Death | 5 (<.1) | 7 (0.1) | 3 (<0.1) | 5 (0.1) |
| Any Treatment-Related Bleeding Event Resulting in Treatment Discontinuation[a] | 180 (1.4) | 322 (2.4) | 99 (1.5) | 213 (3.3) |
| Any Bleeding Event Resulting in Study Discontinuation | 240 (1.8) | 409 (3.1) | 130 (2.0) | 258 (4.0) |
| Any Treatment-Related Bleeding Event Resulting in Discontinuation | 181 (1.4) | 326 (2.5) | 101 (1.6) | 214 (3.3) |
| Any Bleeding Event Resulting in Death | 34 (0.3) | 49 (0.4) | 24 (0.4) | 33 (0.5) |



With regard to ***other than bleeding*** AEs, in the TRA 2ºP-TIMI 50 overall population, the most frequently reported treatment-emergent AEs included non-cardiac chest pain (6%), chest pain (5%), and urinary tract infections (5%), with similar frequency in the vorapaxar and placebo groups. Two noteworthy AEs with different frequency between groups were pulmonary embolism and anaemia. Pulmonary embolism was reported in 26 subjects (0.2%) in the vorapaxar group compared to 52 subjects (0.4%) in the placebo group and anaemia was reported in 437 subjects (3.3%) in vorapaxar group compared to 308 subjects (2.3%) in the placebo group.

In the TRA 2ºP-TIMI 50 Proposed Label Population, the most common treatment emergent other AEs (≥2% in either treatment group during treatment) are presented below in Table S.5. The rate for the two treatment groups was similar for most AEs.

**Table S.5.** TRA 2ºP-TIMI 50 Summary of Treatment Emergent Adverse Events with Annualized Event Rates - Other Adverse events (2.0% Incidence) During Treatment for Proposed Label Population (%) of Subjects

| | Placebo n=8412 | | Vorapaxar n=8444 | |
|---|---|---|---|---|
| | Subjects with Events (%) | Event Rate [a] | Subjects with Events (%) | Event Rate [a] |
| **SUBJECTS REPORTING ANY ADVERSE EVENT** | 6465(76.9) | (90.1) | 6428(76.1) | (89.8) |
| **BLOOD AND LYMPHATIC SYSTEM DISORDERS** | | | | |
| ANAEMIA | 158 (1.9) | (0.8) | 208 (2.5) | (1.1) |
| **CARDIAC DISORDERS** | | | | |
| ANGINA PECTORIS | 264 (3.1) | (1.4) | 257 (3.0) | (1.4) |
| ATRIAL FIBRILLATION | 169 (2.0) | (0.9) | 168 (2.0) | (0.9) |
| PALPITATIONS | 163 (1.9) | (0.9) | 177 (2.1) | (1.0) |
| **GASTROINTESTINAL DISORDERS** | | | | |
| DIARRHOEA | 234 (2.8) | (1.3) | 217 (2.6) | (1.2) |
| DYSPEPSIA | 189 (2.2) | (1.0) | 189 (2.2) | (1.0) |
| NAUSEA | 207 (2.5) | (1.1) | 189 (2.2) | (1.0) |
| **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** | | | | |
| CHEST DISCOMFORT | 187 (2.2) | (1.0) | 184 (2.2) | (1.0) |
| CHEST PAIN | 580 (6.9) | (3.2) | 565 (6.7) | (3.2) |
| FATIGUE | 395 (4.7) | (2.2) | 407 (4.8) | (2.3) |
| NON-CARDIAC CHEST PAIN | 677 (8.0) | (3.8) | 637 (7.5) | (3.6) |
| OEDEMA PERIPHERAL | 266 (3.2) | (1.4) | 269 (3.2) | (1.5) |
| **INFECTIONS AND INFESTATIONS** | | | | |
| BRONCHITIS | 213 (2.5) | (1.1) | 254 (3.0) | (1.4) |
| INFLUENZA | 239 (2.8) | (1.3) | 213 (2.5) | (1.2) |
| NASOPHARYNGITIS | 338 (4.0) | (1.8) | 311 (3.7) | (1.7) |
| UPPER RESPIRATORY TRACT INFECTION | 207 (2.5) | (1.1) | 198 (2.3) | (1.1) |
| URINARY TRACT INFECTION | 341 (4.1) | (1.8) | 363 (4.3) | (2.0) |
| **INJURY, POISONING AND PROCEDURAL COMPLICATIONS** | | | | |
| FALL | 215 (2.6) | (1.2) | 225 (2.7) | (1.2) |
| **INVESTIGATIONS** | | | | |
| ALANINE AMINOTRANSFERASE INCREASED | 159 (1.9) | (0.9) | 177 (2.1) | (1.0) |
| BLOOD CREATINE PHOSPHOKINASE INCREASED | 274 (3.3) | (1.5) | 261 (3.1) | (1.4) |
| GAMMA- GLUTAMYLTRANSFERASE INCREASED | 181 (2.2) | (1.0) | 189 (2.2) | (1.0) |

| | | | | |
|---|---|---|---|---|
| **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** | | | | |
| ARTHRALGIA | 262 (3.1) | (1.4) | 279 (3.3) | (1.5) |
| BACK PAIN | 328 (3.9) | (1.8) | 311 (3.7) | (1.7) |
| MUSCLE SPASMS | 194 (2.3) | (1.0) | 176 (2.1) | (1.0) |
| MUSCULOSKELETAL PAIN | 209 (2.5) | (1.1) | 201 (2.4) | (1.1) |
| MYALGIA | 283 (3.4) | (1.5) | 305 (3.6) | (1.7) |
| PAIN IN EXTREMITY | 331 (3.9) | (1.8) | 309 (3.7) | (1.7) |
| **NERVOUS SYSTEM DISORDERS** | | | | |
| DIZZINESS | 464 (5.5) | (2.6) | 449 (5.3) | (2.5) |
| HEADACHE | 351 (4.2) | (1.9) | 312 (3.7) | (1.7) |
| **PSYCHIATRIC DISORDERS** | | | | |
| DEPRESSION | 169 (2.0) | (0.9) | 194 (2.3) | (1.0) |
| **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** | | | | |
| COUGH | 317 (3.8) | (1.7) | 331 (3.9) | (1.8) |
| DYSPNOEA | 362 (4.3) | (2.0) | 348 (4.1) | (1.9) |
| **VASCULAR DISORDERS** | | | | |
| HYPERTENSION | 456 (5.4) | (2.5) | 437 (5.2) | (2.4) |

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

In TRACER, the differences in event incidence between the two treatment groups were similar for most AEs but there were also some differences. In the vorapaxar group there was at least 0.5 % higher incidence than placebo in hypertension (1.1%), peripheral oedema (0.9%) and anaemia (0.6%) during the study. However, when compared with the overall pool, the difference in occurrence of peripheral oedema was higher for placebo at 0.1% (0.3% for vorapaxar and 0.4% for placebo). The increase incidence of hypertension in the vorapaxar group was not supported by the vital signs data collected.

In the overall pool, the differences between the two treatment groups were marginal for most AEs. The incidence of anaemia was higher in the vorapaxar group (3.5%) than placebo group (2.7%).

Generally, no major differences in the incidence of common AEs were observed between treatment groups across the examined populations. In the most relevant to this application analysis, the TRA 2ºP-TIMI 50 Proposed Label Population, the most common event was chest pain (cardiac or non-cardiac) followed by dizziness. Anaemia was slightly more frequent with vorapaxar and it appears to be related to bleeding.

## Serious adverse events and deaths

- **Deaths**

TRA 2ºP-TIMI 50 trial

Of the 26,449 subjects, 1190 (4.5%) died during the course of the study: 610/13,224 (4.6%) were assigned to placebo and 580/13225 (4.4%) were assigned to vorapaxar (Table S.6). A smaller proportion of subjects died in the Proposed Label Population; of the 16,856 subjects, 98/8,444 (1.2%) on vorapaxar and 113/8,412 (1.3%) on placebo died during treatment. In both, overall and the population of interest, more deaths occurred on or before the last visit compared to after the last visit.

**Table S.6.** All-Cause Death Recorded During the Study in Overall Population and Post-MI Subjects without a History of Stroke or TIA: As-Treated Population [a,b]

| | Overall Population | | Post MI without a History of Stroke or TIA | |
|---|---|---|---|---|
| | Placebo | Vorapaxar | Placebo | Vorapaxar |
| | (n=13224) | (n=13225) | (n=8439) | (n=8458) |
| TOTAL NO. OF DEATHS FROM DEATH or SURVIVAL PAGE | 610 (4.6) | 580 (4.4) | 278 (3.3) | 253 (3.0) |
| TOTAL NO. of DEATHS ON or BEFORE the LAST VISIT | 565 (4.3) | 540 (4.1) | 259 (3.1) | 238 (2.8) |
| TOTAL NO. OF DEATHS AFTER THE LAST VISIT | 45 (0.3) | 40 (0.3) | 19 (0.2) | 15 (0.2) |

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

The following table shows all-cause deaths during the whole study in randomized subjects by subject population: (As-Treated Data Set)

**Table S.7.** All Deaths During Entire study

| Type of event | Placebo n=13224 | SCH 530348 n=13225 |
|---|---|---|
| TOTAL NUMBER OF DEATHS FROM DEATH / SURVIVAL PAGE | 610 (4.6) | 580 (4.4) |
| TOTAL NUMBER OF DEATHS FROM INDIVIDUAL CRF PAGE | 445 (3.4) | 430 (3.3) |
| ADVERSE EVENT | 319 (2.4) | 308 (2.3) |
| BLEEDING | 34 (0.3) | 50 (0.4) |
| MI | 100 (0.8) | 76 (0.6) |
| STROKE | 34 (0.3) | 50 (0.4) |
| TOTAL NUMBER OF DEATHS FROM DEATH / SURVIVAL PAGE AND NOT IN INDIVIDUAL CRF PAGE | 165 (1.2) | 150 (1.1) |
| ADVERSE EVENT | 2 (<.1) | 2 (<.1) |
| CLINICAL EVENT EFFICACY/SAFETY ENDPOINT | 30 (0.2) | 35 (0.3) |
| DISEASE-RELATED COMPLICATIONS | 41 (0.3) | 26 (0.2) |
| OTHER | 70 (0.5) | 68 (0.5) |
| MISSING | 22 (0.2) | 19 (0.1) |

As the above tables suggest the overall mortality rates in TRA 2ºP-TIMI 50 were similar between groups and with an overall trend in favour of vorapaxar. However, a higher proportion of patients receiving vorapaxar than placebo appear to have died from bleeding or stroke.

TRACER

Of the 12,944 subjects who received randomized treatment assignment (overall population), 661 (5.1%) died during the course of the study: 339/6473 (5.2%) in the vorapaxar group and 322/6471 (5.0%) in the placebo group. Noticeable differences between the groups were observed for bleeding (33 [0.5%] vorapaxar vs. 25 [0.4%] placebo), MI (71 [1.1%] vorapaxar vs. 78 [1.2%] placebo), and an undefined "other" category (34 [0.5%] vorapaxar vs. 24 [0.4%] placebo).

Overall pool

For the overall pool ITT population, of the 39,393 subjects who received randomized treatment assignment: 919/19,698 (4.7%) who were assigned vorapaxar and 932/19,695 (4.4%) who were assigned placebo, died during the course of the study. The annualized event rate was identical for both vorapaxar and placebo (2.2 events per 100 subject-years of exposure).

Phase 1 and 2 studies

In the Phase 1 studies, one death (traffic accident) was reported. Three deaths were reported in the three Phase 2 studies, all in Study P03573: two in the PCI population and one in the non-PCI population; all subjects received vorapaxar.

- **Other Serious Adverse Events (SAE)**

All bleeding events were recorded on a bleed event page as opposed to the adverse event page, were adjudicated by the CEC and, per protocol, were not reported as SAEs. Serious non-bleeding adverse events are discussed here.

TRA 2ºP-TIMI 50

For the TRA 2ºP-TIMI 50 overall population, the number of subjects with SAEs were similar between the two treatment groups; vorapaxar (22.1%) and placebo (22.2%). The most frequently reported was non-cardiac chest pain, 3.1% in the vorapaxar group and 3.3% in the placebo group (Table S.8). Most other serious other adverse events were reported in less than 1% of subjects in both treatment groups. Serious anaemia was rare but was more frequently reported in the vorapaxar group (0.3%) compared to placebo (0.1%). Various neoplasms were reported as serious other adverse events in both the placebo and vorapaxar groups. Review of the data indicates that there is no evidence of an excess in reports of cancer associated with vorapaxar treatment. Also noteworthy in review of the SAE data are fewer reports of pulmonary embolism in the vorapaxar group (10/2914; 0.1%) compared with the placebo group (33/2929; 0.3%).

**Table S.8.** Most Frequent Reported Serious Other Adverse Events by Subject Population: Post-MI Subjects without a History of Stroke or TIA: As-Treated Population: Event Accrual Period: Randomization to Last Visit

| Event | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Overall Population | | Post MI and No Prior History of Stroke or TIA | |
| | Placebo (n =13166) | Vorapaxar (n = 13186) | Placebo (n =8412) | Vorapaxar (n =8444) |
| Subjects Reporting Any Serious Other Adverse Event | | | | |
| NON-CARDIAC CHEST PAIN | 428 (3.3) | 411 (3.1) | 365 (4.3) | 338 (4.0) |
| CARDIAC FAILURE | 136 (1.0) | 146 (1.1) | 86 (1.0) | 87 (1.0) |
| PNEUMONIA | 138 (1.0) | 142 (1.1) | 71 (0.8) | 74 (0.9) |
| ATRIAL FIBRILLATION | 86 (0.7) | 112 (0.8) | 49 (0.6) | 67 (0.8) |
| SYNCOPE | 48 (0.4) | 71 (0.5) | 29 (0.3) | 41 (0.5) |
| CARDIAC FAILURE CONGESTIVE | 63 (0.5) | 73 (0.6) | 37 (0.4) | 36 (0.4) |
| OSTEOARTHRITIS | 79 (0.6) | 65 (0.5) | 50 (0.6) | 37 (0.4) |

For the TRA 2ºP-TIMI 50 Proposed Label Population alone, the number of subjects with SAEs was again similar between the two treatment groups; vorapaxar (20.2%) and placebo (21.1%). The most frequently reported SAE was non-cardiac chest pain, 4.0% in the vorapaxar group, and 4.3% in the placebo group (Table S.9).

**Table S.9.** TRA 2ºP-TIMI 50 Summary of Serious Adverse Events - Other Adverse Events for at Least 20 Subjects - During Treatment For Proposed Label Population

| | Placebo n=8412 | | Vorapaxar n=8444 | |
|---|---|---|---|---|
| **SUBJECTS REPORTING ANY ADVERSE EVENT** | **1772** | **(21.1)** | **1702** | **(20.2)** |
| **CARDIAC DISORDERS** | 287 | (3.4) | 287 | (3.4) |
| ATRIAL FIBRILLATION | 49 | (0.6) | 67 | (0.8) |
| CARDIAC FAILURE | 86 | (1.0) | 87 | (1.0) |
| CARDIAC FAILURE CONGESTIVE | 37 | (0.4) | 36 | (0.4) |
| NON-CARDIAC CHEST PAIN | 365 | (4.3) | 338 | (4.0) |
| VENTRICULAR TACHYCARDIA | 20 | (0.2) | 23 | (0.3) |
| **GASTROINTESTINAL DISORDERS** | **170** | **(2.0)** | **180** | **(2.1)** |
| INGUINAL HERNIA | 20 | (0.2) | 24 | (0.3) |
| GASTROENTERITIS | 19 | (0.2) | 21 | (0.2) |
| GASTROOESOPHAGEAL REFLUX DISEASE | 20 | (0.2) | 16 | (0.2) |
| **HEPATOBILIARY DISORDERS** | **57** | **(0.7)** | **68** | **(0.8)** |
| CHOLECYSTITIS | 13 | (0.2) | 22 | (0.3) |
| CHOLELITHIASIS | 26 | (0.3) | 24 | (0.3) |
| **INFECTIONS AND INFESTATIONS** | 311 | (3.7) | 299 | (3.5) |
| PNEUMONIA | 71 | (0.8) | 74 | (0.9) |
| URINARY TRACT INFECTION | 18 | (0.2) | 30 | (0.4) |
| **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** | 200 | **(2.4)** | **167** | **(2.0)** |
| INTERVERTEBRAL DISC PROTRUSION | 24 | (0.3) | 13 | (0.2) |
| MUSCULOSKELETAL CHEST PAIN | 22 | (0.3) | 31 | (0.4) |
| OSTEOARTHRITIS | 50 | (0.6) | 37 | (0.4) |
| **NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** | **210** | **(2.5)** | **203** | **(2.4)** |
| PROSTATE CANCER | 29 | (0.3) | 23 | (0.3) |
| **NERVOUS SYSTEM DISORDERS** | **85** | **(1.0)** | **100** | **(1.2)** |
| SYNCOPE | 29 | (0.3) | 41 | (0.5) |
| **RENAL AND URINARY DISORDERS** | **76** | **(0.9)** | **61** | **(0.7)** |
| NEPHROLITHIASIS | 20 | (0.2) | 12 | (0.1) |
| **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** | **120** | **(1.4)** | **85** | **(1.0)** |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | 35 | (0.4) | 26 | (0.3) |
| PULMONARY EMBOLISM | 21 | (0.2) | 4 | (<.1) |



In general, the rates of individual SAEs (other than bleeding) was low, with very few events like chest pain (non-cardiac) reaching an incidence >1%. Also there were no major differences between treatments, although some events were consistently reported more often in a certain group like anaemia in the vorapaxar treated patients and conversely pulmonary embolism in the placebo groups

TRACER

For TRACER, the overall difference in the occurrence of SAEs was 0.4% between vorapaxar (21.7%) and placebo (21.3%). No one event was particularly prevalent, and differences in occurrences between placebo and vorapaxar were relatively small. The event with the greatest overall occurrence was cardiac failure, not unexpected in this study population under, 119 subjects (1.8%) with vorapaxar vs. 128 subjects (2.0%) with placebo. In the TRACER study, a total of 31 cases of colon cancer were reported; 21 in vorapaxar and 9 in placebo. Given the short, (i.e., < 4 months) median time from exposure to vorapaxar to clinical symptoms, a causal relationship was

considered unlikely but possibly the aggressive antiplatelet therapies, including vorapaxar, administered to these NSTE-ACS subjects helped unveil a pre-existing condition. Additionally, given the relatively small number of subjects for whom individual reports were made, there is no evidence of a meaningful difference in the profile of colon cancer and other serious adverse events between the treatment groups. For the TRA 2ºP-TIMI 50 study (with a larger population and longer exposure), no difference in the rate of colon cancer between treatment groups (32 subjects on vorapaxar group vs. 31 on placebo) using the terms as in TRACER.

Overall Pool

For the overall pool, no one event was particularly prevalent, and differences in occurrences between vorapaxar and placebo were relatively small. The overall difference in occurrence of SAEs was only 0.1 percentage point between vorapaxar (22%) and placebo (21.9%). The event with the greatest overall occurrence was non-cardiac chest pain, 530 (2.7%) subjects with vorapaxar vs. 527 (2.7%) subjects with placebo. The greatest difference in occurrences for an individual SAE between treatments was 0.2 percentage points: anaemia [62 (0.3) vorapaxar subjects vs. 25 (0.1) placebo subjects] and atrial fibrillation [192 (1.0%) vorapaxar subjects vs. 165 (0.8%) placebo subjects

- **Adverse events of special interest**

**BLEEDING**

***Overall Bleeding Events***

As previously mentioned, bleeding risk was considered a major potential safety concern for vorapaxar. The pre-specified bleeding endpoints, individual bleeding events, and other AEs, including deaths, serious AEs, and discontinuations due to AEs, were examined and are presented below for each individual Phase 3 study and pre-defined pools. For both TRACER and TRA 2ºP-TIMI 50, reports of AEs derived from two modules of the eCRF: “bleeding events” and “adverse events.”

The pre-specified bleeding endpoints (see below) were adjudicated by the same independent CEC. The analyses presented in this safety summary are based on the adjudicated results. In the two Phase 3 studies, investigators were to grade the intensity of bleeding events according to the GUSTO criteria in the eCRF as follows:

• *Mild*: bleeding not requiring transfusion or causing hemodynamic compromise, or does not otherwise meet criteria for moderate or severe bleeding

• *Moderate*: bleeding requiring transfusion, but does not result in haemodynamic compromise

• *Severe*: deadly bleeding, intracranial bleeding, or substantial haemodynamic compromise

GUSTO severe is the bleeding subtype most likely to be associated with irreversible damage, whereas GUSTO moderate bleeding does not consider patient clinical stability but only requires the presence of a transfusion. Transfusions were not controlled by protocol and thus were subject to potentially widely varying standards. Given this distinction greater emphasis is placed on GUSTO severe bleeding as the incidence of GUSTO severe bleeding most accurately portrays the overall long-term risk of an antiplatelet agent.

Clinically significant bleeding events were also categorized according to the Thrombolysis in Myocardial Infarction (TIMI) criteria as follows:

• *Major*: (bleeding *not* associated with CABG) 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).

• *Major*: (bleeding associated with CABG) intracranial haemorrhage, or perioperative fatal bleeding, or re-operation for bleeding, or transfusion of ≥5 units of whole blood or packed red blood cells (PRBCs) within a 48 hour period, or chest tube output ≥ 2 L within a 24 hour period.

• *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).

• *Other*: bleeding requiring unplanned medical or surgical treatment, but not meeting TIMI major or minor criteria, or bleeding requiring unplanned laboratory evaluation, but not requiring medical/surgical treatment, and not meeting TIMI major or minor criteria, or other bleeding not meeting any prior criteria.

The bleeding endpoint analyses are based on the '*As-treated'* population; the event accrual period was from randomization to last visit. Study endpoints related to bleeding safety were time from randomized treatment assignment to first occurrence of any component of the following composites, in relative order of importance: GUSTO moderate or GUSTO severe bleeding, Clinically Significant Bleeding, defined as the composite of TIMI Major bleeding, TIMI Minor bleeding, or bleeding that requires unplanned medical or surgical treatment or unplanned laboratory evaluation even if it does not meet the criteria for TIMI Major or TIMI Minor bleeding.

In the overall population, there was a statistically significant increase in major bleeding, including ICH, among subjects taking vorapaxar in addition to standard of care. This increase appeared to be mostly driven by subjects with a history of stroke. In contrast, subjects with no prior stroke history presented a lower overall incidence of ICH and a reduced relative risk associated with vorapaxar that was not significant. It was the aggregate of (a) no relevant evidence of efficacy, (b) no reduction in mortality, and (c) a substantially increased risk of ICH and other serious bleeding events in the population with prior history of stroke that led the DSMB to recommend discontinuing study drug in these subjects (please see *Efficacy* section above, for a detailed account of Phase 3 trial line of events leading to the currently proposed restricted indication).



TRA 2ºP-TIMI 50 *Overall* Population

In the TRA 2ºP-TIMI 50 overall population, the risk of bleeding was greater for subjects on vorapaxar than placebo for all of the pre-specified bleeding endpoints except CABG-related TIMI major bleeding. The differences between the two treatment groups were significant for most of the GUSTO and TIMI categories, including the secondary endpoints of GUSTO moderate/severe bleeding, clinically significant bleeding, and intracranial haemorrhage (Table S.10).

• GUSTO moderate or severe bleeding 3-year Kaplan-Meier (KM) event rates were 4.2% in the vorapaxar group and 2.9% in the placebo group (hazard ratio [HR] 1.51; 95% Confidence Interval (CI) 1.31 to 1.74; p< 0.001).

• A total of 173 cases of ICH were reported, the 3-year KM event rates were 1.0% for vorapaxar and 0.6% for placebo (HR 1.70; 95% CI 1.25 to 2.32; p< 0.001). ICH occurred most commonly in vorapaxar subjects with a prior stroke history (56 subjects [2.7%]). There were 37 subjects who had fatal ICH: 26 (0.2%) on vorapaxar and 11 (0.1%) on placebo. These subjects were also included in the overall fatal bleeding category.

• A total of 65 fatal bleeding cases were reported, the 3-year KM event rates were 0.4% for vorapaxar and 0.3% for placebo (HR 1.40; 95% CI 0.86 to 2.30; p= 0.18).

**Table S.10.** TRA 2ºP-TIMI 50 Bleeding Endpoints Rates with Annualized Event Rates: Overall Population: Event Accrual Period Randomization to Last Visit

| Endpoints | Placebo (n =13166) Subjects With Events (%) | KM%[c] | Annualized Event Rate[d] | Vorapaxar (n = 13186) Subjects With Events (%) | KM%[c] | Annualized Event Rate[d] | Hazard Ratio[a,b] (95% Confidence Interval) | p-value[b] |
|---|---|---|---|---|---|---|---|---|
| **GUSTO Bleeding Categories** | | | | | | | | |
| Severe or Moderate[e] | 313 ( 2.4% ) | 2.9% | 1.0% | 471 ( 3.6% ) | 4.2% | 1.5% | 1.51 ( 1.31 - 1.74) | <0.001 |
| Severe | 146 ( 1.1% ) | 1.4% | 0.5% | 192 ( 1.5% ) | 1.7% | 0.6% | 1.31 ( 1.06 - 1.63) | 0.013 |
| Moderate | 179 ( 1.4% ) | 1.6% | 0.6% | 290 ( 2.2% ) | 2.6% | 0.9% | 1.62 ( 1.35 - 1.96) | <0.001 |
| CABG-Related Severe or Moderate | 13 ( 0.1% ) | 0.1% | <0.1% | 11 ( 0.1% ) | 0.1% | <0.1% | 0.84 ( 0.38 - 1.88) | 0.675 |
| **TIMI Bleeding Categories** | | | | | | | | |
| Major or Minor[e] | 337 ( 2.6% ) | 3.0% | 1.1% | 498 ( 3.8% ) | 4.5% | 1.6% | 1.48 ( 1.29 - 1.70) | <0.001 |
| Major | 243 ( 1.8% ) | 2.2% | 0.8% | 321 ( 2.4% ) | 2.9% | 1.0% | 1.32 ( 1.12 - 1.56) | 0.001 |
| Minor | 105 ( 0.8% ) | 0.9% | 0.3% | 192 ( 1.5% ) | 1.7% | 0.6% | 1.83 ( 1.44 - 2.32) | <0.001 |
| Clinically Significant[f] | 1324 (10.1% ) | 11.3% | 4.4% | 1816 (13.8% ) | 15.4% | 6.2% | 1.41 ( 1.31 - 1.51) | <0.001 |
| NonCABG-Related Major or Minor[e] | 323 ( 2.5% ) | 2.9% | 1.0% | 486 ( 3.7% ) | 4.3% | 1.5% | 1.51 ( 1.31 - 1.74) | <0.001 |
| NonCABG-Related Major | 229 ( 1.7% ) | 2.1% | 0.7% | 309 ( 2.3% ) | 2.8% | 1.0% | 1.35 ( 1.14 - 1.60) | <0.001 |
| CABG-Related Major | 14 ( 0.1% ) | 0.1% | <0.1% | 13 ( 0.1% ) | 0.1% | <0.1% | 0.92 ( 0.43 - 1.97) | 0.838 |
| **Other Categories** | | | | | | | | |
| ISTH Major | 454 ( 3.4% ) | 4.0% | 1.4% | 663 ( 5.0% ) | 5.8% | 2.1% | 1.47 ( 1.30 - 1.66) | <0.001 |
| Intracranial Hemorrhage | 64 ( 0.5% ) | 0.6% | 0.2% | 109 ( 0.8% ) | 1.0% | 0.3% | 1.70 ( 1.25 - 2.32) | <0.001 |
| Fatal ICH | 11 (0.1%) | 0.1% | <0.1% | 26 (0.2%) | 0.2% | 0.1% | 2.36 (1.16-4.77) | 0.017 |
| Fatal Bleeding | 27 ( 0.2% ) | 0.3% | 0.1% | 38 ( 0.3% ) | 0.4% | 0.1% | 1.40 ( 0.86 - 2.30) | 0.179 |

Abbreviations: CABG = coronary artery bypass grafting; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; ICH = intracranial haemorrhage; ISTH = International Society on Thrombosis and Haemostasis; TIMI = Thrombolysis in Myocardial Infarction. Note: Only TIMI major is an appropriate categorization in the context of CABC (in the Clinical Endpoints Committee Manual of Operations).
a. Vorapaxar vs. placebo; a hazard ratio <1 indicates lower hazard associated with vorapaxar relative to placebo.
b. Cox proportional hazards model with covariates of treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use).
c. Kaplan-Meier estimate at 1080 days.
d. Event rate is expressed as number of patients with events per 100 patient-years of exposure
e. Subcategories are mutually exclusive; each subject appears only in the highest intensity subcategory observed for that subject.
f. TIMI Major or Minor bleeding, or bleeding that requires unplanned medical or surgical treatment, or unplanned evaluation via laboratory test

When the risk of bleeding was compared among different subpopulations within TRA 2ºP-TIMI 50, the largest reduction was observed between the overall population and the non-stroke history (NSH) population. In the overall population, GUSTO severe risk was reduced from HR 1.31 (95% CI; 1.06 - 1.63) to HR 1.14 (95% CI 0.88 - 1.45) in the NSH population. In the overall population, the ICH event rate was 0.8% in the vorapaxar group and reduced to 0.5% in the vorapaxar group in the NSH population. Further refinement to post MI with no history of stroke resulted in further reductions in overall bleeding frequency but with modest improvements in treatment related risk (see below).

**Table S.11.** GUSTO and Major Bleeding Endpoints in the Study Subpopulations: Event Accrual Period: Randomization to Last Visit –As-Treated

| Population / Endpoints | Placebo Subjects With Events (%) | KM%[c] | Vorapaxar Subjects With Events (%) | KM%[c] | Hazard Ratio[a,b] (95% Confidence Interval) | P Value[b] |
|---|---|---|---|---|---|---|
| Overall | (n =13166) | | (n = 13186) | | | |
| GUSTO Severe or Moderate[d] | 313 ( 2.4% ) | 2.9% | 471 ( 3.6% ) | 4.2% | 1.51 ( 1.31 - 1.74) | <0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| GUSTO Severe | 146 ( 1.1% ) | 1.4% | 192 ( 1.5% ) | 1.7% | 1.31 ( 1.06 - 1.63) | 0.013 |
| GUSTO Moderate | 179 ( 1.4% ) | 1.6% | 290 ( 2.2% ) | 2.6% | 1.62 ( 1.35 - 1.96) | <0.001 |
| Intracranial Hemorrhage | 64 ( 0.5% ) | 0.6% | 109 ( 0.8% ) | 1.0% | 1.70 ( 1.25 - 2.32) | <0.001 |
| Fatal ICH | 11 (0.1%) | 0.1% | 26 (0.2%) | 0.2% | 2.36 (1.16-4.77) | 0.649 |
| Fatal Bleeding | 27 ( 0.2% ) | 0.3% | 38 ( 0.3% ) | 0.4% | 1.40 ( 0.86 - 2.30) | 0.179 |

| **History of Stroke** | **(n = 2864)** | | **(n = 2855)** | | | |
|---|---|---|---|---|---|---|
| GUSTO Severe or Moderate[d] | 71 ( 2.5% ) | 3.4% | 110 ( 3.9% ) | 5.0% | 1.55 (1.15 - 2.09) | 0.004 |
| GUSTO Severe | 37 ( 1.3% ) | 1.8% | 67 ( 2.3% ) | 3.2% | 1.83 (1.22 - 2.73) | 0.003 |
| GUSTO Moderate | 36 ( 1.3% ) | 1.8% | 44 ( 1.5% ) | 1.8% | 1.21 (0.78 - 1.88) | 0.396 |
| Intracranial Hemorrhage | 22 ( 0.8% ) | 0.9% | 56 ( 2.0% ) | 2.7% | 2.55 (1.56 - 4.18) | <0.001 |
| Fatal ICH | 1 (0%) | 0% | 11 (0.4%) | 0.8% | 10.90 (1.41 – 84.45) | 0.022 |
| Fatal Bleeding | 7 ( 0.2% ) | 0.4% | 16 ( 0.6% ) | 1.3% | 2.28 (0.94 - 5.54) | 0.069 |

| **No History of Stroke** | **(n=10302)** | | **(n=10331)** | | | |
|---|---|---|---|---|---|---|
| GUSTO Severe or Moderate[d] | 242 ( 2.3% ) | 2.7% | 361 ( 3.5% ) | 4.0% | 1.50 (1.27 - 1.76) | <0.001 |
| GUSTO Severe | 109 ( 1.1% ) | 1.3% | 125 ( 1.2% ) | 1.4% | 1.14 (0.88 - 1.48) | 0.308 |
| GUSTO Moderate | 143 ( 1.4% ) | 1.6% | 246 ( 2.4% ) | 2.7% | 1.73 (1.41 - 2.13) | <0.001 |
| Intracranial Hemorrhage | 42 ( 0.4% ) | 0.5% | 53 ( 0.5% ) | 0.6% | 1.25 (0.84 - 1.88) | 0.273 |
| Fatal ICH | 10 (0.1%) | 0.1% | 15 (0.1%) | 0.2% | 1.49 (0.67-3.32) | 0.329 |
| Fatal Bleeding | 20 ( 0.2% ) | 0.3% | 22 ( 0.2% ) | 0.3% | 1.10 (0.60 - 2.01) | 0.767 |
| **Post MI No History of Stroke** | **(n=8556)** | | **(n=8591)** | | | |
| GUSTO Severe or Moderate[d] | 159 ( 1.9% ) | 2.2% | 242 ( 2.8% ) | 3.3% | 1.52 (1.25 - 1.86) | <0.001 |
| GUSTO Severe | 75 ( 0.9% ) | 1.0% | 89 ( 1.0% ) | 1.2% | 1.18 (0.87 - 1.61) | 0.286 |
| GUSTO Moderate | 89 ( 1.0% ) | 1.2% | 159 ( 1.9% ) | 2.1% | 1.79 (1.38 - 2.31) | <0.001 |
| Intracranial Hemorrhage | 32 ( 0.4% ) | 0.5% | 41 ( 0.5% ) | 0.6% | 1.27 (0.80 - 2.02) | 0.309 |
| Fatal ICH | 8 ( 0.1% ) | 0.1% | 11 ( 0.1% ) | 0.2% | 1.36 (0.55 - 3.39) | 0.506 |
| Fatal Bleeding | 14 ( 0.2% ) | 0.2% | 15 ( 0.2% ) | 0.2% | 1.06 (0.51 - 2.20) | 0.867 |
| **Proposed Label Population** | **(n=8412)** | | **(n=8444)** | | | |
| GUSTO Severe or Moderate[d] | 156 (1.9%) | 2.2% | 231 (2.7%) | 3.1% | 1.48 (1.21-1.82) | <0.001 |
| GUSTO Severe | 73 (0.9%) | 1.0% | 85 (1.0%) | 1.2% | 1.16 (0.85-1.59) | 0.352 |
| GUSTO Moderate | 88 (1.0%) | 1.2% | 152 (1.8%) | 2.1% | 1.73 (1.33-2.25) | <0.001 |
| Intracranial Hemorrhage | 30 ( 0.4% ) | 0.5% | 38 ( 0.5% ) | 0.5% | 1.26 ( 0.78 - 2.03) | 0.348 |
| Fatal ICH | 8 (0.1%) | 0.1% | 10 (0.1%) | 0.2% | 1.24 (0.49-3.14) | 0.649 |
| Fatal Bleeding | 14 ( 0.2% ) | 0.2% | 14 ( 0.2% ) | 0.2% | 0.99 ( 0.47 - 2.09) | 0.989 |

a Vorapaxar versus placebo; a hazard ratio <1 indicates lower hazard associated with vorapaxar relative to placebo
b Cox proportional hazard model with covariates of treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use)
c Kaplan-Meier estimate at 1080 days
d Subcategories are mutually exclusive; each subject appears only in the highest intensity subcategory observed for that subject
Abbreviations: CEC = Clinical Endpoints Committee; CV = cardiovascular; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries



TRA 2ºP-TIMI 50 *Proposed Label* Population

In the TRA 2ºP-TIMI 50 Proposed Label Population, results for bleeding endpoints were similar to the results in the overall population, except for GUSTO severe bleeding, TIMI major bleeding and the rate of ICH. In the Proposed Label Population, the rates of GUSTO severe bleeding, TIMI major bleeding, and ICH were not significantly different between the two treatment groups. (Tables S.11 above and S.12 below) The incidence rate of ICH was 0.5% in both treatment groups.

• GUSTO moderate or severe bleeding 3-year KM event rates were 3.1% in the vorapaxar group and 2.2% in the placebo group (HR 1.48; 95% CI 1.21 to 1.82; p< 0.001). The annualized event rate was 1.1 events per 100 subject-years of exposure in the vorapaxar group and 0.8 events per 100 subject-years of exposure in the placebo group.

• Fatal bleeding 3-year KM rate was 0.2 % in both treatment groups (HR 0.99; 95% CI 0.47 to 2.09; p= 0.989).

**Table S.12**. TRA 2ºP-TIMI 50 Bleeding Endpoints with Annualized Event Rates in Subjects with No History of Stroke or TIA Whose Qualifying Condition was CAD: Event Accrual Period Randomization to Last Visit

| Endpoints | Placebo (n =8412 ) | | | Vorapaxar (n =8444 ) | | | Hazard Ratio[a,b] (95% Confidence Interval) | p-value[b] |
|---|---|---|---|---|---|---|---|---|
| | Subjects With Events (%) | KM%[c] | Annualized Event Rate[d] | Subjects With Events (%) | KM%[c] | Annualized Event Rate[d] | | |
| **GUSTO Bleeding Categories** | | | | | | | | |
| Severe or Moderate[e] | 156 (1.9%) | 2.2% | 0.8% | 231 (2.7%) | 3.1% | 1.1% | 1.48 (1.21-1.82) | <0.001 |
| Severe | 73 (0.9%) | 1.0% | 0.4% | 85 (1.0%) | 1.2% | 0.4% | 1.16 (0.85-1.59) | 0.352 |
| Moderate | 88 (1.0%) | 1.2% | 0.4% | 152 (1.8%) | 2.1% | 0.7% | 1.73 (1.33-2.25) | <0.001 |
| CABG-Related Severe or Moderate | 8 (0.1%) | 0.1% | <0.1% | 6 (0.1%) | 0.1% | <0.1% | 0.75 (0.26-2.16) | 0.591 |
| **TIMI Bleeding Categories** | | | | | | | | |
| Major or Minor[e] | 175 ( 2.1% ) | 2.4% | 0.8% | 259 ( 3.1% ) | 3.5% | 1.3% | 1.48 ( 1.22 - 1.80) | <0.001 |
| Major | 133 ( 1.6% ) | 1.8% | 0.6% | 161 ( 1.9% ) | 2.2% | 0.8% | 1.21 ( 0.96 - 1.52) | 0.108 |
| Minor | 47 ( 0.6% ) | 0.6% | 0.2% | 105 ( 1.2% ) | 1.4% | 0.5% | 2.23 ( 1.58 - 3.15) | <0.001 |
| Clinically Significant[f] | 785 (9.3% ) | 10.2% | 4.0% | 1120 (13.3% ) | 14.6% | 5.9% | 1.46 ( 1.34 - 1.60) | <0.001 |
| NonCABG-Related Major or Minor[e] | 167 ( 2.0% ) | 2.3% | 0.8% | 251 ( 3.0% ) | 3.4% | 1.2% | 1.50 ( 1.24 - 1.83) | <0.001 |
| Major | 125 ( 1.5% ) | 1.7% | 0.6% | 153 ( 1.8% ) | 2.1% | 0.7% | 1.22 ( 0.96 - 1.55) | 0.098 |
| CABG-Related Major | 8 ( 0.1% ) | 0.1% | <0.1% | 8 ( 0.1% ) | 0.1% | <0.1% | 1.00 ( 0.37 - 2.66) | 0.996 |
| **Other Categories** | | | | | | | | |
| ISTH Major | 233 ( 2.8% ) | 3.1% | 1.1% | 347 ( 4.1% ) | 4.7% | 1.7% | 1.49 ( 1.26 - 1.76) | <0.001 |
| Intracranial Hemorrhage | 30 ( 0.4% ) | 0.5% | 0.1% | 38 ( 0.5% ) | 0.5% | 0.2% | 1.26 ( 0.78 - 2.03) | 0.348 |
| Fatal ICH | 8 (0.1%) | 0.1% | <0.1% | 10 (0.1%) | 0.2% | <0.1% | 1.24 (0.49-3.14) | 0.649 |
| Fatal Bleeding | 14 ( 0.2% ) | 0.2% | 0.1% | 14 ( 0.2% ) | 0.2% | 0.1% | 0.99 ( 0.47 - 2.09) | 0.989 |

Abbreviations: CABG = coronary artery bypass grafting; CAD = coronary artery disease; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; ICH = intracranial hemorrhage; ISTH = International Society on Thrombosis and Haemostasis; TIA = transient ischemic attack; TIMI = Thrombolysis in Myocardial Infarction. Note: Only TIMI major is an appropriate categorization in the context of CABG (in the Clinical Endpoints Committee Manual of Operations).
a Vorapaxar vs. placebo; a hazard ratio <1 indicates lower hazard associated with vorapaxar relative to placebo.
b Cox proportional hazards model with covariates of treatment and stratification factors.
c Kaplan-Meier estimate at 1080 days.
d Event rate is expressed as number of patients with events per 100 patient-years of exposure
e Subcategories are mutually exclusive; each subject appears only in the highest intensity subcategory observed for that subject.
f TIMI Major or Minor bleeding, or bleeding that requires unplanned medical or surgical treatment, or unplanned evaluation via laboratory test.

In summary, in the *Overall* TRA 2ºP-TIMI 50 a significantly higher risk of bleeding was seen across most categories. GUSTO moderate or severe bleeding event rate during the accrual period was 4.2% in the vorapaxar group compared to 2.9% for placebo with annualised rates (per 100 patient-years of exposure) of 1.5% versus 1.0% respectively. GUSTO severe, TIMI major and ICH rates (including fatal cases) were all considerably higher than placebo. When these findings were further analysed, it was observed that serious events were more common in patients with previous history of stroke; consequently, when those patients were excluded the calculated risk for the remaining patients was much lower.

In this context, the more selected *'Proposed Label Population'* i.e the post-MI patients with no history of stroke or TIA the risk of GUSTO moderate or severe accrued event rate in the vorapaxar group are still higher at 3.1% than placebo at 2.2% but the difference between group is now less than in the overall population. This difference also appears now to be driven by moderate events while GUSTO severe events, although still slightly more frequent with vorapaxar are not significantly different from placebo (event rate 1.2% vs 1.0% respectively with a similar 0.4% annualised rate/100 patient-years

of exposure). Similarly, in this population TIMI major bleeding, ICH and fatal events, although again more common with vorapaxar, were not statistically higher than placebo. The rates of less severe and minor bleedings remained significantly higher in the vorapaxar groups compared to placebo.

In general, the above data suggest that the proposed approach to exclude patients with previous history of stroke and restrict the target population to post-MI patients with no such history appears to reduce considerably the risk of the most severe and life threatening bleeding. However, the risk is not eliminated and its relative importance in the benefit:risk evaluation needs to be considered further.

TRACER

In the TRACER study, the risk of bleeding was greater for subjects on vorapaxar than for subjects on placebo for all bleeding endpoints. The differences between the two treatment groups were significant for most of the GUSTO and TIMI categories, including for the secondary endpoints of GUSTO moderate/severe bleeding and clinically significant bleeding, and for ICH

• GUSTO severe or moderate bleeding 2-year KM event rates were 7.6% in the vorapaxar group and 5.8% in the placebo group (HR 1.36; 95% CI 1.18 to 1.57; p< 0.001).

• Clinically significant bleeding 2-year KM event rates were 19.5% for vorapaxar vs. 14.6% for placebo (HR 1.41; 95% CI 1.29 to 1.54; p< 0.001).

• CABG-related TIMI major 2-year KM event rates were 1.4% for vorapaxar vs. 1.2% for placebo (HR 1.31; 95% CI 0.95 to 1.79; p= 0.098).

A total of 67 cases (0.52%) of ICH were reported, with incidence rates of 0.7% (48 subjects) in the vorapaxar group and 0.3% (19 subjects) in the placebo group. The 2-year KM event rates were 1.0% for vorapaxar and 0.4% for placebo (HR 2.52; 95% CI 1.48 to 4.29; p< 0.001). There were 19 subjects who had fatal ICH, 13 subjects in the vorapaxar group vs. 6 subjects in the placebo group.

A total of 45 cases of fatal bleeding were reported, 29 (0.4%) on vorapaxar and 16 (0.2%) on placebo; nearly one-third occurred in the first 30 days. The 2-year KM event rates were 0.5% for vorapaxar and 0.3% for placebo (HR 1.81; 95% CI 0.98 to 3.34; p = 0.056). Four subjects (3 vorapaxar and 1 placebo) were confirmed to have a fatal bleeding event after the last visit, but were not included in the analysis based on prespecified data censoring schemes.

Generally, in TRACER the bleeding rates were higher than in the TRA 2ºP-TIMI 50 overall population, a rather expected finding considering the likely intensive use of various antithrombotic and antiplatelet therapies in the former study. Severe bleeding including fatal cases and ICH were more common among the vorapaxar treated patients; these findings together with the lack of clear evidence of benefit, as previously mentioned, led to the decision to terminate the trial. As previously discussed, because of the considerable differences between the study populations and patient management between the two Phase 3 trials, the value of TRACER in determining the risk of bleeding in the currently proposed stable post-MI target population is limited.

Chronic Pool

For integrated analyses of bleeding events, the so called *'Chronic Pool'* was considered which includes all bleeding events that occurred ≥ 30 days in TRACER and all bleeding events that occurred in TRA 2ºP-TIMI 50. The rational is that the bleeding events from the first 30 days of subjects' participation in the TRACER trial were not included in this pool in consideration of: 1) the inherent differences in the bleeding rate in the control arms of the two studies attributable to the use of multiple concomitant antithrombotic therapies 2) the invasive procedures during the index hospitalization in TRACER and 3) the differences in the trial populations.

For the chronic pool, the risk of bleeding was significantly greater for subjects on vorapaxar than for subjects on placebo for all bleeding endpoints, except for TIMI major CABG related bleeding.

• GUSTO severe or moderate bleeding annualized event rates were 1.7 events per 100 subject-years of exposure in the vorapaxar group and 1.1 events per 100 subject-years of exposure in the placebo group (HR 1.48; 95% CI 1.32 to 1.67; p< 0.001).

• Clinically significant bleeding annualized event rates were 6.6 events per 100 subject-years of exposure for vorapaxar vs. 4.5 events per 100 subject-years of exposure for placebo (HR 1.45; 95% CI 1.36 to 1.54; p< 0.001).

• TIMI major CABG related bleeding annualized event rates were 0.1 events per 100 subject-years of exposure in both treatment groups (HR 1.29; 95% CI 0.75 to 2.19; p= 0.354)

A total of 229 cases of ICH were reported: 150 (0.8%) subjects in the vorapaxar group and 79 (0.4%) subjects in the placebo group. Annualized event rates were 0.4 events per 100 subject-years of exposure in the vorapaxar group and 0.2 events per 100 subject-years of exposure in the placebo group (HR 1.89; 95% CI 1.44 to 2.48; p< 0.001).

A total of 96 fatal bleeding events were reported: 58 (0.3%) subjects in the vorapaxar group and 38 (0.2%) subjects in the placebo group. The annualized event rate was 0.1 events per 100 subject-years of exposure in both arms (HR 1.52; 95% CI 1.01 to 2.29; p= 0.044). Results in the chronic pool include 20 of the 29 fatal bleeds in the vorapaxar group and 11 of the 16 fatal bleeds in the placebo group from the TRACER trial. The fatal bleeds not included occurred during the first 30 days of the TRACER trial, consistent with the definition of the chronic pool.

Overall, the importance of the Chronic Pool that included events that occurred after the first 30 days in TRACER is questionable; although such events can be seen as happening during the chronic post-ACS phase (thus in the remit of TRA 2ºP-TIMI 50), there are still considerable differences compared to the stable TRA 2ºP-TIMI 50 patients and the relevance of the findings when pooling those two dissimilar groups together is uncertain. In any case the results from the chronic pool add little to the findings from the individual studies.

Phase 2 studies

The incidence of TIMI major and/or minor bleeding among subjects who underwent PCI was not different overall between subjects who received placebo and subjects who received vorapaxar. The difference between treatments was not viewed to be clinically meaningful. Study P03573 showed that vorapaxar was not associated with an increase in TIMI major plus minor bleeding compared with placebo during the protocol-specified treatment phase. In P04772, no notable difference was evident between placebo and vorapaxar, nor in any dosing group, in the proportion of subjects with incidence of TIMI Major, TIMI Minor, and non-TIMI bleeding during the protocol-specified treatment and follow-up phases, and no one event or class of events occurred with notably greater frequency. The incidence of bleeding during follow-up was lower than during the treatment phase. Non-TIMI bleeding was the most commonly reported bleeding in the PCI cohort during the protocol-specified treatment phase. Clinically significant bleeding events were reported for approximately 7% of vorapaxar-treated subjects and no placebo treated subjects. In P05005, during the protocol specified treatment phase, all but one of the bleeding AEs were classified as non-TIMI; no subject had a TIMI major or clinically important bleeding event. During the protocol-specified follow-up phase, as in the protocol-specified treatment phase, most of the bleeding AEs were classified as non-TIMI.

***Intracranial Haemorrhage***

Table S.13 presents a summary of CEC-adjudicated ICH, by location and aetiology for the TRA 2ºP-TIMI 50 overall and Proposed Label Populations as well as the TRACER overall population. Each population is discussed separately below.

**Table S.13**. Intracranial Haemorrhage Location and Aetiology with Annualized Event Rates in TRA 2ºP-TIMI 50 and TRACER: Event Accrual Period Randomization to Last Visit

| | TRA 2ºP-TIMI 50 Overall Population | | | | TRA 2ºP-TIMI 50 Proposed Label Population | | | | TRACER Overall Population | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo n=13166 | | Vorapaxar n=13186 | | Placebo n=8412 | | Vorapaxar n=8444 | | Placebo n=6441 | | Vorapaxar n=6446 | |
| | n (%) | Event rate | n (%) | Event rate | n (%) | Event rate | n (%) | Event rate | n (%) | Event rate | n (%) | Event rate |
| **Intracranial Hemorrhage** | **64 (0.49)** | **(0.2%)** | **109 (0.83)** | **(0.3%)** | **30(0.36)** | **(0.1%)** | **38 (0.45)** | **(0.2%)** | **19 (0.29)** | **(0.2%)** | **48 (0.74)** | **(0.6%)** |
| **Location** | | | | | | | | | | | | |
| Subdural with No Other Extension | 12 (0.09) | (<0.1%) | 13 (0.10) | (<0.1%) | 5 (0.06) | (<0.1%) | 5 (0.06) | (<0.1%) | 2 (0.03) | (<0.1%) | 12 (0.19) | (0.1%) |
| Subdural with Other Extension | 10 (0.08) | (<0.1%) | 9 (0.07) | (<0.1%) | 7 (0.08) | (<0.1%) | 5 (0.06) | (<0.1%) | 4 (0.06) | (<0.1%) | 5 (0.08) | (0.1%) |
| Intraparenchymal with no Other Location | 27 (0.21) | (0.1%) | 52 (0.39) | (0.2%) | 11 (0.13) | (0.1%) | 13 (0.15) | (0.1%) | 6 (0.09) | (0.1%) | 15 (0.23) | (0.2%) |
| Intraparenchymal with Intraventricular Extension | 5 (0.04) | (<0.1%) | 19 (0.14) | (0.1%) | 3 (0.04) | (<0.1%) | 6 (0.07) | (<0.1%) | 4 (0.06) | (<0.1%) | 9 (0.14) | (0.1%) |
| Intraparenchymal and Subarachnoid Only | 3 (0.02) | (<0.1%) | 3 (0.02) | (<0.1%) | 1 (0.01) | (<0.1%) | 2 (0.02) | (<0.1%) | 1 (0.02) | (<0.1%) | 0 | 0 |
| Intraventricular with No Other Extension | 0 | 0 | 4 (0.03) | (<0.1%) | 0 | 0 | 1 (0.01) | (<0.1%) | 0 | 0 | 0 | 0 |
| Intraventricular and Subarachnoid Only | 2 (0.02) | (<0.1%) | 3 (0.02) | (<0.1%) | 1 (0.01) | (<0.1%) | 1 (0.01) | (<0.1%) | 0 | 0 | 0 | 0 |
| Subarachnoid with No Other Location | 3 (0.02) | (<0.1%) | 4 (0.03) | (<0.1%) | 1 (0.01) | (<0.1%) | 3 (0.04) | (<0.1%) | 1 (0.02) | (<0.1%) | 4 (0.06) | (<0.1%) |
| Epidural with No Other Location | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Unknown | 2 (0.02) | (<0.1%) | 2 (0.02) | (<0.1%) | 1 (0.01) | (<0.1%) | 2 (0.02) | (<0.1%) | 1 (0.02) | (<0.1%) | 3 (0.05) | (<0.1%) |
| **Cause** | | | | | | | | | | | | |
| Spontaneous | 17 (0.13) | (0.1%) | 61 (0.46) | (0.2%) | 7 (0.08) | (<0.1%) | 16 (0.19) | (0.1%) | 9 (0.14) | (0.1%) | 24 (0.37) | (0.3%) |
| Without Stroke | 6 (0.05) | (<0.1%) | 11 (0.08) | (<0.1%) | 3 (0.04) | (<0.1%) | 5 (0.06) | (<0.1%) | 4 (0.06) | (<0.1%) | 6 (0.09) | (0.1%) |
| With Stroke | 11 (0.08) | (<0.1%) | 50 (0.38) | (0.2%) | 4 (0.05) | (<0.1%) | 11 (0.13) | (0.1%) | 5 (0.08) | (0.1%) | 18 (0.28) | (0.2%) |
| Hemorrhagic Conversion | 1 (<.01) | (<0.1%) | 3 (0.02) | (<0.1%) | 0 | 0 | 0 | 0 | 2 (0.03) | (<0.1%) | 3 (0.05) | (<0.1%) |
| Primary Intracranial Hemorrhage | 9 (0.07) | (<0.1%) | 46 (0.35) | (0.1%) | 3 (0.04) | (<0.1%) | 11 (0.13) | (0.1%) | 3 (0.05) | (<0.1%) | 14 (0.22) | (0.2%) |
| Subarachnoid Hemorrhage | 1 (<.01) | (<0.1%) | 1 (<.01) | (<0.1%) | 1 (0.01) | (<0.1%) | 0 | 0 | 0 | 0 | 1 (0.02) | (<0.1%) |
| Traumatic | 24 (0.18) | (0.1%) | 24 (0.18) | (0.1%) | 11 (0.13) | (0.1%) | 14 (0.17) | (0.1%) | 6 (0.09) | (0.1%) | 17 (0.26) | (0.2%) |
| Surgery/Procedure | 2 (0.02) | (<0.1%) | 4 (0.03) | (<0.1%) | 1 (0.01) | (<0.1%) | 2 (0.02) | (<0.1%) | 1 (0.02) | (<0.1%) | 5 (0.08) | (0.1%) |
| Mass/Tumor | 4 (0.03) | (<0.1%) | 2 (0.02) | (<0.1%) | 2 (0.02) | (<0.1%) | 1 (0.01) | (<0.1%) | 1 (0.02) | (<0.1%) | 1 (0.02) | (<0.1%) |
| Intracranial Vascular | 4 (0.03) | (<0.1%) | 2 (0.02) | (<0.1%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.02) | (<0.1%) |
| Fibrinolysis | 3 (0.02) | (<0.1%) | 3 (0.02) | (<0.1%) | 2 (0.02) | (<0.1%) | 2 (0.02) | (<0.1%) | 2 (0.03) | (<0.1%) | 0 | 0 |
| Other | 16 (0.12) | (<0.1%) | 19 (0.14) | (0.1%) | 9 (0.11) | (<0.1%) | 5 (0.06) | (<0.1%) | 0 | 0 | 0 | 0 |
| **Outcome** | | | | | | | | | | | | |
| Fatal[a] | 11 (0.08) | (<0.1%) | 26 (0.20) | (0.1%) | 8 (0.10) | (<0.1%) | 10 (0.12) | (<0.1%) | 6 (0.09) | (0.1%) | 13 (0.20) | (0.2%) |
| Non-Fatal [b] | 51 (0.39) | (0.2%) | 80 (0.61) | (0.2%) | 22 (0.26) | (0.1%) | 27 (0.32) | (0.1%) | 12 (0.19) | (0.1%) | 33 (0.51) | (0.4%) |
| ICH Contributing to Death[c] | 2 (0.02) | (<0.1%) | 3 (0.02) | (<0.1%) | 0 | 0 | 1 (0.01) | (<0.1%) | 1 (0.02) | (<0.1%) | 2 (0.03) | (<0.1%) |



TRA 2ºP-TIMI 50 *Overall* Population

In the TRA 2ºP-TIMI 50 overall population, ICH occurred in 173 subjects, 109 (0.83%) on vorapaxar and 64 (0.49%) on placebo with annualized event rates of 0.3 and 0.2 events per 100 subject-years of exposure, respectively (HR 1.70; 95% CI 1.25-2.32; p < 0.001). Compared with the entire overall population (n=26,449), those with ICH were generally older, and more subjects were over 75 years of age (24.8 %). Median body weight was 75 kg, with the majority (88%) of subjects having a weight ≥60 kg. More subjects on vorapaxar than on placebo were over 75 years of age, female, non-white, and had weight less than 60 kg.

In January 2011, the protocol was amended under the DSMB recommendation that subjects with any stroke prior to or post randomization discontinue study treatment, as a result of an increased number of ICHs observed in the vorapaxar group.

Approximately 22% of subjects in the TRA 2ºP - TIMI 50 overall population had a prior history of stroke. As mentioned, in the overall population, there was a statistically significant increase in ICH among subjects taking vorapaxar which was mostly driven by subjects with a history of stroke 2.0% in the vorapaxar group and 0.8% in the placebo group (HR 2.55; 95% CI 1.56 - 4.18; p<0.001). In contrast, subjects with no prior stroke history had a lower overall incidence (0.5% for vorapaxar vs. 0.4% for placebo) and a reduced relative risk associated with vorapaxar that was not significant (HR 1.25; 95% CI 0.84 – 1.88; p=0.273) (Table S.14 below). Based on these findings in the population with prior history of stroke together with efficacy considerations the DSMB recommended to discontinue study drug in these subjects and the Sponsor's decided to contraindicate the use of vorapaxar in patients with a history of stroke or who have a stroke while taking vorapaxar.

TRA 2ºP-TIMI 50 *Proposed Label Population*

The risk of ICH was considered that could be further diminished in the Proposed Label Population that excluded subjects with a history of stroke or TIA (Table S.14). In the Proposed Label Population, ICH occurred in 68 subjects, 38 on vorapaxar and 30 on placebo, with annualized event rates of 0.18 and 0.14 events per 100 subject-years of exposure, respectively.

**Table S.14**. Summary of Intracranial haemorrhage Endpoints by Population in TRA 2ºP-TIMI 50

| | 3 year KM Rate of ICH Endpoints | | | | |
|---|---|---|---|---|---|
| | Treatment Groups Number (%) | | | | |
| | Placebo | KM%[c] | Vorapaxar | KM%[c] | HR(95% CI, p-value)a,b |
| Overall Population | 64/13166 (0.5) | (0.6%) | 109/13186 (0.8) | (1.0%) | 1.70 (1.25-2.32, p<0.001) |
| Prior Stroke History | 22/2864 (0.8) | (0.9%) | 56/2855 (2.0) | (2.7%) | 2.55 (1.56-4.18, p<0.001) |
| No Prior Stroke History (NSH) | 42/10302 (0.4) | (0.5%) | 53/10331 (0.5) | (0.6%) | 1.25 (0.84-1.88, P=0.273) |
| Proposed Label Population | 30/8412 (0.4) | (0.5%) | 38/8444 ( 0.5 ) | (0.5%) | 1.26 (0.78-1.88; p= 0.348) |

Compared with ICH subjects in the overall population, subjects with ICH in the Proposed Label Population were generally younger, and slightly fewer subjects (18.4%) were over 75 years of age. Median body weight was 75.3 kg, with 89.8% of subjects having a weight ≥60 kg. Blood pressure was slightly lower than in subjects who experienced ICH in the overall population. Median systolic blood pressure was 137 mmHg and median diastolic pressure was 79 mmHg. There was no clinically meaningful difference in demographics between the treatment groups. No individual factor associated with significantly higher hazard ratio was identified.

Most of the ICHs were intracerebral in origin. Of the 38 cases in the vorapaxar group, 16 (0.19%) were spontaneous and 11(0.13%) were primary ICH, with an annualized event rate of 0.1 events per 100 subject-years of exposure. Traumatic ICH accounted for 25 (0.18%) of the 68 cases: 14 (0.17%) in the vorapaxar group and 11 (0.13%) in the placebo group. Non-fatal ICH occurred in 49 (0.29%) subjects, 27 (0.32%) on vorapaxar and 22 (0.26%) on placebo. Fatal ICH occurred in 18 (0.11%) subjects, 10 (0.12%) on vorapaxar and 8 (0.10%) on placebo (Table S.13 above).

TRACER

In the TRACER trial, ICH occurred in 67 subjects, 48 on vorapaxar vs. 19 on placebo (Table S.13 above). Subjects with ICH were predominantly white (79.2%) and male (63%). Approximately 40% of subjects were over 75 years of age. Median body weight was 78.5 kg, with 81.3% of subjects having a weight ≥60 kg. Median systolic blood pressure was 136.5 mmHg and median diastolic pressure was 76.5 mmHg. More subjects in the vorapaxar group than in the placebo group were female, nonwhite, and weighed less than 60 kg. Only 5 subjects had a prior history of stroke: 3 on placebo and 2 on vorapaxar.

Compared to ICH subjects in the TRA 2ºP-TIMI 50 overall population, the TRACER ICH subjects were older, with a larger proportion of subjects 75 years of age or older. Approximately half of the ICH cases were spontaneous, often with primary ICH. Approximately one third of the ICH cases were caused by trauma, a frequency greater than that seen in the TRA 2ºP-TIMI 50 trial (25%). Of the 67 ICHs, 35 (52%) were intracerebral in nature, occurring in 24 subjects on vorapaxar vs. 11 subjects on placebo. Non-fatal ICH occurred in 45 cases (67%). There were 19 subjects with fatal ICH and 3 subjects with ICH contributing to death. The incidences of subdural haemorrhage and ICH of traumatic origin were higher in TRACER than in TRA 2ºP-TIMI 50. In contrast to TRA 2ºP-TIMI 50, very few subjects in TRACER (approximately 4% of the overall population) had a prior history of stroke. Among the TRACER subjects who had an ICH, only 2/48 (4.2%) subjects on vorapaxar had a history of stroke prior to ICH, with 1 occurring > 6 months to ≤ 12 months prior to randomization and 1 occurring > 12 months prior to randomization. The more advanced age of the subjects and traumatic causes may have contributed to the ICHs observed in TRACER.

Chronic Pool

In the chronic pool, there were 229 subjects with ICH, 175 (76%) from TRA 2ºP-TIMI 50 and 54 (24%) from TRACER. The 30-days criterion for inclusion in the chronic pool excluded 13 TRACER ICH cases. There were 79 subjects with ICH on placebo and 150 subjects on vorapaxar. Non-fatal ICH occurred in 169 (0.44%) subjects, 108 (0.56%) on vorapaxar and 61 (0.31%) on placebo. Fatal ICH occurred in 54 (0.14%) subjects: 38 (0.20%) on vorapaxar and 16 (0.08%) on placebo.

Phase 1 and 2 Studies

In the Phase 1 studies, one ICH was reported in P03447 nine days after a single dose of vorapaxar 40 mg. In the Phase 2 program, there were 3 cases of ICH, all in subjects treated with vorapaxar.

***Bleeding Endpoints in Subgroups***

TRA 2ºP-TIMI 50 *Overall* Population

In the TRA 2ºP-TIMI 50 overall population, the effect of vorapaxar relative to placebo was shown to be consistent across the majority of subgroups. Only hypertension history revealed a treatment by subgroup interaction (p=0.03): subjects with *no* history of hypertension had more bleeding on vorapaxar compared with placebo than subjects with a history of hypertension. No clinical explanation could be identified for this finding, and this interaction was not seen in the TRACER trial.

In this study, aspirin use was near universal and the majority of subjects were administered DAPT (aspirin and clopidogrel). Subjects taking aspirin had an increased risk for GUSTO severe or moderate bleeding (HR 1.56; 95% CI 1.34 to 1.81). Subjects who were not taking aspirin (n=1703) had a lower bleeding risk than subjects taking aspirin. The risk of GUSTO severe bleeding in subjects with no history of prior stroke was very similar in the two treatment groups (1.4% in vorapaxar and 1.3% in placebo) (HR 1.1; 95% CI 0.88 to 1.48). Concomitant medical conditions or medical history of diabetes mellitus did not significantly impact the bleeding risk.

The following Figure S.1 and Table S.15 shows GUSTO severe and moderate bleeding events by different subgroups

**Figure S.1.** GUSTO-Severe or Moderate Bleeding Events by Subgroups for As-Treated Population (Randomization to Last Visit)

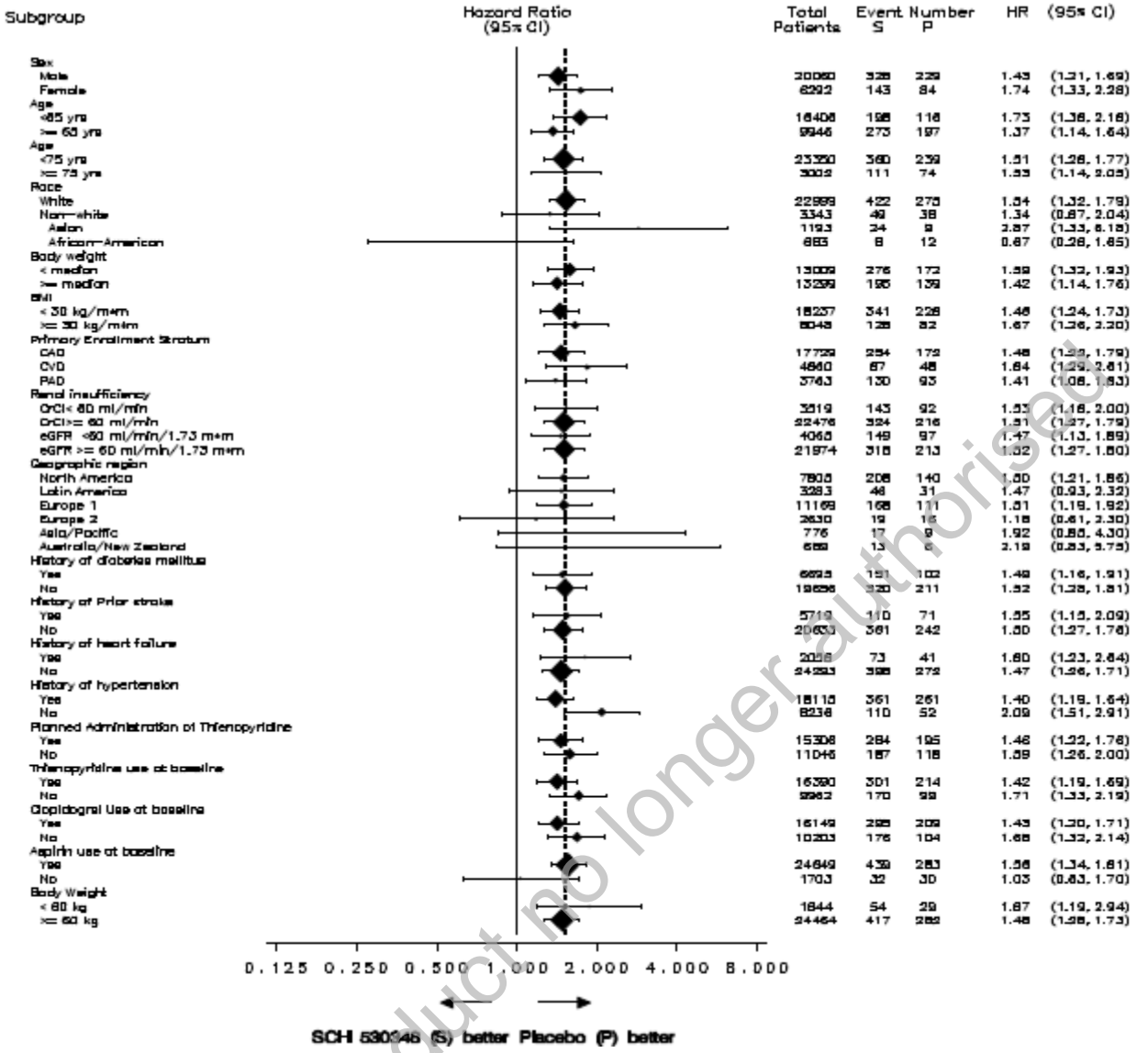



**Table S.15**. Subgroup Analyses for GUSTO Severe or Moderate Bleeding from Randomization to Last Visit: Demographic and Other Baseline Characteristics: As-Treated Population

| Subgroup | Placebo (n =13166 ) | | Vorapaxar (n =13186 ) | | Hazard Ratio[a,b] (95% Confidence Interval) |
|---|---|---|---|---|---|
| | Subjects With Events (%) | KM%[c] | Subjects With Events (%) | KM%[c] | |
| Sex | | | | | |
| Male | 229/10017 ( 2.3%) | 2.7% | 328/10043 ( 3.3%) | 3.8% | 1.43 (1.21 - 1.69) |
| Female | 84/3149 ( 2.7%) | 3.2% | 143/3143 ( 4.5%) | 5.6% | 1.74 (1.33 - 2.28) |
| Age (years) | | | | | |
| <65 | 116/8236 ( 1.4%) | 1.6% | 198/8170 ( 2.4%) | 2.9% | 1.73 (1.38 - 2.18) |
| ≥65 | 197/4930 ( 4.0%) | 5.0% | 273/5016 ( 5.4%) | 6.4% | 1.37 (1.14 - 1.64) |
| <75 | 239/11670 ( 2.0%) | 2.4% | 360/11680 ( 3.1%) | 3.6% | 1.51 (1.28 - 1.77) |
| ≥75 | 74/1496 ( 4.9%) | 6.5% | 111/1506 ( 7.4%) | 8.6% | 1.53 (1.14 - 2.05) |
| Race | | | | | |
| White | 275/11470 ( 2.4%) | 2.9% | 422/11529 ( 3.7%) | 4.3% | 1.54 (1.32 - 1.79) |
| Non-White | 38/1693 ( 2.2%) | 2.9% | 49/1650 ( 3.0%) | 3.9% | 1.34 (0.87 - 2.04) |
| Asian | 9/606 ( 1.5%) | 2.5% | 24/587 ( 4.1%) | 5.3% | 2.87 (1.33 - 6.18) |
| African-American | 12/348 ( 3.4%) | 4.0% | 8/335 ( 2.4%) | 3.4% | 0.67 (0.28 - 1.65) |

| | | | | | |
|---|---|---|---|---|---|
| Body Weight (kg) | | | | | |
| <median (81 kg) | 172/6454 ( 2.7%) | 3.3% | 276/6555 ( 4.2%) | 5.0% | 1.59 (1.32 - 1.93) |
| ≥median (81 kg) | 139/6687 ( 2.1%) | 2.4% | 195/6612 ( 2.9%) | 3.5% | 1.42 (1.14 - 1.76) |
| <60 kg | 29/916 (3.2%) | 4.0% | 54/928 (5.8%) | 7.4% | 1.87 (1.19-2.94) |
| > 60 kg | 282/12225 (2.3%) | 2.8% | 417/12239 (3.4%) | 4.0% | 1.48 (1.28-1.73) |
| Body Mass Index | | | | | |
| <30 kg/$m^2$ | 228/8997 ( 2.5%) | 3.1% | 341/9240 ( 3.7%) | 4.3% | 1.46 (1.24 - 1.73) |
| ≥30 kg/$m^2$ | 82/4136 ( 2.0%) | 2.3% | 128/3912 ( 3.3%) | 4.0% | 1.67 (1.26 - 2.20) |
| Primary Enrollment Stratum | | | | | |
| CAD | 172/8849 ( 1.9%) | 2.3% | 254/8880 ( 2.9%) | 3.3% | 1.48 (1.22 - 1.79) |
| CVD | 48/2437 ( 2.0%) | 2.6% | 87/2423 ( 3.6%) | 4.9% | 1.84 (1.29 - 2.61) |
| PAD | 93/1880 ( 4.9%) | 5.1% | 130/1883 ( 6.9%) | 7.2% | 1.41 (1.08 - 1.83) |
| Renal Function[d] | | | | | |
| CrCl <60 Ml/min | 92/1725 ( 5.3%) | 6.6% | 143/1794 ( 8.0%) | 9.3% | 1.53 (1.18 - 2.00) |
| CrCl ≥60 Ml/min | 216/11264 ( 1.9%) | 2.3% | 324/11212 ( 2.9%) | 3.4% | 1.51 (1.27 - 1.79) |
| eGFR <60 Ml/min•1.73$m^2$ | 97/1963 ( 4.9%) | 6.3% | 149/2102 ( 7.1%) | 8.1% | 1.47 (1.13 - 1.89) |
| eGFR ≥60 Ml/min•1.73$m^2$ | 213/11051 ( 1.9%) | 2.2% | 318/10923 ( 2.9%) | 3.4% | 1.52 (1.27 - 1.80) |
| History of Prior Stroke | | | | | |
| Yes | 71/2864 ( 2.5%) | 3.4% | 110/2855 ( 3.9%) | 5.0% | 1.55 (1.15 - 2.09) |
| No | 242/10302 ( 2.3%) | 2.7% | 361/10331 ( 3.5%) | 4.0% | 1.50 (1.27 - 1.76) |
| History of Heart Failure | | | | | |
| Yes | 41/1033 ( 4.0%) | 4.9% | 73/1025 ( 7.1%) | 8.2% | 1.80 (1.23 - 2.64) |
| No | 272/12132 ( 2.2%) | 2.7% | 398/12161 ( 3.3%) | 3.9% | 1.47 (1.26 - 1.71) |
| History of Diabetes Mellitus[f] | | | | | |
| Yes | 102/3343 ( 3.1%) | 3.5% | 151/3352 ( 4.5%) | 5.3% | 1.49 (1.16 - 1.91) |
| No | 211/9823 ( 2.1%) | 2.6% | 320/9833 ( 3.3%) | 3.8% | 1.52 (1.28 - 1.81) |
| History of Hypertension | | | | | |
| Yes | 261/9094 ( 2.9%) | 3.5% | 361/9021 ( 4.0%) | 4.7% | 1.40 (1.19 - 1.64) |
| No | 52/4071 ( 1.3%) | 1.5% | 110/4165 ( 2.6%) | 3.1% | 2.09 (1.51 - 2.91) |
| Planned Administration of Thienopyridine | | | | | |
| Yes | 195/7647 ( 2.6%) | 3.1% | 284/7659 ( 3.7%) | 4.3% | 1.46 (1.22 - 1.76) |
| No | 118/5519 ( 2.1%) | 2.5% | 187/5527 ( 3.4%) | 4.1% | 1.59 (1.26 - 2.00) |
| Thienopyridine Use at Baseline | | | | | |
| Yes | 214/8204 ( 2.6%) | 3.1% | 301/8186 ( 3.7%) | 4.2% | 1.42 (1.19 - 1.69) |
| No | 99/4962 ( 2.0%) | 2.4% | 170/5000 ( 3.4%) | 4.2% | 1.71 (1.33 - 2.19) |
| Clopidogrel Use at Baseline | | | | | |
| Yes | 209/8091 ( 2.6%) | 3.1% | 295/8058 ( 3.7%) | 4.2% | 1.43 (1.20 - 1.71) |
| No | 104/5075 ( 2.0%) | 2.5% | 176/5128 ( 3.4%) | 4.2% | 1.68 (1.32 - 2.14) |
| Aspirin Use at Baseline | | | | | |
| Yes | 283/12312 ( 2.3%) | 2.7% | 439/12337 ( 3.6%) | 4.2% | 1.56 (1.34 - 1.81) |
| No | 30/854 ( 3.5%) | 5.2% | 32/849 ( 3.8%) | 4.6% | 1.03 (0.63 - 1.70) |

Note: Median body weight was 65 kg.
a Vorapaxar versus placebo; a hazard ratio <1 indicates lower hazard associated with vorapaxar relative to placebo.
b Cox proportional hazard model with covariates treatment and stratification factors, with the exception of those subgroup variables
related to the stratification factors.
c For subgroup variable of stratification factor, qualifying atherosclerotic disease (or planned thenopyridine use), hazard ratio is

calculated
from Cox proportional hazard model with covariates treatment and the other stratification factor, planned thenopyridine use (or qualifying atherosclerotic disease).
d Kaplan-Meier estimate at 1080 days.
e Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault equation. Estimated glomerular filtration rate (Egfr) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.
f See Section 14.1.1.6 for identification of countries in each region.
g Self-reported in the Cardiovascular History Module of the eCRF.

Generally, subgroup analyses with regard to bleeding risk in the *Overall* TRA 2ºP-TIMI 50 population did not show any clear evidence of a clinically significant interaction, including the effect of factors like age, sex, weight, renal status or background therapy. However, across both active and control groups the risk of bleeding was higher among females, older patients, those with weight less 60kgr, patients with renal impairment, those with history of heart failure or in patients were taking aspirin. Although some relevant warnings about subgroups at higher risk of bleeding are included in the SmPC, more information will need to be added. Some of these points are further discussed in section *Safety in special populations* below.

In terms of concomitant antiplatelet therapy in the Overall TRA 2ºP-TIMI 50, subjects taking aspirin had an HR of 1.56 (95% CI; 1.34 – 1.81). Conversely subjects (1703) who were not taking aspirin, showed no increase in bleeding risk with vorapaxar i.e. GUSTO severe/moderate bleeding reported in 32 subjects in the vorapaxar group compared to 30 subjects the placebo group (HR 1.03; 95% CI; 0.63-1.70) but the numbers are small and the CI wide. Concomitant clopidogrel therapy did not appear to increase further the risk. Most of the patients on clopidogrel were also receiving aspirin; therefore, the bleeding rates reported for clopidogrel reflect those on dual antiplatelet treatment. In general, at baseline the majority of patients (more than 3/4) were on DAPT.

TRA 2ºP-TIMI 50 *Proposed Label Population*

The effect of vorapaxar relative to placebo in the Proposed Label Population was shown to be consistent across many of the subgroups. Concomitant medical conditions or medical history of diabetes mellitus, and history of heart failure or hypertension did not significantly impact on the bleeding risk. Assessment of bleeding risk relative to the use of concomitant anti-platelet therapy cannot be easily made because only 282 subjects (of 16,856) were not taking aspirin at baseline and approximately 3700 were not taking clopidogrel.

Table S.16 shows GUSTO severe and moderate bleeding events by different subgroups in the Proposed Label Population.

**Table S.16**. TRA 2ºP-TIMI 50 GUSTO Severe or Moderate Bleeding by Subgroups in Proposed Label Population: Event Accrual Period: Randomization to Last Visit

| | Placebo n=8412 | | | Vorapaxar n=8444 | | | |
|---|---|---|---|---|---|---|---|
| **Subgroup** | **Subjects with Events m/n (%)** | **Event Rate[a]** | **KM[b]** | **Subjects with Events m/n (%)** | **Event Rate[a]** | **KM[b]** | **Hazard Ratio [c,d] (95% CI)** |
| **Sex** | | | | | | | |
| Male | 120/6747 (1.8%) | 0.7% | 2.1% | 169/6727 (2.5%) | 1.0% | 2.8% | 1.42 (1.12 - 1.79) |
| Female | 36/1665 (2.2%) | 0.9% | 2.6% | 62/1717 (3.6%) | 1.5% | 4.5% | 1.69 (1.12 - 2.55) |
| **Age** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| <65 yrs | 79/6033 (1.3%) | 0.5% | 1.5% | 120/5952 (2.0%) | 0.8% | 2.3% | 1.54 (1.16 - 2.05) |
| >= 65 yrs | 77/2379 (3.2%) | 1.3% | 4.0% | 111/2492 (4.5%) | 1.8% | 5.2% | 1.39 (1.04 - 1.85) |
| <75 yrs | 132/7809 (1.7%) | 0.7% | 2.0% | 192/7811 (2.5%) | 1.0% | 2.8% | 1.46 (1.17 - 1.82) |
| >= 75 yrs | 24/603 (4.0%) | 1.7% | 4.9% | 39/633 (6.2%) | 2.6% | 7.0% | 1.57 (0.94 - 2.61) |
| **Race** | | | | | | | |
| White | 135/7389 (1.8%) | 0.7% | 2.1% | 208/7467 (2.8%) | 1.1% | 3.2% | 1.53 (1.23 - 1.90) |
| Non-white | 21/1020 (2.1%) | 0.9% | 2.7% | 23/971 (2.4%) | 1.0% | 2.9% | 1.16 (0.64 - 2.10) |
| Asian | 4/340 (1.2%) | 0.5% | 1.7% | 7/321 (2.2%) | 0.9% | 2.2% | 2.09 (0.61 - 7.16) |
| African-American | 8/176 (4.5%) | 2.0% | 5.4% | 3/172 (1.7%) | 0.7% | 2.1% | 0.37 (0.10 - 1.38) |
| **Body weight** | | | | | | | |
| < median | 81/3721 (2.2%) | 0.9% | 2.7% | 120/3824 (3.1%) | 1.3% | 3.7% | 1.46 (1.10 - 1.93) |
| >= median | 75/4679 (1.6%) | 0.6% | 1.8% | 111/4610 (2.4%) | 1.0% | 2.7% | 1.50 (1.12 - 2.01) |
| **BMI** | | | | | | | |
| < 30 kg/m*m | 114/5582 (2.0%) | 0.8% | 2.4% | 163/5795 (2.8%) | 1.2% | 3.2% | 1.38 (1.09 - 1.75) |
| >= 30 kg/m*m | 41/2813 (1.5%) | 0.6% | 1.7% | 68/2632 (2.6%) | 1.0% | 3.1% | 1.77 (1.20 - 2.61) |
| **Primary Enrollment Stratum** | | | | | | | |
| CAD | 156/8412 (1.9%) | 0.8% | 2.2% | 231/8444 (2.7%) | 1.1% | 3.1% | 1.48 (1.21 - 1.82) |
| **Renal insufficiency** [e,f] | | | | | | | |
| CrCl< 60 ml/min | 30/713 (4.2%) | 1.7% | 5.2% | 53/797 (6.6%) | 2.8% | 7.5% | 1.59 (1.01 - 2.48) |
| CrCl>= 60 ml/min | 124/7590 (1.6%) | 0.7% | 1.9% | 176/7541 (2.3%) | 1.0% | 2.7% | 1.43 (1.14 - 1.80) |
| eGFR $ <60 ml/min/1.73 m*m | 33/922 (3.6%) | 1.5% | 4.8% | 59/1046 (5.6%) | 2.2% | 6.2% | 1.54 (1.01 - 2.36) |
| eGFR >= 60 ml/min/1.73 m*m | 121/7393 (1.6%) | 0.7% | 1.8% | 170/7302 (2.3%) | 1.0% | 2.7% | 1.43 (1.13 - 1.81) |
| **History of diabetes mellitus** | | | | | | | |
| Yes | 42/1808 (2.3%) | 1.0% | 2.7% | 61/1805 (3.4%) | 1.4% | 4.1% | 1.47 (0.99 - 2.18) |
| No | 114/6604 (1.7%) | 0.7% | 2.0% | 170/6638 (2.6%) | 1.0% | 2.9% | 1.49 (1.17 - 1.89) |
| **History of Prior stroke** | | | | | | | |
| No | 156/8412 (1.9%) | 0.8% | 2.2% | 231/8444 (2.7%) | 1.1% | 3.1% | 1.48 (1.21 - 1.82) |
| **History of heart failure** | | | | | | | |
| Yes | 22/713 (3.1%) | 1.3% | 3.5% | 35/697 (5.0%) | 2.1% | 6.1% | 1.60 (0.94 - 2.73) |
| No | 134/7698 (1.7%) | 0.7% | 2.1% | 196/7747 (2.5%) | 1.0% | 2.9% | 1.46 (1.17 - 1.82) |
| **History of hypertension** | | | | | | | |
| Yes | 124/5200 (2.4%) | 1.0% | 2.8% | 159/5168 (3.1%) | 1.3% | 3.6% | 1.29 (1.02 - 1.63) |
| No | 32/3211 (1.0%) | 0.4% | 1.2% | 72/3276 (2.2%) | 0.9% | 2.5% | 2.22 (1.47 - 3.37) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Thienopyridine use at baseline** | | | | | | | |
| Yes | 136/6609 (2.1%) | 0.8% | 2.4% | 192/6593 (2.9%) | 1.2% | 3.3% | 1.42 (1.14 - 1.77) |
| No | 20/1803 (1.1%) | 0.4% | 1.3% | 39/1851 (2.1%) | 0.8% | 2.7% | 1.86 (1.09 - 3.20) |
| **Clopidogrel Use at baseline** | | | | | | | |
| Yes | 135/6551 (2.1%) | 0.8% | 2.4% | 190/6527 (2.9%) | 1.2% | 3.3% | 1.42 (1.14 - 1.77) |
| No | 21/1861 (1.1%) | 0.5% | 1.3% | 41/1917 (2.1%) | 0.8% | 2.7% | 1.86 (1.10 - 3.15) |
| **Aspirin use at baseline** | | | | | | | |
| Yes | 153/8272 (1.8%) | 0.8% | 2.2% | 227/8302 (2.7%) | 1.1% | 3.1% | 1.49 (1.21 - 1.82) |
| No | 3/140 (2.1%) | 0.9% | 2.3% | 4/142 (2.8%) | 1.2% | 4.0% | 1.25 (0.28 - 5.61) |
| **Body Weight** | | | | | | | |
| < 60 kg | 11/426 (2.6%) | 1.1% | 3.0% | 19/431 (4.4%) | 1.9% | 5.2% | 1.78 (0.85 - 3.74) |
| >= 60 kg | 145/7974 (1.8%) | 0.7% | 2.1% | 212/8003 (2.6%) | 1.1% | 3.0% | 1.46 (1.18 - 1.80) |

a. Event rate is expressed as number of patients with events per 100 patient-years of exposure
b. Kaplan-Meier estimate at 1080 days
c. Hazard Ratio is vorapaxar group vs. placebo group
d. Hazard Ratio is calculated based on Cox PH model with covariates treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use), with the exception for those subgroup variables related to the stratification factors. For subgroup variable of stratification factor, qualifying atherosclerotic disease (or planned thienopyridine use), hazard ratio is calculated from Cox PH model with covariates treatment and the other stratification factor, planned thienopyridine use (or qualifying atherosclerotic disease).
e. Creatinine Clearance is calculated using Cockcroft-Gault equation.
f. eGFR is calculated using Modification of Diet in Renal Disease (MDRD) formula.

Generally, the subgroup analyses of bleeding in the Proposed Label Population were consistent with those in the Overall TRA 2ºP-TIMI 50 population.

**In the Proposed Label Population of TRA 2°P-TIMI 50, 76.3% of subjects reported dual antiplatelet therapy (DAPT) at baseline. A total of 98% of the subjects were taking aspirin and 78% were taking clopidogrel at baseline. In response to a question from CHMP the Applicant submitted additional information and analyses about the use of aspirin and clopidogrel for the whole duration of the study and associated bleedings. It appears that the percentages of the Proposed Label Population patients who were actually treated with aspirin and a thienopyridine were 99% and 80.3% respectively (thienopyridine numbers reflect in fact DAPT as almost all patients were on aspirin, and almost all concern clopidogrel), which is consistent with the numbers previously provided for patients who had 'reported' such a treatment at baseline.**

However, although most patients continued on aspirin for the whole duration of the trial (median = 902 days) many (exact percentage uncertain) discontinued their clopidogrel treatment at some point (overall, remaining on treatment only for a median of 517 days. The Applicant states that the exact reasons for stopping thienopyridines are not known and while bleeding may be the cause in some cases, these figures are likely to reflect the recommendations in the label and the clinical guidelines on DAPT use after an MI. It is reassuring that the numbers are similar between vorapaxar and placebo groups, suggesting that the reasons for therapy cessation may be unrelated to vorapaxar therapy. It is worth noting here that in current guidelines use of DAPT after STEMI (with variations depending on reperfusion strategies) beyond 12 months is generally not recommended. Therefore, if this application is approved, it is anticipated that in practice after the first year post-MI in most (uncomplicated) cases vorapaxar will be co-administered with aspirin alone.

In terms of bleeding (GUSTO severe/moderate) in relation to background therapy during the trial, the Applicant provided an analysis showing that most events (~63%) during the trial occurred while patients were on background DAPT. This is not surprising since the majority of patients were receiving dual antiplatelet therapy for most of the study. The interesting finding is that the relative proportion

of patients who had a bleeding event while of DAPT or when thienopyridine was stopped was similar between vorapaxar and placebo groups. The Applicant suggests that this indicates no differential effect of concomitant therapy with thienopyridine by treatment group assignment with respect to bleeding. Indeed, more patients on vorapaxar than placebo had a bleeding event while receiving aspirin+thienopyridine but a similarly higher proportion of patients on vorapaxar than placebo had bleeding events when not taking a thienopyridine. Therefore, it can be concluded that the concomitant use of thienopyridine (on top of aspirin) with vorapaxar during the trial did not increase disproportionally the risk in comparison to placebo.

Taken together the above suggest that most patients in the Proposed Label Population of TRA 2ºP-TIMI 50 remained on aspirin for the duration of the trial but this was not the case with clopidogrel. Overall, compared to placebo vorapaxar was associated with an increased risk of bleeding but this was not disproportionally higher in patients on DAPT compared to those who stopped clopidogrel therapy.

TRACER

With the exceptions of weight, negative troponin status, and no clopidogrel use at baseline, population subgroups identified by baseline characteristics (i.e., gender, race, and GPIIb-IIIa, antithrombin and aspirin use) were not associated with any meaningful changes in bleeding risk compared with that in the overall patient population. Of note, subjects below the median body weight (80 kg) demonstrated a higher risk of bleeding with an increase in the hazard ratio from 1.15 to 1.63 for GUSTO severe or moderate bleeding. However, subjects weighing less than 60 kg did not show a significant interaction (p = 0.405). Concomitant medical conditions or medical history of diabetes mellitus, history of heart failure, or hypertension did not significantly impact bleeding risk. These findings are consistent with TRA 2ºP-TIMI 50 overall population.

As noted, the TRACER population differs from that of TRA 2ºP-TIMI 50 in many ways. In TRA 2ºP-TIMI 50, thienopyridine use did not impact bleeding risk. In TRACER, approximately 1700 (13.6%) subjects were not receiving thienopyridine and were on aspirin alone at baseline. Although a small minority of the overall study cohort, the risk of GUSTO severe or moderate bleeding in the vorapaxar group appeared to be prevented in those subjects not receiving a thienopyridine at randomization (HR 0.90; 95% CI 0.63 to 1.28), whereas the risk was increased in subjects who were receiving a thienopyridine (HR 1.47; 95% CI 1.26 to 1.72). Although these populations are small, the discordances from TRA 2ºP-TIMI 50 are another example of the TRACER population being distinct from TRA 2ºP-TIMI 50.

Chronic Pool

In the chronic pool, the effect of vorapaxar relative to placebo in the chronic pool was consistent across many of the subgroups. Bleeding rates, regardless of treatment, increased across the majority of subgroups. Vorapaxar-related bleeding risk was noted in several subgroups, including females (HR 1.71 female vs. 1.41 males) and hypertensives (HR 1.42 for positive hypertension history vs. 1.81 for no hypertension history). In the chronic pool, vorapaxar was not associated with increased bleeding risk in subjects with prior stroke history, diabetes, or heart failure history. Subjects below the median body weight demonstrated an increased risk of bleeding, with an HR 1.15 to 1.63 (p=0.017) for GUSTO moderate or severe bleeding those weighing less than 60 kg did not achieve a significant interaction. There were discordant results in subjects with renal dysfunction, with an increased risk associated with CrCl < 60 mL/min that was not substantiated by an eGFR of < 60 mL/ min/1.73m$^2$. Subjects aged ≥ 75 years had a HR of 1.60 vs. 1.45 for <75 years, yet when the cut-off of age ≥ 65 years was used, there was a reduction in the risk of vorapaxar-related bleeding. In general, the results of the pooled analyses of the chronic population are consistent with the TRA 2ºP-TIMI 50 overall population.

***Individual Bleeding Events***

For TRA 2ºP-TIMI 50, the frequency of bleeding/other adverse events (treatment emergent, treatment-related, and serious) were similar between the vorapaxar and placebo groups. Larger differences in incidences between the two groups were noted for bleeding events in vorapaxar (25.5%) compared to placebo (18.4%). The frequency of any 'other' AEs was similar (77%) between the two treatment groups. In addition, differences between the treatment groups were also observed for treatment-related bleeding events (17.1% for vorapaxar vs. 11% for placebo), and serious bleeding events (5.2% for vorapaxar vs. 3.6% for placebo). For TRACER, the frequencies of bleeding/other AEs were similar between the subjects on vorapaxar (78.4%) and on placebo (75.3%). Larger differences in incidences between the two groups were noted for bleeding events (31.9% for vorapaxar vs. 24.1% for placebo) than for other AEs (74.4% for vorapaxar vs. 72.2% for placebo).

TRA 2ºP-TIMI 50 *Overall* Population

Table S.17 summarizes the most frequently reported TE bleeding events during treatment for the Overall and Proposed Label Population. In the TRA 2ºP-TIMI 50 overall population:

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

• The most frequently reported bleeding event was epistaxis, 6.2% for vorapaxar group compared to placebo group, 3.1% with next most frequently reported haematuria: 2.6% in the vorapaxar group and 2.0% in the placebo group.

**Table S.17**. Summary of Treatment-Emergent Bleeding Events Reported for ≥ 0.2% of Subjects in Either Treatment Group Overall As-Treated and Subjects with No History of Stroke or TIA Whose Qualifying Condition Was CAD (Proposed Label Population): As-Treated Population

| | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Overall Population | | CAD Subjects with No History of Stroke or TIA | |
| System Organ Class and Adverse Events | Placebo (n = 13166) | Vorapaxar (n = 13186) | Placebo (n=8412) | Vorapaxar (n=8444) |
| **SUBJECTS REPORTING ANY AE** | 2260 (17.2) | 3211 (24.4) | 1526 (18.1) | 2166 (25.7) |
| **BLOOD & LYMPH SYSTEM DISORDERS** | | | | |
| HAEMORRHAGIC DIATHESIS | 30 (0.2) | 52 (0.4) | 20 (0.2) | 37 (0.4) |
| **EYE DISORDERS** | | | | |
| CONJUNCTIVAL HAEMORRHAGE | 33 (0.3) | 65 (0.5) | 14 (0.2) | 47 (0.6) |
| EYE HAEMORRHAGE | 45 (0.3) | 43 (0.3) | 29 (0.3) | 25 (0.3) |
| **GASTROINTESTINAL DISORDERS** | | | | |
| GI HAEMORRHAGE | 32 (0.2) | 68 (0.5) | 16 (0.2) | 39 (0.5) |
| GINGIVAL BLEEDING | 60 (0.5) | 131 (1.0) | 44 (0.5) | 101 (1.2) |
| HAEMATEMESIS | 21 (0.2) | 37 (0.3) | 13 (0.2) | 21 (0.2) |
| HAEMATOCHEZIA | 52 (0.4) | 49 (0.4) | 30 (0.4) | 27 (0.3) |
| HAEMORRHOIDAL HAEMORRHAGE | 79 (0.6) | 96 (0.7) | 62 (0.7) | 67 (0.8) |
| MELAENA | 68 (0.5) | 114 (0.9) | 39 (0.5) | 71 (0.8) |
| RECTAL HAEMORRHAGE | 132 (1.0) | 176 (1.3) | 83 (1.0) | 122 (1.4) |

| | | | | |
|---|---|---|---|---|
| **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** | | | | |
| CATHETER SITE HAEMORRHAGE | 37 (0.3) | 29 (0.2) | 28 (0.3) | 19 (0.2) |
| CATHETER SITE HAEMATOMA | 20 (0.2) | 20 (0.2) | 16 (0.2) | 13 (0.2) |
| **INJURY, POISONING AND PROCEDURAL COMPLICATIONS** | | | | |
| CONTUSION | 296 (2.2) | 386 (2.9) | 216 (2.6) | 293 (3.5) |
| LACERATION | 42 (0.3) | 40 (0.3) | 24 (0.3) | 31 (0.4) |
| OPERATIVE HAEMORRHAGE | 37 (0.3) | 33 (0.3) | 21 (0.2) | 12 (0.1) |
| POST PROCEDURAL HAEMORRHAGE | 42 (0.3) | 54 (0.4) | 25 (0.3) | 39 (0.5) |
| WOUND HAEMORRHAGE | 49 (0.4) | 85 (0.6) | 38 (0.5) | 58 (0.7) |
| **INVESTIGATIONS** | | | | |
| OCCULT BLOOD POSITIVE | 22 (0.2) | 27 (0.2) | 10 (0.1) | 14 (0.2) |
| **NERVOUS SYSTEM DISORDERS** | | | | |
| HAEMORRHAGE INTRACRANIAL | 32 (0.2) | 59 (0.4) | 17 (0.2) | 20 (0.2) |
| **RENAL AND URINARY DISORDERS** | | | | |
| HAEMATURIA | 265 (2.0) | 343 (2.6) | 172 (2.0) | 213 (2.5) |
| HAEMORRHAGE URINARY TRACT | 14 (0.1) | 25 (0.2) | 11 (0.1) | 18 (0.2) |
| **REPRODUCTIVE SYSTEM & BREAST DISORDERS** | | | | |
| MENORRHAGIA | 11 (0.1) | 23 (0.2) | 8 (0.1) | 18 (0.2) |
| **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** | | | | |
| EPISTAXIS | 412 (3.1) | 821 (6.2) | 306 (3.6) | 608 (7.2) |
| HAEMOPTYSIS | 47 (0.4) | 68 (0.5) | 24 (0.3) | 42 (0.5) |
| PHARYNGEAL HAEMORRHAGE | 12 (0.1) | 23 (0.2) | 10 (0.1) | 15 (0.2) |
| **SKIN & SUBCUT TISSUE DISORDERS** | | | | |
| ECCHYMOSIS | 43 (0.3) | 74 (0.6) | 30 (0.4) | 54 (0.6) |
| INCREASED TENDENCY TO BRUISE | 190 (1.4) | 311 (2.4) | 152 (1.8) | 237 (2.8) |
| SKIN HAEMORRHAGE | 83 (0.6) | 126 (1.0) | 51 (0.6) | 87 (1.0) |
| **VASCULAR DISORDERS** | | | | |
| HAEMATOMA | 177 (1.3) | 272 (2.1) | 125(1.5) | 194 (2.3) |
| HAEMORRHAGE | 48 (0.4) | 93 (0.7) | 28 (0.3) | 57 (0.7) |



TRA 2ºP-TIMI 50 *Proposed Label Population*

For the Proposed Label Population, the results were similar to the overall population:

• More subjects reported bleeding events in the vorapaxar group (24.4%) compared to the placebo group (18.1%) with annualized event rates of 14.2 and 9.3 events per 100 subject-years of exposure, respectively.

• The most frequently reported bleeding event was epistaxis, 6.2% for vorapaxar group compared to 3.6% for placebo with an annualized event rate of 3.4 and 1.7 events per 100 subject-years of exposure, respectively.

• For the other most frequently reported treatment-related bleeding events— contusion and haematuria—the differences between vorapaxar and placebo were smaller (0.6 to 0.7 percentage points respectively).

TRACER

• More subjects had bleeding events with vorapaxar (31.9%) than with placebo (24.1%) during the study. 95% of these events occurred during treatment, and about half during the index hospitalization. The majority of the events related to surgical procedures, such as catheter site haematoma, catheter site haemorrhage and post procedural haemorrhage occurred during index hospitalization.

• The most common bleeding events were epistaxis and haematuria during the study. Epistaxis was the most frequently reported treatment-related bleeding event during the study occurring in 5.1% of the vorapaxar group vs. 2.5% in the placebo group.

• For the remaining three; catheter site haemorrhage, contusion, and hematoma, the differences between vorapaxar and placebo were 0.4 to 0.7 %.

For the Chronic pool, the results were similar to the TRA 2ºP-TIMI 50 overall and Proposed Label populations:

***Interventions Associated With Bleeding Events***

Interventions to manage bleeding events were examined. An analysis was performed to assess what procedures were performed following the start of the subject's first CEC adjudicated GUSTO moderate or severe bleed event.

TRA 2ºP-TIMI 50

The results for the overall population TRA 2ºP-TIMI 50 as well as the Proposed Label Population are shown in Table S.18.

**Table S.18**. Summary Results for Subjects Who Had a Bleeding Event, that Began (per Investigator) On or After Randomization During the Study, And Received One or More Transfusions that Began Within 2 Days After Any Bleeding Event For Subjects with CEC-Adjudicated GUSTO Moderate/Severe Bleeding Events: Number (%) of Subjects Who Received the Indicated Transfusate for TRA 2ºP-TIMI 50 overall and Proposed Label Populations

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

| | | | | |
|---|---|---|---|---|
| Platelet Transfusion | 30 (9.5) | 44 (9.3) | 13 (8.3) | 24 (10.3) |
| Fresh-Frozen Plasma Transfusion | 35 (11.1) | 44 (9.3) | 13 (8.3) | 27 (11.6) |
| Cryoprecipitate Transfusion | 1 (0.3) | 7 (1.5) | 1 (0.6) | 6 (2.6) |
| Missing | 0 | 3 (0.6) | 0 | 1 (0.4) |

Note: Units are as entered in the eCRF, and do not imply a predefined standard volume. Number of units is total for two consecutivecalendar days, beginning with first day of transfusion(s). Subsequent transfusions, if any, begin a new 2-day transfusionrecord. Units represent the single largest 2-day total for the indicated transfusate. Note: Subject may have had more than one type of transfusion and can be counted in multiple rows. PRBC=Packed Red Blood Cells

In the *Overall* population, the most common procedures that occurred in close proximity of the first GUSTO severe/moderate event were endoscopies (126/260 subjects in the vorapaxar group and 87/189 subjects in the placebo group). There were 473 subjects on vorapaxar and 316 subjects on placebo who received one or more transfusions that began within two days after any bleeding event (see table above). Although bleeding was more common in the vorapaxar treatment group, the duration of bleeding was similar between treatment groups. The median (25th to 75th percentile) duration was 3.0 (1.0 – 5.0) for both treatment groups. The minimum-maximum duration was 1.0 – 233.0 in vorapaxar group and 1.0 – 230.0 in placebo group.

In *the Proposed Label Population*, there were 234 subjects on vorapaxar and 157 subjects on placebo who experienced a CEC-adjudicated GUSTO moderate or severe bleeding event with 128/234 vorapaxar subjects and 84/157 placebo subjects having a procedure to stop the bleeding. As in the analysis of the overall TRA 2ºP-TIMI 50 population, the most common therapeutic procedures were endoscopies (74/128 subjects in the vorapaxar group and 47/84 subjects in the placebo group). The median duration of the bleeding event was 3.0 (1.0-6.0) days in the vorapaxar group and 3.0(1.0-5.0) days in the placebo group. There were 233 subjects on vorapaxar and 157 subjects on placebo who received one or more transfusions that began within two days after any bleeding event (see table above).

In summary, more subjects on vorapaxar experienced a bleeding event with a greater frequency of GUSTO moderate and severe bleeding events. In the *Overall* population, there were 475 subjects on vorapaxar and 317 subjects on placebo who experienced a CEC-adjudicated GUSTO moderate or severe bleeding event with 260/475 vorapaxar subjects and 189/317 placebo subjects having a procedure to stop the bleeding. Using GUSTO moderate/severe as the threshold, the most frequent bleeding site was gastrointestinal. Although of greater frequency, there was a relatively similar need for intervention mostly endoscopic procedures with 132/260 (51%) vorapaxar treated subjects vs. 92/189 (50%) placebo treated subjects during the first GUSTO moderate/severe bleeding event. It should be noted that the study did not pre-specify assessment of these measures and thus they should be considered estimates; nevertheless, the short time to resolution and similar hospitalization periods suggest that conventional supportive measures are effective in controlling bleeding events associated with vorapaxar.

**OCULAR SAFETY**

Because of early preclinical findings with respect to the retina (see Non-Clinical reports), the Sponsor, in dialogue with regulatory agencies, carried out a program evaluating vorapaxar ocular safety in parallel with the vorapaxar clinical development program. The pre-clinical findings concerned a low incidence of vacuoles in the inner nuclear layer of the retina of the eye bilaterally in rats which was noted when they were administered ≥10 mg/kg of vorapaxar. To address the potential safety concerns raised by the preclinical ocular findings, the Sponsor conducted two clinical studies examining potential ocular effects of vorapaxar. One study **P05185** was a Phase 1 study in healthy volunteers as well as a few subjects with atherosclerosis. The second study **P05183** was conducted as a substudy of the TRA 2ºP-TIMI 50 trial.

**P05185** was a multicenter, randomized, double-blind, placebo-controlled, parallel group Phase 1 study to determine the ocular safety of vorapaxar when administered orally for a minimum of 1 month and a maximum of 3 months, with respect to any changes occurring in the retina, both anatomic and functional, in healthy volunteers (118, 86%) and in subjects with documented atherosclerotic disease (19, 14%). A loading dose of vorapaxar 40 mg or matching placebo was administered at the time of randomisation followed by daily maintenance dosing with 2.5 mg or matching placebo. Subjects received 1, 2, or 3 months maintenance dose, as follows: Group 1 = 1 month; Group 2 = 2 months; Group 3 = 3 months. Clinic visits for safety evaluations were scheduled monthly during the treatment phase and at 1 month and 2 months after the end of treatment. Spectral domain optical coherence tomography (SD-OCT), best corrected visual acuity following standardized refraction, and fundus photography were performed at screening, at each monthly treatment visit, and at each monthly follow-up visit. The primary endpoint was the incidence of vacuolation in the inner nuclear layer (INL) of the retina through treatment and follow-up defined as the presence of more than one vacuole (defined as a clear, round structure in the INL of the retina of at least 30 µm in diameter) compared to baseline. SD-OCT was used to detect vacuoles.

Only one subject, (1% of the vorapaxar treated population), developed vacuolation, which was observed at end of treatment and end of study. The patient was a 25-year-old healthy black man with pre-study quadranopsia (visual field loss in one quarter of the visual field of the eye) and a 1-year history of intermittent visual floaters, who received 3 months of treatment with vorapaxar. With regard to secondary parameters, numerically, slightly more vorapaxar-treated than placebo subjects experienced a decrease in visual acuity score of at least 7 letters from baseline. In a post-hoc analysis for vorapaxar-treated subjects, a change of more than 15 letters at the end of treatment was noted for 3 subjects (2 subjects with positive change, 1 subject with negative change); no placebo-treated subject met this criterion. At the end of the follow-up period, 5 vorapaxar-treated subjects showed a change in visual acuity score of more than 15 letters (4 subjects showing positive change, 1 subject showing negative change). No placebo-treated subject had a visual acuity score change of more than 15 letters during this time. It was concluded that the numerical differences observed for either an increase or decrease in visual acuity using a change from baseline of either seven or 15 letters support that vorapaxar did not have an effect on visual acuity.

Center point thickness measured by SD-OCT was analysed for a change from baseline of greater than 15 µm in either the left or right eye. Although the number of subjects was very small, there was numerically a slightly greater proportion of vorapaxar-treated subjects who met the defined endpoint at end of treatment; however, this difference disappeared by the end of study.

Overall, it was concluded that vorapaxar did not show any ocular safety signal as compared to placebo with respect to any of the ocular safety parameters assessed in this study. The study was designed to rule out a difference in safety signal of 18% or more between vorapaxar and control assuming a 0% event rate in the control. Comparisons of the aforementioned ocular safety parameters did not reach statistical significance in this study.

**P05183** was a multicenter, randomized, double-blind, placebo-controlled in subjects with established atherosclerotic disease who were enrolled in TRA 2ºP-TIMI 50. Eligible subjects should not have any of the following: age-related macular degeneration; History of diabetic macular oedema, or evidence of treated diabetic retinopathy; other retinal diseases, including retinal injury; retinal surgery, including laser photocoagulation; glaucoma; high intraocular pressure of >22 mm Hg; evidence of center foveal thickness of >190 µm or presence of vacuoles in the retina on baseline OCT examination. Eligible patients were randomized to treatment through TRA 2ºP-TIMI 50 and received treatment from the investigator participating in TRA 2ºP-TIMI 50. Subjects received daily maintenance dosing with 2.5 mg vorapaxar or matching placebo. Ocular safety was assessed for 1 year, with ophthalmology clinic visits scheduled at 4, 8, and 12 months of treatment. Masked ocular

data were reviewed by a Safety Review Committee (SRC) throughout the subject's participation in the trial.

A total of 258 subjects were referred to ophthalmology sites, 65 of whom did not participate in P05183 beyond the screening visit and were not included in the analysis of ocular safety. Of the 193 subjects included in the ocular safety analysis, 140 (73%) were men and 53 (27%) were women. Median age was 56.0 years, ranging from 22 to 82 years. The majority of subjects, 150 (78%), were <65 years. Subjects were distributed between the treatment groups as follows: Placebo: 95 subjects; vorapaxar: 98 subjects.

The primary endpoint was the incidence of vacuolation in the inner nuclear layer (INL) of the retina through treatment and follow-up. Vacuolation, as defined in the protocol, was the presence of more than one vacuole (defined as a clear, round structure in the INL of the retina of at least 30 µm in diameter) compared to baseline. Optical coherence tomography (OCT) was used to detect vacuoles.

Two subjects, 2% of the vorapaxar-treated population, developed vacuolation:

• Subject 11/060025 at the 4-month visit; no vacuoles in the INL were observed at the 8- and 12-month visits; the subject was on study treatment for all 3 visits

• Subject 35/060018 at the 8-month visit, which occurred 5 months after the subject prematurely discontinued treatment; no vacuoles in the INL were observed at the 4-month visit when the subject was on treatment; the subject did not have a 12-month visit.

With regard to secondary endpoints of the study, the number of subjects experiencing a decrease in visual acuity score of at least seven letters from baseline was similar in the placebo and vorapaxar groups. Center point thickness measured by OCT was analyzed for a change from baseline of greater than 15 µm in either the left or right eye. At 4 and 8 months, the number of subjects with a change of greater than 15 µm was similar in the placebo and vorapaxar groups. At 12 months and the P05183 end of study, numerically fewer subjects in the vorapaxar group met the defined endpoint compared with the placebo group. There were no clinically relevant differences in the mean change of graded abnormalities as measured by OCT during the study. Overall, the individual scores were low, ranging from 0 to 17. There were no clinically relevant differences in the mean change of graded abnormalities as measured by fundus photography during the study. Overall, the individual scores were low, ranging from 0 to 25.

It was concluded that the effect of vorapaxar on the ocular safety parameters assessed in this study was similar to that of placebo. In addition, there were no clinically relevant ocular findings in these patients with established atherosclerotic disease.

**Ocular Adverse Events**

In the TRA 2°P-TIMI 50 overall population there were no apparent differences between vorapaxar and placebo in the frequency or types of retinal disorders reported. Retinal disorder AEs were reported in 1.5% of subjects in each treatment group. The most frequently reported AEs were vision blurred, visual acuity reduced, and visual impairment (0.4%, 0.2% and 0.2% for vorapaxar, and 0.3%, 0.2% and 0.2% each for placebo, respectively). All other individual retinal AEs were reported in 0.1% or less of subjects in either treatment group.

In TRACER there were no apparent differences between vorapaxar and placebo in the frequency or types of retinal disorders reported. Retinal AEs were reported in 1% of subjects in each treatment group. The most common AEs were vision blurred and visual impairment (0.4% and 0.2% for vorapaxar, and 0.3% each for placebo, respectively). All other individual retinal AEs were reported in 0.1% or less of subjects in either treatment group.

For the overall pool (TRA 2ºP-TIMI 50 and TRACER as-treated populations), there were no apparent differences between vorapaxar and placebo in the frequency or types of retinal disorders reported. Retinal AEs were reported in 1.3% of subjects in each treatment group. The most frequently reported retinal AEs were vision blurred, visual acuity reduced, and visual impairment (0.3%, 0.2% and 0.2% for vorapaxar, and 0.4%, 0.1% and 0.2% each for placebo, respectively). All other individual retinal AEs were reported in 0.1% or less in either treatment group.

Overall, the results of the ocular safety studies, due to the very small number of events and the insignificant differences between groups, are difficult to interpret. Similarly the low incidence of the relevant AEs reported in the clinical trials does not allow drawing conclusions. Clearly, these are rare events and the possible ocular effects of vorapaxar cannot be established at this stage. Although the findings so far do not raise any major concerns this is an issue that will need to remain under monitoring.

**HEPATIC SAFETY**

The Sponsor monitored hepatic safety throughout the vorapaxar development program using routine serum testing and adverse event reporting. The following postbaseline laboratory results were considered as potential event of drug-induced liver injury (DILI): -ALT and/or AST activity ≥3xULN and total bilirubin concentration ≥2xULN and alkaline phosphatase concentration <2xULN.

TRA 2ºP-TIMI 50

In the TRA 2ºP-TIMI 50 overall population and Proposed Label Population, the numbers of subjects and percentages of potential DILI were generally small for each category. In the TRA 2ºP-TIMI 50 overall population, in the vorapaxar treatment group, there were 14 subjects who met all relevant criteria compared to 11 on placebo, and 26 subjects who met the criteria ALT and/or AST ≥3xULN, total bilirubin ≥2xULN (same as placebo). There were no Hy's Law case. For the Proposed Label Population, in the vorapaxar treatment group, there were 8 subjects who met all criteria compared to 9 in placebo, and 17 subjects who met the criteria ALT and/or AST ≥3xULN, total bilirubin ≥2xULN (same as placebo).

TRACER

The numbers of subjects and percentages of potential DILI were generally small for each category. There were 9 vorapaxar and 10 placebo subjects who met all criteria, and 18 vorapaxar and 23 placebo subjects who met the criteria ALT and/or AST ≥3xULN, total bilirubin ≥2xULN. Compared with the large numbers of subjects randomized into both groups, the finding did not lead to detection of any potential DILI in the overall population.

**PLATELET SAFETY**

Although there was no pre-clinical effect of vorapaxar on platelet number, throughout the development program, the Sponsor monitored platelet levels. Platelet counts of <50,000/$mm^3$ were to be reported as a serious adverse event.

In the TRA 2ºP-TIMI 50 overall population, 30(0.2%) of the 13,186 subjects on vorapaxar, and 27(0.2%) of the 13,166 subjects on placebo had a platelet count of <50 ($10^9$/L). In the vorapaxar group, 248 (1.9%) and in placebo 260 (2.0%) had decrease of ≥50% in platelet count. Similar percentages were seen in the Proposed Label Population.

In TRACER, 28 (0.4%) patients on vorapaxar had a platelet value of <50 ($10^9$/L) and 33 (0.5%) on placebo had a platelet value of <50 ($10^9$/L). In the vorapaxar treatment group 206 (3.2%) and in the placebo group 247 (3.9%) had decrease of ≥ 50% in platelet count.

**OVERDOSE**

Across the TRACER study and TRA 2ºP-TIMI 50 study, 39 adverse events of vorapaxar overdose were reported (29 subjects in TRA 2ºP-TIMI 50 and 10 in TRACER). Thirty-five cases of overdose were not associated with an adverse event while in 5 an event was reported. Of the five reports of overdose with events, four were associated with intake of 5 mg of vorapaxar per day for ≥ 28 consecutive days and one involved intake of a single dose greater than 120 mg:

Subject 0112/003672 developed diarrhoea which resolved after study drug was interrupted. There were no reports of diarrhoea after treatment with study drug restarted.

Subject 3525/050009 reported increased creatinine and worsening of renal insufficiency. Study drug was eventually discontinued. Both adverse events resolved. The investigator believed that the overdose possibly affected the subject's high creatinine/worsening kidney function.

- Subject 3661/020522 experienced mild bleeding from a pre-existing vascular angioma of the lip which required cauterization. Therapy was not interrupted. The subject recovered.
- Subject 1714/050207 experienced skin bleeding (multiple skin hematomas), headache, fatigue and dyssomnia. Laboratory results showed a low platelet count. Study drug was discontinued. The subject's condition improved.
- Subject 2410/000209 (suicide attempt) experienced spontaneous ecchymosis of the right arm one day after an intentional overdose. Study drug was interrupted. The bleeding resolved and did not recur when study drug therapy resumed.

There were 2 other cases with vorapaxar overdose involving family members or acquaintances of participants in the vorapaxar clinical trial TRA 2ºP-TIMI 50 without sequelae.

In conclusion, there were 39 patients and 2 relatives/acquaintances of study subjects who were reported with vorapaxar overdose. Most cases involved subjects who inadvertently took two tablets per day instead of one. Five of these subjects had associated adverse events including three with bleeding events. All subjects recovered. There were no reports of overdose in the Phase 1 and 2 studies.

Although the limited data from the overdose cases with no reported major events are somewhat reassuring the lack of an antidote and the long half life of vorapaxar are of concern. This should be taken into account in the benefit:risk evaluation.

### Laboratory findings

***Haematology and Coagulation***

TRA 2ºP-TIMI 50

For the TRA 2ºP-TIMI 50 *Overall* population the highest percentages of subjects in both treatment groups who had values above the upper limit of normal were those with significant bleeding within 2 weeks of sample collection for haemoglobin and haematocrit. The largest absolute difference observed between the treatments was for haematocrit within 2 weeks of bleeding (2.3%). The percentages for the *Proposed Label Population* were generally slightly lower for both treatment groups in comparison to the overall population. In general, similar patterns in the differences between treatment groups were observed for both populations. There were no important differences between the treatment groups for any of the platelet or white blood cell categories. Similar results were observed for post baseline platelet values and total and differential white blood cell counts in subjects with no history of stroke or TIA and CAD. For PT and INR, there were no clear and meaningful differences between the treatment groups in the percentage of subjects meeting the specified criteria for any of the coagulation parameters.

TRACER

For TRACER, more subjects on vorapaxar than on placebo met the specified parameters for the coagulation assays, regardless of bleeding events. However, none of the differences between the treatment groups was greater than 2 percentage points for the postbaseline values. The percentages

were generally well balanced between the two treatment groups. Only postbaseline lymphocyte values less than 1.0 X $10^9$/L showed a 1.0 percentage point difference between treatment groups (22.5% for vorapaxar and 21.1% for placebo). More subjects on vorapaxar (907, 18.1%) than placebo (832, 16.7%) showed PT greater than 12 seconds. The overall percentages in other categories were similar between the two groups, with difference of percentages not greater than 0.5%.

Phase 3 Overall Pool

For the overall pooled population, higher percentages of subjects on vorapaxar than those on placebo met the specified parameters. Percentage point differences of approximately 2% among the vorapaxar group over placebo were observed for haemoglobin (g/L) and haematocrit (%) in subjects with significant bleeding within 2 weeks before sample collection. For the postbaseline values of platelets and the total and differential white blood cell counts, the overall percentages in the values of platelets counts between treatment groups were very similar and did not reveal a decrease in platelet counts for vorapaxar. For the total and differential white blood cell counts, the percentages between treatment groups were also very similar except for the lymphocyte values less than 1.0x$10^9$/L which revealed a 1.0% difference between the groups (15.8% vorapaxar and 14.8% placebo). For PT and INR, there were no meaningful differences between treatment groups in the percentage of subjects meeting the specified upper limit criteria for any of the coagulation parameters in the combined (central and local) laboratory data or in the central and local laboratory data alone.

***Hepatic Tests***

TRA 2ºP-TIMI 50

The distribution of subjects with postbaseline values above each specified upper limit, defined as ≥ 3 times the upper limit of normal, was similar between the two treatment groups. The largest difference was a 0.7% difference between treatments observed in GGT≥3xULN (902, 6.9% vorapaxar vs. 807, 6.2% placebo). There were no meaningful differences between the treatment groups for the observed values. Similar results were observed in the Proposed Label Population.

TRACER

In TRACER, the distribution of subjects with postbaseline values above each specified upper limit was similar between the two groups. A greater than 0.3 percentage point difference between placebo and vorapaxar was observed only in GGT≥3xULN. About 77% (4561/5913) in the vorapaxar group and 76% (4443/5861) subjects in the placebo group showed normal AST values at baseline, compared with greater than 90% of the subjects with normal baseline values of ALT, AST and/or ALT, and alkaline phosphatase in both treatment groups. The postbaseline hepatic function of this subset of subjects did not reveal any apparent difference between the two populations.

Phase 3 Overall Pool

The overall percentages of subjects for most of the categories were very similar between placebo and vorapaxar and reveal no meaningful differences between the treatment groups. A similar pattern was observed for post-baseline hepatic function tests in subjects with normal values at baseline.

***Renal/Urine Tests***

TRA 2ºP-TIMI 50

The data did not indicate any increase in percentages of subjects exceeding the prespecified limit for either BUN or creatinine in the vorapaxar group compared to the placebo group. As expected, increases in BUN and creatinine were more prevelant for both treatment groups in subjects with low CrCl or low eGFR at baseline. Similar results were observed in post-baseline values of renal function tests in the Proposed Label Population. Urine analysis, showed no significant differences

between groups generally but the rates of red blood cells per high power field were higher for vorapaxar than placebo.

TRACER

In TRACER, the observed values were similar between the treatment groups. The greatest difference was observed in the following two subsets: • BUN >14.28 mmol/L (> 40 mg/dL)/ Baseline CrCl <60 mL/min (118/595 (19.8%) for vorapaxar and 114/623 (18.3%) for placebo) • BUN >14.28 mmol/L (>40 mg/dL)/ Baseline eGFR <60 mL/min/1.73m$^2$ (150/672 (22.3% ) for vorapaxar and 134 / 651 (20.6%) for placebo). In urine analysis the percentages of abnormal values were balanced between the two treatment groups with only the RBC (number/HPF) and blood (by dipstick) subsets showing greater than 1% differences between the groups.

***Electrolytes, Lipids, and Other Blood Chemistry Variables***

There were no meaningful differences between treatment groups for the postbaseline electrolyte, lipid and other blood chemistry values for the overall and Proposed Label Population of TRA 2ºP-TIMI 50. In TRACER, the following subsets showed greater than 1% differences between the groups: • More subjects on vorapaxar (665, 12.4%) than placebo (573, 10.7%) had a calcium level less than 2.125 mmol (8.5 mg/dL) after baseline, a difference of 1.7 percentage points. More subjects on vorapaxar (849, 55.0%) than placebo (820, 53.6%) had a glucose level greater than 8.8 mmol (>160 mg/dL) after baseline, a difference of 1.4 percentage points. In the Phase 3 Overall Pool there were no meaningful differences between treatment groups for the postbaseline electrolyte, lipid and other blood chemistry values.

***Vital Signs, Physical Findings and Electrocardiograms***

The analyses for systolic and diastolic blood pressure, heart rate and ECG recordings revealed no consistent differences of clinical relevance between treatment groups in TRA 2ºP-TIMI 50 or TRACER.

## Safety in special populations

### Demographics and concomitant diseases

***Age***

In TRA 2ºP-TIMI 50 more than 25% patients were older than 65 years and those 75yrs or older were approximately 11%. The Proposed Label Population included younger patients but still more than 20% and 7% were older than 65yrs and 75yrs respectively; yet because of the large size of the study the numbers are sufficient to assess vorapaxar safety, at least for the most common events, in these older groups.

In TRA 2°P-TIMI 50, approximately 75% of subjects <65 years of age (both vorapaxar and placebo) reported adverse events and in subjects ≥65 years of age, 77.4% on vorapaxar compared to 78.3% on placebo reported adverse events. In TRACER, approximately 73% of subjects <65 years of age on vorapaxar compared to 70% on placebo reported adverse events and 76.3% of subjects ≥65 years of age on vorapaxar compared to 74.6% on placebo reported adverse events. Thus, the number of subjects reporting adverse events was similar, regardless of age or treatment with vorapaxar.

The relative risk of bleeding (vorapaxar compared with placebo) was similar across age groups as well, although bleeding in the placebo group increased with age. For the Proposed Label Population, the placebo KM 3-year rate for GUSTO severe/moderate bleed, for subjects <65 years of age was 1.5% compared to 4.0% for ≥65 years of age and 2.0% for <75 years of age compared to 4.9% ≥ 75 years of age.

PK data suggested that there is a small increase in vorapaxar exposure in older patients. The Applicant supports that since the risk of non-bleeding related and bleeding related AEs was not affected by age, the exposure increase in older patients is not considered to be clinically important. Therefore, no special labelling guidance with respect to dosage and administration is needed for age.

Overall, the available data indicate a higher risk of GUSTO severe-moderate bleeding in older patients; however, the hazard ratios for vorapaxar were similar across age groups, suggesting that vorapaxar may not increase further the risk in older patients. The TIMI major or minor bleedings analyses revealed similar findings. The extract from subgroup analyses for age below shows GUSTO severe/moderate bleeding in TRA 2ºP-TIMI 50 Proposed Label Population.

| | Placebo n=8412 | | | Vorapaxar n=8444 | | | |
|---|---|---|---|---|---|---|---|
| **Subgroup** | **Subjects with Events m/n (%)** | **Event Rate[a]** | **KM[b]** | **Subjects with Events m/n (%)** | **Event Rate[a]** | **KM[b]** | **Hazard Ratio [c,d] (95% CI)** |
| **Age** | | | | | | | |
| <65 yrs | 79/6033 (1.3%) | 0.5% | 1.5% | 120/5952 (2.0%) | 0.8% | 2.3% | 1.54 (1.16 - 2.05) |
| >= 65 yrs | 77/2379 (3.2%) | 1.3% | 4.0% | 111/2492 (4.5%) | 1.8% | 5.2% | 1.39 (1.04 - 1.85) |
| <75 yrs | 132/7809 (1.7%) | 0.7% | 2.0% | 192/7811 (2.5%) | 1.0% | 2.8% | 1.46 (1.17 - 1.82) |
| >= 75 yrs | 24/603 (4.0%) | 1.7% | 4.9% | 39/633 (6.2%) | 2.6% | 7.0% | 1.57 (0.94 - 2.61) |

Other bleeding events were also more common in older patients but again the relative risk with vorapaxar appeared similar between age groups.

With regard to 'Other non-bleeding events' older subjects (≥ 65 years), and especially those ≥ 75 years generally reported more AEs in both treatment groups. A few events such as, chest pain, fatigue and non-cardiac chest pain, were more frequent among the younger age groups.

In general, as expected, older patients especially those ≥75yrs are at much higher risk of bleeding, although the impact of vorapaxar treatment may not be greater than in their younger counterparts. The SmPC includes a warning that older age is a risk factor for bleeding but there are no other warnings or recommendations for dose adjustments (this issue is also discussed in the *Pharmacokinetics* section above). As with other specific subgroups of patients likely at increased risk, further advice should be included in the SmPC that vorapaxar use in the elderly should follow careful assessment of the individual potential benefits and bleeding risks as well as need for co medications.

***Gender***

In TRA 2ºP-TIMI 50, during the study, females assigned to placebo reported about 5% more AEs than males (75.5% males vs. 79.1% females). Treatment with vorapaxar did not adversely impact gender related AE reporting (74.7% males vs. 79.1% females) compared to placebo (75.5% males and 79.1% females). A 3% difference on vorapaxar was seen in TRACER where 73.5% males vs. 76.8% females on vorapaxar reported adverse events compared to 70.9% males and 75.6% females on placebo. Thus, overall there were slightly more females than males reporting adverse events, but there was minimal effect of vorapaxar on adverse event reporting in general. The relative risk of bleeding events (vorapaxar compared with placebo) was similar for gender as well.

Population PK analysis predicted that females have a 32% higher exposure of vorapaxar than males, although this finding was not initially observed in the Phase I data. Since the risk of non-bleeding related and bleeding related adverse events was not affected by gender, the increase in vorapaxar exposure in women is not considered to be clinically important. Therefore, the Applicant suggests that no special advice with respect to posology is needed. As with older age, for females there was no clear evidence of a less favourable benefit:risk compared to men.

***Race/Ethnicity***

In the TRA 2ºP-TIMI 50 study, 75.3% of white subjects on vorapaxar and 78.5% non-white subjects reported AEs during the study compared to those on placebo (76.3% and 76.1%, respectively). In TRACER, 74.1% of white subjects on vorapaxar and 76% non-white subjects reported AEs during

the study compared to those on placebo (71.9% and 74.4%, respectively). While subjects self-identifying as Asian appear to have a slightly increased hazard for GUSTO moderate to severe bleeding, subjects treated in the Asia/Pacific geographical area do not have an increased risk of bleeding events. Thus, there is no consistent signal suggesting a higher bleeding risk among Asian subjects in the vorapaxar Phase 3 program. No relevant dosing recommendations are considered necessary.

***Weight***

Patients weighing < 60 kg may be at increased risk for severe bleeding events when treated with anti-platelet agents like prasugrel. PK data suggest there is a statistically significant inverse relationship between weight/BMI and vorapaxar AUC/Cmax. Post-hoc subgroup analyses were performed to examine the pharmacokinetics of vorapaxar in subjects weighing <60 kg and the risk of bleeding events in this cohort. In TRACER, lower body weight was associated with an increase in bleeding.

In TRA 2ºP-TIMI 50, based on a safety subgroup analysis of the as-treated population, a higher rate of ICH was observed in subjects weighing < 60 kg that were treated with vorapaxar compared to subjects weighing ≥ 60 kg. Most of the affected subjects had a history of stroke or TIA and hence limiting the Proposed Label Population to individuals with no history of stroke or TIA can mitigate the risk of ICH. Nevertheless, as an additional safeguard for patients, given the increased risk of ICH in the as treated population, the Applicant proposes that vorapaxar at a daily dose of 2.5 mg in the Proposed Label Population should be used with caution in patients with a body weight <60 kg.

Overall, the data suggest that the risk of GUSTO severe/moderate bleeding is generally higher in patients with lower weight and slightly more in the vorapaxar groups. The extract from subgroup analyses for weight and BMI below shows GUSTO severe/moderate bleeding in TRA 2ºP-TIMI 50 Proposed Label Population.

| Subgroup | Placebo (n =8412 ) | | Vorapaxar (n =8444 ) | | Hazard Ratio[a,b] (95% Confidence Interval) |
|---|---|---|---|---|---|
| | Subjects With Events (%) | KM%[c] | Subjects With Events (%) | KM%[c] | |
| Body Weight (kg) | | | | | |
| <median (81 kg) | 81/3721 ( 2.2%) | 2.7% | 120/3824 ( 3.1%) | 3.7% | 1.46 (1.10 - 1.93) |
| ≥median (81 kg) | 75/4679 ( 1.6%) | 1.8% | 111/4610 ( 2.4%) | 2.7% | 1.50 (1.12 - 2.01) |
| < 60 kg | 11/426 ( 2.6%) | 3.0% | 19/431 ( 4.4%) | 5.2% | 1.78 (0.85 - 3.74) |
| > 60 kg | 145/7974 ( 1.8%) | 2.1% | 212/8003 ( 2.6%) | 3.0% | 1.46 (1.18 - 1.80) |
| Body Mass Index | | | | | |
| <30 kg/m$^2$ | 114/5582 ( 2.0%) | 2.4% | 163/5795 ( 2.8%) | 3.2% | 1.38 (1.09 - 1.75) |
| ≥30 kg/m$^2$ | 41/2813 ( 1.5%) | 1.7% | 68/2632 ( 2.6%) | 3.1% | 1.77 (1.20 - 2.61) |

An additional analysis (see table below) of the key secondary events (CV death, MI, and stroke) against GUSTO severe bleeding did not show any benefit with vorapaxar in patients <60kgr compared to placebo; instead it confirmed an increase in the risk of severe bleeding.

Subgroup Analysis for Key Secondary Efficacy Endpoint (CV Death, MI, and Stroke) and GUSTO Severe Proposed Label Population: ITT Event Accrual Period: Randomization to Last Visit

| | Placebo | | Vorapaxar | | |
|---|---|---|---|---|---|
| Subgroup | Subjects with Events m/n (%) | KM % [1] | Subjects with Events m/n (%) | KM % [1] | Hazard Ratio [2] [3] (95% CI) |
| **Body Weight** | | | | | |
| **< 60 kg** | | | | | |
| Key Secondary | 29/429 (6.8%) | 7.9% | 31/432 (7.2%) | 8.9 % | 1.06 (0.64 - 1.76) |
| GUSTO Severe | 4/426 (0.9%) | 1.5% | 7/431 (1.6%) | 1.7 % | 1.76 (0.51 - 6.01) |
| **>= 60 kg** | | | | | |
| Key Secondary | 642/7996 (8.0%) | 9.1% | 500/8016 (6.2%) | 7.3 % | 0.77 (0.68 - 0.86) |
| GUSTO Severe | 69/7974 (0.9%) | 1.0% | 78/8003 (1.0%) | 1.1 % | 1.13 (0.81 - 1.56) |

*[2]: Hazard Ratio is vorapaxar group versus placebo group*

*[3]: Hazard Ratio is calculated based on Cox PH model with covariates treatment and stratification factors (planned thienopyridine use), with the exception for those subgroup variables related to the stratification factors. For subgroup variable of stratification factor, qualifying atherosclerotic disease (or planned thienopyridine use), hazard ratio is calculated from Cox PH model with covariate treatment and the other stratification factor, planned thienopyridine use (or qualifying atherosclerotic disease).*

Overall, for patients weighting less than 60kg the data suggest an increased risk of bleeding without clear evidence of benefit, indicating a questionable benefit:risk. However, it is accepted that the numbers are very small and patients with low body weight is a heterogeneous group that also includes women for whom the overall effect of vorapaxar was positive. It can be argued that drawing conclusions from such small numbers is problematic but considering the seriousness of the complications a cautious approach is warranted. The SmPC advises that vorapaxar should only be prescribed after very careful assessment of individual potential risks and benefits.

***Multiple risk factors***

Following a request, the Applicant examined the potential additive effect of multiple factors, for example advanced age, or female gender with low body weight that may increase the risk of bleeding. The analyses of patients with more than one risk factor did not reveal any noteworthy findings over and above the examination of the individual parameters. Certainly, the limitations due to the low numbers of patients and events are even more prominent here.

***Hepatic failure***

The Applicant refers to the PK data which are discussed in the *Clinical Pharmacology* section. They indicate that exposure to vorapaxar and M20 metabolite was shown to be lower in subjects with severe hepatic impairment compared to matched healthy subjects; however considering the inherently higher risk of bleeding in these patients SmPC advises that the risks should be considered before starting vorapaxar in these patients.

Indeed, patients with "known active hepatobiliary disease, or known unexplained persistent increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) activity to two times or more the upper limit of the reference range (upper limit of "normal" [≥2xULN])" were excluded from the Phase 3 trials. Therefore, the safety of vorapaxar in these patients is uncertain. Considering, as also pointed out by the Applicant, the likely increased risk of bleeding in this group, until further data become available, the use of vorapaxar in such patients should be contraindicated

***Renal failure***

Subgroup analyses of subjects with renal insufficiency (CrCl <60 ml/min or eGFR < 60 ml/min/1.73 $m^2$) showed no increased risk with vorapaxar for bleeding events compared to CrCl ≥60 ml/min or eGFR ≥ 60 ml/min/1.73$m^2$. Based on the available PK and these safety data the Applicant concluded that there is no need for specific label guidance for patients with any degree of renal failure. The effects of renal insufficiency on vorapaxar pharmacokinetics are discussed in the *Clinical Pharmacology* section above.

Overall in TRA 2ºP-TIMI 50 patients with impaired renal function i.e. (CrCl <60 ml/min or eGFR < 60 ml/min/1.73 $m^2$) were generally almost twice as likely to experience a GUSTO severe/moderate bleeding event compared to their normal/mildly impaired counterparts. However, the hazard ratios across groups were similar suggesting, as the Applicant support, that vorapaxar treatment might not be more likely to cause bleeding in the former group. The extract from subgroup analyses for renal impairment below shows GUSTO severe/moderate bleeding in TRA 2ºP-TIMI 50 Proposed Label Population.

| Subgroup | Placebo (n =8412 ) | | Vorapaxar (n =8444 ) | | Hazard Ratio[a,b] (95% Confidence Interval) |
|---|---|---|---|---|---|
| | Subjects With Events (%) | KM%[c] | Subjects With Events (%) | KM%[c] | |
| Renal Function[d] | | | | | |
| CrCl <60 Ml/min | 30/713 ( 4.2%) | 5.2% | 53/797 ( 6.6%) | 7.5% | 1.59 (1.01 - 2.48) |
| CrCl ≥60 Ml/min | 124/7590 ( 1.6%) | 1.9% | 176/7541 ( 2.3%) | 2.7% | 1.43 (1.14 - 1.80) |
| eGFR[e] <60 Ml/min•1.73$m^2$ | 33/922 ( 3.6%) | 4.8% | 59/1046 ( 5.6%) | 6.2% | 1.54 (1.01 - 2.36) |
| eGFR ≥60 Ml/min•1.73$m^2$ | 121/7393 ( 1.6%) | 1.8% | 170/7302 ( 2.3%) | 2.7% | 1.43 (1.13 - 1.81) |

However, there were very few patients with severe renal disease (placebo n=49, vorapaxar n=56) in the TRA 2ºP-TIMI 50 Proposed Label Population, and the very low number of events does not allow any meaningful assessment of the potential risks in this potentially more vulnerable group. This limitation should be adequately reflected in the SmPC that needs to advice use with caution in such patients.

***Diabetes Mellitus***

The bleeding rates (GUSTO Severe or Moderate) for patients with or without diabetes in the phase 3 trials are shown in Table S.19.

**Table S.19**. Annualized Event Rates for GUSTO Severe or Moderate Bleeding by Subgroups: As-treated Population Event Accrual Period: Randomization to Last Visit

| | TRA 2ºP- TIMI 50 | | | | TRACER | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo n=13166 | | Vorapaxar n=13186 | | Placebo n=6441 | | Vorapaxar n=6446 | |
| | Subjects with Events m/n (%) | Event Rate[a] | Subjects with Events m/n (%) | Event Rate[a] | Subjects with Events m/n (%) | Event Rate[a] | Subjects with Events m/n (%) | Event Rate[a] |
| History of diabetes mellitus | | | | | | | | |
| Yes | 102/3343 (3.1%) | 1.3% | 151/3352 (4.5%) | 1.9% | 121/2020 (6.0%) | 4.8% | 170/2034 (8.4%) | 6.8% |
| No | 211/9823 (2.1%) | 0.9% | 320/9833 (3.3%) | 1.3% | 211/4421 (4.8%) | 3.6% | 279/4411 (6.3%) | 4.9% |

In the Proposed Label Population for GUSTO severe/moderate bleeding the HR in diabetics was 1.47 (95% CI 0.99 - 2.18) while the HR was 1.49 (95% CI 1.17 - 1.89) in non-diabetics. For clinically significant bleed events, the HR was 1.44 (95% CI 1.19 - 1.74) for diabetics and 1.47 (95% CI 1.33 - 1.63) for non-diabetics. For ICH, the HR was 1.21 (95% CI 0.52 - 2.79) and 1.29 (95% CI 0.72 - 2.31) respectively.

***Pregnancy and Lactation***

Women who were breast-feeding, pregnant, or who intended to become pregnant were excluded from the clinical studies. There were no pregnancies in TRACER or phase 2 studies. In TRA 2ºP-TIMI 50 trial there were three unwanted pregnancies that led to abortion. In one case the study drug was interrupted and there was a mild bleeding event considered unlikely related to study drug. In the other two cases the study drug was discontinued. There were also two cases in Phase 1 studies, one was a spontaneous abortion and the other case concerned a positive pregnancy test after completing rosiglitazone dosing in Period 1 of study P05361.

***Coronary Artery Bypass Grafting (CABG)***

In both TRA 2ºP-TIMI 50 and TRACER trials, patients underwent CABG, as deemed appropriate by the investigators and the treating physicians. The information available at the time (including specific CABG experience in TRA-PCI Phase II study) supported the continuation of vorapaxar during surgical procedures such as CABG. As a result, during the conduct of the study, discontinuation of study drug treatment for CABG was not recommended. However, at the discretion of the investigators and the treating physicians or surgeons, study drug treatment could be temporarily interrupted. Modifications in the therapy with other common concomitant medications, such as aspirin or thienopyridine, were as per local standard of care.

To better evaluate CABG-related bleeding, TIMI major CABG-related bleeding, a CABG-specific bleeding endpoint was pre-defined and adjudicated, in accordance with the CEC charter as follows: Any haemorrhage that meets any of the following criteria:

a. Fatal bleeding (i.e., bleeding that directly results in death), or

b. Peri-operative intracranial bleeding, or

c. Re-operation following closure of the sternotomy incision for the purpose of controlling bleeding, or

d. Transfusion of ≥5 units of whole blood or PRBCs within a 48 hour period, or

e. Chest tube output >2L within a 24 hour period.

In addition, the number of subjects requiring transfusion and re-operation, as well as the extent of chest tube drainage was captured in the eCRF. The analyses did not evaluate the effect of interruption or termination other concomitant medications such as aspirin or clopidogrel that might have influenced the bleeding outcomes.

TRA 2ºP-TIMI 50

In the *Overall* population, 419 subjects underwent CABG surgery, 230 on placebo vs. 189 on vorapaxar. The bleeding rates were low with only 25 subjects with confirmed TIMI major CABG related bleeding, 13 on placebo, and 12 on vorapaxar (HR 1.06; CI 0.48-2.33) (Table S.20).

**Table S.20**. TRA 2ºP-TIMI 50Bleeding Endpoints who Underwent CABG: Event Accrual Period; From Randomization to Last Visit: Overall Population

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

Note: Subjects who had > 1 CABG during the interval, bleeding associated with 1st CABG is used. Abbreviations: CABG = coronary artery bypass grafting; CEC = Clinical Endpoints Committee; TIMI =Thrombolysis in Myocardial Infarction.
a. CABG-related fatal bleeding is defined as having a CEC adjudicated fatal bleeding event occurred within 7 days from CABG. The subject should also have major bleeding events associated with the CABG surgery itself such as TIMI major CABG related bleeding or GUSTO Severe bleeding within 48 hours of CABG.

The blood transfusion rate was relatively low; approximately 30% of the subjects received any transfusion, with similar distribution between treatment groups. Similarly, there was no significant difference observed in the volume of chest tube drainage or need for reoperation for bleeding between groups. There was only one CABG-related fatal bleeding, and it was in the placebo group.

As mentioned above, during the study, routine interruption of the study drug was not recommended. Vorapaxar is slowly eliminated and has a terminal half-life of 187 hours. Therefore, the study drug was likely to have a pharmacodynamic effect in subjects who stopped the study medication less than 7 days prior to CABG surgery as effects may persist for up to 2 to 4 weeks. However, 31 subjects in the placebo group and 36 subjects in the vorapaxar group interrupted study treatment prior to surgery. The results for CABG-related bleeding endpoints (TIMI major, GUSTO severe or moderate and GUSTO severe bleeding) are presented in Table S.21.

**Table S.21.** Bleeding Endpoints Associated with CABG in Subjects Whose Treatment Was or Was Not Interrupted Prior to Surgery: As-Treated Population

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

Note: Subjects who permanently discontinued study medication prior to CABG were excluded from this table. a "Treatment interruption" is defined as an interruption of >2 days prior to CABG. b Only TIMI Major is an appropriate categorization in the context of CABG

The need for transfusion of any blood products, packed red blood cell or platelets was similar between the two treatment groups whether study drug was continued or discontinued at the time of CABG surgery

Similar results as for the *Overall* study were observed for bleeding endpoints among the 131 subjects who underwent CABG surgery within the *Proposed Label Population*. The bleeding rate was similarly low; there were only 14 TIMI major CABG-related bleeding, 7 on placebo vs. 7 on vorapaxar (HR 1.17; 95% CI 0.41-3.34). In general, rates for transfusion and chest tube drainage volume were similar between treatment groups. Again, only 1 CABG-related fatal bleeding event occurred and was in the placebo group.

Generally, the numbers of events are too small to allow definite conclusions and the available data from TRA 2ºP-TIMI 50 do not suggest a significant increase in the risk of major CABG related bleeding with vorapaxar but there are concerns about the small benefit observed compared to the bleeding risk (patients with TIMI major bleeding events 4.5% versus 5.3% in vorapaxar in the Proposed Label Population). There is no information about possible discontinuation of concomitant antiplatelet therapy in the two groups that could potentially confound the results but given the small number of events further subanalyses would be unlikely to provide any additional useful information.

Overall, the available clinical data so far do not raise major concerns about an unacceptably high risk of bleeding in patients undergoing CABG and possibly other procedures. However, the long half life and duration of the vorapaxar effect on platelets remains a concern. PK/PD data suggest a persistent

high level of TRAP-induced platelet aggregation inhibition for at least four weeks after discontinuation of vorapaxar although the association to bleeding risk, in particular in case of surgery, is difficult to determine. There is also evidence from preclinical data that triple therapy with aspirin and clopidogrel may increase bleeding time. 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 that standard measures to manage bleeding is uncertain. Of course, this is not unique to vorapaxar as this is a common problem for all modern antiplatelets.

The above issues and uncertainties are reflected in the product information to help clinicians decide the best course of action for their patients and provide advice, where possible (see also *Pharmacodynamics* section above). The rates of CABG-related bleeding are also shown in section 4.8 of the SmPC

TRACER

In the TRACER study, among the 12,994 subjects, 1880 (14.5%) subjects underwent CABG during the study, with 1317 (70%) of the operations performed during index hospitalization during which the subjects had received a 40 mg loading dose of vorapaxar. It should be noted that eight subjects, four on placebo and four on vorapaxar, received their first CABG surgery after last visit. These subjects were included in analysis with the accrual period "since randomization during the study" but not included in those defined as "since randomization to last visit".

A total of 157 (8.3%) subjects reported CABG-related TIMI bleeding endpoint during the study, 68 (7.2%) on placebo and 89 (9.6%) on vorapaxar. There was no excess in fatal bleeding or increase in re-operation. There were 2 subjects who had CABG related fatal bleeding in the placebo group and none in the vorapaxar group.

Phase 3 Chronic Pool

This analysis included 419 subjects from TRA 2ºP-TIMI 50 and 390 subjects from TRACER i.e. those with CABG surgery after the first 30 days from randomization. These 390 TRACER subjects represented approximately 20% of the 1880 CABG subjects in TRACER, with most of the CABG taking place following the index hospitalization. Even though slightly less than half of the 809 cases were derived from TRACER, because the bleeding rates were generally higher in TRACER, the results shown below are weighted towards TRACER. Furthermore, this post hoc analysis for this post-randomization procedure is potentially influenced by the imbalances between the treatment groups, given fewer subjects on vorapaxar received CABG surgery. The results should therefore be interpreted with caution.

More subjects on vorapaxar had confirmed TIMI major CABG related bleeding: 23 (5.3%) in the placebo group vs. 30 (8.0%) in the vorapaxar group (HR 1.49; 95% CI 0.87-2.57). In this population, subjects in the placebo group required slightly more transfusions compared to the vorapaxar group. Subjects requiring re-operations for bleeding was higher in the vorapaxar group, 22 compared to placebo 13. The volume of chest tube drainage was slightly greater in the vorapaxar group.

## Immunological events

N/A

## Safety related to drug-drug interactions and other interactions

Potential drug-drug interactions are discussed in Pharmacokinetics section above. On the basis of the knowledge that CYP3A4 inhibitors can affect the PK of vorapaxar and since drugs identified as weak or moderate CYP3A4 inhibitors were allowed in the Phase 3 trials, the sponsor assessed their potential impact on the bleeding risk.

Phase 3 trials enrolled a total of 22,748 subjects (in the "as-treated population") who received weak or moderate CYP3A4 inhibitors for ≥ 7 days (11,223 in TRA 2ºP-TIMI 50 and 5268 in TRACER). Table S.22 summarizes the rate of bleeding associated with systemic use of CYP3A4 inhibitors in Phase 3 "as-treated population". More subjects on vorapaxar than those on placebo had bleeding events regardless of CYP3A4 usage. Bleeding events were also more common among subjects taking a weak or moderate CYP3A4 compared to subjects who did not take a systemic CYP3A4 inhibitor. These data should be interpreted with caution as subjects were not stratified based on their use of CYP3A4 agents. In addition, subjects taking CYP3A4 inhibitors may have had additional co-morbidities which could confound the interpretation of this analysis.

Overall, the difference in bleeding events among vorapaxar treated subjects compared to placebo subjects was similar in those taking concomitant weak or moderate CYP3A4 inhibitors to those not receiving concomitant CYP3A4 inhibitors. Thus, it was concluded that co-administration of a weak or moderate CYP3A4 inhibitor with vorapaxar does not increase the hazard for bleeding.

**Table S.22.** Bleeding Endpoints Were Reported During the Study, With or Without Use of a Systemic Weak or Moderate CYP3A4 Inhibitor for at Least Seven Consecutive Days: Overall Population

| | TRA 2ºP-TIMI 50 | | | | TRACER | | | |
|---|---|---|---|---|---|---|---|---|
| | Number (%) of Subjects | | | | Number (%) of Subjects | | | |
| | Bleeding in Subjects Who Did Not Take a Systemic CYP3A4 Inhibitor for ≥7 Days | | Bleeding Associated With Use of a Systemic CYP3A4 Inhibitor Taken for ≥7 Days | | Bleeding in Subjects Who Did Not Take a Systemic CYP3A4 Inhibitor for ≥7 Days | | Bleeding Associated With Use of a Systemic CYP3A4 Inhibitor Taken for ≥7 Days | |
| Endpoints | Placebo (n =5600 ) | Vorapaxar (n =5623 ) | Placebo (n =7566 ) | Vorapaxar (n =7563 ) | Placebo (n = 2623) | Vorapaxar (n =1350 ) | Placebo (n =3818 ) | Vorapaxar (n = 3801) |
| **GUSTO Bleeding Categories** | | | | | | | | |
| GUSTO Severe or Moderate | 105 ( 1.9% ) | 159 ( 2.8% ) | 195 ( 2.6% ) | 280 ( 3.7% ) | 106 (4.0% ) | 161 ( 6.1% ) | 172 (4.5% ) | 225 (5.9% ) |
| GUSTO Severe | 47 ( 0.8% ) | 63 ( 1.1% ) | 93 ( 1.2% ) | 117 ( 1.5% ) | 37 (1.4% ) | 65 ( 2.5% ) | 50 (1.3% ) | 82 (2.2% ) |
| **TIMI Bleeding Categories** | | | | | | | | |
| TIMI Major or Minor | 115 ( 2.1% ) | 43 (1.6%) | 209 (2.8% ) | 288 ( 3.8% ) | 89 (3.4% ) | 142 (5.4% ) | 119 ( 3.1% ) | 186 (4.9%) |
| nonCABG TIMI Major or Minor | 110 ( 2.0% ) | 42 (1.5%) | 201 (2.7% ) | 278 ( 3.7% ) | 64 (2.4% ) | 120 (4.5% ) | 95 (2.5% ) | 144 (3.8%) |
| Not TIMI Major/Minor and Requiring Medical Attention[a] | 403 ( 7.2% ) | 195 (7.1%) | 574 (7.6% ) | 803 ( 10.6% ) | 223 (8.5% ) | 310 (11.7% ) | 327 (8.6% ) | 446 (1.7%) |
| **Other Categories** | | | | | | | | |
| Clinically Significant Bleeding[b] | 499 ( 8.9% ) | 661 (11.8%) | 751 (9.9% ) | 1028 (13.6%) | 299 (1.4%) | 428 (6.2%) | 426 (1.2%) | 591 (5.5%) |

Note: CEC-adjudicated components were used as appropriate. Abbreviations: CABG = coronary artery bypass grafting; CEC = Clinical Endpoints Committee; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; ISTH = International Society on Thrombosis and Haemostasis; TIMI = Thrombolysis in Myocardial Infarction Study Group.
a. "Medical attention" comprises unplanned medical or surgical treatment, or unplanned evaluation via laboratory test.
b. TIMI major or minor bleeding or bleeding that requires medical attention.

It appears that severe/moderate bleeding events tended to be more common in patients who had received CYP3A4 inhibitors but this was seen across both vorapaxar patients and controls. Hence, there is no clear evidence that weak-moderate CYP3A4 inhibitors in this setting increase the risk when given together with vorapaxar but, as noted by the Applicant, the data should be interpreted with caution as subjects were not stratified based on use of CYP3A4 agents and also the effect of confounders is uncertain. Still, CYP3A4 is the main enzyme responsible for vorapaxar metabolism. Therefore, it cannot be excluded that the slightly increased number of bleeding events was due to the concomitant use of CYP3A4 inhibitors. A general warning with regard to the co-administration of vorapaxar and weak to moderate CYP3A4 inhibitors should be added to the SmPC. It should be recommended that alternative drugs not known to inhibit CYP3A4 should be used whenever possible. Drug-drug interactions are discussed also in the Pharmacokinetics section.

## Discontinuation due to AES

TRA 2ºP-TIMI 50 *Overall* Population

Bleeding events

For the TRA 2ºP-TIMI 50 overall population, more subjects in the vorapaxar group (3.0%) discontinued treatment due to bleeding events compared to subjects in the placebo group (1.8%). Epistaxis was the most frequently reported bleeding event resulting in treatment discontinuation in both treatment groups (Table S.23)

**Table S.23.** Number (%) of Subjects Reporting Bleeding Events Resulting in Treatment Discontinuation Reported for at least 10 Subjects During Treatment: As Treated Population

| | Placebo (n=13166) | Vorapaxar (n=13186) |
|---|---|---|
| **SUBJECTS REPORTING ANY ADVERSE EVENT** | **234 (1.8)** | **401 (3.0)** |
| **GASTROINTESTINAL DISORDERS** | 82 (0.6) | 122 (0.9) |
| GASTROINTESTINAL HAEMORRHAGE | 11 (0.1) | 17 (0.1) |
| HAEMATEMESIS | 7 (0.1) | 10 (0.1) |
| HAEMORRHOIDAL HAEMORRHAGE | 7 (0.1) | 12 (0.1) |
| MELAENA | 15 (0.1) | 30 (0.2) |
| RECTAL HAEMORRHAGE | 18 (0.1) | 24 (0.2) |
| VOMITING | 0 | 1 (<.1) |
| **INJURY, POISONING AND PROCEDURAL COMPLICATIONS** | 20 (0.2) | 43 (0.3) |
| CONTUSION | 8 (0.1) | 18 (0.1) |
| **NERVOUS SYSTEM DISORDERS** | 22 (0.2) | 53 (0.4) |
| HAEMORRHAGE INTRACRANIAL | 19 (0.1) | 40 (0.3) |
| **RENAL AND URINARY DISORDERS** | 19 (0.1) | 26 (0.2) |
| HAEMATURIA | 18 (0.1) | 25 (0.2) |
| **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** | 32 (0.2) | 66 (0.5) |
| EPISTAXIS | 23 (0.2) | 57 (0.4) |
| **SKIN AND SUBCUTANEOUS TISSUE DISORDERS** | 15 (0.1) | 37 (0.3) |
| INCREASED TENDENCY TO BRUISE | 6 (<.1) | 23 (0.2) |
| SKIN HAEMORRHAGE | 5 (<.1) | 11 (0.1) |
| **VASCULAR DISORDERS** | 22 (0.2) | 27 (0.2) |
| HAEMATOMA | 9 (0.1) | 10 (0.1) |
| HAEMORRHAGE | 10 (0.1) | 15 (0.1) |

*Other Adverse Events*

For the TRA 2ºP-TIMI 50 overall population, the numbers of events that resulted in discontinuation of treatment over the course of the study were similar between both treatment groups; 7.0% in the vorapaxar group and 7.3% in the placebo group. Most events occurred at a relative low frequency of ≤0.1% for either of the treatment groups. Of the individual events reported, anaemia was the most frequently reported event with a higher incidence observed between vorapaxar and placebo (0.3% for vorapaxar and 0.1% for placebo).

TRA 2ºP-TIMI 50 *Proposed Label Population*

For the Proposed Label Population, discontinuation due to *bleeding events* was similar to the overall population. More subjects in the vorapaxar group (2.9%) discontinued treatment due to bleeding compared to subjects in the placebo group (1.7%). Epistaxis was again the most frequently reported bleeding event resulting in treatment discontinuation in both treatment groups: 40 (0.5%) for subjects who took vorapaxar and 16 (0.2%) for subjects who took placebo.

As with the overall population, a similar number of subjects reported *other adverse events* resulting in treatment discontinuation (6.0% for vorapaxar and 6.2% for placebo). Also, of the individual events, anaemia was the most frequently reported event with a higher incidence observed between vorapaxar and placebo (0.3% for vorapaxar and 0.1% for placebo).

TRACER

Although the occurrence of discontinuation of treatment because of *bleeding events* was relatively low (approximately 3%), approximately twice as many subjects discontinued treatment with

vorapaxar (4.0%) compared with placebo (1.9%), reflecting both the greater occurrence of bleeding events and the greater occurrence of more severe types of bleeding. Epistaxis was the most common bleeding event resulting in treatment discontinuation in both treatment groups: 13/6441 (0.2%) subjects who took placebo, and 33/6446 (0.5%) subjects who took vorapaxar.

Many different *other AEs* resulted in discontinuation of treatment, most responsible for only a few subjects. Other adverse events resulting in discontinuation of treatment that might be described as having a greater occurrence with one treatment over the other, vorapaxar vs. placebo, were anaemia (20 [0.3%] vs. 8 [0.1%] subjects), cardiogenic shock (5 [0.1%] vs. 11 [0.2%] subjects), and rash (20 [0.3%] vs. 10 [0.2%] subjects.

Phase 3 Overall Pool

The occurrence of *bleeding events* that led to the discontinuation of study drug was 2.8% for vorapaxar vs. 1.6% for placebo. Melaena, ICH, haematuria, epistaxis, and the general category of increased tendency to bruise were the events most reported. In all cases, the between group difference for each was <0.2%.

For the overall pool, the numbers of *other events* that resulted in discontinuation over the course of the study were similar between both treatment groups (6.8% in the vorapaxar group vs. 6.7% in the placebo group). Most events occurred at a relative low frequency of 0.1% or less for either of the treatment groups.

***Withdrawal and rebound effects***

From a theoretical point of view, it is suggested that the long terminal half-life of vorapaxar should reduce the possibility of rebound platelet hyperaggregability allowing endogenous mechanisms to counteract possible compensatory pathways that might take over after the drug is discontinued. In addition, PAR 1 platelet receptors are not upregulated when blocked, which would also decrease the risk of rebound effects. In the multiple-dose study P03450, platelet function recovered after cessation of dosing with vorapaxar, but the time to recovery was dose dependent, and took from several weeks to more than 2 months, without raising specific safety or tolerability concerns. In the three Phase 2 studies P03573, P04772, P05005, no statistically significant differences were noted between the vorapaxar treatment groups and placebo for TIMI major and minor bleeding or non TIMI bleeding during the protocol specified follow-up phases. To further examine the possibility of rebound hypercoagulability Phase 3 data were examined in various analyses.

TRA 2ºP-TIMI 50 ITT versus 'On-Treatment' Analysis

The ITT analysis includes data from all subjects through their final study visit, and data from subjects who have discontinued study drug but continued in the study. The 'On Treatment' analysis includes only subjects administered study drug and censors the data at the time of the last dose of study drug plus 3 days. It was hypothesised that a smaller treatment effect in the ITT compared to the 'On Treatment' populations could suggest an excess of events due to hypercoagulability in subjects who discontinued active treatment. The actual analyses showed that the 'on treatment' effect was slightly less than the ITT analysis, suggesting lack of rebound effect (i.e. no excess of endpoint events) following the discontinuation of vorapaxar.

Efficacy Endpoints 30 Days Following Treatment Discontinuation in TRA 2ºP-TIMI 50

In an analysis of the primary and secondary endpoints that occurred within 30 days after the final dose of study drug for subjects who discontinued the TRA 2ºP-TIMI 50 trial prematurely but continued to be followed up there was no excess of observed efficacy endpoints in the vorapaxar vs. the placebo groups suggesting no rebound effect. The event rate of 2.6% in the placebo group in this case is consistent with the event rate during the trial. There were similar findings in the Proposed Label Population.

Efficacy Endpoints 30 Days Following Treatment Discontinuation in TRACER

Analyses of the TRACER trial, in the population of all subjects who had events within 30 days following the discontinuation of study drug show a slight excess of events in the vorapaxar group which consisted mainly of MI, CV deaths, and recurrent ischemic revascularization (RIR); however, the number of events is very small. Examining the events over time, it appears that the excess of CV deaths occurred during the first week of stopping vorapaxar, which may indicate that other events had transpired to prompt the stop of study drug. The excess of MI and RIR occurred later during the 30 day period off drug.

Subjects who discontinued study drug and continued to be followed in the trial may provide a better evaluation of possible withdrawal effects. The analysis of the primary and secondary endpoints that occurred within 30 days after the final dose of study drug for subjects, in TRACER who discontinued the trial prematurely suggest no excess of events in the vorapaxar vs. the placebo group.

Overall, the available evidence does not indicate an increased risk of major thromboembolic events after cessation of therapy with vorapaxar, suggesting absence of a clinically significant rebound effect.

**Post marketing experience**

The are no available post-marketed data for vorapaxar.

## 2.6.1. Discussion on clinical safety

The safety database includes data from across the whole vorapaxar clinical program but mostly from the two largest phase 3 trials TRA 2ºP-TIMI 50 and TRACER. Because of the differences between the populations in the two trials the focus is on TRA 2°P-TIMI 50, which is considered the pivotal study for this application, with TRACER having a supporting role. The Applicant submitted a comprehensive review of the safety data, with analyses in various datasets and assessments of events of special interest across the whole program.

The overall exposure to vorapaxar, in terms of number of patients included in the clinical program and duration of treatment, is considered sufficient to establish the key aspects of its safety profile. In the Phase 3 program 19,632 subjects (13,186 subjects in TRA 2°P-TIMI 50 and 6446 in TRACER) received at least one dose of vorapaxar with an estimated compliance greater than 90% in 17,276 (88%) of subjects. In TRA 2ºP-TIMI 50 subjects randomized to vorapaxar received treatment for a median of 823 days with at least 60% taking the treatment for more than 2 years (720 days) and 15% for more than 3 years. In the overall population, more than 76% of the subjects were on treatment for at least 2 years and the median duration of treatment was 2.5 years.

The study population across the whole development program comprised a range of patients with atherosclerotic disease. In TRA 2ºP-TIMI 50, patient characteristics reflected a stable secondary prevention population with the '*Proposed Label Population'* restricted to a selected post-MI group with a range of background risk factors and co-morbidities but no history of stroke/TIA. Overall, there was a sufficient number of older patients over 65yrs or ≥75yrs (although in the generally younger *Proposed Label Population* the percentage of the latter was lower at around 7% compared to approximately 17% in the Overall population), one quarter were diabetics, the majority were also hypertensives or hyperlipidaemic, and approximately 10% had impaired renal function. The vast majority of patients in TRA 2ºP-TIMI 50 were on aspirin and most of them were also receiving clopidogrel but there were very few patients on other antiplatelet agents like prasugrel or ticagrelor, or on anticoagulants. In view also of the SAG recommendations, relevant warnings are included in the SmPC advising against the use of vorapaxar with prasugrel and ticagrelor. Also use with warfarin and

other oral anticoagulants should be avoided while caution is advised when using heparin (including low molecular weight heparin [LMWH]) as it might be associated with an increased risk of bleeding.

As expected for an antiplatelet drug the risk of bleeding was considered the major potential concern and the Phase 3 studies were designed to examine bleeding as the main safety endpoint. Bleeding events were adjudicated by an independent clinical events committee and were graded according to GUSTO as well as TIMI criteria.

In TRA 2ºP-TIMI 50 trial significantly more subjects reported bleeding events in the vorapaxar group (24.4%) compared to the placebo group (17.2%) with epistaxis (6.2% for vorapaxar vs 3.1% for placebo) being the most common followed by haematuria, gingival bleeding, melaena and other GI bleeding. Epistaxis was also the most common bleeding event leading to treatment discontinuation in both treatment groups. Generally, more subjects (2.9%) discontinued treatment due to bleeding in the vorapaxar group compared to placebo (1.7%).

In the *Overall* population, GUSTO moderate or severe bleeding event rate during the accrual period was 4.2% in the vorapaxar group compared to 2.9% (HR: 1.51; 95% CI: 1.31 to 1.74; p< 0.001). GUSTO severe, TIMI major rates and intracranial haemorrhages including fatal cases were all considerably higher than placebo. ICH occurred in 173 subjects, 109 (0.83%) on vorapaxar and 64 (0.49%) on placebo with an annualized event rate of 0.3 and 0.2 events per 100 subject-years of exposure, respectively (HR 1.70; 95% CI 1.25-2.32; p < 0.001). When these findings were further analysed, it was observed that serious events were more common in patients with previous history of stroke; when such patients were excluded the risk was found to be lower in the remaining population, which led to the restricted, current *'Proposed Label Population'*.

In the *Proposed Label Population* i.e the post-MI patients with no history of stroke or TIA the rate of GUSTO moderate or severe accrued event rate in the vorapaxar group is still higher at 3.1% than placebo at 2.2% but the difference between active group and control is smaller than that observed in the overall TRA 2ºP-TIMI 50 population (HR 1.48; 95% CI 1.21 to 1.82; p< 0.001). This difference also appears now to be driven mainly by moderate events while GUSTO severe events, although still slightly more frequent with vorapaxar are not significantly different from placebo (event rate 1.2% vs 1.0% respectively with a similar 0.4 annualised rate/100 patient-years of exposure). Fatal bleeding 3-year KM rate was 0.2 % in both treatment groups. ICH occurred in 38(0.5%) patients on vorapaxar and 30(0.4%) on placebo, with annualized event rates of 0.18 and 0.14 events per 100 subject-years of exposure (HR 1.26; 95% CI 0.78 to 1.88; p= 0.348).

In general, the above data suggest that the proposed approach to exclude patients with previous history of stroke and restrict the target population to post-MI patients with no such history (plus no history of TIA) appears to reduce considerably the risk of the most severe and life threatening bleeding, including ICH. However, the risk is not eliminated and even in the currently restricted target group, patients will still be at higher risk of moderate/severe bleeding when vorapaxar is added to their standard therapy. The relative importance of this incremental risk will need to be weighed against the expected benefits in the overall benefit:risk evaluation.

The subgroup analyses in TRA 2ºP-TIMI 50 did not provide any strong evidence of a clinically significant effect of any single factor. However, across both active and control groups the risk of bleeding was higher among females, older patients, those with weight less 60kg, patients with renal impairment or history of heart failure. Individually none of these parameters was shown to considerably increase the risk of severe/moderate bleeding with vorapaxar as a similar increase was seen across both active and control groups, but often the number of events was quite small to allow conclusions.

The above points were discussed in the SAG (see minutes). With regards to the population at risk of bleeding the CHMP discussed the SAG recommendations and considered the following. For patients weighting less than 60kg the data suggest an increased risk of bleeding and although drawing

conclusions from such small numbers is problematic considering the seriousness of the complications a conservative approach is warranted.

Examination of potential additive effect of multiple factors, for example advanced age with low body weight, did not reveal any noteworthy findings over and above the examination of the individual parameters. The limitations due to the low numbers of patients and events are even more prominent here. Overall, for patients with low body weight and the elderly, the CHMP, in view of the SAG advice considered the need for further update of the SmPC that caution is recommended in case of use of vorapaxar in patients with low body weight and elderly should follow careful assessment of the individual potential benefits and individual bleeding risks as well as the need for co-medications that may further increase the risk of bleeding.

Further to the above there is little information for certain special groups like patients with severe renal failure. Very few patients with severe renal impairment were among the TRA 2ºP-TIMI 50 Proposed Label Population and the very low number of events does not permit any meaningful assessment of the potential risks. This limitation is adequately reflected in the SmPC that needs to advise use with caution in such patients.

In addition, patients with significant hepatic disease were not included in the trial. Considering the higher risk of bleeding in this group, the use of vorapaxar in patients with significant liver disease should be contraindicated.

In terms of concomitant antiplatelet therapy in TRA 2ºP-TIMI 50 almost 95% of patients were taking aspirin at baseline. Patients (n=1703) not on aspirin, showed no higher bleeding risk with vorapaxar compared to placebo i.e. GUSTO severe/moderate bleeding reported in 32 subjects in the vorapaxar group compared to 30 subjects the placebo group (HR 1.03; 95% CI; 0.63-1.70) but the numbers are small and the CI wide. Concomitant clopidogrel therapy did not appear to increase further the risk.

The Applicant also examined the risk of bleeding in patients who underwent CABG (n=419) during TRA 2ºP-TIMI 50 as they were not required to discontinue therapy for the operation. The numbers of TIMI major bleedings were small and there was a small increase in the risk with vorapaxar. Although the available clinical data so far do not raise major concerns about an unacceptably high risk of bleeding in patients undergoing CABG and possibly other procedures the long half life and duration of the vorapaxar effect on platelets remains a concern and there are circumstances that an antiplatelet effect during surgery may not be desired. 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 that standard measures to manage bleeding is uncertain. The above issues and uncertainties are reflected in the product information to help clinicians decide the best course of action for their patients and provide advice, where possible, but some further information should be included in the SmPC.

In TRACER trial the bleeding rates were generally even higher than in TRA 2ºP-TIMI 50, a rather expected finding considering the ACS population of the former and the likely intensive use of antithrombotic and antiplatelet therapies. Again severe bleeding including fatal cases and ICH were more common among the vorapaxar treated patients; these findings together with the lack of clear evidence of benefit led to the decision to terminate the trial. As previously mentioned, due to the important differences between the study populations the usefulness of TRACER in the assessment of bleeding risk for the currently proposed target group is limited.

With regard to other non-bleeding adverse events in the TRA 2ºP-TIMI 50 (In the Overall but also in the Proposed Label Population) there were no major differences in the incidence of common AEs between treatment groups across the examined populations. Among the most frequently reported were chest pain (cardiac or non-cardiac), dizziness and urinary tract infections. Anaemia was consistently more common with vorapaxar (in the overall study, 3.3% in vorapaxar vs 2.3% in the placebo group) and appears to be related to bleeding.

The incidence of serious events (other than bleeding) was generally low, with very few events like chest pain (non-cardiac) reaching >1%. Again in most cases there were no major differences between treatments but anaemia was more common in the vorapaxar treated patients and conversely pulmonary embolism in the placebo group. Total mortality was slightly lower in the vorapaxar patients (for the Overall population, 4.4% in the vorapaxar vs 4.6% in the placebo group) but a higher proportion of patients receiving vorapaxar than placebo died from bleeding or stroke.

There is no clear evidence that vorapaxar adversely affects renal or hepatic function, and there were no clinically meaningful differences between groups or findings of major concern in the examined laboratory tests, vital signs or ECG parameters. Also the results of two ocular safety studies and relevant AEs reported in the clinical trials did not raise any major concerns but the very small number of events does not allow firm conclusions. Clearly these are rare events and the possible ocular effects of vorapaxar cannot be established at this stage. This is an issue that will need to remain under monitoring in the PSURs.

There were a small number of overdose cases with no reported major events, which is somewhat reassuring but the lack of an antidote and the long half-life of vorapaxar are of concern. These issues are addressed in the RMP and the SmPC.

Overall, the main safety issue with vorapaxar remains bleeding. Although restricting the target population appears to lower the likelihood of severe bleeding including intracranial haemorrhages, patients will still be at higher risk when vorapaxar is added to their therapy. These issues have been addressed in the RMP and the SmPC.

### 2.6.2. Conclusions on the clinical safety

A large safety database has provided sufficient information to determine the key aspects of the vorapaxar safety profile, although there are some important limitations, including the lack of data on co-administration with newer antiplatelet agents and anticoagulants, or data in patients with renal or hepatic disease.

The decision to restrict the target population excluding patients with previous stroke or TIA appears well justified. Nevertheless the risk of bleeding, remains a concern and patients who will prescribed vorapaxar on top of their standard therapy will still be more likely to experience a bleeding event.

Other than bleeding, there were no major issues or signals. The product information has been updated to include all clinically relevant safety information.

## *2.7. Pharmacovigilance*

**Detailed description of the pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

A statement has been submitted that the Applicant has the services of a fully Qualified Person responsible for pharmacovigilance, who has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC

## *2.8. Risk Management Plan*

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

The PRAC considered that the risk management plan version 1.3 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice with the following changes:

For the proposed EU PASS to characterize normal conditions of use and safety following administration of vorapaxar included in the Pharmacovigilance Plan, a due date for the submission of the Final Report has been added (e.g. "no later than December 2026"). Section V on "Risk minimisation measures" has been updated accordingly.

The applicant implemented the changes in the RMP as requested by the CHMP.

The CHMP endorsed the Risk Management Plan version 1.5 with the following content:

***Safety concerns***

**Table Summary of Ongoing Safety Concerns**

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

***Pharmacovigilance plan***

**Table Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan: Imposed Activities, Specific Obligations and Required Activities (Categories 1 - 3)**

| Study / Activity | Objectives | Safety Concerns Addressed | Status | Date for Submission of Interim / Final Reports (target dates) |
|---|---|---|---|---|
| Category 3: Observational postauthorization safety study (PASS) to characterize normal conditions of use and safety following administration of vorapaxar. | Describe physician prescribing patterns in an outpatient setting during the post-licensure period with regards to key aspects of the product label in | Intracranial haemorrhage, especially among patients with a history of stroke/TIA<br>Medically important bleeding risks, excluding ICH | Planned | EU PASS: Progress reports will be submitted with each PSUR until completion of the study. Data on prescribing patterns will be submitted 2 years after EMA protocol approval and commercial launch in at least one participating PASS country, which is anticipated 6-12 months after EC marketing |

**Table** **Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan: Imposed Activities, Specific Obligations and Required Activities (Categories 1 - 3)**

| Study / Activity | Objectives | Safety Concerns Addressed | Status | Date for Submission of Interim / Final Reports (target dates) |
|---|---|---|---|---|
| | terms of appropriate patient selection (medical history, contraindications) and concomitant drug administration, and to estimate rates of hospitalization for bleeding events (e.g. intracranial hemorrhage (ICH), GI hemorrhage) in a real-world clinical setting.<br>Evaluate the effectiveness of the risk minimization measures. | Drug-drug interaction: strong inhibitor of CYP3A4<br>Patients with severe hepatic dysfunction<br>Co-administration with oral anticoagulants (e.g. warfarin), prasugrel, or ticagrelor<br>Off-label use | | authorization. Additional reports with prescribing data will be submitted every two years thereafter until completion of the study. The timeline for the interim report with outcomes data and final study report will be included with the full protocol, submitted to the EMA approximately 6 months after EC marketing authorization.<br>The final report with outcomes data and baseline data for all patients exposed to vorapaxar will be submitted once the required amount of person years of exposure has been accumulated, but no later than December 2020. The timeline for this report will depend on sample size and the rate of marketing uptake, for which limited information is available at this time. |

***Risk minimisation measures***

**Table** **Summary of Safety Concerns and Risk Minimization Activities**

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| **Important Identified Risks** | | |
| Medically important bleeding, including intracranial hemorrhage | SmPC: Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, Section 4.5 Interaction with other medicinal products and other forms of interaction, Section 4.8 Undesirable effects, and Section 5.1 Pharmacodynamic properties | None |
| Drug-drug interaction: strong inhibitor of CYP3A4 | SmPC: Section 4.5 Interaction with other medicinal products and other forms of interaction, and Section 5.2 Pharmacokinetic properties | None |
| Drug-drug interaction: strong inducer of CYP3A4 | SmPC: Section 4.5 Interaction with other medicinal products | None |

**Table Summary of Safety Concerns and Risk Minimization Activities**

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

## *2.9. Product information*

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling for readability purpose has been submitted by the applicant and has been found unacceptable by the QRD Group for the following reasons:

The request of the applicant was rejected. The Group agreed that the information on the blister had to be rearranged to accommodate all particulars. The short term for the pharmaceutical form ('tablets' instead of 'film-coated tablets') could also be used.

# 3. Benefit-Risk Balance

***Benefits***

**Beneficial effects**

Anti-thrombotic therapy options in patients with stable atherosclerosis are not well-established. Long-term therapies to effectively modulate the key components responsible for atherothrombosis in secondary prevention of ischemic CV disease are therefore required. The Sponsor has investigated whether a new class of antiplatelet agents, PAR-1 antagonists, can further decrease the risk of cardiovascular events with an appropriate balance of efficacy and bleeding risk in a population of established atherothrombosis when added to standard of care by studying vorapaxar, a first-in-class PAR-1 receptor antagonist, in secondary prevention of ischemic diseases.

In the current application, the Applicant presents the results from two Phase III studies TRACER and TRA 2P-TIMI. TRACER study in patients with ACS was stopped early due to an increased bleeding risk. The indication sought in the current application "reduction of atherothrombotic events in patients with a history of myocardial infarction" is supported by the efficacy results of the TRA 2P-TIMI study.

In the proposed Label Population CAD subjects without a history of stroke or TIA (64% of subjects enrolled in this study), had efficacy results that favoured vorapaxar (18% relative risk reduction on top of standard care). In this population, the primary efficacy composite endpoint was a 3-year KM event rate of 9.8% in the vorapaxar group compared to 11.4% in the placebo group (HR; 0.82; 95% CI 0.74-0.90, P<0.001). All *key* components of the composite endpoint were in the same direction, in favour of vorapaxar. Yet, the individual component of the composite endpoints that most contributed to the difference between vorapaxar and placebo was the reduction of the rate of MI. MI was reported in 374 vorapaxar subjects (4.4%) vs. 451 placebo subjects (5.3%) as a component of the primary endpoint.

The efficacy results in all the analysed populations of TRA 2ºP-TIMI 50 including the Proposed Label Population were consistent and in favour of vorapaxar. However, the results showed that vorapaxar was more efficacious (greater clinical benefit and with higher statistical significance) in the Proposed Label Population.

**Uncertainty in the knowledge about the beneficial effects**

Vorapaxar treatment, in the restricted population of patients with history of MI but with no previous stroke or TIA, has demonstrated statistically and clinically relevant results in the composite endpoint of CV death, MI, stroke and UCR mainly driven by the reduction of MI events.

The vast majority of patients were taking aspirin and therefore the efficacy of vorapaxar seems to be highly related to the effect of aspirin. This needs to be better reflected in the SmPC and the indications. Similarly important is for the SmPC to reflect that patients in the pivotal trial mostly had a history of a recent (12 months or less) myocardial infarction. Relevant recommendations the time of initiation of treatment after an MI are included in the SmPC. Also, treatment duration in TRA 2P-TIMI study was at least 1 year for all patients; however, the median participation in the study was more than 2.5 years. Considering uncertainties about the longer term effects, taking into account the SAG recommendation, the CHMP recommended that continued therapy after 24 months must be based on the re-evaluation of the benefits and risks for the individuals.

There was also some uncertainty about the appropriate course of action in case that a patient suffers an acute coronary event while on treatment with vorapaxar. The Applicant submitted further analyses that provide reassurance that the continued use of vorapaxar during an ACS was not associated with increased bleeding rates above what was observed in subjects who had not experienced any such event.

Therefore, it can be accepted that stopping Zontivity in case that a patient suffers an ACS may not be warranted. Moreover, due the long-half-life of the drug and the prolonged effect on platelets, discontinuation of therapy would be unlikely to have a significant effect during the acute phase.

Further to the above, especially when considering the negative results of TRACER and the continuum of the CAD disease and atherosclerotic plaque pathophysiology following an acute event, is was which patient group would benefit more and should receive vorapaxar following an acute MI and the place of vorapaxar in the modern management of patients with a recent MI was questioned and SAG view sought. Taking also further into account the relevant recommendations of the latest Clinical Guidelines and the newer antiplatelet agents (such as prasugrel and ticagrelor), it is agreed that not all patients with an acute MI will be able or suitable to start therapy with one of the newer antiplatelets prasugrel or ticagrelor. After discharge some will be treated with aspirin or clopidogrel alone and many will be prescribed dual (ASA+clopidogrel) antiplatelet therapy. Those patients can receive vorapaxar.

Also not all patients who will start therapy with either prasugrel or ticagrelor during the acute phase will be able to remain on them during the post-MI phase because of tolerability, safety or compliance issues. Finally, those patients who will be treated with prasugrel or ticagrelor will normally receive therapy for up to a year (their SmPC recommends treatment for up to 12 months as experience beyond that period is limited). In contrast, vorapaxar has demonstrated a favourable benefit:risk beyond the first year post MI.

The above suggest that a proportion of MI patients will be treated with aspirin with or without clopidogrel in the post MI phase and there is sufficient evidence from the large pivotal trial that they could benefit from vorapaxar addition to their treatment. This is appropriately reflected in the indication as follows;

*Zontivity, 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).*

In addition Vorapaxar should not be used in combination with prasugrel nor ticagrelor and should be stopped in case of initiation of treatment with these agents.

**Risks**

**Unfavourable effects**

A large safety database has provided sufficient information to determine the key characteristics of vorapaxar safety profile. As expected for an antiplatelet agent the risk of bleeding is considered the major safety issue and relevant events were analysed across different settings and subgroups.

In the pivotal trial TRA 2ºP-TIMI 50 the risk of bleeding was greater for subjects on vorapaxar than placebo for all pre-specified bleeding endpoints (except CABG-related TIMI major bleeding) and the differences between the two treatment groups were significant for most GUSTO and TIMI categories including intracranial haemorrhage.

In the proposed *Label Population* that includes only post-MI patients from TRA 2ºP-TIMI 50 with no previous history of stroke or TIA, the event rate of GUSTO moderate or severe bleeding with vorapaxar was lower than the *Overall* TRA 2ºP-TIMI 50 population, with much less common GUSTO severe events (including ICH). However, even in this restricted population the risk of moderate/severe events is not eliminated and data suggest that patients who will be prescribed vorapaxar as add-on to their standard therapy will still face an increased risk of bleeding (calculated rate 1.1 events per 100 subjects per year) although life-threatening or fatal events are likely to be very rare (rate of severe GUSTO and fatal bleeding: 0.4 and 0.1 per 100 subjects per year respectively; similar to placebo). The relative importance of this incremental risk will need to be weighed against the expected benefits in the overall benefit:risk evaluation.

Further to more severe events, patients receiving vorapaxar will also be likely to experience less serious bleedings like epistaxis, haematuria, gingival bleeding more frequently, and in some cases these will lead to discontinuation of therapy, although the data from the TRA 2ºP-TIMI 50 trial suggest that this may not be happen very often (for the Proposed Label Population, discontinuation rate due to bleeding events in the vorapaxar group was 2.9% compared to 1.7% in placebo). Patients on vorapaxar will also be more likely to require a procedure to investigate a bleeding event or a transfusion; however, it is reassuring that the median duration of a bleeding event in TRA 2ºP-TIMI 50 was similar between vorapaxar patients and controls suggesting that the interventions implemented to manage bleeding were generally similarly effective in both groups.

Further to the bleeding risk, there was no indication of other significant safety issues of major concerns. Yet, anaemia was consistently more common with vorapaxar and appears to be related to bleeding. Serious events (other than bleeding) were generally rare with no major differences between treatment groups and there was a trend in overall mortality in favour of vorapaxar. There is also no clear evidence that vorapaxar adversely affects renal or hepatic function.

## Uncertainty in the knowledge about the unfavourable effects

As noted above, the safety database was of a reasonable size in a range of patients with atherosclerotic disease. TRA 2ºP-TIMI 50 included a stable secondary prevention population with the 'Proposed Label Population' restricted to a selected post-MI group with a range of background risk factors and co-morbidities but no history of stroke/TIA. Overall, there were a sufficient number of older patients over 65yrs or ≥75yrs, diabetics, patients with hypertension, hyperlipidaemia or some degree of renal impairment. However, there are areas with little or missing information. For example, patients with significant hepatic disease were not included in the phase 3 trials; also very few patients with severe renal failure were studied.

With regard to background therapies, the vast majority of patients in TRA 2ºP-TIMI 50 were on aspirin and most of them were also receiving clopidogrel but there were very few patients on other antiplatelet agents including prasugrel or ticagrelor, or anticoagulants. All the above are limitations and gaps in the currently submitted evidence. Areas where the safety of vorapaxar cannot be

established from the available evidence need to be adequately reflected in the product information making clear that use of vorapaxar with such agents which may further increase the risk of bleeding should be avoided.

As previously discussed, bleeding is the key safety issue and in general there are sufficient data to evaluate the relevant hazards at different settings and conditions, allowing a reasonable confidence in the estimation of the relative risks that a patient is likely to face if he/she is prescribed vorapaxar on top of his/her standard treatment.

The risk of bleeding appears to be higher in certain subgroups, irrespective of vorapaxar therapy, such as females, older patients, those with weight less 60kgr, patients with significant hepatic disease or patients with renal impairment. As mentioned above, in some of those groups, like patients with hepatic disease of severe renal failure the impact of vorapaxar treatment is uncertain. In other, like older patients≥75yrs when examined separately, there was no strong evidence of an additional risk with vorapaxar but the absolute risk of bleeding increases with age. For patients weighting less than 60kg the data suggest an increased risk of bleeding without clear evidence of benefit indicating a questionable benefit:risk. The SmPC reflects the need of caution prior starting therapy and the relevant risks in special subgroups and particularly in patients with low body weight and the elderly.

The need to avoid Vorapaxar therapy in case of treatment with NOACs or warfarin is also reflected in the SmPC whereas caution is advised in case of combination with heparin.

There are still also some uncertainties about the bleeding risk and best course of action during surgery but the overall data so far do not raise major concerns. The product information includes a relevant warning to reflect the available data and provide advice based on the existing evidence. An additional issue is the increasing complexity, with multiple tablets, of the therapy of patients in the secondary prevention and to what extent this can affect overall compliance and adherence to the most critical aspects of their management.

There were a small number of overdose cases with no reported major events, which is somewhat reassuring but the lack of an antidote and the long half-life of vorapaxar are of concern, which are addressed in the RMP and reflected in the SmPC.

The review of adverse events other than bleeding did not raise any major concerns, and some areas of special interest like ocular safety did not reveal any significant findings. However, despite the size of the vorapaxar phase 3 program, very rare events may be difficult to be captured and post-marketing monitoring will be required to evaluate the potential longer-term impact of vorapaxar therapy.

## Balance

### Importance of favourable and unfavourable effects

Vorapaxar treatment, in the restricted population of patients with history of MI but with no previous stroke or TIA, has demonstrated statistically and clinically relevant results in the composite endpoint of CV death, MI, stroke and UCR mainly driven by the reduction of MI events.

In the currently *Label Population* the event rate of GUSTO moderate or severe bleeding with vorapaxar was lower than the *Overall* TRA 2ºP-TIMI 50 population, with much less common GUSTO severe events (including ICH). However, even in this restricted population the risk of moderate/severe events is not eliminated and data suggest that patients who will be prescribed vorapaxar as add-on to their standard therapy will still face an increased risk of bleeding (calculated rate 1.1 events per 100 subjects per year) although life-threatening or fatal events are likely to be very rare (rate of severe GUSTO and fatal bleeding: 0.4 and 0.1 per 100 subjects per year respectively; similar to placebo).

Compared with placebo, vorapaxar prevented 80 (95% CI: 41, 120) CV deaths, MIs, strokes and urgent coronary revascularisations per 10,000 patient-years, while causing 6 severe bleeds (Table B1).

**Table B1.** Risk Differences of Main Efficacy and Safety Endpoints: Subjects with No History of Stroke or TIA Whose Qualifying Condition Was CAD

| | Number of events per 10,000 patient years | | |
|---|---|---|---|
| **Efficacy Endpoints** | Vorapaxar (n = 8458) | Placebo (n = 8439) | Risk Difference (95% CI) |
| CV Death / MI / Stroke / UCR | 357 | 437 | -80 (-120 , -41) |
| CV Death / MI / Stroke | 260 | 332 | -72 (-106 , -39) |
| CV Death / MI | 239 | 296 | - 57 ( -89 , -26) |
| All-Cause Death | 113 | 124 | -11 ( -31 , 10) |
| CV Death | 62 | 76 | -14 ( -30 , 2) |
| MI | 192 | 239 | - 48 ( -76 , -19) |
| Stroke | 30 | 48 | -18 ( -31 , -7) |
| Ischemic Stroke | 20 | 39 | -19 ( -30 , -9) |
| **Safety Endpoints** | Vorapaxar (n = 8444) | Placebo (n = 8412) | Risk Difference (95% CI) |
| GUSTO Severe or Mod. Bleeding | 112 | 75 | 36 ( 18 , 55) |
| GUSTO Severe Bleeding | 41 | 35 | 6 ( -6 , 18) |
| GUSTO Moderate Bleeding | 73 | 42 | 31 ( 16 , 46) |
| Fatal Bleeding | 7 | 7 | 0 ( -5 , 5) |
| ICH | | | |
| Fatal ICH | 5 | 4 | 1 ( -3 , 5) |
| Non-fatal ICH | 13 | 11 | 2 ( -4 , 9) |
| ICH Contributing to Death | 0 | 0 | 0 ( -1 , 3) |
| GUSTO Severe Non-fatal Non-ICH | 20 | 19 | 1 ( -7 , 10) |

Note: it is assumed that discrepancies between the risk difference presented in column 4 is different to (column 2 – column 3) because of rounding.

***Benefit-risk balance***

Long-term therapies to effectively modulate the key components responsible for atherothrombosis in secondary prevention of ischaemic CV disease are still required. The applicant has investigated vorapaxar as a new class of antiplatelet agents, PAR-1 antagonists. Vorapaxar efficacy results in the restricted label population, particularly in the prevention of myocardial infarction, is considered clinically relevant as compared to the small increase in severe bleeding events.

It is considered that the benefit-risk balance is positive. The recommended indication is as follows: *Zontivity, 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).*

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zontivity (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) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to medical prescription.

***Conditions and requirements of the Marketing Authorisation***

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.***

Not applicable.

These conditions fully reflect the advice received from the PRAC.

***New Active Substance Status***

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Vorapaxar is qualified as a new active substance.