CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204886Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review Memo

Date	April 18, 2014
From	Thomas A. Marciniak, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supp #	NDA 204-886 000
Proprietary / Established (USAN) names	Zontivity / vorapaxar sulfate
Dosage forms / strength	oral tablet / 2.5 mg (equivalent to 2.08 mg of vorapaxar)
Proposed Indication(s)	for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI)
Recommended:	approval for history of MI and peripheral arterial disease (PAD) without a history of stroke or transient ischemic attack (TIA)

1. Introduction to Review

Vorapaxar is a first-in-class platelet inhibitor working by antagonism of the protease activated receptor 1 (PAR-1). PAR-1 is the primary thrombin receptor on human platelets. As an antagonist of PAR-1 vorapaxar blocks thrombin-mediated platelet aggregation and therefore may have efficacy in the treatment of atherothrombotic cardiovascular (CV) disease for which other platelet inhibitors, such as aspirin and the $P2Y_{12}$ receptor inhibitors, have shown efficacy.

Vorapaxar has been tested in two large placebo-controlled CV outcome trials: TRACER in 12,944 moderate-to-high risk patients with non-ST segment elevation acute coronary syndromes (NSTE-ACS) and TRA2P in 26,449 patients with CV risk defined by a history of MI, stroke, or peripheral arterial disease (PAD). TRACER failed on its primary endpoint and showed an increased risk of intracranial hemorrhage (ICH) in patients with a history of stroke. Because TRA2P showed similar findings patients with a history of stroke were discontinued from TRA2P. Subsequently TRA2P was successful on its primary endpoint and serves as the substantial evidence for the proposed indication and the primary focus of the clinical and statistical reviews.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

As the primary clinical review summarizes, the applicant discussed the plans for the phase 3 studies at an end of phase 2 meeting with the Division on February 27, 2007. The applicant declined the Division's invitation to submit special protocol assessments for the phase 3 studies.

There have been no previous FDA actions regarding vorapaxar. There are no foreign approvals.

3. CMC/Microbiology/Device

The CMC reviewer, Dr. Thomas Wong, recommends approval of the application from a CMC perspective. He judged that the applicant provided adequate information to allow a satisfactory evaluation of the quality of both drug substance and drug product. An early minor issue was resolved regarding labeling: While the tablets contain 2.5 mg of vorapaxar sulfate, the labeling should indicate that the amount of vorapaxar is 2.08 mg.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Dr. Patricia Harlow, states that the application is approvable from a pharmacology/toxicology perspective. She summarized that most of the toxicities identified in the non-clinical studies have adequate safety margins relative to human therapeutic exposures. However, the effect of vorapaxar treatment on memory in F1 female rat offspring has only a 4-fold safety margin based on the NOAEL dose. The label needs to warn women of child-bearing age of the potential risks for effects on their off-spring. In addition, the high levels of vorapaxar in milk of lactating rats, suggests the potential for vorapaxar exposure levels leading to inhibition of platelet aggregation and resulting bleeding in nursing neonates and infants.

A preclinical finding that was followed-up in the clinical studies was retinal vacuolation. Vacuoles in the inner nuclear layer of the retina consisting of distended cellular organelles and cell processes without evidence of phospholipidosis or any degenerative changes, were observed in most rat studies. Retinal vacuolation was not found in the rat carcinogenicity study, in any mouse study, or in any monkey study. Retinal vacuolation was found in rat studies after seven, but not after three, doses. The finding was reversible after four weeks of recovery. Retinal vacuolation was observed when the eyes were fixed under a number of conditions with an aldehyde-based fixative but not after 24 hours refrigeration *in situ* or with acetic acid-based Carnoy's fixative. Dr. Harlow noted that the applicant considers retinal vacuolation to be a vorapaxar-related exaggeration of a common retinal artifact associated with aldehyde-based fixation.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewers, Drs. Sudharshan Hariharan, AbuAsal Bilal, and Fang Li, recommend approval pending agreement with the applicant on labeling. They recommend avoiding use of vorapaxar in patients with body weight < 60 kg due to unfavorable benefit-risk. The biopharmaceutics reviewer, Dr. Okpo Eradiri, found that the dissolution method and acceptance criterion for vorapaxar tablets are agreed upon and are acceptable for release and stability. Dr. Eradiri recommends approval from a biopharmaceutics perspective.

The most relevant findings from the clinical pharmacology reviews are the following:

- Vorapaxar has a long half-life. The terminal elimination half-life is 7-11 days while the effective half-life based on accumulation at steady state is 3 to 4 days. Steady state is obtained by day 21 with once daily dosing and accumulation is about 6-fold. Time to offset of platelet inhibition is slow with ~50% of platelet function recovered by 4 weeks post-last dose.

- Increases in exposure of 20 – 40% are observed with older age, Asian race, female gender, and moderate renal insufficiency. Because the clinical trials did not show variations in efficacy or safety by these characteristics, dosage adjustment for them is not recommended. While exposure was not increased substantially in patient with moderate hepatic insufficiency, because patients with hepatic impairment are at increased risk of bleeding the clinical pharmacology reviewers recommend avoiding use in hepatically-impaired patients.

- Vorapaxar is metabolized by CYP3A4 and CYP2J2. Ketoconazole, a strong CYP3A inhibitor, increases the systemic exposures to vorapaxar by 2-fold, while rifampin, a strong CYP3A inducer, decreases the systemic exposure to vorapaxar by 55%. Because concomitant administration of these drugs was prohibited in the phase 3 studies, the clinical pharmacology reviewers recommend avoiding concomitant use. Concomitant use of weak to moderate inhibitors or inducers does not require dosage adjustment.

- Vorapaxar is extensively bound (≥ 99.8%) to serum albumin. Conditions for displacement are not known.

- Vorapaxar demonstrates a steep exposure-platelet inhibition relationship. Over a narrow range of vorapaxar concentration (~1 to 5 ng/mL), inhibition of TRAP-induced platelet aggregation changes from non-effect to maximal inhibition in most studies. However, two studies showed exceptionally high, unexplained EC_{50} values. The applicant predicted that vorapaxar 2.5 mg once daily should achieve the target ≥ 80% platelet inhibition in almost all patients by day 7. However, the exposure-response and or inhibition-response relationships for both efficacy and safety are unknown.

- In Phase 1 studies vorapaxar did not affect blood coagulation tests (thrombin time, prothrombin time, activated partial thromboplastin time, activated clotting time, and ecarin clotting time). Standard tests may not be helpful in assessing bleeding risk in overdose situations. The applicant measured bleeding time in the Phase 1 studies by an unvalidated assay. The effects of vorapaxar upon bleeding time are not known.

- Vorapaxar sulfate converts partially to the amorphous free base upon manufacturing and storage. A bioequivalence study demonstrated that the low base product (23%) and high base product (46%) were bioequivalent in the presence of a proton pump inhibitor, the worst case scenario.

6. Clinical Microbiology

Vorapaxar is an oral non-antimicrobial drug for which there are no clinical microbiology concerns.

7. Clinical/Statistical

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The applicant selected the dose based on platelet inhibition studies summarized in Section 5 above and detailed in the clinical pharmacology review. A limitation is that we do not know the exposure-response or inhibition-response relationship for either efficacy or safety.

7.1.2. Studies essential for approval

The pivotal study supporting approval is the Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA2P) trial. TRA2P was a large (26,449 subject), international, multi-center, randomized, double-blind, parallel group, cardiovascular (CV) outcomes trial in patients with a history of myocardial infarction (MI), cerebrovascular disease, or peripheral arterial disease (PAD). Dosing was vorapaxar 2.5 mg daily and the median duration of treatment was 823 days with follow-up to 4 years. TRA2P was successful on its primary endpoint of CV death, MI, stroke, or urgent coronary revascularization (UCR).

Another large (12,944 subject), international, multi-center, randomized, double-blind, parallel group, cardiovascular (CV) outcomes trial failed on its primary endpoint. This other study, the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial, was conducted in patients with acute coronary syndromes (ACS). TRACER used a loading dose of vorapaxar 40 mg followed by 2.5 mg daily for a median treatment duration of about 1 year. While TRACER failed on its primary endpoint analysis, it did provide valuable safety information regarding risks of intracerebral hemorrhage (ICH).

7.1.3. Other studies

The applicant conducted 21 phase 1 clinical studies in 1215 subjects, 1060 of whom received vorapaxar. The clinical pharmacology review addresses these studies. The applicant also conducted 3 phase 2 studies. The first was a multicenter dose-ranging study in 1030 subjects undergoing PCI (TRA-PCI) and the two others were small studies in the Japanese population.

The primary objective of TRA-PCI was to evaluate bleeding rates at sequential randomized combinations of loading doses (10, 20, or 40 mg) and maintenance doses (0.5, 1, and 2.5 mg). MACE was a secondary endpoint. Vorapaxar did not appear to

affect TIMI major or minor bleeding rates. Non-TIMI bleeding rate was higher in the 40/2.5 mg sequential group than in the placebo arm. MACE rates were slightly lower in the vorapaxar arms than in the placebo arm. The applicant interpreted TRA-PCI as justifying the phase 3 studies.

7.1.4. Primary clinical and statistical reviewers' findings and conclusions

The primary clinical reviewers, Dr. Martin Rose (efficacy) and Jonathan Levine (safety), recommend that vorapaxar be approved for the reduction of atherothrombotic events in patients with a history of MI or with PAD. (While their initial filed review recommends approval only with a history of MI, Dr. Rose presented at the advisory committee meeting arguments favoring approval with PAD and subsequently they have changed their recommendation to include with PAD.) They based their recommendation on the "robustly" positive results for the primary and key secondary endpoints in TRA2P. The hazard ratio (HR) for the primary endpoint was 0.88 (95% confidence interval [CI] 0.82 to 0.95, p=0.001.) They note that the key secondary endpoints including all randomized patients favored vorapaxar at the $p \leq 0.001$ level.

Their subgroup finding that is most relevant to labeling is that the risk of ICH was substantially increased in vorapaxar arm subjects with a prior history of stroke coupled with no observed benefit of vorapaxar for the primary endpoint in that subgroup. In the PAD stratum, which included only 14% of TRA2P patients, there was a 5% reduction in the rate of the primary endpoint with vorapaxar ($p>0.5$), but the results improved when prior stroke/TIA patients were removed from the analysis.

The primary statistical reviewer, Dr. Yeh-Fong Chen, confirmed the applicant's analysis results for the primary, key secondary and other important secondary endpoints in both TRACER and TRA2P studies. She observes that the efficacy results for vorapaxar demonstrated from TRA2P appear positive in all different patient populations and the findings appear robust throughout the trial. She is concerned with the unplanned interim efficacy analyses conducted, though she concedes that the trial still seems to achieve significance level of 0.01 for both the primary and the key secondary endpoints. It is unclear to her whether such unplanned unblinded interim efficacy analyses, sample size re-estimation and change of patient population might have some impact on trial integrity. She also notes that vorapaxar's effect seems larger as the body weight increases and seems little or negative in patients with weight ≤ 60 kg, but the apparent significant treatment by body weight interactions are difficult to interpret.

COMMENT: I agree with the primary clinical reviewers (although see my comments on PAD in Section 7.2.2). Regarding the unplanned interim efficacy analyses, they were performed for the DSMB to support the DSMB's mission of assessing safety and benefit-risk. I do agree that this DSMB appeared overconcerned with the narrower definition of benefit stipulated by the pre-specified primary composite endpoint and should have focused predominantly on the individual risks such as death, MI, stroke, ICH, etc. I have observed this overconcern with the pre-specified composite by

DSMBs in other trials. Because benefit-risk assessment is an integral part of the DSMB's mission and because the interim analyses did not affect trial conduct (other than the prior stroke and ICH issue discussed elsewhere), I judge that the DSMB's interim analyses did not affect trial integrity. I comment further in Section 7.1.6 below regarding the other specific issues.

7.1.5. Pediatric use

Myocardial infarctions and atherosclerotic peripheral arterial disease are not pediatric diseases so that pediatric studies of them are not possible and not needed.

7.1.6. Discussion of notable efficacy issues

Most issues impact both efficacy and safety and are relevant to benefit-risk assessments. I discuss specific issues in this section and address both the efficacy and safety aspects.

7.1.6.1. Data quality

The clinical reviewers judged the datasets were generally of good quality. They did find that some patients discontinued study early but were censored on an earlier date without information available on any component of the primary endpoint. At their request the applicant later conducted a sensitivity analysis in which the identified 110 subjects were censored on the last date when ascertainment of subjects' cardiovascular efficacy and safety status was made. The applicant confirmed that the primary and key secondary efficacy results were not impacted. The statistical reviewer found one variable for capturing events' adjudication status in TRACER that was problematic. The source variable code was wrong but events were properly included in the analyses.

Regarding completeness of follow-up the primary reviewers primarily quote the applicant's statistics. In TRA2P determining completeness of follow-up is complicated by the discontinuations of the patients with a history of stroke and who suffered a stroke during the study (and by a CRF flaw I describe below). These stroke patients were not followed after their early termination visits, making ITT assessments impossible for the study as a whole. For the indicated subgroup (patients without a history of stroke/TIA), incomplete follow-up for withdrew consent for follow-up was about 2.4% and for lost was 0.15%, so vital status follow-up was about 97.5% complete. Because about 2.1% had vital status follow-up only, follow-up for events was about 95.3% complete by these applicant statistics. I present below my analyses of follow-up for TRA2P.

In TRACER about 6.3% and 5.5% of subjects in the placebo and vorapaxar arms, respectively, discontinued follow-up alive. Many of these subjects had vital status assessed; only 2.0 and 1.8% of subjects in the placebo and vorapaxar arms, respectively had no vital status available at the end of study. However, subjects

who discontinued follow-up alive had no information on other study endpoints (MI, stroke, bleeding, etc.) after their last follow-up date.

I examined data completeness and quality in the TRA2P and identified two additional flaws:

- Serious adverse events (SAEs) were only to be reported until 60 days after the last dose of study drug. While this limitation is not critical for bleeding events, it is problematic for SAEs, such as cancers and ALS, that take time to develop and be detected.

- Patients who discontinued treatment were followed by phone contacts. The phone contacts consisted of a Visit case report form (CRF or screen) with fields for date of visit and type of contact (visit, phone) and possibly a Patient Status CRF with fields for patient status (continuing on treatment, discontinuing treatment, discontinuing study) and flags (yes/no) for adverse events, ischemic events, etc. with directions to the more detailed CRFs for the events. Unfortunately there was no date of visit field for the Patient Status CRF. In the data sets submitted there are examples of the last Patient Status CRF not corresponding to the last Visit phone contact. Hence we have no way of verifying from the datasets the last dates upon which the sites solicited events from patients whose last contacts were phone calls.

Within the limitation described above I tried to characterize the completeness of follow-up for the indicated population (without a prior stroke/TIA). About 80% of vorapaxar and 82% of placebo patients without a prior stroke/TIA died on-study or had a visit with vital signs on or after the earliest last follow-up date of August 1, 2011. However, as noted above, by protocol the last contact could be a phone call in patients who discontinued treatment. About 96.5% of patients without a prior stroke/TIA died on-study or had a visit or phone contact on or after the earliest last follow-up date of August 1, 2011 (although this estimate is subject to the uncertainty described in the previous paragraph.) The median follow-up for the 3.5% of these patients with incomplete follow-up was less than one year (0.93 year) compared to about 2.6 years for patients alive at study end with complete follow-up.

COMMENT: While the follow-up rate in TRA2P was better than those in recent trials such as PLATO and ATLAS, I would not characterize incomplete follow-up of 3.5% as good. It exceeds substantially the difference between arms in the primary endpoint rates of 1.15% and the difference in the mortality rates of 0.4%. While the follow-up rate is sufficient that we should not reject the TRA2P results, it is less than ideal such that we may still have lingering doubts about their validity.

7.1.6.2. Informative censoring

We should be concerned about the potential for informative censoring in trials of antiplatelet drugs in atherothrombotic disease because of the following potential

mechanism: the new antiplatelet drug causes more bleeding that leads to discontinuation of study drug, less complete follow-up, and more cardiac events. We may have less concern in TRA2P because the protocol specified following all patients who discontinued study drug until the end of the study. However, as I document above, while follow-up appeared adequate it was not optimal. We still need to examine the data available relevant to the potential for information censoring.

That patients with bleeds in CV trials suffer more cardiac events and deaths is widely but not universally appreciated. I summarized the evidence for it in the FDA briefing document for the January 16, 2014, AC meeting regarding another drug (rivaroxaban) causing more bleeding in its CV trial. Cardiac event and death rates for patients who have moderate or severe bleeds in CV trials are typically about 5-fold more frequent than for patients who don't have that severity of bleeding. Regardless, we do not have to rely upon references to other trials. Patients who had moderate or more severe bleeds in TRA2P fared worse than those who did not as shown in Table 1.

Table 1: Primary Endpoint Rates in Patients with and without GUSTO Moderate/Severe Bleeds in TRA2P

	GUSTO moderate/severe bleed	
	no	yes
placebo	10.1%	37% (of 317)
vorapaxar	8.5%	40% (of 476)

Primary endpoints were about 4-fold higher in patients who suffered a GUSTO moderate/severe bleed in TRA2P than those who did not.

For the endpoint rates to be biased it is not necessary that the bleed be causative of the endpoint. Frailty leading to both the bleed and the endpoint can also bias the endpoint rates. Incomplete follow-up in the patients who bled could bias the rates because more vorapaxar patients (476) had GUSTO moderate/severe bleeds than placebo patients (317). Hence more endpoint events could be missed in vorapaxar patients. Differential follow-up by arm, i.e., more incomplete follow-up in the vorapaxar, would increase the bias. There is slight evidence for both problems as shown in Table 2.

Table 2: Follow-up Rates in Patients with and without GUSTO Moderate/Severe Bleeds in TRA2P

	GUSTO moderate/severe bleed	
	no	yes
placebo	96.4%	97.8%
vorapaxar	96.6%	95.6%

The follow-up rate was lowest in patients in the vorapaxar arm with GUSTO moderate/severe bleeds and highest in the patients in the placebo arm with such bleeds. The interaction between vorapaxar use and GUSTO moderate/severe bleeding for follow-up is significant at the $p < 0.1$ level as shown in Table 3.

Table 3: Logistic Regression of Complete Follow-up by Treatment and GUSTO Moderate/Severe Bleeding in TRA2P

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Logistic regression                               Number of obs   =      26449
                                                  LR chi2(3)      =       4.33
                                                  Prob > chi2     =     0.2279
Log likelihood =  -4014.792                       Pseudo R2       =     0.0005

------------------------------------------------------------------------------
complete f/u | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   vorapaxar |   1.085265    .073768     1.20   0.229     .9498991     1.23992
     gustoms |   1.673565    .644464     1.34   0.181      .786789    3.559813
 vor#gustoms |
(interaction)|   .4508125   .2018709    -1.78   0.075     .1874276    1.084322
             |
       _cons |    26.4617   1.243437    69.71   0.000     24.13347    29.01455
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```

However, the follow-up rates in all subgroups would appear to be adequate and the endpoint differences explained by the differential follow-up are small: The difference in primary endpoints between arms is 148. The number of vorapaxar patients with incomplete follow-up who had a GUSTO moderate/severe bleed but no primary endpoint is 16 for vorapaxar vs. 6 for placebo.

COMMENT: While there appears to be some informative censoring, it does not explain or eliminate the primary endpoint advantage for vorapaxar. This conclusion depends upon the follow-up statistics being accurate.

7.1.6.3. Exclusion of prior stroke and inclusion of MI and PAD

Whether to exclude patients with a history of stroke and whether to include PAD patients in addition to those with a history of MI are questions of both efficacy and safety, i.e., of benefit-risk. I discuss these questions under Section 7.2.2 below.

7.1.6.4. Age, sex, and race

Because age is associated with some variations in efficacy (and safety) I will discuss it last. Sex does not appear to be associated with such variations. Women had slightly higher endpoint and bleeding rates than men but there are no interactions between treatment and sex. Some of the differences may be related to the fact that women were older than men (mean age 63.2 vs. 60.2 in TRA2P), as is typical of most cardiovascular trials because women develop atherosclerotic cardiac disease later in life than men.

Regarding race, about 87% of TRA2P patients were white, 5.3% were multiracial, 4.5% were Asian, and 2.6% were black.

COMMENT: This race distribution does not facilitate sensitive analyses regarding racial variations. We would like to see better representation of the US population in CV studies but, with the trend towards greater international participation in CV trials, that goal is not being realized. Atherosclerotic cardiac disease appears to have the same pathophysiology and similar clinical courses among different racial populations so the predominance of whites in the vorapaxar studies is not a critical issue.

The mean and median ages in the TRA2P indicated population were about 60 years. About 33.4% were age 65 or older and about 9.2% were age 75 or older. I show the primary endpoint rates for the TRA2P population by age quintile in Table 4 and the GUSTO moderate/severe bleeding rates by age quintile in Table 5.

Table 4: Primary Endpoint Rates by Age Quintile in the TRA2P Indicated Population

quintile	placebo	vorapaxar
≤51	9.6%	7.7%
52-58	10.0%	7.1%
59-64	9.2%	8.4%
65-71	11.3%	9.5%
>71	14.9%	14.5%

Table 5: GUSTO Moderate/Severe Bleeding Rates by Age Quintile in the TRA2P Indicated Population

quintile	placebo	vorapaxar
≤51	0.9%	1.5%
52-58	1.7%	2.2%
59-64	1.9%	3.4%
65-71	3.1%	4.0%
>71	5.1%	7.0%

By the quintile analyses efficacy appears reduced in those age 72 or older while bleeding rates increase with increasing age for both placebo and vorapaxar. However, an interaction between age and vorapaxar for efficacy is not clear: For patients 75 or older the point estimates for the primary endpoint favor vorapaxar and the interaction between age 72 and older and vorapaxar is not statistically significant as shown by the Cox regression in Table 6.

Table 6: Cox Regression of the Primary Endpoint with Age ≥ 72 and Selected Other Cofactors for the TRA2P Indicated Population

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Stratified Cox regr. -- Breslow method for ties

No. of subjects =        20172                     Number of obs   =     20172
No. of failures =         1991
Time at risk    =     17821356
                                                   LR chi2(7)      =    317.06
Log likelihood  =   -17034.557                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
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          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   vorapaxar |   .7964017   .0406344    -4.46   0.000     .7206124    .8801619
     agege72 |   1.323648   .1038919     3.57   0.000     1.134913     1.54377
 vor#agege72 |
(interaction)|   1.177796   .1278934     1.51   0.132     .9520076    1.457134
             |
        male |   .9613515   .0510057    -0.74   0.458     .8664044    1.066704
       asian |   .7260381   .1047661    -2.22   0.027     .5471828    .9633551
    egfrlt60 |   1.546764   .0886011     7.61   0.000     1.382502    1.730543
    diabetes |   1.845257   .0908462    12.44   0.000     1.675522    2.032186
------------------------------------------------------------------------------
                                                        Stratified by strata
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For TRACER, the point estimates by age quintile for the primary endpoint favor vorapaxar except for the lowest age quintile ≤ 56. GUSTO moderate/severe bleeding was substantially higher with vorapaxar in the highest age quintile ≥ 74 (about 8.4% placebo vs. 13% vorapaxar.)

COMMENT: Whether vorapaxar efficacy is reduced in the elderly, i.e., age ≥ 72 or age ≥ 75, is not clear. Bleeding risk is increased in the elderly regardless of treatment.

7.1.6.5. Body weight and renal function

The clinical pharmacology reviewers have raised the issue of whether low body weight, e.g., < 60 kg, is associated with less favorable benefit-risk. They postulate decreased efficacy and increased bleeding based predominantly on point estimates of hazard ratios from subgroup analyses, e.g., by weight < 60 kg or ≥ 60 kg. I show in Table 7 the primary endpoint rates by this dichotomization and treatment for TRA2P.

Table 7: Primary Endpoint Rates by Weight < or ≥ 60 kg and Treatment in TRA2P

	N	placebo	vorapaxar
< 60 kg	1,852	8.4%	10.6%
≥ 60 kg	24,587	11.0%	9.6%

The < 60 kg subgroup is small, about 7% of the study, but the vorapaxar effect is strikingly reversed. The interaction between treatment and dichotomized weight by logistic regression is "statistically" significant (p = 0.012, remembering that this is a non-prespecified subgroup analysis.)

The primary endpoint rates by weight quintile in TRA2P are interesting as I show in Table 8.

Table 8: Primary Endpoint Rates by Weight Quintile and Treatment in TRA2P

quintile	placebo	vorapaxar
≤68.6	9.8%	9.9%
68.7-77	10.2%	9.7%
77.1-88	10.4%	9.0%
88.1-95.2	11.5%	9.5%
>95.2	12.3%	10.4%

The endpoint rates in the placebo arm monotonically increase with increasing weight while those in the vorapaxar arm form a flat U or J-shaped distribution across the weight quintiles.

I show in Table 9 the GUSTO moderate/severe bleeding rates by weight quintile and treatment in TRA2P.

Table 9: GUSTO Moderate/Severe Bleeding Rates by Weight Quintile and Treatment in TRA2P

quintile	placebo	vorapaxar
≤68.6	2.7%	4.4%
68.7-77	2.9%	4.2%
77.1-88	2.4%	3.5%
88.1-95.2	1.7%	2.9%
>95.2	2.2%	3.0%

Bleeding rates in TRA2P are higher for the two lowest weight quintiles for both placebo and vorapaxar.

For the indicated population (without history of stroke/TIA) the interaction between weight < 60 kg and treatment remains significant and bleeding rates remain higher in the two lowest weight quintiles. However, the distributions of primary endpoint rates by weight quintiles is slightly different than for the ITT population as shown in Table 10.

Table 10: Primary Endpoint Rates by Weight Quintile and Treatment in TRA2P for the Indicated Population

quintile	placebo	vorapaxar
≤68.6	10.3%	9.5%
68.7-77	9.8%	8.7%
77.1-88	9.8%	7.8%
88.1-95.2	10.9%	9.1%
>95.2	12.5%	10.2%

For the lowest quintile the point estimate for the primary endpoint rate for the placebo arm patients is slightly greater than the point estimate for the vorapaxar patients.

It is informative to examine the same statistics for TRACER. I show the primary endpoint rates by weight dichotomization and treatment for TRACER in Table 11

Table 11: Primary Endpoint Rates by Weight < or ≥ 60 kg and Treatment in TRACER

	N	placebo	vorapaxar
< 60 kg	1,046	18.2%	19.3%
≥ 60 kg	11,898	16.9%	15.6%

The < 60 kg subgroup is similarly small, about 8% of the study and the vorapaxar effect is numerically reversed. The interaction between treatment and dichotomized weight is not statistically significant by logistic regression.

I show the primary endpoint rates by weight quintile for TRACER in Table 12.

Table 12: Primary Endpoint Rates by Weight Quintile and Treatment in TRACER

quintile	placebo	vorapaxar
≤68	17.0%	17.7%
68.1-77	17.0%	14.3%
77.1-85	15.7%	15.3%
85.1-95.5	17.0%	16.5%
>95.5	18.8%	16.0%

In TRACER the primary endpoint rates by weight quintile appear more random than in TRA2P.

I show in Table 13 the GUSTO moderate/severe bleeding rates by weight quintile and treatment in TRACER.

Table 13: GUSTO Moderate/Severe Bleeding Rates by Weight Quintile and Treatment in TRACER

quintile	placebo	vorapaxar
≤68	5.4%	9.5%
68.1-77	5.6%	7.8%
77.1-85	5.4%	6.3%
85.1-95.5	5.4%	5.4%
>95.5	4.6%	6.2%

In TRACER the placebo bleeding rates vary little by weight quintile. The TRACER placebo bleeding rates are higher than in TRA2P, likely related to the TRACER ACS population having higher procedure rates and greater use of dual antiplatelet therapy than in TRA2P. The vorapaxar bleeding rates in TRACER are highest in the two lowest weight quintiles.

I also examined the results by weight for the prasugrel TRITON trial in ACS. Prasugrel, like vorapaxar, has substantially higher exposure in patients with lower

body weight. For prasugrel exposure is about 50% higher for 60 kg when compared to 85 kg according to FDA clinical pharmacologists. The clopidogrel arm of TRITON is similar to the placebo arm of TRACER. I show in Table 14 the primary endpoint (MACE) rates by weight dichotomization and treatment in prasugrel TRITON.

Table 14: Primary Endpoint Rates by Weight < or ≥ 60 kg and Treatment in Prasugrel TRITON

	N	clopidogrel	prasugrel
< 60 kg	657	11.5%	9.7%
≥ 60 kg	12,951	11.6%	9.4%

Prasugrel shows little difference in efficacy for patients < 60 kg (odds ratio 0.82 vs. 0.80). By weight quintiles both arms show slightly higher endpoint rates for the lowest two quintiles. TIMI minor/major bleeding rates were substantially higher in patients < 60 kg (about 2-fold) and highest with prasugrel but the interaction term for weight < 60 kg and prasugrel use is not statistically significant by logistic regression (although the < 60 kg subgroup is small as shown in Table 14.)

COMMENT: I do not see a consistent pattern in the above analyses that low body weight, e.g., <60 kg, is associated with reduced efficacy of vorapaxar. While the interaction between vorapaxar and weight <60 kg in TRA2P is striking, it appears explained by better "efficacy" at lower body weights in the placebo arm. TRACER results are equivocal and TRITON, particularly the results in the clopidogrel arm that is similar to the placebo arm of TRACER, is not supportive. All three trials suggest that bleeding rates are higher in patients with lower body weight. The latter observation appears real. I'm not convinced that the efficacy results by body weight in TRA2P are real but I suspect that they may be chance subgroup variations.

While low body weight increases vorapaxar exposure, reduced renal function has less impact upon PK: The estimated increase in exposure is 17% for mild (estimated creatine clearance 60 to 89 mL/min by Cockcroft-Gault formula) and 34% for moderate (30 to 59 mL/min) renal impairment. The TRA2P results for efficacy by glomerular filtration rate estimated by the MDRD formula (eGFR) show little effect of eGFR upon relative efficacy as shown in Table 15.

Table 15: Primary Endpoint Rates by eGFR < or ≥ 60 mL/min/1.73m^2 and Treatment in TRA2P Indicated Population

	N	placebo	vorapaxar
≥60	17,313	9.7%	7.9%
<60	2,859	17.0%	15.6%

Endpoint rates were higher (about double) in patients with eGFR<60. The point estimate of the vorapaxar benefit is slightly lower in patients with eGFR <60 but the interaction between treatment and eGFR<60 by logistic regression is insignificant.

Bleeding rates were also higher (about 2.6-fold) with reduced renal function as shown in Table 16.

Table 16: GUSTO Moderate/Severe Bleeding Rates by eGFR < or ≥ 60 mL/min/1.73m^2 and Treatment in TRA2P Indicated Population

	N	placebo	vorapaxar
≥60	17,313	1.9%	2.7%
<60	2,859	5.1%	7.3%

Of the subgroup <60, only 171 patients had eGFR<30. There is no interaction between treatment and eGFR<60 for bleeding. In logistic regressions eGFR seems to be a better predictor of bleeding than weight. I show the most complete model I tested in Table 17.

Table 17: Logistic Regression of GUSTO Moderate/Severe Bleeds with Selected Baseline Cofactors in TRA2P Indicated Population

```
Logistic regression                               Number of obs   =      20140
                                                  LR chi2(9)      =     377.75
                                                  Prob > chi2     =     0.0000
Log likelihood = -2415.5334                       Pseudo R2       =     0.0725

------------------------------------------------------------------------------
     gustoms | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   vorapaxar |   1.469261   .1282002     4.41   0.000     1.238304    1.743293
         pad |    1.75948   .1865636     5.33   0.000     1.429317    2.165909
         age |   1.039721   .0049642     8.16   0.000     1.030036    1.049496
        male |   1.024737   .1072836     0.23   0.815     .8346353    1.258137
       asian |   1.169588    .341179     0.54   0.591      .660283    2.071743
         usa |   2.209129     .20564     8.51   0.000     1.840712    2.651285
       p2y12 |   1.483985   .1526577     3.84   0.000     1.213016    1.815485
      weight |   .9959116   .0028549    -1.43   0.153     .9903317    1.001523
       egfr0 |   .9882023   .0023314    -5.03   0.000     .9836434    .9927822
       _cons |   .0036196   .0018574   -10.95   0.000     .0013239     .009896
------------------------------------------------------------------------------
```

There are no significant interactions with treatment.

COMMENT: Moderate renal functional impairment is a risk factor for bleeding. We should mention the increased risk in the label.

7.1.6.6. Use with other platelet inhibitors and anticoagulants

In TRA2P, while there was frequent use of aspirin (98%) and clopidogrel (78%) in the indicated population, use of other antiplatelet agents was rare (ticlopidine 0.5%, prasugrel 0.2%, and no ticagrelor). Use of anticoagulants, including warfarin or other vitamin K antagonists, was also rare (0.1%). Please see the primary clinical review for more details on concomitant drug use.

COMMENT: The label should reflect the lack of experience with platelet inhibitors other than aspirin and clopidogrel and with anticoagulants.

7.1.6.7. Aspirin dosage

Aspirin dosage, i.e., ≤100 mg vs. ≥ 300 mg daily, was an issue for another platelet inhibitor, ticagrelor. For ticagrelor efficacy appeared to be reduced while bleeding was higher with concomitant use of ticagrelor and the higher aspirin dosages. The ticagrelor label recommends use with aspirin 75-100 mg per day. Hence we should examine aspirin dosage with vorapaxar.

For both TRA2P and TRACER I estimated oral aspirin dosage from the concomitant medication datasets. I did not include rectal administration and the occasional intravenous aspirin dosing in Europe. I used two methods: (1) the earliest post-randomization aspirin dose; and (2) the aspirin dose with the most days of administration post-randomization, the "modal" aspirin dose. Because the earliest post-randomization dose is closest to a baseline factor, I present primarily the results for it, commenting if the modal dose results are different and appear informative.

Aspirin dosage in TRA2P and TRACER shows geographic variation similar to that seen in ticagrelor PLATO. I show the aspirin dosage by geographic region for the TRA2P indicated population in Table 18 and for TRACER in Table 19.

Table 18: Initial Oral Aspirin Dosage by Outside United States vs. US for the TRA2P Indicated Population

	OUS*	US
N	15,280	4,892
0 or missing	3%	2%
≤100	85%	48%
101-299	11%	5%
≥300	2%	45%

*OUS = outside United States

Table 19: Initial Oral Aspirin Dosage by Outside United States vs. US for TRACER

	OUS*	US
N	10,131	2,813
0 or missing	2%	2%
≤100	82%	29%
101-299	8%	3%
≥300	8%	67%

*OUS = outside United States

Higher aspirin dosage in TRA2P and TRACER, as in PLATO, was predominantly in the US. Modal use of dosages ≥ 300 mg daily was slightly lower (TRA2P 1% and 39%, TRACER 2% and 50%, OUS vs. US). For the "0 or missing" category I cannot determine from the data sets whether the patient did not take aspirin or

whether the site did not record the aspirin administration. Because this category is infrequent as well as indeterminate, I do not include it in the remainder of the analyses.

I examined baseline factors associated with aspirin dosages ≥ 300 mg in TRA2P by logistic regression. I show the most informative model in Table 20.

Table 20: Logistic Regression of Initial Oral Aspirin Dosage ≥ 300 mg with Selected Baseline Cofactors for the TRA2P Indicated Population

```
Logistic regression                               Number of obs   =      19685
                                                  LR chi2(9)      =    5650.25
                                                  Prob > chi2     =     0.0000
Log likelihood = -4656.2848                       Pseudo R2       =     0.3776

------------------------------------------------------------------------------
   asa0ge300 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   vorapaxar |   1.020918   .0538119     0.39   0.694     .9207137    1.132028
         age |   .9875395   .0025354    -4.88   0.000     .9825827    .9925213
        male |   1.308733   .0825255     4.27   0.000     1.156582      1.4809
       asian |    .721173   .1711046    -1.38   0.168     .4529857    1.148139
             |
    diabetes |   1.851498   .2481358     4.60   0.000      1.42379    2.407689
          us |   21.43683    3.63952    18.05   0.000     15.36896    29.90037
 diabetes#us |
(interaction)|   .5844022   .0876921    -3.58   0.000     .4354971    .7842208
             |
     priormi |    .711126   .1136203    -2.13   0.033      .519931    .9726294
  us#priormi |
(interaction)|    2.72325   .4781515     5.71   0.000     1.930334    3.841869
             |
       _cons |   .0393934   .0092069   -13.84   0.000     .0249164    .0622821
------------------------------------------------------------------------------
```

Randomized treatment was unrelated to aspirin dosage (as it should be.) Older patients were less likely to receive the higher dosages while men were more likely. Diabetics were more likely, at least OUS. In the US patients with prior MI were more likely to receive the higher dosages. Logistic regressions of the TRACER data produce similar associations except for no clear association with diabetes.

I show the primary endpoint rates by initial oral aspirin dosage for the TRA2P indicated population in Table 21 and for TRACER in Table 22.

Table 21: Primary Endpoint Rates by Initial Oral Aspirin Dosage for the TRA2P Indicated Population

	placebo	vorapaxar
≤100	10%	8%
101-299	12%	8%
≥300	13%	14%

Table 22: Primary Endpoint Rates by Initial Oral Aspirin Dosage for TRACER

	placebo	vorapaxar
≤100	17%	15%
101-299	19%	14%
≥300	18%	19%

For both TRA2P and TRACER the primary endpoint point estimates are favorable for the lower aspirin dosages while the point estimates favor placebo for aspirin dosages ≥ 300 mg. The interactions between vorapaxar and aspirin dosages ≥ 300 mg are marginally statistically significant as shown in Cox regressions for TRA2P in Table 23 and for TRACER in Table 24.

Table 23: Cox Regression of the Primary Endpoint with Initial Oral Aspirin Dosage ≥ 300 mg Cofactor Interaction for the TRA2P Indicated Population

```
Stratified Cox regr. -- Breslow method for ties

No. of subjects =        19685                     Number of obs   =     19685
No. of failures =         1940
Time at risk    =     17370069
                                                   LR chi2(3)      =     46.37
Log likelihood  =   -16717.015                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   vorapaxar |   .8115709   .0406506    -4.17   0.000     .7356831    .8952867
   asa0ge300 |   1.251511   .1081732     2.60   0.009     1.056481    1.482544
vor#asa0ge300|
(interaction)|   1.271253   .1540373     1.98   0.048     1.002518    1.612025
------------------------------------------------------------------------------
                                                        Stratified by strata
```

Table 24: Cox Regression of the Primary Endpoint with Initial Oral Aspirin Dosage ≥ 300 mg Cofactor Interaction for TRACER

```
Stratified Cox regr. -- Breslow method for ties

No. of subjects =        12718                     Number of obs   =     12718
No. of failures =         2091
Time at risk    =      5534381
                                                   LR chi2(3)      =     10.37
Log likelihood  =   -17189.043                     Prob > chi2     =    0.0157

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   vorapaxar |   .8830731   .0442103    -2.48   0.013     .8005381    .9741175
   asa0ge300 |   1.011367   .0751137     0.15   0.879     .8743605    1.169842
vor#asa0ge300|
(interaction)|   1.203853   .1244213     1.80   0.073     .9831047    1.474169
------------------------------------------------------------------------------
                                                        Stratified by strata
```

The results for modal aspirin dosages are not as differentiated. For TRA2P the point estimate of the primary endpoint rate is slightly higher for placebo for the patients receiving a modal aspirin dosages ≥ 300 mg while for TRACER the point estimates are nearly identical in each arm with modal aspirin dosages ≥ 300 mg.

Bleeding shows as different pattern as shown by GUSTO moderate/severe bleeding rates for the TRA2P indicated population in Table 25 and for TRACER in Table 26.

Table 25: GUSTO Moderate/Severe Bleeding Rates by Initial Oral Aspirin Dosage for the TRA2P Indicated Population

	placebo	vorapaxar
≤100	2.1%	3.3%
101-299	1.7%	2.0%
≥300	4.0%	4.9%

Table 26: GUSTO Moderate/Severe Bleeding Rates by Initial Oral Aspirin Dosage for TRACER

	placebo	vorapaxar
≤100	5.2%	6.5%
101-299	3.4%	5.4%
≥300	6.4%	8.9%

Bleeding rates were always slightly higher with vorapaxar than with placebo. Bleeding rates were highest in the patients receiving aspirin dosages ≥ 300 mg. There is no interaction between vorapaxar and aspirin dosage for bleeding.

COMMENT: Aspirin dosages were not randomized and we do not know how they were assigned in the US, while use of higher dosages was uncommon OUS. The greater use of higher dosages in TRACER compared to TRA2P and the greater use of higher dosages in TRA2P patients with prior MIs suggest that patients treated with the higher dosages were higher risk. Conversely, the lower use in the elderly does not confirm that patients treated with higher dosages were consistently higher risk.

The vorapaxar results appear to be consistent with but not as extreme as the ticagrelor PLATO results: Efficacy was slightly worse with the higher aspirin dosages and the more potent other platelet inhibition while bleeding was substantially worse. Particularly because of the increased bleeding rates I recommend that the label suggests aspirin dosages of 75 to 100 mg daily for concomitant use with vorapaxar.

7.1.6.8. Vorapaxar use with surgery

For all antiplatelet agents a clinically relevant question is what to do with them prior to surgery. Continuing them may lead to procedure-related bleeding while discontinuing them may lead to cardiac events. In the vorapaxar clinical trials the protocols recommended continuing vorapaxar despite surgery. The best documented surgical procedures in the trials were coronary artery bypass grafting (CABG). It is informative to examine bleeds and cardiac events post-CABG in the vorapaxar trials.

To assign CABG-related bleeds I examined bleeding rates post-CABG regardless of treatment arm. The bleeding rates were highest immediately post-CABG but did not appear to return to a low level until about 21 days post-CABG. Hence I counted any bleed occurring within 21 days post-CABG as a CABG-related bleed. I counted similarly for deaths and primary endpoints.

About 199 placebo and 177 vorapaxar patients in the TRA2P indicated population had a CABG reported, including after the earliest last follow-up date. In TRACER about 953 placebo and 935 vorapaxar patients had a CABG reported. In both studies the majority of patients had vorapaxar continued until the day of surgery. In TRA2P the 25th percentile was discontinuation 10 days prior and in TRACER 3 days prior.

I show selected bleeding and efficacy rates for 21 days post-CABG in the TRA2P indicated population in Table 27 and for TRACER in Table 28.

Table 27: Bleeding and Efficacy Rates in the TRA2P Indicated Population for 21 Days Post-CABG

	placebo	vorapaxar
Number of CABGs	199	177
GUSTO moderate/severe bleed	12.1%	15.8%
TIMI minor/major bleed	9.1%	10.2%
TIMI major bleed	7.0%	7.9%
Intracranial hemorrhage	0.5%	0.0%
Primary endpoint*	8.1%	2.2%
Deaths	2.5%	1.7%

* Excluding 115 placebo and 92 vorapaxar patients with primary endpoints prior to CABG

Table 28: Bleeding and Efficacy Rates in TRACER for 21 Days Post-CABG

	placebo	vorapaxar
Number of CABGs	953	935
GUSTO moderate/severe bleed	17.0%	21.1%
TIMI minor/major bleed	8.5%	11.1%
TIMI major bleed	8.1%	11.0%
Intracranial hemorrhage	0.0%	0.3%
Primary endpoint*	8.3%	5.9%
Deaths	3.9%	1.7%

*Excluding 85 placebo and 92 vorapaxar patients with primary endpoints prior to CABG

Bleeding rates were slightly higher with vorapaxar post-CABG. Both the primary endpoint rates and death rates were substantially lower with vorapaxar post-CABG. The results in the two studies appear consistent.

COMMENT: There appears to be strong justification from the trials for continuing vorapaxar despite surgery.

7.2. Safety

7.2.1. General safety considerations

The major safety concern for vorapaxar is bleeding.

7.2.2. Safety findings

The primary clinical review covers the bleeding findings in detail, including the ICH findings that lead to exclusion of patients with a history of stroke from the indicated population. I will not repeat the findings here. The analyses that I consider most relevant are the bleeding—and primary efficacy endpoint—rates by indication subgroup and thienopyridine use (the original strata except including all patients with a prior history of stroke/TIA in the stroke subgroup.)

Table 29: ITT GUSTO Moderate/Severe Bleeding and Primary Efficacy Endpoint Rates by Indication Subgroup and Thienopyridine Use in TRA2P

sub group	thieno-pyridine	N		primary endpoint		GUSTO mod/sev	
		placebo	vorapaxar	placebo	vorapaxar	placebo	vorapaxar
MI	yes	6,207	6,203	10.6%	8.9%	2.1%	3.0%
	no	2,232	2,256	9.6%	8.1%	1.3%	2.2%
stroke*	yes	945	959	15.0%	17.9%	3.6%	5.4%
	no	2,189	2,184	9.5%	8.9%	2.2%	3.9%
PAD	yes	527	515	14.6%	13.4%	6.5%	9.5%
	no	1,124	1,108	11.6%	10.0%	3.8%	5.0%

*includes MI and PAD strata patients with a prior history of stroke/TIA

In Table 29 I provide the ITT rates (or as close as one can approximate given the discontinuations for stroke history and otherwise) for both the primary efficacy endpoint and the bleeding rates so that the rates can be compared for benefit-risk assessment.

COMMENT: The benefit-risk in the stroke subgroup without thienopyridine use appears favorable above because Table 29 does not break out ICH, for which the rate in the stroke subgroup without thienopyridine use was about 2%. I consider the contraindication in patients with a history of stroke to be justified by the safety data.

For the MI and PAD subgroups, the benefit-risk by the rates in Table 29 appears favorable with the possible exception of the PAD patients already receiving a thienopyridine. The point estimate rates for these latter patients suggest a small efficacy benefit (1.2%) that must be weighed against a substantial rate of bleeding (3% higher.) The counterargument is that we may be slicing-and-dicing the results excessively if we also contraindicate these patients. My preference is not to exclude them from the indication but to characterize the results for them in the label.

7.2.3. Safety update

There were no active vorapaxar clinical studies so the 120-day safety update did not provide additional safety data.

7.2.4. Immunogenicity

Immunogenicity is not a significant concern for this small molecule.

7.2.5. Special safety concerns

The nonclinical studies raised issues regarding the safety of vorapaxar in pregnant and nursing women and regarding retinal toxicity. Because there are no clinical studies in pregnant or nursing women and such studies are infeasible because pregnant or nursing women rarely have PAD or histories of MI, we will address this issue with appropriate labeling.

Regarding possible retinal toxicity, there were no clinically or statistically significant differences in ocular or visual adverse event rates between vorapaxar and placebo except for diplopia (which is an ocular muscle disorder rather than a retinal disorder) and conjunctival and scleral bleeds (also not retinal but expected effects of an antiplatelet drug.) The ocular substudy in 102 TRA2P subjects included spectral domain optical coherence tomography, visual acuity, refraction, and fundus photography. Dr. Boyd, an FDA ophthalmology consultant, concluded that "There does not appear to be an increased ocular risk associated with the use of SCH 530348 [vorapaxar] based on the evaluations performed."

The diplopia appears to be a real finding because rates of diplopia were increased in the vorapaxar arms of both TRACER and TRA2P. The mechanism for the excess diplopia is unclear. Per the primary safety reviewer the risk appears to be small, about 1 extra case of diplopia per 1000 treated subjects.

There was also a numeric excess of amyotrophic lateral sclerosis (ALS) or upper motor neuron disorders in the vorapaxar arm of TRA2P. The difference is not statistically significant and the primary reviewers calculate that the incidence of ALS in the studies is consistent with expectations based on epidemiological studies. Most likely this is a chance finding. Regardless, an increased rate of a rare event like ALS should be detectable in the post-marketing data if the association is real.

7.2.6. Primary reviewers' comments and conclusions

The primary clinical reviewers recognized bleeding as the major safety consideration for vorapaxar. They noted that there is a higher rate of bleeding with vorapaxar compared to placebo across all general bleeding categories with hazard ratios of about 1.2 to 1.8 for the as-treated (+ 30 days) proposed label population. They noted

additionally that, while fatal bleeding is higher, it was still a rare event (about 0.2% in TRA2P) and that CABG-related bleeding was similar between vorapaxar and placebo.

They balanced safety and efficacy with a benefit-risk analysis. Their estimated advantages of vorapaxar in the proposed label population of TRA2P were 5 fewer fatal events and 45 fewer non-fatal serious events vs. 33 additional GUSTO moderate bleeds.

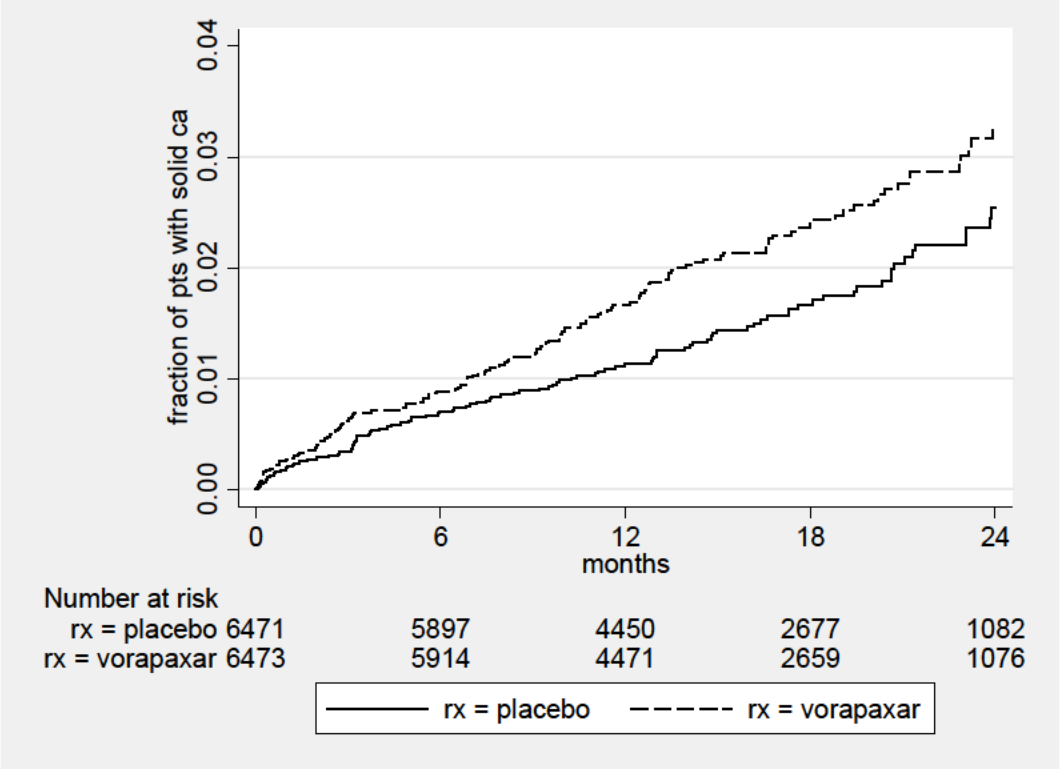
7.2.7. Discussion of notable safety issues

Bleeding is the major safety concern for vorapaxar. I have discussed it above as well as the special safety concerns of retinal toxicity, diplopia, and ALS. There is one more safety issue worth discussing: For other antiplatelet and anticoagulant drugs we have observed increased rates of solid cancers in the arms having more bleeding. Whether the increased rates are simply detection biases resulting from bleeding leading to more cancer diagnoses or whether there is a cancer promotion effect is unclear. Regardless, we should comment upon cancer rates in the vorapaxar outcomes trials.

The primary clinical reviewers commented upon deaths caused by solid cancers. In TRACER they reported 27 such deaths for vorapaxar vs. 18 for placebo. In TRA2P they reported 111 such deaths for vorapaxar for 97 for placebo.

I show the times to first solid cancer events by arm in Figure 1. The solid cancer results for TRACER look very similar to those for prasugrel TRITON, the trial that initiated the controversy regarding bleeding and cancer. In TRACER, as in TRITON, deaths in solid cancer patients were high: 37 in vorapaxar patients vs. 24 in placebo patients.

Figure 1: Times to First Solid Cancer Events by Arm in TRACER

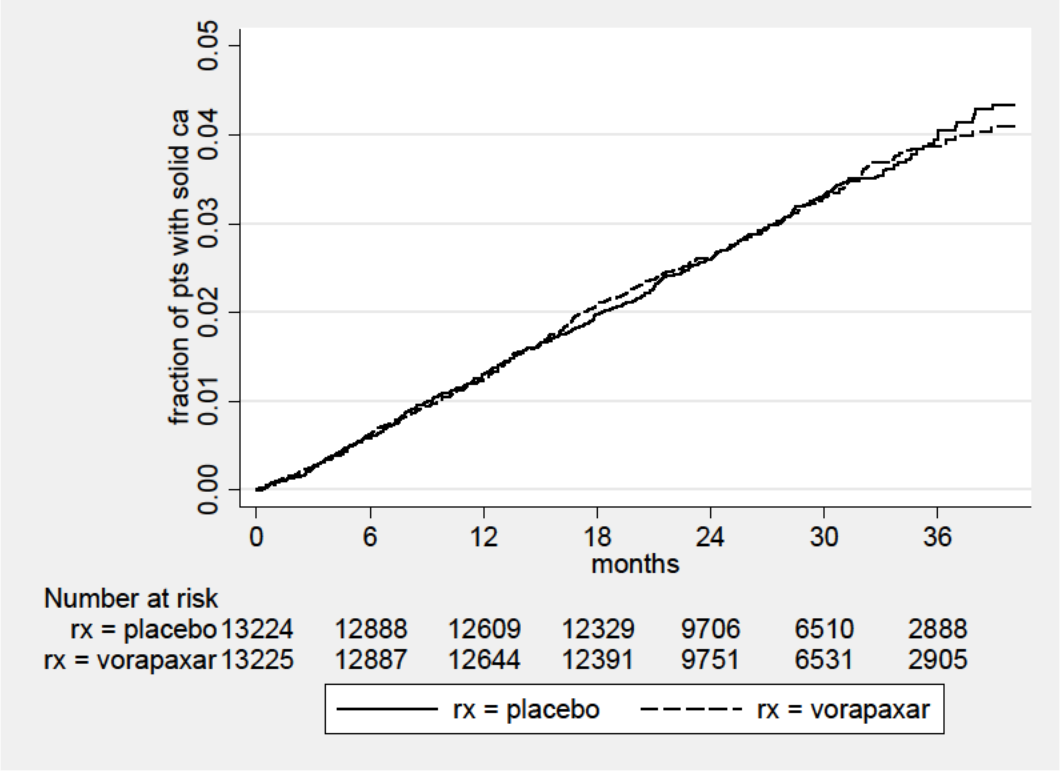


Hazard ratio 1.4 (95% CI 1.1 to 1.8, p = 0.012)

However, the solid cancer incidence in TRA2P is completely different. Times to first solid cancer events were virtually identical by arm as shown in Figure 2. As noted by the primary clinical reviewers, there was a slight excess of solid cancer deaths in the vorapaxar arm in TRA2P.

COMMENT: I find it difficult to reconcile the disparate results for solid cancers in TRACER and TRA2P. TRACER results look similar to TRITON as well as most other recent anticoagulant trials: The arm with more bleeding has more solid cancers. TRA2P, on the other hand, is inconsistent in that, while there was more bleeding in the vorapaxar arm, solid cancer incidence rates were similar. One has to wonder whether the incomplete follow-up on patients who discontinued study drug is contributory—although there is no suggestion in the curves of an early effect and TRACER shared the 60-day cutoff after treatment discontinuation on adverse event follow-up. One can argue that the larger size of TRA2P provides the better estimate than TRACER. Without a clear resolution of the disparity and no signal of a problem in TRA2P I judge that vorapaxar does not show a different effect on solid cancers than other antiplatelets and anticoagulants and that there is no need to describe these results in label until we have resolved the question of the relationship between bleeding and solid cancers.

Figure 2: Times to First Solid Cancer Events by Arm in TRA2P



8. Advisory Committee Meeting

We presented vorapaxar at the meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) on January 15, 2014. The committee voted 10 to 1 for approval. While a large majority of members judged the benefit-risk to be favorable, the one member voting against approval expressed concern about the size of the clinical benefit, particularly relative to harder end points such as CV death. He also expressed concern about bleeding in the general population compared to a clinical trial population.

9. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

10. Financial Disclosure

Of 6030 investigators for TRA2P 14 had disclosable financial interests. However, the total number of investigators lacking at least some element of disclosure is 1057. The primary clinical efficacy reviewer Dr. Rose has filed a review providing the details of the incomplete disclosures and the lack of an impact upon study results. His summary is relevant:

> "The study was a large double blind, placebo controlled RCT with >26,000 subjects, > 1000 sites and > 6000 investigators worldwide. There was a blinded, centralized adjudication process for efficacy and safety endpoints. The sponsor describes a diligent

process for follow-up in cases where investigators failed to provide disclosure. Patients at sites where at least one investigator disclosed an interest constitute a very small fraction of the total number of patients. When sites where at least one investigator had an interest are removed from the primary efficacy and safety analyses, the results for these endpoints are unchanged. Also, there is no notable effect on the safety and efficacy results when sites with at least one investigator who had an interest are combined with sites where at least one investigator failed to provide complete disclosure and then removed from the primary safety and efficacy analyses. There is no substantial reason to be concerned about the integrity of the study due to known financial interests or failure to disclose such interests."

11. Labeling

11.1. Proprietary name

We have accepted the proprietary name Zontivity.

11.2. Physician labeling

We have various recommendations regarding the proposed physician labeling that we will communicate to the applicant during label negotiations. One major change is to extend the indication from only patients with a history of MI to include also patients with PAD. We will also insure that the risk of ICH in patients with a history of stroke is addressed adequately.

11.3. Carton and immediate container labeling

The CMC reviewer Dr. Thomas Wong recommended, and the applicant adopted, that the tablet strength should be expressed as 2.08 mg, equivalent to 2.5 mg vorapaxar sulfate in the entire labeling. The final carton and immediate container labeling is acceptable.

11.4. Patient labeling/medication guide

The primary clinical reviews recommend that a medication guide be required with the following risk information:

- An increased risk of bleeding with vorapaxar overall;
- Contraindications in patients with prior ICH, ischemic stroke or TIA; or current overt pathological bleeding
- Discontinue treatment in the event of stroke or TIA on treatment
- Subgroups with increased risk of bleeding:
  - Elderly
  - Weight < 60 kg
  - Severe hepatic impairment
- Drug interactions (CYP3A strong inducers and inhibitors, warfarin).

COMMENT: We should add reduced renal function to the subgroups with increased risk of bleeding.

12. OSI Audits

OSI audited four foreign and one domestic clinical investigator sites internationally and an applicant site. OSI found minor regulatory violations for three sites, e.g., failure to ensure proper monitoring, failure to follow the investigational plan, and not discontinuing drug shipments to a site that had been discontinued due to GCP noncompliance. OSI judged that these violations are unlikely to impact significantly the primary efficacy or safety analyses for the study and concluded that the data from this study may be considered reliable.

13. Conclusions and Recommendations

13.1. Recommended regulatory action

I recommend approval of vorapaxar for the reduction of atherothrombotic events in patients with a history of MI or with PAD and without a history of stroke or TIA. I judge the favorable efficacy results of TRA2P to be reliable enough and the increased bleeding to be tolerable such that the risk-benefit is favorable for the subgroups of history of MI and PAD. I judge that the exclusion of patients with a history of stroke or TIA is justified by the increased ICH rates in TRA2P for these patients as well as similar experiences with other platelet inhibitors such as prasugrel.

13.2. Safety concerns to be followed postmarketing

While the bleeding risk appears to have been characterized reasonably in the clinical trials, variations in bleeding when a new antiplatelet drug moves from the trial to the general population are always of concern. The safety topic of special concern for vorapaxar that should be followed postmarketing is diplopia. Lastly, ALS is likely not a concern but should manifest itself in the postmarketing reports if it is a real association.

13.3. Risk Minimization Plan

Clinicians understand the risk of bleeding with antiplatelet drugs. While the increased risk of ICH in patients with a history of stroke is not unique to vorapaxar, it is a serious enough risk that clinicians should be informed adequately about it. The primary clinical reviewers do not recommend a formal Risk Evaluation and Mitigation Strategy (REMS) but consider a medication guide to be adequate in addition to the boxed warning. The Division of Risk Management also does not recommend a REMS beyond professional labeling at this time.

I do recommend that the label suggest using vorapaxar with aspirin dosages of 75 to 100 mg. While this recommendation is similar to that in the ticagrelor label, the recommendation for vorapaxar is not as compelling as that for ticagrelor and I do not recommend that the aspirin dosage be included in a boxed warning in the vorapaxar label. I do not recommend a REMS for vorapaxar regarding aspirin dosage.

13.4. Postmarketing studies

The applicant did not characterize the effects of vorapaxar on bleeding time with a validated assay. Knowing whether vorapaxar affects bleeding time should be useful clinically, e.g., in combination with aspirin or clopidogrel and after aspirin and clopidogrel effects have worn off for overdoses and for suitability for surgery for which bleeding is a critical problem. The latter would seem to be a rare problem because, as I documented in Section 7.1.6.8, it appears beneficial to continue vorapaxar until the time of CABG and likely other procedures. I recommend a postmarketing requirement for a PK/PD study of the effects of vorapaxar on bleeding time alone and in combination with aspirin, clopidogrel, and both aspirin and clopidogrel but my recommendation is not a strong one.

13.5. Comments to be conveyed to the applicant

We have various recommendations regarding the proposed label that we will communicate to the applicant during the label negotiations.

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/s/

THOMAS A MARCINIAK
04/18/2014