Office of Drug Evaluation-I: Decisional Memo

Date	May 8, 2014
From	Ellis F. Unger, MD, Director Office of Drug Evaluation 1, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
NDA #	204886
Applicant Name	Merck Sharp and Dohme Corp.
Date of Submission	May 10, 2013
PDUFA Goal Date	May 10, 2014
Proprietary Name/ Established (USAN) Name	Zontivity (vorapaxar)
Dosage Forms/ Strengths	Tablet 2.08 mg
Indication	Reduction of thrombotic events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization.
Action:	Approval

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Alison Blaus, RAC
Medical Officer Clinical Review	Martin Rose, MD, JD (efficacy) Jonathan Levine, MD (safety)
Clinical Pharmacology Review	Sudharshan Hariharan, PhD, AbuAsal Bilal, PhD, Rajanikanth Madabushi, PhD, Yaning Wang, PhD
Statistical Review	Yeh Fong Chen, PhD
Pharmacovigilance Review	Susan Lu, PhD, Oanh H. Dang, PhD
Pharmacology Toxicology	Patricia Harlow, PhD
Executive Cancer Assessment Committee	Adele S. Seifried
Chemistry Manufacturing and Controls	Ramesh Sood, PhD, Thomas M. Wong, PhD
ONDQA Biopharmaceutics Review	Okponanabofa Eradini, PhD
Method Validation – Product Quality Reviewer	Thomas M. Wong, PhD
Statistical Review - Carcinogenicity Study	Mohammad Atiar Rahman, PhD, Karl Lin, PhD
Proprietary Name Review	Kimberly DeFronzo, RPh, MS, MBA
Division of Good Clinical Practice Compliance, Office of Scientific Investigations	Sharon Gershon, Susan Thompson, MD
MVP Coordinator	Michael L. Trehy
Division of Medication Error Prevention and Analysis	Janine Stewart, PharmD, Lisa Khosla, PharmD, MHA, Irene Z. Chan
Epidemiology Reviewer	Jie J. Li
Risk Evaluation and Mitigation Strategy (REMS) Review	Jamie C. Wilkins Parker, PharmD, Kim Lehrfeld, Pharm D, BCPS, Kellie A. Taylor, PharmD, MPH
Cross-Discipline Team Leader	Thomas Marciniak, MD
Director, Division of Cardiovascular and Renal Products	Norman Stockbridge, MD

Regulatory Action:

The applicant, Merck Sharp and Dohme Corp., is seeking approval of vorapaxar for reduction of thrombotic events in patients with a history of myocardial infarction (MI) or peripheral arterial disease (PAD), based on reduction in the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization. The review team recommends approval, and I agree with their recommendation.

Description/Mechanism of Action:

Vorapaxar is a first-in-class anti-platelet agent that inhibits platelet aggregation through antagonism of the protease activated receptor 1 (PAR-1), a platelet thrombin receptor. PAR-1 receptors exist in many tissues; however, the pharmacodynamic effects of vorapaxar, beyond its platelet effects, are not known at this time. Although inhibition of PAR-1 is reversible, the half-life of the drug exceeds the typical 5- to 9-day lifespan of platelets.

Disease Background:

Use of anti-platelet therapies for 2° prevention in patients with cardiovascular disease is well established and described by Dr. Rose.

Aspirin is labeled for several indications relevant to the proposed vorapaxar indication:
- prior MI or unstable angina: to reduce the risk of death and nonfatal MI; 81 to 325 mg daily
- suspected acute MI: to reduce the risk of vascular mortality; ≥162 mg daily for 30 days
- transient ischemic attack (TIA) and 2° prevention of atherothrombotic cerebral infarction: 81 to 325 mg daily

Clopidogrel is labeled for use in patients with:
- Acute coronary syndrome (ACS) in combination with aspirin
- history of recent MI, recent stroke, or peripheral arterial disease (PAD)…to reduce the rate of a combined endpoint of ischemic stroke…, MI…, and other vascular death"

Ticagrelor and prasugrel have indications for patients with ACS that are similar to those of clopidogrel; coadministration of aspirin is recommended for both. Prasugrel's indications are only for patients who are to be managed with PCI. Neither ticagrelor nor prasugrel have 2° prevention indications, or indications relevant to PAD.

Regulatory History:

Vorapaxar is a new molecular entity that has not been approved in or outside the U.S. The drug was developed under Merck's IND 071384, submitted December 17, 2004. Significant milestones and agreements are summarized below:

An End of Phase 2 meeting was held February 27, 2007. The minutes of that meeting include the following recommendations and agreements:
- FDA indicated that it "had no major objections to Schering's dosing proposal," and found "the endpoints and study designs of the Phase 3 ACS and 2° prevention trials acceptable."
- The Division suggested that the sponsor submit special protocol assessments for the Phase 3 studies, but the sponsor declined, indicating that they wanted to start the studies expeditiously without waiting to negotiate protocol details.

- The Division agreed with the sponsor's serious adverse event (SAE) reporting plans.
- The Division agreed to the sponsor's approach to clinical exploration of the rat retinal findings.
- The Division suggested that the sample sizes of the phase 3 studies should be based on the 2° endpoints, which would be critical to approval. One study in each indication could support approval with supportive phase 2 data.

Chemistry Manufacturing and Controls:

There are no pending chemistry manufacturing and controls (CMC) issues. The CMC reviewer, Dr. Thomas Wong, recommends approval. He determined that the applicant provided adequate information to allow a satisfactory evaluation of the quality of both the drug substance and drug product.

One minor issue was resolved regarding labeling: whereas the tablets contain 2.5 mg of vorapaxar sulfate, the mass of vorapaxar is 2.08 mg. Ultimately, we agreed that the labeling will indicate that Zontivity tablets are supplied as 2.08 mg vorapaxar; or 2.5 mg vorapaxar sulfate. I have some difficulty with the inconsistency in the numbers of significant figures, but could not convince the team to round 2.08 mg to 2.1 mg, and expressing the total mass to 3 significant figures, i.e., 2.50 mg, seems senseless. Thus, somewhat reluctantly, I accept expression of the salt to 2 significant figures, with expression of the active moiety to 3 significant figures.

Pharmacology/Toxicology:

The pharmacology/toxicology reviewer, Dr. Patricia Harlow, determined the application to be approvable from a pharmacology/toxicology perspective. Most of the toxicities identified in the non-clinical studies have adequate safety margins. One exception was memory in F1 female (but not male) rat offspring, however, with only a 4-fold safety margin based on the no observed adverse effect level (NOAEL) dose. The label states that "Zontivity should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus."

In addition, Dr. Harlow and the applicant estimated that exposure to vorapaxar and/or its metabolites in infants, via milk consumption, would be approximately 7% of the dose administered to the mother. The label will state that female patients should discontinue nursing or discontinue vorapaxar.

A preclinical finding that was followed up in the clinical studies was retinal vacuolization. Ophthalmology was consulted, and did not think that the finding merited mention in labeling, based on vacuolization observed in one animal species.

Carcinogenicity:

The primary carcinogenicity review was conducted by Dr. Patricia Harlow, and the primary statistical review was conducted by Dr. Mohammad Rahman. The applicant submitted two animal carcinogenicity studies, one in rats and one in mice, to assess the carcinogenic potential of vorapaxar when administered once daily via gavage.

There was an increased incidence of hepatocellular adenomas in high-dose female rats, but the difference did not meet the statistical threshold necessary for a positive finding for a common tumor. Tests in mice were negative.

The Executive Carcinogenicity Assessment Committee found the studies adequate in both rats and mice, and determined that there were no drug-related neoplasms in either males or females.

Site Inspections:

The Office of Scientific Investigation (OSI) audited four foreign clinical sites, one domestic clinical site, and an applicant site. They found minor regulatory violations for three sites, which they considered unlikely to impact the primary efficacy or safety analyses for the study. They deemed the data from this study to be reliable.

Pharmacokinetics:

Dr. Sudharshan Hariharan conducted the clinical pharmacology review. Vorapaxar is essentially 100% bioavailable; T_{max} occurs 1-2 hours after oral administration, independent of food. The effective half-life based on accumulation at steady state is 3 to 4 days; steady state accumulation is 5- to 6-fold.

Vorapaxar is extensively metabolized by CYP3A and CYP2J2. Following oral administration, <2% of vorapaxar is excreted unchanged in feces, and none is detectable in urine. Strong CYP3A inhibitors (ketoconazole) and inducers (rifampin) increase and decrease exposure by a factor of 2 and should be avoided. There is at least one active metabolite (M20) whose kinetics mirror those of the parent; it probably does not contribute importantly to PAR-1 inhibition. Vorapaxar is >99% protein-bound, and its volume of distribution is 634 L. Systemic exposures of vorapaxar and M20 were not measured in TRA2°P - TIMI 50; exposure data were collected in only a small subset of patients (95) in TRA•CER, such that there were no assessments of the relationships between exposure and clinical outcomes.

Pharmacodynamics:

The exposure-response of vorapaxar was assessed on the basis of TRAP-induced platelet aggregation. There appears to be a steep exposure-response relationship. Over a narrow range of vorapaxar concentrations, ~1 to 5 ng/mL, inhibition of TRAP-induced platelet aggregation varied from no effect to maximal inhibition in most studies, but the half-maximal effective concentration (EC_{50}) varied markedly among studies. In particular, the EC_{50} was strikingly higher in two phase 1 studies than in the other studies, but the reasons for this difference are unknown.

It might have been useful to understand the effect of vorapaxar on bleeding time, but as Dr. Marciniak discovered, 'bleeding time' was assessed with what was essentially a pin prick rather than the standard template assay, such that the data are not informative. The actual effect of vorapaxar on bleeding time is unknown. Dr. Marciniak would like to have had the applicant assess bleeding time post-approval, but given that the effects of vorapaxar on bleeding have been assessed in >100 patients who underwent coronary artery bypass graft (CABG) surgery in the phase 3 studies, the added value of formal studies of bleeding time it is not clear to me.

Abuse Potential:

There was no evidence suggesting drug abuse or dependence.

QT Effects:

Vorapaxar's effects on the QTc interval were evaluated in a thorough QT study, and there was no effect at single doses up to 120 mg.

Evidence of Effectiveness:

Study Designs

a. The principal evidence of efficacy is provided by the Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P) trial. This was a 26,449-subject, international, randomized, double-blind, placebo-controlled, parallel group, cardiovascular (CV) outcomes trial in patients with a history of MI, cerebrovascular disease, or PAD. Study enrollment was intended to be unequal in these 3 qualifying subgroups, with a target of 70% of subjects in the prior MI (CAD) stratum and 15% in each of the prior stroke (CVD) and PAD strata. Subjects were randomized 1:1 to vorapaxar 2.5 mg once daily or placebo, with stratification by their qualifying underlying condition and planned thienopyridine use. Subjects were to receive a background of standard care for each condition.

The 1° endpoint was time to the first instance of CV death, MI, stroke, or urgent coronary revascularization (UCR). *For the purpose of this memorandum, this endpoint will be referred to as MACE+, to denote major adverse cardiovascular event + UCR.* The key 2° endpoint was time to first instance of CV death, MI, or stroke. *For the purpose of this memorandum, this endpoint will be referred to as MACE.* This was a superiority trial, with placebo as the comparator group.

b. TRA•CER, the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome trial, conducted in patients with ACS, provided supportive data. This was another large (12,944 subjects), international, randomized, double-blind, placebo-controlled parallel group, CV outcomes trial. Patients were randomized 1:1 to vorapaxar or placebo. The vorapaxar dose was also 2.5 mg daily, except that a 40 mg loading dose was given on Day 1.

The 1° endpoint was time to the first instance of CV death, MI, stroke, recurrent ischemia with re-hospitalization (RIR) or urgent coronary revascularization (UCR). *For the purpose of this memorandum, this endpoint will be referred to as MACE+, to denote major adverse cardiovascular event + RIR or UCR.* The key 2° endpoint was time to first instance of CV death, MI, or stroke. *For the purpose of this memorandum, this endpoint will be referred to as MACE.* This was a superiority trial, with placebo as the comparator group.

Dr. Chen confirmed the applicant's analysis results for the 1°, key 2°, and other important endpoints in both TRA•CER and TRA 2°P studies. TRA 2°P was successful on both its 1° and 2° endpoints, MACE+ and MACE. TRA•CER failed on MACE+, its 1° endpoint, but succeeded on MACE, the 2° endpoint.

Results: TRA 2°P

Interim Analyses – Exclusion of Patients with a History of Cerebrovascular Event

The two studies shared a single Clinical Endpoint Committee (CEC) charter and a Data Safety Monitoring Board (DSMB). Eleven DSMB meetings were held during the course of the studies,

and it is clear from the meeting minutes that the Board was concerned about excess numbers of patients who experienced intracerebral hemorrhage (ICH) in one of the treatment groups. Ultimately, on Jan 8, 2011, they issued a recommendation to discontinue treatment of patients with a prior history of stroke, and those who experienced a stroke during the course of the study (TRA 2°P). They also recommended close-out of TRA•CER.

Dr. Yeh-Fong Chen, the biostatistical reviewer, had concerns regarding the interim safety and efficacy evaluations and change in the study protocols. I will note that although ICH is a safety concern, it was also one of the components of the 1° efficacy endpoints for both studies, which complicates interpretation.

Neither Dr. Marciniak nor Dr. Stockbridge considered the change to be problematic, and I agree. It is important to point out that the primary analysis included all patients, as randomized.

Overall Results

A total of 26,449 patients were randomized (13,224 subjects receiving placebo and 13,225 receiving vorapaxar). The Kaplan-Meier (KM) event rates for the 1° endpoint (MACE+) were 12.4% in the placebo group, and 11.2% in the voraxapar group, HR 0.88, 95% CI 0.82 – 0.95, p=0.001. For the 2° endpoint (MACE), the KM event rates were 10.5% in the placebo group, and 9.3% in the voraxapar group, HR 0.87, 95% CI 0.80 – 0.94, p<0.001.

Patient Populations

Having observed an unfavorable benefit-risk profile in patients with a history of stroke (because of excessive ICH), the applicant subsequently decided that the benefit-risk profile in the PAD patient population was unfavorable as well, and decided to exclude such patients from the indicated population.

In their study reports, analyses, and summaries, therefore, the applicant focused on the following 4 populations of interest:

- Overall population – all subjects, regardless of the qualifying condition
- No stroke history population – subjects with no history of stroke, regardless of the qualifying condition
- CAD (post MI) and no history of stroke – subjects whose qualifying condition was CAD, and who had no documented history of stroke.

Recognizing the difficulty of distinguishing stroke and transient ischemic attack (TIA) by history alone, the applicant subsequently placed the same level of concern on TIA as they had on stroke. This led to the proposed label population:

- Proposed label population – subjects whose qualifying condition was CAD (post MI), with no history of stroke or TIA.

When the NDA was received, the review team initially focused on the populations of interest identified by the applicant, but wrestled two key issues:

- Was it reasonable to exclude patients with a history of stroke and TIA?

- Was it reasonable to exclude patients with PAD from the indicated patient population? As noted by Dr. Rose, the results in the overall PAD population favored vorapaxar (hazard ratio [HR] = 0.95), but the results were not statistically significant. When patients with prior stroke or TIA were excluded from the PAD population, the HR improved to 0.87 – essentially the same as the HR for the study overall; however the results were still not statistically significant. Notably, the PAD population comprised only 14% of the overall population – about 1/5 the size of the prior MI population.

In the end, the review team reached the conclusion that patients with strokes and TIAs could be removed from the indicated population for safety reasons, and that the results shown in labeling could reflect only the indicated population. This was possible because the trial had succeeded overall, even with such patients included. The team also decided that patients with PAD should be included in the indicated population along with patients with recent MI.

It is noteworthy, however, that the applicant did not analyze the combined CAD + PAD patient population, per se, because it was never their intention to seek such an indication for this group. Similarly, the review team conducted few if any analyses of efficacy or safety in what they determined to be the labeled patient population. Many of the analyses that follow, therefore, were generated by me for the purpose of this memorandum, and are not found in the reviews.

The applicant's analyses of the 1° and 2° endpoints of TRA 2°P are shown in Table 1.

Table 1: TRA 2°P: Time to First Event in Post-MI or PAD Patients Without History of Stroke/TIA

	Placebo (n=10,090)		ZONTIVITY (n=10,080)		Hazard Ratio‡,§	p-value§
Endpoints	**Patients with events* (%)**	**K-M %†**	**Patients with events* (%)**	**K-M %†**	**(95% CI)**	
Primary Efficacy Endpoint (CV death/MI/stroke /UCR)*,§	1073 (10.6%)	11.8%	896 (8.9%)	10.1%	0.83 (0.76-0.90)	<0.001
Secondary Efficacy Endpoint (CV death/MI/stroke)*,§	851 (8.4%)	9.5%	688 (6.8%)	7.9%	0.80 (0.73-0.89)	<0.001

* Each patient was counted only once (first component event) in the component summary that contributed to the primary efficacy endpoint.

† K-M estimate at 1,080 days.

‡ Hazard ratio is ZONTIVITY group versus placebo group.

§ Cox proportional hazard model with covariates treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use).

Results on both the 1° and 2° endpoints are highly statistically significant, although the absolute risk reductions are less than impressive. The absolute risk reduction for the MACE + UCR 1° endpoint is 1.7% over 1080 days – approximately 0.6% per year. Based on these results, one would need to treat ~170 patients for 1 year (1 ÷ 0.006) to prevent an MI, stroke, CV death, or UCR in 1 patient. The absolute risk reduction for MACE, the 2° endpoint, is similar: 1.6% over 1080 days, and the number needed to treat is similar, about 180 patients.

All 4 components of the 1° endpoint are directionally consistent (Table 2), which bolsters support for the overall study composite. The study is nominally statistically significantly successful on MI and stroke (the upper limit of the 95% CI is <1), with a good trend on cardiovascular death, where the upper limit of the 95% CI is 1.04, slightly over 1.

Table 2: TRA 2°P: Components of the Primary Endpoint

	Placebo n=10,090		Vorapaxar n=10,080		Hazard Ratio (95% CI)
	events (%)	K-M %	events %	K-M %	
CV Death	239 (2.4%)	2.80%	205 (2.0%)	2.40%	0.86 (0.71-1.03)
MI	569 (5.6%)	6.40%	470 (4.7%)	5.40%	0.82 (0.73-0.93)
Stroke	145 (1.4%)	1.60%	98 (1.0%)	1.20%	0.67 (0.52-0.87)
UCR	283 (2.8%)	3.00%	249 (2.5%)	2.80%	0.88 (0.74-1.04)

Table 3: TRA 2°P: MI by Type

MI Type	%
Type 1 (Spontaneous)	77.7%
Type 2 (Secondary)	10.3%
Type 3 (SCD due to suspected MI)	0.3%
Type 4a (Peri-PCI)	1.1%
Type 4b (Stent-Thrombosis)	10.3%
Type 5 (Peri-CABG)	0.2%
	100%

Some on the advisory committee expressed concern regarding the seemingly small reduction in absolute risk. One must recognize, however, that the events prevented are medically important and often life-changing. Patients in TRA 2°P were stable at study entry, and the MIs prevented were generally spontaneous in nature (Table 3), unlike trials in patients with ACS, where many of the MIs prevented are peri-procedural Type 4a events (some consider these questionable in clinical importance). Moreover the event rate in the placebo group is only 11.8% over 3 years, a mere 3.9% per year. Even a truly remarkable therapy, e.g., one that reduces by relative risk by 50%, would decrease the annual event rate by only 1.95% per year. As advances in therapies and patient management decrease the absolute risk over time, drugs for 2° prevention become more "vaccine-like." In other words, as the absolute benefit declines, so must the risk decline in order to be acceptable. For this application, the benefit outweighs the risk by a narrow margin.

Figure 1 and Figure 2 show the Kaplan-Meier plots for the 1° (MACE+) and 2° (MACE) endpoints, respectively, the time to first occurrence of any composite event in the subset of patients: a) in the post-MI or PAD strata; and b) without prior history of stroke or TIA. Some modification of the upper plot will be used in labeling. In both plots, the blue curves show how the differences between the treatment groups increase as a function of time. For MACE + UCR (Figure 1), there appears to be little further divergence of the curves after 18 months, whereas for MACE (Figure 2), the curves continue to separate slightly throughout the study.

Once the review team became comfortable with the exclusion of patients with cerebrovascular disease and the addition of patients with PAD to the indication, much of the analysis and discussion focused on efficacy and safety in a number of subgroups, particularly where the balance between benefit-risk seemed unfavorable.

Figure 2: TRA 2°P: Kaplan-Meier Plot, 1° Efficacy Endpoint, Time to First Cardiovascular Death, MI, Stroke, or Urgent Coronary Revascularization (MACE+) – Labeled Population

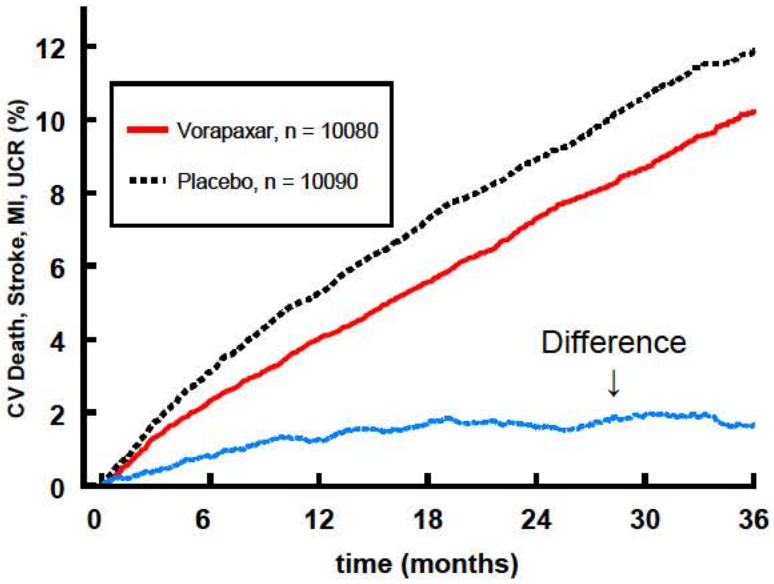
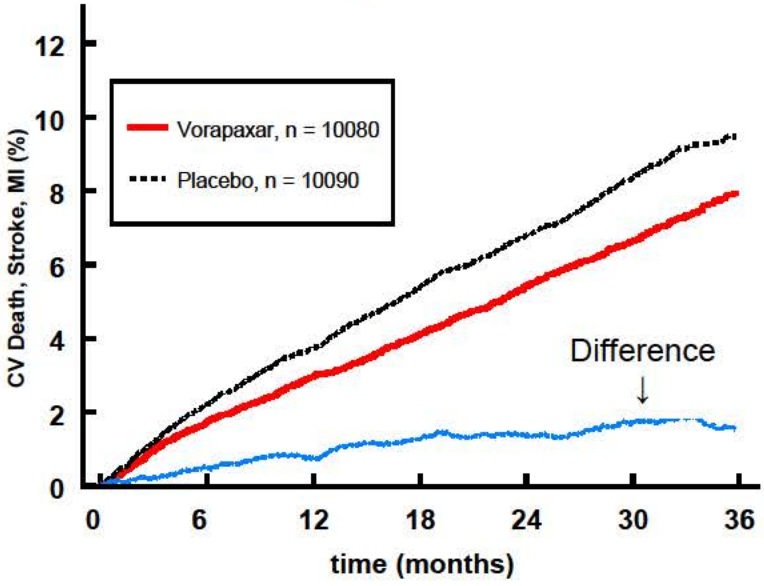


Figure 1: TRA 2°P: Kaplan-Meier Plot, 2° Efficacy Endpoint, Time to First Cardiovascular Death, MI, Stroke (MACE) – Labeled Population



***Concerns of the Review Team*:**

The main concerns of the review team were:

- completeness of follow-up
- patient weight (less efficacy at lower weight, which seems counter-intuitive)
- patient age (less efficacy and greater absolute risk of bleeding with advancing age)
- baseline ASA dose (less efficacy with higher ASA doses, similar to the finding with ticagrelor)
- use of proton pump inhibitors (PPIs). Certain PPIs decrease the efficacy of clopidogrel; Dr. Stockbridge noted that efficacy of vorapaxar was greater when PPIs were used, possibly because clopidogrel was less effective in that setting.

The 4 latter concerns are based on various subgroup analyses. The reviewers performed a number of examinations, but they were difficult to reconcile because they were based on disparate cutoffs (age or weight dichotomized at various cut points, increments [with unequal n's], or quintile), and on different populations. Most of the analyses were based on the overall population in TRA 2°P, and not on the to-be-labeled population.

My subgroup analyses are shown in a number of tables that follow. These subgroups were defined on the basis of parameters present prior to randomization, such that they could not be affected by treatment. Nevertheless, it is important to recognize that a myriad of analyses were performed, and comparisons between strata lack the benefit of randomization. Thus, even for particular subgroup analyses that were pre-planned and delineated in the statistical analytical plan, the findings must be interpreted with healthy skepticism.

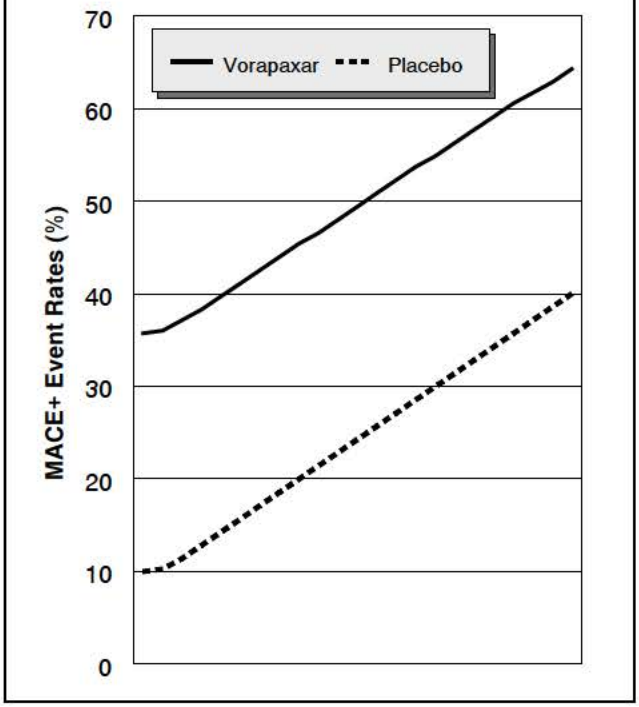
Data Quality – Completeness of Follow-up

The majority of the review team viewed the data quality as acceptable, although there were concerns. Dr. Marciniak noted that the follow-up (96.5%) was better than in recent trials, but he would not characterize the rate of incomplete follow-up (3.5%) as 'good.' He noted that the 3.5% figure substantially exceeds the difference between arms in the primary endpoint rates of 1.15% and the difference in the mortality rates of 0.4%.

Whereas the overall event rate for the 1° endpoint was ~9% in TRA 2°P, Dr. Marciniak notes that the event rate for the 1° endpoint was 4-fold higher, approximately 40%, for patients who experienced a GUSTO moderate or severe bleeding event.

A high event rate in the 3.5% of patients with missing data would have little impact on the study results, unless missingness was not random, i.e., there was a higher event rate in

Figure 3: Disparity in Event Rates (MACE+) in Missing Data in TRA 2°P that would be Needed to Abolish Statistical Significance



patients in the vorapaxar arm. The concern, therefore, is the potential that there were more patients in the vorapaxar group who dropped out of the study because of significant bleeding. Given this possibility, Figure 3 reflects my calculations of the range of disparities in event rates that would be necessary, in the 3.5% of patients with missing data, to abolish the statistical significance of the overall study results. For example, if the rate of MACE+ were 10% in the placebo group, a rate consistent with the overall study, the rate in the vorapaxar group would need to be 36% to render the results statistically non-significant (left side of the plot). If the event rate were as high as 40% in the placebo group, the rate in the vorapaxar group would need to be 64% to abolish the statistical significance of the results (right side of figure). Thus, there would have to be a marked disparity between event rates in the two treatment groups to overturn the statistical significance of the overall study, and such a difference seems unlikely.

Weight

There was concern by the clinical pharmacology and medical reviewers that efficacy was lower in patients with low body mass. In TRA 2°P, the hazard ratio for the ~7% of patients with body mass < 60 kg was > 1.0 (unfavorable), and the interaction between treatment and weight dichotomized at 60 kg was nominally statistically significant by Dr. Marciniak's logistic regression. Drs. Marciniak and Stockbridge discussed the body weight interaction in some detail, and neither was impressed. Table 4 shows the 1° endpoint (MACE+) by weight quartiles, by weight quartiles for each sex, and by decile.

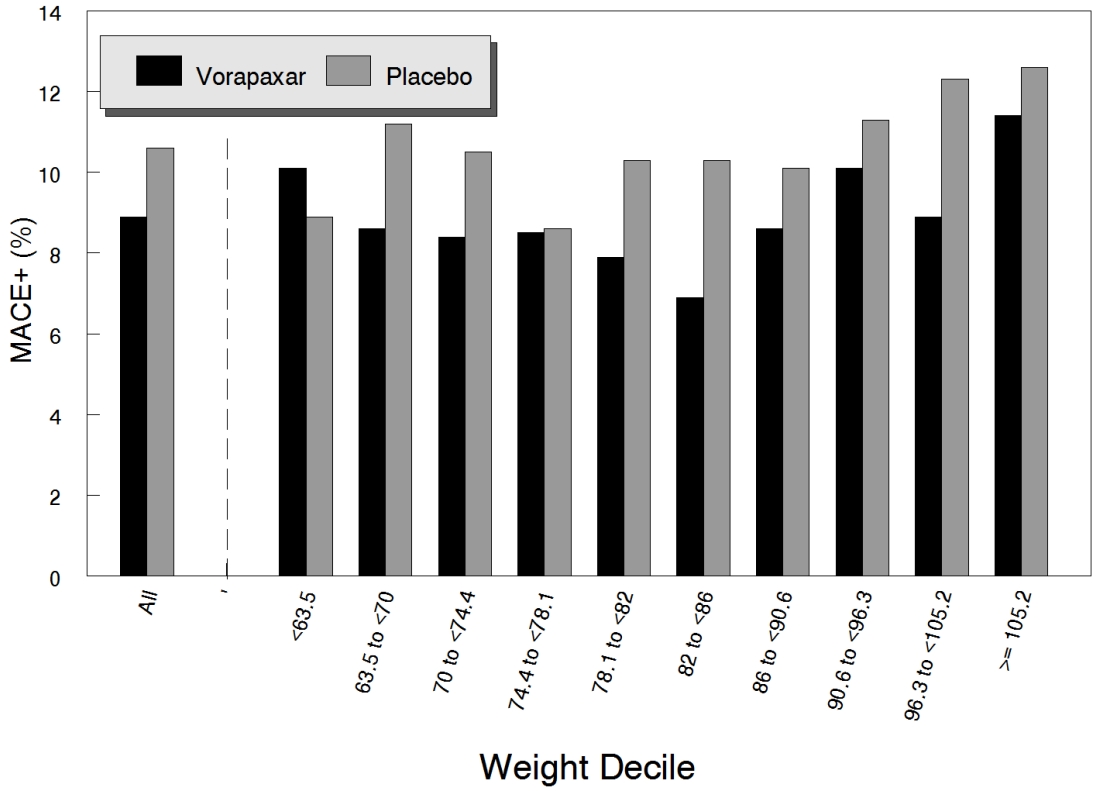
Table 4: TRA 2°P Primary Endpoint by Weight Subgroup – Labeled Population: MACE + UCR

Subgroup		Vorapaxar			Placebo			Delta	RR (95% CI)
		events	N	%	events	N	%		
Overall	-->	896	10080	8.9%	1073	10090	10.6%	1.7%	0.84 (0.77, 0.91)
Weight quartile	<72 kg	227	2432	9.3%	251	2382	10.5%	1.2%	0.89 (0.75, 1.05)
	72 to <82	204	2509	8.1%	234	2499	9.4%	1.2%	0.87 (0.73, 1.04)
	82 to <93.4	217	2685	8.1%	266	2589	10.3%	2.2%	0.79 (0.66, 0.93)
	>=93.4	247	2441	10.1%	322	2601	12.4%	2.3%	0.82 (0.7, 0.96)
Weight quartile, males	<74.8 kg	154	1861	8.3%	168	1820	9.2%	**1.0%**	0.9 (0.73, 1.1)
	74.8 to <83.7	159	2100	7.6%	193	2074	9.3%	1.7%	0.81 (0.67, 0.99)
	83.7 to <94.3	164	1935	8.5%	196	1903	10.3%	1.8%	0.82 (0.68, 1)
	>=94.3	194	1968	9.9%	255	2111	12.1%	2.2%	0.82 (0.68, 0.97)
Weight quartile, females	<62 kg	57	543	10.5%	53	543	9.8%	**-0.7%**	1.08 (0.75, 1.53)
	62 to <70.7	57	551	10.3%	72	532	13.5%	3.2%	0.76 (0.55, 1.06)
	70.7 to <82	51	563	9.1%	59	528	11.2%	2.1%	0.81 (0.57, 1.16)
	>=82	59	546	10.8%	77	560	13.8%	2.9%	0.79 (0.57, 1.08)
weight decile	<63.5	101	997	10.1%	91	1018	8.9%	**-1.2%**	1.13 (0.87, 1.48)
	63.5 to <70	88	1023	8.6%	110	981	11.2%	2.6%	0.77 (0.59, 1)
	70 to <74.4	86	1021	8.4%	106	1008	10.5%	2.1%	0.8 (0.61, 1.05)
	74.4 to <78.1	88	1040	8.5%	85	989	8.6%	**0.1%**	0.98 (0.74, 1.31)
	78.1 to <82	69	873	7.9%	93	904	10.3%	2.4%	0.77 (0.57, 1.03)
	82 to <86	76	1108	6.9%	106	1034	10.3%	3.4%	0.67 (0.5, 0.89)
	86 to <90.6	94	1095	8.6%	104	1033	10.1%	1.5%	0.85 (0.65, 1.11)
	90.6 to <96.3	89	883	10.1%	107	950	11.3%	1.2%	0.89 (0.69, 1.17)
	96.3 to <105.2	96	1084	8.9%	137	1113	12.3%	3.5%	0.72 (0.56, 0.92)
	>= 105.2	109	956	11.4%	134	1060	12.6%	1.2%	0.9 (0.71, 1.14)

When considered by quartile, there is a trend for decreasing efficacy (i.e., increasing relative risk [RR]) with decreasing weight (Table 4, top). This is evident in both males and females, but particularly females, where the RR is 1.08 for female patients who weigh <62 kg. Note that this is driven primarily by a lower event rate in the placebo arm in females of low body weight, and not a higher rate in the voraxapar group.

To provide more detail, TRA 2ºP results for the 1° efficacy endpoint are shown by weight decile at the bottom of Table 4, and displayed graphically in Figure 4. Because this was a large study that included ~10,000 patients in each group, each bar represents ~1,000 patients. The bars on the left of the dotted line represent the entire labeled population (all weights).

Figure 4: TRA 2ºP: Primary Endpoint (MACE + UCR) by Weight Decile – Labeled Population



There appear to be U-shaped relationships between MACE+ and weight for both the voraxapar and placebo groups. Event rates tend to be higher at the lower and higher extremes of weight, and event rates are consistently lower in the voraxapar group, with one exception. In the lowest weight decile, weight <63.5 kg, the event rate is higher with voraxapar than placebo. Whereas the event rates in the voraxapar group conform to a U-shaped pattern, with gradually rising event rates as weight declines through the lowest deciles, the event rate in lowest weight decile in the placebo group defies the general trend, and appears lower than predicted. In other words, voraxapar's unfavorable relative risk in the lowest (<63.5 kg) weight group appears to be a function of an aberrantly low event rate in the placebo group, i.e., play of chance. Given the multiple comparisons made here, some aberrations and inconsistencies are expected. There is an inconsistency in the lowest weight decile, such that any analysis that assesses efficacy by body mass will appear unfavorable for voraxapar in the lowest weight group. But based on this analysis, the finding seems factitious.

In TRA•CER, the relative risk for MACE+ by weight quartiles seems inconsistent (see Table 7). From lowest to highest weight quartile, the relative risks from MACE+ are 1.02, 0.89, 1.00, and 0.84. This pattern does not suggest that efficacy is lower in patients with low weight.

Age

Dr. Marciniak noted that the mean age in the TRA 2ºP indicated population was ~60 years. He noted that efficacy seemed lower in the highest age quintile of TRA 2P (age >72), whereas the opposite was true in TRA•CER, where the 1° endpoint did not favor voraxapar in the *lowest* age quintile (≤56).

In my quartile analysis of TRA 2ºP (Table 5, top), the RR is less favorable for voraxapar (closer to 1) as age increases. But when expressed in deciles, (Table 5, bottom; Figure 5), the superiority of voraxapar seems consistent across age. Again, because the study included approximately 10,000 patients in each group, each bar in Figure 6 represents ~1,000 patients.

Table 5: TRA 2ºP Primary Endpoint by Age Subgroup – Labeled Population: MACE + UCR

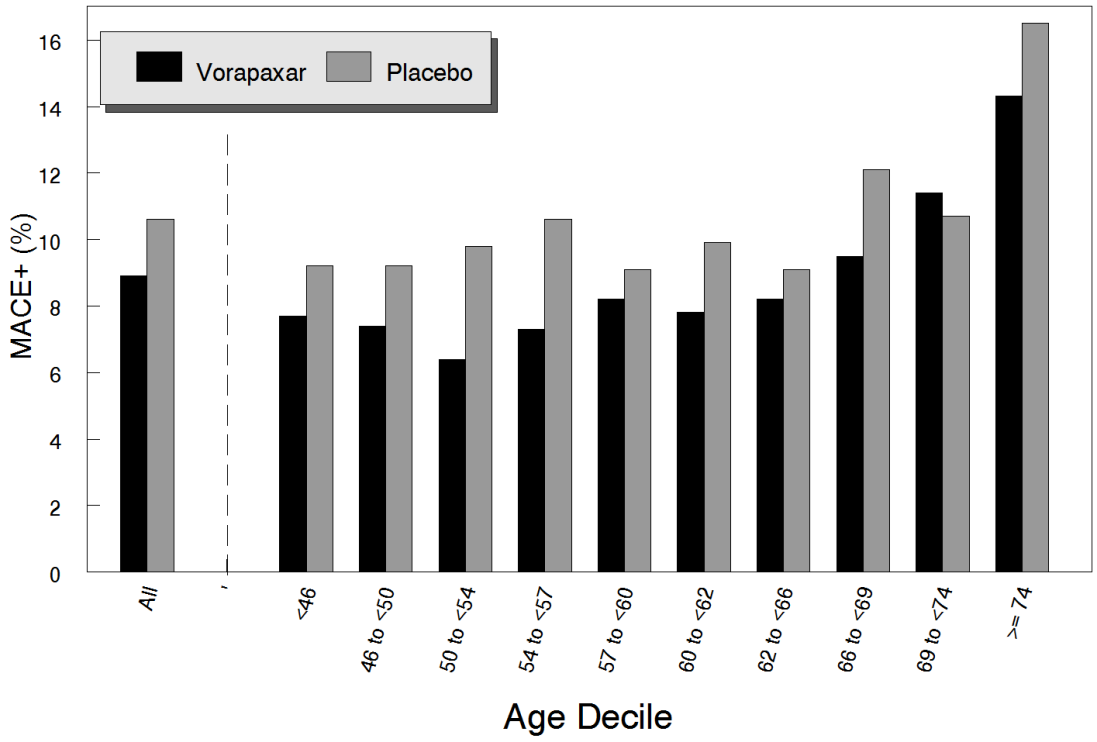
Subgroup		Vorapaxar			Placebo			Delta	RR (95% CI)
		events	N	%	events	N	%		
Overall	-->	896	10080	8.9%	1073	10090	10.6%	1.7%	0.84 (0.77, 0.91)
Age	<53	191	2585	7.4%	248	2625	9.4%	2.1%	0.78 (0.65, 0.94)
	53 to <61	203	2695	7.5%	274	2792	9.8%	2.3%	0.77 (0.65, 0.91)
	61 to <69	219	2591	8.5%	257	2512	10.2%	1.8%	0.83 (0.7, 0.98)
	>=69	283	2209	12.8%	294	2161	13.6%	**0.8%**	0.94 (0.81, 1.1)
age decile	<46	73	951	7.7%	86	933	9.2%	1.5%	0.83 (0.62, 1.12)
	46 to <50	63	854	7.4%	79	860	9.2%	1.8%	0.8 (0.58, 1.1)
	50 to <54	69	1076	6.4%	111	1127	9.8%	3.4%	0.65 (0.49, 0.87)
	54 to <57	73	997	7.3%	114	1073	10.6%	3.3%	0.69 (0.52, 0.91)
	57 to <60	85	1042	8.2%	93	1021	9.1%	**1.0%**	0.9 (0.68, 1.19)
	60 to <62	58	748	7.8%	77	781	9.9%	2.1%	0.79 (0.57, 1.09)
	62 to <66	104	1272	8.2%	117	1290	9.1%	**0.9%**	0.9 (0.7, 1.16)
	66 to <69	88	931	9.5%	102	844	12.1%	2.6%	0.78 (0.6, 1.02)
	69 to <74	127	1118	11.4%	115	1079	10.7%	**-0.7%**	1.07 (0.84, 1.35)
	>= 74	156	1091	14.3%	179	1082	16.5%	2.2%	0.86 (0.71, 1.05)

Within the oldest age quintile (the highest 2 *deciles* in the figure), the quintile of concern in Dr. Marciniak's analysis, the RR is more favorable for voraxapar at the *higher* age. In other words, in the highest age decile, the results are favorable for voraxapar. Based on inspection of Figure 5, it would be difficult to conclude that efficacy is not consistent across age.

ASA Dose

Drs. Marciniak and Rose considered the effect of aspirin dose on efficacy and safety. Some of the concern was driven by the notable finding in the ticagrelor NDA, where efficacy was lower

Figure 5: TRA 2ºP: Primary Endpoint (MACE + UCR) by Age Decile – Labeled Population



(relative to clopidogrel) in PLATO, the pivotal study, with higher aspirin doses. Both Dr. Rose and Marciniak found the voraxapar results to be similar to those of ticagrelor in PLATO, but not as extreme: they found that efficacy was slightly worse with the higher aspirin dosages whereas bleeding was substantially worse. In his Clinical Addendum, Dr. Rose suggested a warning regarding loss of efficacy when vorapaxar is used with aspirin doses of ≥ 300 mg daily. Dr. Marciniak's view was that the label should suggest aspirin dosages of 75 to 100 mg daily. He favored the lower dose, particularly because of the increased bleeding risk.

Table 6 shows benefit and risk, side-by-side, in TRA 2ºP by subgroup. Aspirin doses are categorized overall, and categorized separately for patients enrolled inside and outside the U.S. Only 13% of patients received a baseline aspirin dose >299 mg, of whom 11% were in the U.S. In the overall study, for patients who received >299 mg of aspirin daily at baseline, there was no salutary effect on MACE+; RR was 1.01. (In the U.S., baseline aspirin doses were evenly divided between high and low dose, with ~11% of the total study population receiving each.)

Outside the U.S., very few patients received a baseline aspirin dose >299 mg (2% of the study overall), and such patients did poorly with respect to MACE+ on vorapaxar (RR 1.72 – worse in any subgroup examined). Both inside and outside the U.S., the bleeding risk was actually numerically *lower* with high-dose aspirin than low-dose aspirin. In any case, the recommendation to use lower aspirin doses seems prudent because of the question regarding efficacy, and use of the lower dose is consistent with good medical practice.

Table 6: TRA 2ºP: Benefit-Risk Assessment by Subgroup – MACE+ (Events Prevented, Left) vs. GUSTO Moderate and Severe Bleeding (Events Caused, Right)

			BENEFIT				RISK				
			Efficacy (MACE +)				Bleeding (GUSTO Moderate or Severe)				
		%	Vorapaxar	Placebo	Delta	RR	Vorapaxar	Placebo	Delta	RR	ΔΔ%
All		20170	8.9%	10.6%	1.7%	0.84	3.0%	2.0%	-1.0%	1.52	0.7%
Age	<53	26%	7.4%	9.4%	2.1%	0.78	1.3%	0.8%	-0.5%	1.64	1.5%
	53 to <61	27%	7.5%	9.8%	2.3%	0.77	2.2%	1.5%	-0.7%	1.47	1.6%
	61 to <69	25%	8.5%	10.2%	1.8%	0.83	3.3%	2.1%	-1.2%	1.60	**0.5%**
	>=69	22%	12.8%	13.6%	**0.8%**	0.94	5.7%	4.0%	**-1.7%**	1.42	**-0.9%**
Sex	Male	78%	8.5%	10.2%	1.7%	0.83	2.8%	1.9%	-0.9%	1.48	0.8%
	Female	22%	10.2%	12.1%	1.9%	0.84	3.7%	2.3%	**-1.4%**	1.61	**0.5%**
Race	Caucasian	89%	8.6%	10.5%	1.9%	0.82	3.1%	2.0%	-1.1%	1.53	0.8%
	Black	2%	15.6%	15.5%	**0.0%**	1.00	2.6%	3.4%	0.8%	0.77	0.7%
	Asian	3%	7.8%	7.1%	**-0.7%**	1.11	2.4%	0.8%	**-1.6%**	2.84	**-2.3%**
	Other/unkn	6%	11.1%	13.4%	2.3%	0.83	2.2%	1.6%	-0.7%	1.44	1.6%
Weight	<60 kg	6%	10.7%	8.6%	**-2.1%**	1.24	5.0%	2.9%	**-2.1%**	1.71	**-4.2%**
	<72 kg	24%	9.3%	10.5%	1.2%	0.89	3.4%	2.6%	-0.8%	1.31	**0.4%**
	72 to <82	25%	8.1%	9.4%	1.2%	0.87	3.4%	2.0%	**-1.4%**	1.73	**-0.2%**
	82 to <93.4	26%	8.1%	10.3%	2.2%	0.79	2.6%	1.9%	-0.8%	1.43	1.4%
	>=93.4	25%	10.1%	12.4%	2.3%	0.82	2.6%	1.6%	-1.0%	1.66	1.2%
eGFR	<66.7	23%	13.1%	15.0%	1.9%	0.88	5.3%	3.5%	**-1.7%**	1.50	**0.1%**
	66.7 to <79.8	25%	8.5%	9.8%	1.3%	0.86	3.2%	1.7%	**-1.5%**	1.87	**-0.1%**
	79.8 to <93.5	25%	7.6%	9.8%	2.2%	0.78	2.1%	1.4%	-0.7%	1.52	1.5%
	>=93.5	26%	6.8%	8.5%	1.8%	0.79	1.8%	1.5%	-0.3%	1.21	1.5%
Location	US	24%	13.2%	14.9%	1.7%	0.88	5.5%	3.2%	**-2.3%**	1.71	**-0.6%**
	Outside US	76%	7.5%	9.3%	1.8%	0.81	2.2%	1.6%	-0.6%	1.39	1.1%
ASA dose at baseline	0 mg /unknown	3%	11.7%	13.7%	2.0%	0.85	3.3%	3.3%	0.0%	1.01	2.0%
	1 - 101	75%	8.1%	10.0%	1.9%	0.81	2.9%	1.8%	-1.1%	1.62	0.8%
	102 - 299	9%	8.0%	10.8%	2.8%	0.74	1.9%	1.2%	-0.7%	1.62	2.1%
	> 299	13%	13.3%	13.1%	**-0.1%**	1.01	4.2%	3.3%	-0.9%	1.29	**-1.1%**
Location and ASA dose at baseline	OUS 1 - 101	64%	7.2%	9.1%	1.8%	0.80	2.2%	1.6%	-0.7%	1.42	1.2%
	OUS 102 - 299	8%	7.9%	11.2%	3.3%	0.71	1.6%	1.1%	-0.5%	1.49	2.7%
	OUS > 299	2%	10.5%	6.1%	**-4.4%**	1.72	3.3%	2.5%	-0.8%	1.34	**-5.2%**
	US 1 - 101	11%	13.2%	15.7%	2.5%	0.84	6.7%	3.0%	**-3.6%**	2.20	**-1.2%**
	US 102 - 299	1%	8.9%	8.0%	**-0.9%**	1.11	5.1%	2.0%	**-3.1%**	2.53	**-3.9%**
	US > 299	11%	13.6%	14.1%	**0.5%**	0.96	4.4%	3.4%	-0.9%	1.28	**-0.5%**
Thieno at baseline	Yes	67%	9.1%	10.8%	1.8%	0.84	3.0%	2.1%	-0.9%	1.44	0.8%
	No	33%	8.5%	10.2%	1.7%	0.83	3.0%	1.8%	-1.2%	1.69	**0.5%**
Disease location	CAD	84%	8.5%	10.3%	1.8%	0.83	2.5%	1.7%	-0.8%	1.51	0.9%
	PAD	16%	10.9%	12.5%	1.6%	0.87	5.6%	3.6%	**-2.0%**	1.54	**-0.4%**
Half of study	1st	51%	10.8%	12.2%	1.4%	0.89	3.8%	2.5%	-1.4%	1.55	**0.1%**
	2nd	49%	6.9%	9.0%	2.1%	0.77	2.2%	1.5%	-0.7%	1.47	1.4%
Stent at baseline	No	34%	9.0%	10.0%	1.0%	0.90	4.0%	2.3%	**-1.7%**	1.74	**-0.7%**
	Yes	66%	8.8%	11.0%	2.1%	0.81	2.5%	1.8%	-0.7%	1.37	1.5%
Any PPI use > 7	No	65%	7.5%	9.3%	1.8%	0.81	1.7%	1.1%	-0.6%	1.52	1.2%
	Yes	35%	11.4%	13.2%	1.8%	0.87	5.5%	3.6%	**-1.8%**	1.50	**0.0%**
omep/eso use >7	No	79%	8.0%	10.0%	2.0%	0.80	2.5%	1.5%	-1.0%	1.65	1.0%
	Yes	21%	12.0%	12.9%	**0.9%**	0.93	5.0%	3.8%	-1.2%	1.31	**-0.3%**

PPI Use

Both omeprazole and esomeprazole significantly reduce the antiplatelet activity of clopidogrel; therefore, results in patients taking, and not taking, these that proton pump inhibitors (PPI) are of interest. Dr. Stockbridge noted that PPI use had an impact on outcomes: in the placebo group, MACE+ event rates were 12.1% among subjects on any PPI for ≥ 7 days vs. 9.9% for subjects not on a PPI. For use of omeprazole or esomeprazole, the corresponding rates were 13.7% vs. 10%. I would add that bleeding rates are also strikingly higher in patients who were taking PPI at baseline than in those who were not. It is possible that patients who took PPIs at baseline were more likely to have had some form of peptic ulcer disease, and/or their physicians deemed them to be a higher risk of gastrointestinal bleeding. Dr. Stockbridge noted that treatment differences were directionally the same regardless of PPI use, but smaller among subjects not taking PPIs. He concluded that vorapaxar adds less efficacy to clopidogrel when clopidogrel is used under optimal conditions, i.e., in the absence of a PPI. In TRA 2ºP, this was evident in the 21% of subjects who took omeprazole or esomeprazole, where the RR was closer to unity (Table 6, bottom). As Dr. Stockbridge points out, however, the RR for efficacy was favorable, even in patients who were taking PPI at baseline. But because of their higher propensity to bleed, patients who were taking PPI at baseline had a greater absolute increase in bleeding risk, and a marginal or negative benefit-risk profile overall. I believe the risk is related to the underlying substrate, however, i.e., higher risk of bleeding, rather than an interaction between voraxapar and PPI.

Results: TRA•CER

Table 7 shows the corresponding analysis for TRA•CER, and compares the 1° efficacy endpoint (MACE + UCR + RIR, left) with GUSTO moderate or severe bleeding (right). The RR is slightly unfavorable in a number of subgroups, not surprising because the study did not succeed on the 1° endpoint.

Efficacy Summary:

Overall, TRA 2°P provides substantial evidence of efficacy, although this is more a function of the sample size than the effect size. The results are statically robust, consistent across the components of the 1° endpoint (Table 2), and consistent across major subgroups. The completeness of data collection (96.5%) could have been better, but is in line with most of the applications we've received in recent years.

As noted in Guidance (Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products; May, 1998), a single, large, multicenter, adequate and well-controlled study can support effectiveness in situations where a drug prevents mortality or irreversible morbidity, and this is certainly the case here. Moreover, the evidence of effectiveness is supported by TRA•CER. Although TRA•CER failed on its primary endpoint with a HR of 0.82, p=0.072, it did succeed on MACE, the key 2° endpoint, with HR 0.89 (95% CI 0.18, 0.98), p=0.018. TRA 2ºP could support efficacy in isolation, but the data from TRA•CER buttress the evidence.

Table 7: TRA•CER: Benefit-Risk Assessment by Subgroup – MACE+ (Events Prevented, Left) vs. GUSTO Moderate and Severe Bleeding (Events Caused, Right)

			BENEFIT				RISK				
			Efficacy (MACE +)				Bleeding (GUSTO Moderate or Severe)				
		%	Vorapaxar	Placebo	Delta	RR	Vorapaxar	Placebo	Delta	RR	ΔΔ%
All		12944	15.9%	17.0%	1.1%	0.94	7.1%	5.3%	**-1.8%**	1.34	**-0.7%**
Age	<53	24%	14.6%	13.8%	**-0.9%**	1.06	3.8%	2.6%	-1.1%	1.42	**-2.0%**
	53 to <61	24%	13.7%	15.6%	1.9%	0.88	5.4%	3.9%	**-1.6%**	1.40	**0.3%**
	61 to <69	26%	15.3%	17.1%	1.8%	0.90	7.1%	6.0%	-1.1%	1.18	0.7%
	>=69	25%	20.0%	21.5%	1.5%	0.93	11.8%	8.4%	**-3.4%**	1.41	**-2.0%**
Sex	Male	72%	15.6%	17.2%	1.6%	0.91	6.5%	4.9%	**-1.6%**	1.33	**-0.1%**
	Female	28%	16.7%	16.6%	**-0.1%**	1.01	8.4%	6.3%	**-2.1%**	1.34	**-2.3%**
Race	Caucasian	85%	15.6%	16.9%	1.2%	0.93	6.9%	5.3%	**-1.6%**	1.31	**-0.4%**
	Black	2%	19.2%	21.1%	1.9%	0.91	10.6%	4.3%	**-6.2%**	2.44	**-4.3%**
	Asian	8%	15.3%	15.2%	**-0.1%**	1.01	7.1%	6.6%	-0.5%	1.08	**-0.6%**
	other/unknown	4%	21.7%	22.1%	**0.3%**	0.98	7.9%	3.2%	**-4.7%**	2.46	**-4.3%**
Weight	<60 kg	8%	19.3%	18.2%	**-1.1%**	1.06	9.9%	7.5%	**-2.5%**	1.33	**-3.6%**
	<72 kg	23%	17.7%	17.3%	**-0.4%**	1.02	9.5%	5.7%	**-3.8%**	1.68	**-4.2%**
	72 to <82	23%	14.4%	16.3%	1.9%	0.89	7.6%	5.2%	**-2.3%**	1.44	**-0.5%**
	82 to <93.4	29%	16.2%	16.3%	**0.0%**	1.00	5.8%	5.7%	-0.1%	1.02	**-0.1%**
	>=93.4	25%	15.5%	18.5%	3.0%	0.84	6.0%	4.5%	**-1.6%**	1.35	1.4%
Creatinine clearance	<72.9	24%	22.6%	23.0%	**0.4%**	0.98	12.4%	7.9%	**-4.5%**	1.56	**-4.0%**
	72.9 to <95.2	24%	14.1%	16.2%	2.1%	0.87	6.6%	5.8%	-0.8%	1.15	1.2%
	95.2 to <121.4	24%	13.0%	14.5%	1.5%	0.89	4.9%	4.2%	-0.7%	1.16	0.8%
	>=121.4	24%	14.4%	13.6%	**-0.8%**	1.06	4.2%	3.3%	-0.9%	1.26	**-1.7%**
Location	US	22%	19.7%	21.5%	1.8%	0.91	9.4%	7.3%	**-2.2%**	1.30	**-0.3%**
	Outside US	78%	14.9%	15.8%	**0.9%**	0.94	6.4%	4.7%	**-1.7%**	1.35	**-0.7%**
ASA dose at baseline	0 mg /unknown	3%	16.5%	17.6%	1.1%	0.94	8.7%	7.0%	**-1.6%**	1.23	**-0.5%**
	1 - 101	58%	15.2%	16.8%	1.6%	0.91	6.6%	5.3%	-1.3%	1.25	**0.3%**
	102 - 299	8%	14.9%	20.0%	5.1%	0.74	5.2%	2.9%	**-2.3%**	1.80	2.8%
	> 299	30%	17.5%	16.7%	**-0.8%**	1.05	8.3%	5.7%	**-2.5%**	1.44	**-3.3%**
Location and ASA dose at baseline	OUS 1 - 101	54%	14.8%	16.1%	1.3%	0.92	6.3%	4.9%	**-1.4%**	1.28	**-0.1%**
	OUS 102 - 299	7%	14.4%	18.0%	3.6%	0.80	4.7%	2.8%	**-1.9%**	1.69	1.7%
	OUS > 299	15%	15.0%	12.9%	**-2.1%**	1.16	7.0%	4.9%	**-2.1%**	1.42	**-4.2%**
	US 1 - 101	5%	19.5%	23.8%	4.3%	0.82	9.6%	9.4%	-0.2%	1.02	4.1%
	US 102 - 299	1%	19.2%	37.0%	17.8%	0.52	9.6%	3.7%	**-5.9%**	2.60	11.9%
	US > 299	15%	19.9%	20.6%	**0.7%**	0.97	9.4%	6.6%	**-2.9%**	1.44	**-2.2%**
Thieno at baseline	Yes	87%	16.2%	17.0%	**0.8%**	0.95	7.1%	4.9%	**-2.1%**	1.44	**-1.4%**
	No	13%	14.0%	17.4%	3.4%	0.81	7.0%	7.7%	0.7%	0.90	4.1%
Half of study	1st	50%	18.2%	19.6%	1.5%	0.92	7.9%	5.5%	**-2.4%**	1.43	**-0.9%**
	2nd	50%	13.7%	14.4%	**0.7%**	0.95	6.2%	5.1%	-1.2%	1.23	**-0.5%**
Stent at baseline	No	45%	15.5%	16.2%	**0.7%**	0.95	9.3%	7.4%	**-1.8%**	1.25	**-1.1%**
	Yes	55%	16.3%	17.7%	1.4%	0.92	5.2%	3.5%	**-1.8%**	1.50	**-0.3%**
Any PPI use > 7 days	No	59%	14.5%	15.6%	1.1%	0.93	4.7%	3.8%	-0.9%	1.22	**0.2%**
	Yes	41%	17.9%	19.0%	1.1%	0.94	10.4%	7.4%	**-3.0%**	1.41	**-1.9%**
omep/esomep use >7 days	No	80%	15.2%	16.2%	1.0%	0.94	6.0%	4.7%	-1.3%	1.28	**-0.3%**
	Yes	20%	18.7%	20.3%	1.6%	0.92	11.1%	7.6%	**-3.4%**	1.45	**-1.9%**

Support of Safety:

Voraxapar's principal safety concern is bleeding, and the risk is well summarized in the applicant's analysis of bleeding events for TRA 2ºP, shown in Table 8. Of note, the overall RR for GUSTO moderate or severe bleeding in TRA•CER (1.34) was slightly lower than that in TRA 2ºP (1.55), yet TRA•CER offered a more severe 'test,' given that patients were hospitalized with ACS and underwent invasive procedures as a routine matter.

Table 8: TRA 2°P – Non-CABG-Related Bleeds in the Labeled Population (First Dose to Last Dose + 30 Days)

	Placebo (n=10,049)		ZONTIVITY (n=10,059)		Hazard Ratio
Endpoints	Patients with events (%)	K-M %	Patients with events (%)	K-M %	(95% CI)
GUSTO Severe	82 (0.8%)	1%	100 (1.0%)	1.30%	1.24 (0.92-1.66)
GUSTO Moderate or Severe	199 (2.0%)	2.40%	303 (3.0%)	3.70%	1.55 (1.30 - 1.86
GUSTO Moderate, Severe, or Mild	1769 (17.6%)	19.80%	2518 (25.0%)	27.70%	1.52 (1.43 - 1.61
Fatal	14 (0.1%)	0.2%	16 (0.2%)	0.20%	1.15 (0.56-2.36)
ICH	31 (0.3%)	0.4%	45 (0.4%)	0.60%	1.46 (0.92-2.31)
Clinically Significant Bleeding	950 (9.5%)	10.9%	1349 (13.4%)	15.50%	1.47 (1.35-1.60)
GI bleeding	297 (3.0%)	3.5%	400 (4.0%)	4.70%	1.37 (1.18-1.59)

In the categories where there are large numbers of events, GUSTO moderate, severe, or mild bleeding events (4287 events) and clinically significant bleeding events (2299 events), the RR is ~1.5. Assuming that bleeding events of lesser severity are surrogates for bleeding events of greater severity, it is fair to say that voraxapar increases bleeding by 50%.

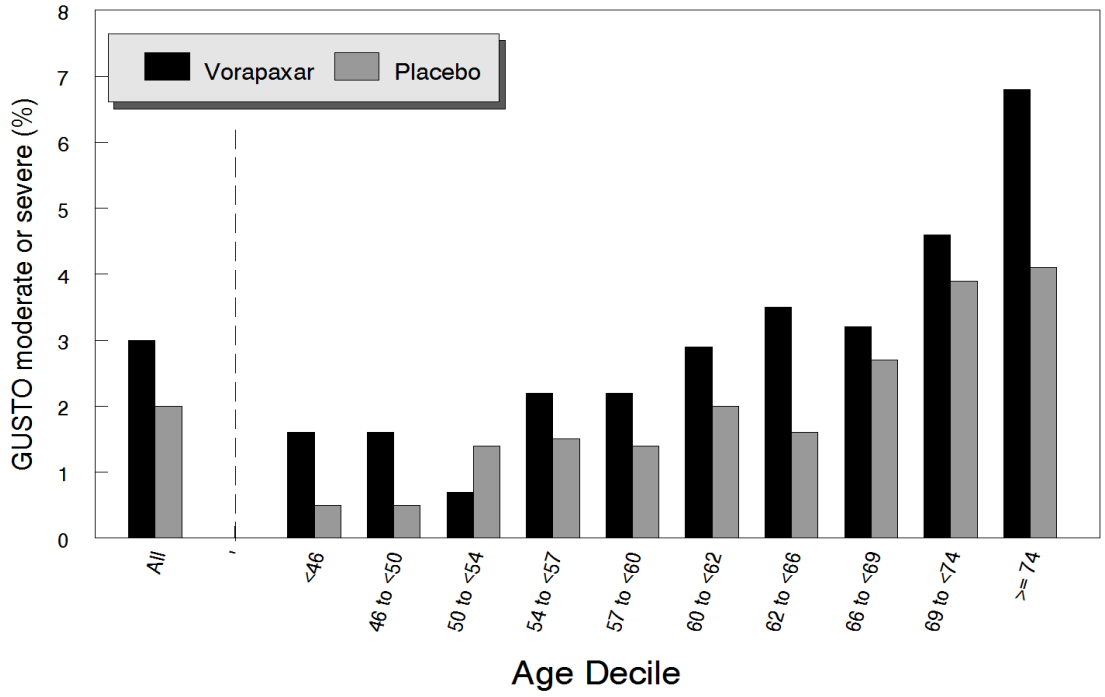
Bleeding Subset Analyses:

In both studies, the RR of bleeding is fairly consistent across the multiple subsets represented. There are some notable exceptions: Asians do poorly in TRA 2ºP with respect to bleeding (Table 6), although they only account for 3% of the study population; Blacks do poorly in TRA•CER (Table 7), but comprise only 2% of the study population. It is clear that in future studies we should be proactive and encourage sponsors to enroll higher numbers of minorities so that we have a better chance of estimating risk (and benefit).

Whereas the RR of bleeding seems relatively consistent across subgroups, the absolute risk is a function of the baseline risk. This point is well illustrated in a plot of GUSTO moderate or severe bleeding vs. age deciles in TRA 2ºP (Figure 6). As age increases, the risk of bleeding

increases, such that the voraxapar's incremental *absolute* risk generally increases as age increases.

Figure 6: TRA 2ºP: GUSTO Moderate or Severe Bleeding by Age Decile – Labeled Population



Other subgroups with higher baseline risk of bleeding include:

- female sex
- lower weight
- patients with renal dysfunction (reduced glomerular filtration rate [GFR])
- PAD (rather than coronary artery disease), and
- PPI use at baseline.

There was also a considerable disparity in bleeding rates between U.S. and non-U.S. patients; this is evident in the placebo groups of both studies: 4.2 vs. 1.7 for U.S. and non-U.S. patients, respectively in TRA 2ºP; 7.3 vs. 4.6% for U.S. and non-U.S. patients, respectively in TRA•CER. Taking the two studies together, the bleeding rate in the U.S. is roughly double that outside the U.S. Whether this has to do with practice of medicine, completeness of reporting, or both, or play of chance, is unknown.

What is clear from these analyses is that the higher a patient's inherent risk of bleeding, the greater vorapaxar's additive risk in absolute terms, and this message will be included in labeling.

Other Safety (Non-Bleeding)

The applicant tabulated adverse events by preferred term, and there was little attempt, by the applicant or in the reviews, to categorize related or seemingly identical terms together. For example, the following 20 terms, all representing anemia, were categorized and tabulated separately:

- aplasia pure red cell
- iron deficiency anaemia
- nephrogenic anaemia
- anaemia
- anaemia folate deficiency
- anaemia haemolytic autoimmune
- anaemia megaloblastic
- anaemia of chronic disease
- anaemia vitamin B12 deficiency
- cold type haemolytic anaemia
- haemorrhagic anaemia
- hypochromic anaemia
- microcytic anaemia
- normochromic normocytic anaemia
- pernicious anaemia
- anaemia postoperative
- haematocrit abnormal
- haematocrit decreased
- haemoglobin decreased
- red blood cell count decreased

Such analyses, with preferred terms split among several groups, are deceptive. I recognize that under particular circumstances, some would say certain terms should not be combined, for example, some might say that the anemia of vitamin B12 deficiency has a distinct pathophysiology and deserves separate tabulation and analysis. That may be true, but for a high-level view, these terms should be combined. And certainly the terms haematocrit decreased, haemoglobin decreased, red blood cell count decreased, and anaemia, etc. cannot be differentiated, and should be combined.

I created groupings of preferred terms in order to categorize serious and non-serious adverse events. For example, the preferred terms listed above were analyzed as “anemia.”

Serious Adverse Reactions:

Serious adverse events reported at higher rates for voraxapar than placebo, which seemed plausibly drug-related included: anemia, iron deficiency, retinal disorders, and depression.

Table 9 shows my tabulation of serious adverse events that occurred in at least 9 patients (0.05%) in the voraxapar group, at a RR of at least 1.1. They are shown by decreasing order of RR.

Table 9: Serious Adverse Reactions in TRA 2ºP and TRA•CER: On Treatment; Rate in Voraxapar ≥ 0.05%, Relative Risk ≥1.1, by Decreasing RR

	Voraxapar 19632	Placebo 19607	RR
	n (%)	n (%)	
Fe Deficiency	21 (0.11)	6 (0.31)	3.50
anemia	92 (0.47)	34 (1.73)	2.71
esophagitis, Hiatal Hernia	23 (0.12)	11 (0.56)	2.09
hernia, incarcerated or ruptured	9 (0.05)	5 (0.26)	1.80
tendon rupture	12 (0.06)	7 (0.36)	1.71
benign prostatic hypertrophy	44 (0.22)	30 (1.53)	1.47
gout, high uric acid	13 (0.07)	9 (0.46)	1.44
retinopathy, retinal disorders	10 (0.05)	7 (0.36)	1.43
atrial flutter	42 (0.21)	31 (1.58)	1.35
UTI	117 (0.6)	89 (4.54)	1.31
low EF, low CO, cardiomyopathy, LV dys	36 (0.18)	28 (1.43)	1.29
depression	36 (0.18)	28 (1.43)	1.29
dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis, gastric ulcer, H pylori infection	95 (0.48)	74 (3.77)	1.28
AV block	43 (0.22)	34 (1.73)	1.26
Ileus, obstruction	36 (0.18)	29 (1.48)	1.24
wheeze, bronchospasm, asthma	16 (0.08)	13 (0.66)	1.23
Fall	22 (0.11)	18 (0.92)	1.22
syncope	108 (0.55)	90 (4.59)	1.20
high or third deg AV Block	24 (0.12)	20 (1.02)	1.20
diabetes, glucose intolerance, hyperglycemia,	85 (0.43)	71 (3.62)	1.20
pulm edema	31 (0.16)	26 (1.33)	1.19
sepsis	80 (0.41)	68 (3.47)	1.18
AF	192 (0.98)	165 (8.42)	1.16
bacteremia	86 (0.44)	74 (3.77)	1.16
hypoglycemia	29 (0.15)	25 (1.28)	1.16
Angina	201 (1.02)	174 (8.87)	1.16
pre-syncope or syncope	129 (0.66)	114 (5.81)	1.13
appendicitis	27 (0.14)	24 (1.22)	1.13
dizziness, light-headedness	18 (0.09)	16 (0.82)	1.13
infection, viral	46 (0.23)	41 (2.09)	1.12
supra-ventricular	249 (1.27)	224 (11.42)	1.11
palpitations	10 (0.05)	9 (0.46)	1.11
DVT	22 (0.11)	20 (1.02)	1.10

Adverse reactions (serious and non-serious) reported at a frequency of ≥0.1% and a RR of ≥1.1 are tabulated in Table 10 by decreasing RR. At our request, the applicant provided a number of new tabulations of adverse reactions. Section 6 of the label will include anemia, depression, and rash in the table (rate ≥0.2% and RR ≥1.1). Section 6 will also include text below the table describing excess adverse reactions of: iron deficiency, retinopathy or retinal disorder, and diplopia/oculomotor disturbances.

Table 10: Adverse Reactions in TRA 2ºP and TRA•CER: On Treatment; Rate in Voraxapar ≥ 0.1%, Relative Risk ≥1.1, by Decreasing RR

	Voraxapar 19632	Placebo 19607	RR
	n (%)	n (%)	
diplopia	30 (0.15)	10 (0.05)	3.00
hepatitis	24 (0.12)	15 (0.08)	1.60
retinopathy, retinal disorders	65 (0.33)	44 (0.22)	1.48
Fe Deficiency	120 (0.61)	83 (0.42)	1.45
emothional mood disturbance (non-depressive)	31 (0.16)	23 (0.12)	1.35
Ileus, obstruction	50 (0.25)	39 (0.2)	1.28
anemia	982 (5)	783 (3.99)	1.25
eosinophilia	35 (0.18)	28 (0.14)	1.25
leukopenia	31 (0.16)	25 (0.13)	1.24
motor vehicle accident	64 (0.33)	53 (0.27)	1.21
infection, fungal	193 (0.98)	160 (0.82)	1.21
polyuria, increased frequency	48 (0.24)	40 (0.2)	1.20
suicidal ideation, suicide	30 (0.15)	25 (0.13)	1.20
dysuria	51 (0.26)	43 (0.22)	1.19
abscess, boil, furuncle	185 (0.94)	157 (0.8)	1.18
depression	477 (2.43)	405 (2.07)	1.18
herpes virus	161 (0.82)	137 (0.7)	1.18
memory loss, impairment	94 (0.48)	82 (0.42)	1.15
cellulitis, erysipelas	213 (1.08)	186 (0.95)	1.15
Bili, alk phos, jaundice	357 (1.82)	312 (1.59)	1.14
AV block	89 (0.45)	78 (0.4)	1.14
hernia	165 (0.84)	145 (0.74)	1.14
hypoglycemia	149 (0.76)	131 (0.67)	1.14
esophagitis, Hiatal Hernia	128 (0.65)	113 (0.58)	1.13
stone, renal colic	188 (0.96)	168 (0.86)	1.12
reflux, GERD	235 (1.2)	211 (1.08)	1.11
sepsis	100 (0.51)	90 (0.46)	1.11
diverticular disease	163 (0.83)	147 (0.75)	1.11
bacteremia	113 (0.58)	102 (0.52)	1.11
hepatic steatosis	52 (0.26)	47 (0.24)	1.11
erectile dysfunction	142 (0.72)	129 (0.66)	1.10
infection, bacterial	134 (0.68)	122 (0.62)	1.10
hearing loss	56 (0.29)	51 (0.26)	1.10

Cancer:

Dr. Marciniak analyzed times to first solid cancer events in TRA 2ºP and TRA•CER. Inexplicably, there was a nominally statistically significant increase in solid cancer events in TACER, but no difference whatsoever in TRA 2ºP. The meaning of these findings is not clear, and Dr. Marciniak did not believe the excess cancers in TRA•CER should be described in labeling. Dr. Stockbridge did not comment on cancer, but I agree with Dr. Marciniak's conclusion.

BENEFIT-RISK

Despite much recent interest in benefit-risk assessment, benefit and risk are difficult to compare as a general principle. Benefit and risk are usually difficult to quantify, and if they lend themselves to quantification at all, they can be difficult to weigh. For example, one has to decide how to compare the short- and long-term consequences of an MI with those of a life-threatening hemorrhage. Even more difficult is the comparison of, for example, a 3-point change on a depression scale with an imbalance in a serious adverse reaction. Such decisions are inherently subjective and difficult, which makes benefit-risk assessment elusive.

In recent years, the Division of Cardiovascular and Renal Products has received a number of NDAs for antiplatelet drugs and anticoagulants with large outcome trials – where benefit and risk have been quantifiable on the basis of numbers of patients in whom cardiovascular events are prevented (generally MIs, strokes, and cardiovascular death) vs. numbers of patients in whom there is excess harm (generally bleeding). All of these applications, however, have compared the new drug to an active control.

Unlike these recent NDAs for anti-platelet agents and anticoagulants, this NDA presents a unique opportunity to assess *absolute* benefit and risk, because here voraxapar was compared to placebo, and so the benefits and risks are relative to no drug; voraxapar (or placebo) was used *in addition to* standard therapy.

The overall benefit-risk assessment is 0.7%, favoring voraxapar. That is to say that the decrease in MACE+ is 1.7% over 3 years, compared to a GUSTO severe or moderate bleeding rate of 1.0%.

But that analysis presupposes that GUSTO severe or moderate bleeding should carry a weight similar to the events prevented (MACE+). It is important to consider benefit and risk by the severity of bleeding (Table 11). Assuming a 50% increase in bleeding of all types, the absolute increase in bleeding events is as low as 0.4% for GUSTO severe bleeding events, but as high as 8.8% for GUSTO severe, moderate, or mild events.

Table 11: Benefit and Risk in TRA 2P: Absolute Risk Depends on Severity of Bleeding

	Rate in Placebo Group	RR	Fractional Change	Loss/Gain
Benefit				
MACE+ reduction	10.6%	0.084	-0.16	**-1.7%**
Risk				
GUSTO severe	0.8%	1.5	0.5	**0.4%**
GUSTO severe, moderate	2.0%	1.5	0.5	**1.0%**
GUSTO severe, moderate, mild	17.6%	1.5	0.5	**8.8%**
Clinically significant	9.5%	1.5	0.5	**4.8%**

Thus, for each MACE+ event prevented, there will be an estimated 5 GUSTO severe, moderate, or mild bleeding events. It is critical to communicate this considerable bleeding risk in labeling.

Bleeding risk will be highlighted in a boxed warning. In addition, Section 6 will have a prominent table and a large forest plot to highlight and describe the bleeding risk.

Table 6 shows a side-by-side comparison of benefit and risk by subgroup in TRA 2ºP, and there is a corresponding table for TRA•CER in Table 7. The benefit represents the numbers of MACE+ events prevented. Risk represents GUSTO moderate or severe bleeding. Event rates and relative risks were calculated as simple comparisons of numerators and denominators. Deltas represent simple subtractions. For example, for all patients (top), the "Delta" for benefit (1.7%) represents the difference between 10.6% and 8.9% for the placebo and voraxapar groups, respectively. The ΔΔ column on the right represents the difference between benefit and risk: the higher the number, the more favorable the benefit-risk. Negative numbers are unfavorable. Benefit and risk are given equal weight: they are simply subtracted. Some would argue that MIs, strokes and certainly deaths have permanent consequences, whereas hemorrhages do not. But some MIs have limited consequences, and many GUSTO moderate and severe bleeding events are clinically important. Thus, they are given equal weight in this analysis. Outliers are shown in bold font.

Subgroups where benefit-risk is less favorable include higher age, Asian race, weight <60 kg, and U.S. location. It should not be surprising that one can identify particular subgroups where benefit-risk is less favorable, but such subset analyses, with multiple comparisons, have important limitations, as noted above. For example, the most favorable benefit-risk profile in TRA 2ºP (Table 6) is in the 8% of study subjects, outside the U.S., who received a daily dose of aspirin between 102 and 299 mg at study entry – plainly a preposterous finding! The point is that one has to be careful not to over-interpret these subgroup findings.

SUMMARY/CONCLUSION

Voraxapar represents a new, third prong of anti-platelet therapy, to be used in addition to aspirin and clopidogrel for the prevention of MI, stroke, need for urgent coronary revascularization, and cardiovascular death in patients with a history of MI or PAD. But the leap from dual anti-platelet therapy to triple anti-platelet therapy is a serious step that should not be taken lightly. I believe that TRA 2ºP alone provides substantial evidence of efficacy and would support approval in its own right. But approval of voraxapar could herald a potential change in the overall practice of cardiovascular medicine – a very serious matter, such that approval here is not a straightforward decision.

Given the sheer size of TRA 2ºP with its 1,971 primary endpoint events, we can be confident of the results with respect to efficacy. The upper limit of the 95% confidence interval for MACE+ is 0.90. The bleeding risk is also well characterized, at approximately 50% (RR 1.5).

In recent months, (b) (4) I agree with that line of thinking. Although

TRA•CER did not succeed on its 1° MACE+ endpoint (MACE plus UCR plus RIR), it did succeed nominally on MACE, and it was able to characterize bleeding risk in a high-risk ACS patient population.

Thus, I believe there is sufficient evidence here to change practice, provided that the bleeding risk is well-described and highlighted in labeling. With a boxed warning, contraindications for patients with prior stroke and TIA, and both a table and figure in Section 6 of labeling, I am satisfied that communication of the bleeding risk will be adequate.

Whether one should assume the risk of bleeding for a 1.7% reduction in MACE and urgent revascularization over 3 years will require an informed decision that can be made by patients and physicians. The labeling should insure that such decisions are well informed.

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/s/

ELLIS F UNGER
05/08/2014