CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204886Orig1s000

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION
ADDENDUM

NDA/Serial Number:	204886 (S0000)
Drug Name:	MK-5348/SCH 530348 (Vorapaxar Sulfate)
Indication:	Secondary Prevention of Ischemic Events
Applicant:	Merck
Dates:	Date of Document: May 10, 2013
	PDUFA Due Date: May 10, 2014
Review Priority:	Standard
Biometrics Division:	Biometrics I
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardiovascular and Renal Drug Products
Clinical Team:	Martin Rose, M.D.
	Thomas Marciniak, M.D.
Project Manager:	Alison Blaus, RAC

Reference ID: 3426523

The sponsor is proposing restricting the indication to a subgroup of patients based on Study TRA-2P. Among many subgroups for which vorapaxar performed differently in terms of primary and key secondary efficacy endpoints, it is particularly noted and seems to have drawn special attention that patients with body weight less than 60 kg showed little or adverse effect, in contrast to the beneficial effect in the patients with body weight 60 kg or above. We further assessed the vorapaxar's performance by assessing treatment by patient's body weight interaction.

I performed Cox regression analyses by adding patient's body weight (as a continuous variable) and its interaction with treatment in the primary analysis model for both primary and key secondary efficacy endpoints. The results are given in Table 1. As seen from the table, the 'Treatment' factor is no longer significant in the model. Thus, the apparent significant treatment by body weight interactions are difficult to interpret.

Table 1 Statistical Reviewer's P-Values for Assessing Vorapaxar's Efficacy in Presence of Body Weight and its Interaction with Treatment Factors for the ITT Population

Factor	Primary Efficacy Endpoint	Key Secondary Efficacy Endpoint
Treatment	0.26	0.12
Body Weight	0.001	0.003
Body Weight×Treatment	0.07	0.02

_____
Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 204,886
HFD-110/Dr. Stockbridge
HFD-110/Dr. Grant
HFD-110/Dr. Marciniak
HFD-110/Dr. Levine
HFD-110/Dr. Rose
HFD-110/Ms. Alison
HFD-700/Ms. Patrician
HFD-710/Dr. Hung

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/s/

YEH FONG CHEN
12/20/2013

HSIEN MING J HUNG
12/20/2013

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STATISTICAL REVIEW AND EVALUATION

Clinical Studies

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1. EXECUTIVE SUMMARY

The vorapaxar's efficacy in addition to the standard of care for preventing patients' atherothrombotic ischemic events appears to be demonstrated in TRA 2°P-TIMI 50 trial for the overall study population and also for the proposed label population, i.e., post MI patients without history of stroke or TIA. We are concerned about several unplanned interim analyses, sample size increase and change of patient population, even though these analyses are performed by an independent statistician through the Data Safety Monitoring Board (DSMB). Whether these analyses might have impacted the trial integrity is uncertain.

2. INTRODUCTION

2.1 OVERVIEW

The sponsor's vorapaxar Phase III clinical program included two placebo-controlled clinical outcome studies, TRACER and TRA 2°P-TIMI 50 Trials (hereafter referred to as TRA-2P in this review) that were designed to test the hypothesis that vorapaxar added to standard of care would reduce the incidence of atherothrombotic events compared to placebo with standard of care in two distinct patient populations. They were two independent, long-term, large outcome studies intended to support different indications of acute coronary syndromes (ACS) and secondary prevention of post myocardial infaction (MI), post stroke or PAD separately.

According to the sponsor, TRACER enrolled subjects in the midst of an acute episode during hospitalization that invariably resulted in parenteral use of anti-coagulants and loading dose regimens of both anti-coagulants and anti-platelet agents. However, TRA-2P, on the other hand, enrolled subjects that were clinically stable as they were 2 weeks to 1 year post the index event (median 77 days). Due to the remote qualifying events for TRA-2P inclusion, subjects with good tolerance to anti-platelet agents could have been selected.

The primary endpoint of TRACER study was the composite of cardiovascular (CV) death, MI, stroke, recurrent ischemia with rehospitalization (RIR) and recurrent ischemia leading to urgent coronary revascularization (UCR) and the key secondary endpoint was the composite of CV death, MI and stroke. In TRACER study, 12,944 subjects (6,471 receiving placebo and 6,473 receiving vorapaxar) were randomized and the final results showed a non-significant hazard reduction of 8% with p-value equal to 0.072, even though vorapaxar reduced the hazard of the key secondary composite of CV death, MI or stroke by 11%.

The primary endpoint of TRA-2P was the composite of CV death, MI, stroke and UCR and the key secondary endpoint was the composite of cardiovascular death, MI and stroke. In TRA-2P study, 26,449 subjects (13,224 subjects receiving placebo and 13,225 receiving vorapaxar) were randomized and the sponsor's final results demonstrated hazard reduction of 12 % with p-value of 0.001 for the primary endpoint and a hazard reduction of 13% with p-value less than 0.001 for the key secondary endpoint.

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Although two studies showed different efficacy conclusions, the two studies had some similar design elements; both studies had one official interim analysis planned and they shared the same Clinical Endpoint Committee (CEC) charter and the Data Safety Monitoring Board (DSMB). As a result, the principal investigators of the two trials were to engage in routinely scheduled communication to assess the conduct and consistency of adjudication process within the two trials and the DSMB members knew both trials' interim analysis findings. Due to the large size of the TRA-2P study, it was also noted that although TRA-2P was conducted about three months earlier than TRACER study but completed about six months later than the TRACER study.

Now that TRACER was a non-positive study, our evaluation was mainly on TRA-2P. Although based on the sponsor's results, which clearly demonstrated that TRA-2P had positive findings in the overall ITT patient population, during an interim analysis, the DSMB observed an increased incidence and relative risk of ICH in subjects with prior history of stroke and thus recommended discontinuing the study drug in all subjects with a prior history of stroke or a stroke occurring during the course of the study. The sponsor decided to update and pre-define in the data analysis plan the following supplementary secondary objectives including the evaluation of the first occurrence of the primary and key secondary endpoints in populations including the following:

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

Post MI or CAD with no history stroke – subjects whose qualifying condition was Coronary Artery Disease (CAD), and did not have a documented history of stroke prior to randomization

Following data-base lock and unblinding, the sponsor and trial's Executive Committee determined that, for the purpose of clinical clarity and patient safety, subjects with a history of TIA be granted the same consideration as subjects with a history of stroke given that the clinical diagnosis of stroke vs. TIA can be difficult, especially when based on patient medical history alone. This TIA subgroup was then removed from the pre-specified post MI with no history of stroke population, yielding this definition for the proposed label population:

Proposed Label Population (post MI with no history of stroke or TIA) – subjects whose qualifying condition was CAD and did not have a documented history of stroke or TIA prior to randomization

The following Table 1 shows the sponsor's analysis results for different types of patient population. Based on their findings, they concluded that efficacy in both the primary and key secondary endpoint was evident in the pre-specified NSH population, as well as in the pre-specified, post MI (CAD) subjects without a history of stroke and in the Proposed Label Population.

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Table 1 Sponsor's Efficacy Findings for Different Patient Population for TRA-2P Study

Population	Placebo		Vorapaxar		Hazard Ratio (95% CI) , P-value
	Events (%)	KM %	Events (%)	KM %	
Overall	n = 13224		n = 13225		
Primary Endpoint	1417 (10.7%)	12.4%	1259 (9.5%)	11.2%	0.88 (0.82-0.95) 0.001
Key Secondary Endpoint	1176 (8.9%)	10.5%	1028 (7.8%)	9.3%	0.87 (0.80-0.94) <0.001
No Stroke History (NSH)	n = 10344		n = 10355		
Primary Endpoint	1104 (10.7%)	11.8%	959 (9.3%)	10.6%	0.86 (0.79-0.94) <0.001
Key Secondary Endpoint	878 (8.5%)	9.6%	742 (7.2%)	8.3%	0.84 (0.76-0.93) <0.001
Post MI NSH	n = 8583		n = 8608		
Primary Endpoint	887 (10.3%)	11.5%	757 (8.8%)	10.1%	0.84 (0.76-0.93) <0.001
Key Secondary Endpoint	687 (8.0%)	9.1%	564 (6.6%)	7.7%	0.81 (0.73-0.91) <0.001
Proposed Label	n = 8439		n = 8458		
Primary Endpoint	867 (10.3%)	11.4%	719 (8.5%)	9.8%	0.82 (0.74-0.90) <0.001
Key Secondary Endpoint	671 (8.0%)	9.0%	532 (6.3%)	7.4%	0.78 (0.70- 0.88) <0.001

Source: Sponsor's Table 4 of clinical overview.pdf

2.2 DATA SOURCES

The sponsor's original submission including data files and clinical study reports is stored in the following link: \\Cdsesub1\evsprod\NDA204886\0000.

During the NDA review cycle, we requested the sponsor to respond to the questions listed in the 74 Days' letter. The statistical questions include the unplanned interim analysis and also the needed alpha adjustment, the clarification of sample size increase as well as the interim analysis results. The relevant submissions are stored in the following links:

\\CDSESUB1\evsprod\NDA204886\0032 (for unplanned IAs and alpha adjustment)
\\CDSESUB1\evsprod\NDA204886\0034 (for unplanned sample size re-estimation)
\\CDSESUB1\evsprod\NDA204886\0039 (for interim analysis results)

3. STATISTICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

The submitted data and the quality of the analyses performed by the sponsor appear to be acceptable. However, during the review cycle, the statistical reviewer noted that the sponsor did not include their interim analysis (IA) results and also the interim data in the submission, thus requested the sponsor to submit them. It is interesting to note that the interim analyses were conducted by an independent statistician through the company appointed Data Monitoring Committee and the sponsor indicated that they did not further verify the IA results as the study had been completed, thus no need to perform the verification. Another issue is that during the review cycle, the medical reviewer Dr. Rose found that some patients discontinued study early but were censored on an earlier date without information available on any component of the primary endpoint. Per our request, the sponsor 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. They confirmed that the primary and key secondary efficacy results are not impacted. Finally, during the review cycle, the statistical reviewer found that one variable for capturing events'

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adjudication status in TRACER study was problematic. The sponsor confirmed that it was due to a mistake in their SAS program, but ensured us the primary efficacy analysis results were not affected by this mistake in any way.

3.2 EVALUATION OF EFFICACY

3.2.1 Study Design and Endpoints

Description of Study TRA 2°P – TIMI 50

Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 (Vorapaxar) in Addition to Standard of Care in Subjects with a History of Atherosclerotic Disease: Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events

The following study description was mostly extracted from the sponsor's clinical study report.

3.2.1.1 Study Objectives

Primary Objective

To evaluate the hypothesis that vorapaxar added to standard of care will reduce the incidence of atherothrombotic ischemic events relative to standard of care alone, as measured by the composite of cardiovascular (CV) death, myocardial infarction (MI), stroke, and urgent coronary revascularization.

Secondary Objectives

The key secondary objective was to evaluate clinical benefit with respect to the composite of CV death, MI, and stroke. Other secondary efficacy objectives included evaluation of the incidence of and time to the following composites or individual components as indicated:

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

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3.2.1.2 Study Design

TRA 2°P – TIMI 50 (Protocol P04737) was a multicenter, international, randomized, double-blind, placebo-controlled, balanced-parallel-groups, events-driven investigation of orally administered vorapaxar in the secondary prevention of ischemic events conducted in conformance with GCP.

Men and women at least 18 years old who had evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems were eligible to participate. Following completion of informed consent, subjects were considered enrolled, and were to receive randomized assignment of daily treatment with either vorapaxar at 2.5 mg or placebo, with assignment stratified for

- underlying presentation history at the time of enrollment, in the following hierarchical order of priority
  1. CAS as manifested by MI
  2. Ischemic (presumed thrombotic) CVD
  3. PAD

- planned treatment with a thienopyridine (being taken or added at enrollment versus not taken and not added)

Subjects were to receive randomized treatment assignment no later than 10 days after enrollment (giving informed consent), and were to begin taking daily treatment immediately, or as soon as possible, after randomized treatment assignment.

Treatment was to continue until study completion; that is, when a statistically defined number of efficacy endpoint events had been observed and every subject had the opportunity to participate in the study for at least 1 year.

Up to 25,000 subjects were anticipated to participate at approximately 1000 centers. This sample size was required to provide adequate power to test the hypothesis of a 15% relative risk reduction with vorapaxar relative to placebo, each added to the existing standard of care, for occurrence of the primary and key secondary composite efficacy endpoints, plus adjust for potential dropouts during the study.

One interim efficacy analysis was planned for when approximately 50% of the primary and 50% of the key secondary efficacy endpoints (best available data: total of adjudicated and unadjudicated) required for completion of the TRA-2P-TIMI 50 trial were available and was conducted on 24 FEB 2010. The purpose of the interim analysis was to confirm initial estimates of event rates and to allow the DSMB to make recommendations to the Executive Committee; these recommendations could have included continuing under the current protocol, amending the current protocol, or stopping the study.

The following Figure 1 shows a schematic representation of the study design.

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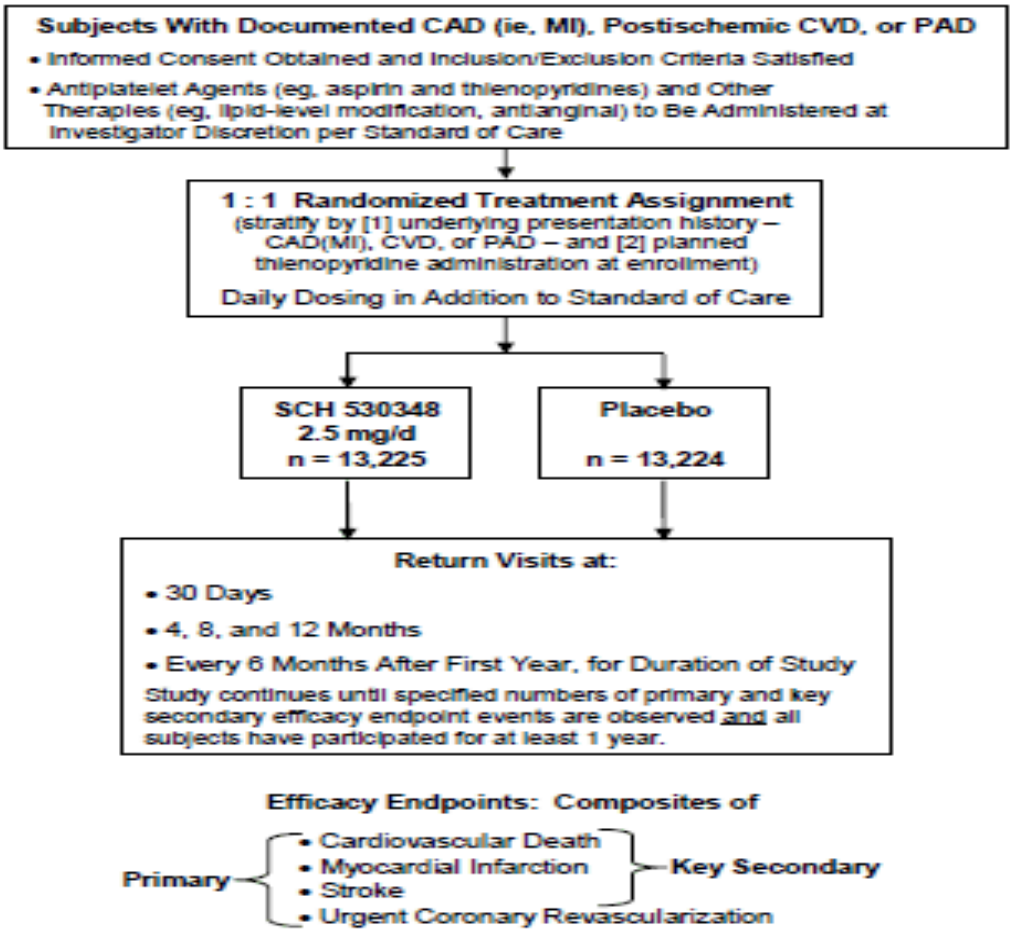
Figure 1 Schematic Representation of the Study Design for TRA-2P Study



Source: Sponsor's Figure 1 from CSR

3.2.1.3 Efficacy Endpoints

The primary efficacy endpoint was the first occurrence of any component of the composite of CV death, MI, stroke, and urgent coronary revascularization.

The key secondary efficacy endpoint was the first occurrence of any component of the composite of CV death, MI, or stroke.

Other secondary endpoints included the first occurrence of the following composites or individual components, as shown:

- all-cause death, MI, stroke, and urgent coronary revascularization
- CV death and MI
- CV death, MI, stroke, urgent coronary revascularization, or urgent hospitalization for vascular cause of ischemic nature
- all-cause death, MI, stroke, and any revascularization

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- CV death, MI, stroke, any revascularization, or urgent hospitalization for vascular cause of ischemic nature
- The following individual components of the primary endpoint
  1. CV death
  2. MI
  3. urgent coronary revascularization
  4. stroke
- all-cause death

3.2.2 Statistical Methodologies

Efficacy analyses will be carried out on an intent-to-treat basis, and all evaluations will include all subjects who receive treatment, or who receive randomization assignment without receiving treatment. Safety evaluations will include all subjects who receive at least one dose of study treatment. The statistical methods described here are intended for the analyses of the primary and key secondary efficacy endpoints. The primary efficacy analysis will be based on the time from randomized treatment assignment until the first occurrence of one of the following: cardiovascular death, MI, stroke, or urgent coronary revascularization. A Cox proportional-hazard model with covariates of treatment and stratification factors will be used to perform this analysis. Estimates of the hazard ratios and associated 95% confidence intervals comparing placebo with vorapaxar will be provided with the use of this model. The key secondary efficacy endpoint, first occurrence of cardiovascular death, MI, or stroke, will be evaluated using similar methodology. Kaplan-Meier estimates for the time to the primary and key secondary efficacy endpoints will be plotted. The potential influence of baseline risk factors and concomitant therapies such as statins, thienopyridines, and aspirin dosing on the occurrences of the primary and key secondary efficacy endpoints will be explored using the Cox proportional-hazard model.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

A total of 26,449 subjects were enrolled in the study and received randomized treatment assignment at 1029 study sites in 32 different countries. Of the total subjects enrolled, 13,224 subjects were assigned to receive placebo and 13,225 were assigned to receive vorapaxar at 2.5 mg daily. These subjects comprised the “Intent to Treat” population.

Following the DSMB recommendation of 08 Jan 2011 to stop treatment in all subjects with a medical history of stroke or who had a stroke during the study, a series of communications that included new risk information to subjects were sent to the study sites on 13 Jan 2011 to guide them on treatment discontinuation and follow-up.

Of the total 26,449 subjects who were assigned to receive randomized treatment assignment (ITT population), 97 subjects did not receive treatment (58 were assigned to receive placebo and 39 who were assigned to receive vorapaxar). The remaining 26,352 subjects (13,166 placebo and 13,186 vorapaxar) comprised the “As Treated” population. Of note, a low percent

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of subjects withdrew consent for telephone follow-up (255 subjects on placebo; 277 subjects on vorapaxar). A total of 32 subjects were lost to follow-up.

Of these 26,449 subjects, the DSMB recommendation involved 4,510 subjects who had either a prior history of stroke or had experienced a stroke endpoint during the study. Therefore, subjects randomized and stratified to the CVD stratum who had a history of stroke had their study drug and participation in the trial discontinued. The remaining subjects with a history of stroke or stroke endpoint who were randomized and stratified to the CAD and PAD strata and 25 subjects in the stroke stratum who did not have a history of stroke (and thus were incorrectly stratified) had their study drug discontinued but continued participation in the trial.

A detailed description of the disposition of subjects through the study is shown in the following Table 2.

Table 2 Subject Disposition for TRA-2P Study

Number (%) of Subjects	Placebo	SCH 530348	Total
Randomized	13,224 (100)	13,225 (100)	26,449 (100)
Never Received Study Drug	58 (0.4)	39 (0.3)	97 (0.4)
Discontinued Study Drug Prematurely	2,948 (22.3)	3,145 (23.8)	6,093 (23.0)
Adverse/Bleeding/Clinical Experience	1,299 (9.8)	1,381 (10.4)	2,680 (10.1)
Withdrew Consent to Study Treatment	1,211 (9.2)	1,257 (9.5)	2,468 (9.3)
Did not Meet Protocol Eligibility	48 (0.4)	42 (0.3)	90 (0.3)
Non-compliance with Protocol	297 (2.2)	355 (2.7)	652 (2.5)
Required Prohibited Medication	57 (0.4)	67 (0.5)	124 (0.5)
Other/Missing	36 (0.3)	43 (0.3)	79 (0.3)
Subjects with History of Stroke or New Stroke Discontinued Study Drug at Recommendation of DSMB	2,248 (17.0)	2,262 (17.1)	4,510 (17.1)
Completed Treatment	7,970 (60.3)	7,779 (58.8)	15,749 (59.5)
Died	589 (4.5)	556 (4.2)	1,145 (4.3)
Lost to Follow-up	15 (0.1)	17 (0.1)	32 (0.1)
Withdrew Consent for Follow-up	277 (2.1)	255 (1.9)	532 (2.0)

Source: Sponsor's Display A-1.4 on Page 769 of CSR.

Demographic and Baseline Characteristics

The following Tables 3 to 5 summarize patients' demographic and baseline characteristics for the overall subjects, subjects without a history of stroke prior randomization, and the Proposed Label Population (i.e., post MI subjects without history of stroke or TIA). According to the sponsor, at study entry, the qualifying and stratifying conditions were well balanced between the treatment groups, and the two treatment groups overall were well balanced in terms of demographic characteristics at baseline. Subjects were predominately white (87%), male (76%), and a median of 61 years. Additionally, 11% of subjects were over 75 years old. Median body weight for subjects was 81 kg with 93% of subjects having a weight ≥ 60 kg. Median body mass index was 27.6 kg/m^2, in the midrange of 'overweight' (25-<30 kg/m^2), and approximately one quarter of the subjects were obese (≥30 kg/m^2).

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Table 3 Demographic and Other Baseline Characteristics for All Randomized Patients in TRA-2P Study

Number (%) of Subjects	Placebo N=13,244	Voparaxar N=13,225	Total N=26,449
Age (years), Mean (SD)	60.9 (10.84)	61.0 (10.90)	60.9 (10.87)
Sex, n (%)			
Female	3,172 (24.0)	3,154 (23.8)	6,326 (23.9)
Male	10,052 (76.0)	10,071 (76.2)	20,123 (76.1)
Race, n (%)			
White	11,524 (87.1)	11,562 (87.4)	23,086 (87.3)
Non-White	1,695 (12.8)	1,656 (12.5)	3,351 (12.7)
American Indian or Alaskan Native	30 (0.2)	19 (0.1)	49 (0.2)
Asian	606 (4.6)	588 (4.4)	1,194 (4.5)
Black or African American	350 (2.6)	339 (2.6)	689 (2.6)
Multiracial	694 (5.2)	696 (5.3)	1,390 (5.3)
Native Hawaiian or Other Pacific Islander	15 (0.1)	14 (0.1)	29 (0.1)
Missing	5 (<0.1)	7 (0.1)	12 (<0.1)
Ethnicity, n (%)			
Arab	27 (0.2)	37 (0.3)	64 (0.2)
Asian Indian	163 (1.2)	158 (1.2)	321 (1.2)
Bangladeshi	1 (<0.1)	2 (<0.1)	3 (<0.1)
Cambodian	1 (<0.1)	0	1 (<0.1)
Chinese	62 (0.5)	63 (0.5)	125 (0.5)
Filipino	11 (0.1)	11 (0.1)	22 (0.1)
Hispanic or Latino	1,836 (13.9)	1,857 (14.0)	3,693 (14.0)
Indonesian	8 (0.1)	10 (0.1)	18 (0.1)
Japanese	299 (2.3)	297 (2.2)	596 (2.3)
Korean	2 (<0.1)	2 (<0.1)	4 (<0.1)
Malaysian	31 (0.2)	27 (0.2)	58 (0.2)
Middle Easterner / North African	98 (0.7)	96 (0.7)	194 (0.7)
Pakistani	9 (0.1)	10 (0.1)	19 (0.1)
Thai	1 (<0.1)	0	1 (<0.1)
Vietnamese	2 (<0.1)	4 (<0.1)	6 (<0.1)
Other	10,629 (80.4)	10,604 (80.2)	21,233 (80.3)
Missing	44 (0.3)	47 (0.4)	91 (0.3)
Weight (kg), Mean (SD)	82.8 (17.3)	82.3 (16.9)	82.5 (17.1)
Height (cm), Mean (SD)	170.6 (9.6)	170.6 (9.6)	170.6 (9.6)
Calculated Body Mass Index (kg/m^2), Mean (SD)	28.3 (5)	28.2 (4.9)	28.3 (4.9)
Heart Rate (beats/minute), Mean (SD)	66.5 (11.5)	66.5 (11.6)	66.5 (11.5)
Systolic Blood Pressure (mm Hg), Mean (SD)	133.4 (19.4)	133.5 (19.5)	133.5 (19.5)
Diastolic Blood Pressure (mm Hg), Mean (SD)	78.1 (10.8)	78.0 (10.9)	78.0 (10.8)
Waist Circumference (cm), Mean (SD)	99.5 (12.8)	99.2 (13.0)	99.3 (12.9)
Ankle/Brachial Index, Mean (SD)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)

Source: Sponsor's Display A-10.1 from Pages 578 to 581 of CSR.

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Table 4 Demographic and Other Baseline Characteristics for Patients With No History of Stroke Prior to Randomization in TRA-2P Study

Number (%) of Subjects	Placebo N=10,344	Vorapaxar N=10,355	Total N=20,699
Age (years), Mean (SD)	59.9 (10.84)	60.0 (10.80)	60 (10.7)
Sex, n (%)			
Female	2,228 (21.5)	2,274 (22.0)	4,502 (21.7)
Male	8,116 (78.5)	8,081 (78.0)	16,197 (78.3)
Race, n (%)			
White	9,160 (88.6)	9,197 (88.8)	18,357 (88.7)
Non-White	1,181 (11.4)	1,151 (11.1)	2,332 (11.3)
American Indian or Alaskan Native	24 (0.2)	16 (0.2)	40 (0.2)
Asian	357 (3.5)	333 (3.2)	690 (3.3)
Black or African American	245 (2.4)	239 (2.3)	484 (2.3)
Multiracial	542 (5.2)	553 (5.3)	1,095 (5.3)
Native Hawaiian or Other Pacific Islander	13 (0.1)	10 (0.1)	23 (0.1)
Missing	3 (<0.1)	7 (0.1)	10 (<0.1)
Ethnicity, n (%)			
Arab	19 (0.2)	20 (0.2)	39 (0.2)
Asian Indian	155 (1.5)	149 (1.4)	304 (1.5)
Bangladeshi	1 (<0.1)	2 (<0.1)	3 (<0.1)
Cambodian	1 (<0.1)	0	1 (<0.1)
Chinese	42 (0.4)	42 (0.4)	84 (0.4)
Filipino	8 (0.1)	9 (0.1)	17 (0.1)
Hispanic or Latino	1,393 (13.5)	1,419 (13.7)	2,812 (13.6)
Indonesian	8 (0.1)	10 (0.1)	18 (0.1)
Japanese	85 (0.8)	77 (0.7)	162 (0.8)
Korean	2 (<0.1)	1 (<0.1)	3 (<0.1)
Malaysian	31 (0.3)	25 (0.2)	56 (0.3)
Middle Easterner / North African	73 (0.7)	71 (0.7)	144 (0.7)
Pakistani	7 (0.1)	10 (0.1)	17 (0.1)
Thai	1 (<0.1)	0	1 (<0.1)
Vietnamese	2 (<0.1)	4 (<0.1)	6 (<0.1)
Other	8,479 (82.0)	8,476 (81.9)	16,955 (81.9)
Missing	37 (0.4)	40 (0.4)	77 (0.4)
Weight (kg), Mean (SD)	83.89 (17.30)	83.35 (16.85)	83.62 (17.08)
Height (cm), Mean (SD)	171.31 (9.4)	171.18 (9.4)	171.3 (9.4)
Calculated Body Mass Index (kg/m^2), Mean (SD)	28.5 (5.03)	28.4 (4.9)	28.4 (4.9)
Heart Rate (beats/minute), Mean (SD)	65.4 (11.2)	65.4 (11.3)	65.4 (11.2)
Systolic Blood Pressure (mm Hg), Mean (SD)	131.9 (19.1)	132.1 (19.4)	132.0 (19.3)
Diastolic Blood Pressure (mm Hg), Mean (SD)	77.5 (10.7)	77.4 (10.8)	77.5 (10.7)
Waist Circumference (cm), Mean (SD)	99.8 (12.7)	99.5 (12.9)	99.6 (12.8)
Ankle/Brachial Index, Mean (SD)	1.03 (0.23)	1.03 (0.22)	1.03 (0.23)

Source: Sponsor's Display A-10.2 from Pages 582 to 585 of CSR.

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Table 5 Demographic and Other Baseline Characteristics for Proposed Label Population in TRA-2P Study

Number (%) of Subjects	Placebo N=8,439	Vorapaxar N=8,458	Total N=16,897
Age (years), Mean (SD)	58.5 (10.46)	58.7 (10.58)	58.6(10.52)
Sex, n (%)			
Female	1,676 (19.9)	1,723 (20.4)	3,399 (20.1)
Male	6,763 (80.1)	6,735 (79.6)	13,498 (79.9)
Race, n (%)			
White	7,415 (87.9)	7,481 (88.4)	14,896 (88.2)
Non-White	1,021 (12.1)	971 (11.5)	1,992 (11.8)
American Indian or Alaskan Native	18 (0.2)	11 (0.1)	29 (0.2)
Asian	340 (4.0)	321 (3.8)	661 (3.9)
Black or African American	177 (2.1)	172 (2.0)	349 (2.1)
Multiracial	474 (5.6)	457 (5.4)	931 (5.5)
Native Hawaiian or Other Pacific Islander	12 (0.1)	10 (0.1)	22 (0.1)
Missing	3 (<0.1)	6 (0.1)	9 (0.1)
Ethnicity, n (%)			
Arab	18 (0.2)	16 (0.2)	34 (0.2)
Asian Indian	150 (1.8)	146 (1.7)	296 (1.8)
Bangladeshi	1 (<0.1)	2 (<0.1)	3 (<0.1)
Cambodian	1 (<0.1)	0	1 (<0.1)
Chinese	42 (0.5)	42 (0.5)	84 (0.5)
Filipino	8 (0.1)	9 (0.1)	17 (0.1)
Hispanic or Latino	1,154 (13.7)	1,170 (13.8)	2,324 (13.8)
Indonesian	7 (0.1)	9 (0.1)	16 (0.1)
Japanese	75 (0.9)	70 (0.8)	145 (0.9)
Korean	2 (<0.1)	1 (<0.1)	3 (<0.1)
Malaysian	31 (0.4)	25 (0.3)	56 (0.3)
Middle Easterner / North African	55 (0.7)	60 (0.7)	115 (0.7)
Pakistani	7 (0.1)	9 (0.1)	16 (0.1)
Thai	1 (<0.1)	0	1 (<0.1)
Vietnamese	0	4 (<0.1)	4 (<0.1)
Other	6,872 (81.4)	6,880 (81.3)	13,752 (81.4)
Missing	15 (0.2)	15 (0.2)	30 (0.2)
Weight (kg), Mean (SD)	84.7 (17.3)	84.0 (16.8)	84.3 (17.1)
Height (cm), Mean (SD)	171.72 (9.4)	171.51 (9.4)	171.62 (9.4)
Calculated Body Mass Index (kg/m^2), Mean (SD)	28.6 (5.0)	28.5 (4.8)	28.6 (4.9)
Heart Rate (beats/minute), Mean (SD)	64.6 (10.8)	64.5 (11)	64.5 (10.9)
Systolic Blood Pressure (mm Hg), Mean (SD)	130.2 (18.6)	130.3 (18.8)	130.2 (18.7)
Diastolic Blood Pressure (mm Hg), Mean (SD)	77.8 (10.7)	77.6 (10.7)	77.7 (10.7)
Waist Circumference (cm), Mean (SD)	99.9 (12.6)	99.6 (12.87)	99.8 (12.7)
Ankle/Brachial Index, Mean (SD)	1.08 (0.19)	1.08 (0.18)	1.07 (0.18)

Source: Sponsor's Display A-10.2 from Pages 606 to 609 of CSR.

3.2.4 Results and Conclusions

3.2.4.1 Sponsor's Efficacy Results-Primary Endpoint and Key Secondary Endpoint

Due to an increased number of ICH events, the DSMB provided the recommendation to discontinue study drug in all subjects with a prior history of stroke or stroke that occurred during the course of the study. The DSMB members also decided unanimously to recommend that the TRP-2P study continue in subjects without history of stroke until the requisite number

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of clinical events had been met. In light of the DSMB recommendation, in an effort to determine the subject population with the optimal benefit/risk profile for vorapaxar, the sponsor predefined populations of interest:

- Overall Population- subjects, regardless of the qualifying condition, who received randomized treatment assignment; this was the efficacy population originally defined in the protocol and the data analysis plan
- NSH population- subjects with no stroke history, regardless of the qualifying condition, who received randomized treatment assignment
- Post MI (CAD) and no history of stroke – subjects whose qualifying condition was CAD and did not have a documented history of stroke prior to randomization

In assessing benefit/risk, an additional population was defined following database lock:

- Proposed Label Population (Post MI with no history of stroke or TIA) – subjects whose qualifying condition was CAD and did not have a documented history of stroke or TIA prior to randomization. This population was defined post-hoc to account for the difficulty in diagnosis of stroke versus TIA based on subject history alone.

The sponsor's analysis results for the primary endpoint and key secondary endpoint for the overall patient population, the NSH patient population, the CAD subjects with no prior history of stroke and the proposed label population are shown in Table 6 to Table 9 respectively. Their Kaplan Meier survival curves for the overall and proposed label population are shown in Figure 2 and 3, respectively.

Table 6 Sponsor's Results for Primary and Key Secondary Endpoints for the Overall ITT Population for TRA-2P Study

Endpoint and Contributing Component	Placebo (n=13,224)		Vorapaxar (n=13,225)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Primary Efficacy Endpoint	1,417 (10.7%)	12.4%	1,259 (9.5%)	11.2%	0.88 (0.82-0.95)	0.001
CV Death	199 (1.5%)		172 (1.3%)			
MI	629 (4.8%)		536 (4.1%)			
Stroke	297 (2.2%)		297 (2.2%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	256 (1.9%)		210 (1.6%)			
Hemorrhagic Stroke	27 (0.2%)		67 (0.5%)			
Uncertain	14 (0.1%)		20 (0.2%)			
UCR	292 (2.2%)		254 (1.9%)			
Key Secondary Efficacy Endpoint	1,176 (8.9%)	10.5%	1,028 (7.8%)	9.3%	0.87 (0.80-0.94)	<0.001
CV Death	207 (1.6%)		175 (1.3%)			
MI	665 (5.0%)		554 (4.2%)			
Stroke	304 (2.3%)		299 (2.3%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	260 (2.0%)		212 (1.6%)			
Hemorrhagic Stroke	28 (0.2%)		67 (0.5%)			
Uncertain	16 (0.1%)		20 (0.2%)			

Source: Sponsor's Table 30 of CSR.

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Table 7 Sponsor's Results for Primary and Key Secondary Endpoints for NSH Population for TRA-2P Study

Endpoint and Contributing Component	Placebo (n=10,344)		Vorapaxar (n=10,355)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Primary Efficacy Endpoint	1,104 (10.7%)	11.8%	959 (9.3%)	10.6%	0.86 (0.79-0.94)	<0.001
CV Death	161 (1.6%)		137 (1.3%)			
MI	546 (5.3%)		473 (4.6%)			
Stroke	127 (1.2%)		113 (1.1%)			
UCR	270 (2.6%)		236 (2.3%)			
Key Secondary Efficacy Endpoint	878 (8.5%)	9.6%	742 (7.2%)	8.3%	0.84 (0.76-0.93)	<0.001
CV Death	167 (1.6%)		140 (1.3%)			
MI	578 (5.6%)		488 (4.7%)			
Stroke	133 (1.3%)		114 (1.1%)			

Source: Sponsor's Table 31 of CSR.

Table 8 Sponsor's Results for Primary and Key Secondary Endpoints for CAD Subjects With No Prior History of Stroke for TRA-2P Study

Endpoint and Contributing Component	Placebo (n=8,583)		Vorapaxar (n=8,608)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Primary Efficacy Endpoint	887 (10.3%)	11.5%	757 (8.8%)	10.1%	0.84 (0.76-0.93)	<0.001
CV Death	98 (1.1%)		86 (1.0%)			
MI	462 (5.4%)		388 (4.5%)			
Stroke	86 (1.0%)		73 (0.85%)			
UCR	241 (2.8%)		210 (2.4%)			
Key Secondary Efficacy Endpoint	687 (8%)	9.1%	564 (6.5%)	7.7%	0.81 (0.73-0.91)	<0.001
CV Death	103 (1.2%)		88 (1.0%)			
MI	493 (5.7%)		402 (4.7%)			
Stroke	91 (1.1%)		74 (0.86%)			

Source: Sponsor's Table 32 of CSR.

Table 9 Sponsor's Results for Primary and Key Secondary Endpoints for the Proposed Label Population for TRA-2P Study

Endpoint and Contributing Component	Placebo (n=8,439)		Vorapaxar (n=8,458)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Primary Efficacy Endpoint	867 (10.3%)	11.4%	719 (8.5%)	9.8%	0.82 (0.74-0.90)	<0.001
CV Death	96 (1.1%)		82 (1.0%)			
MI	451 (5.3%)		374 (4.4%)			
Stroke	84 (1.0%)		60 (0.7%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	69 (0.8%)		38 (0.4%)			
Hemorrhagic Stroke	11 (0.1%)		16 (0.2%)			
Uncertain	4 (0.0%)		6 (0.1%)			
UCR	236 (2.8%)		203 (2.4%)			
Key Secondary Efficacy Endpoint	671 (8.0%)	9.0%	532 (6.3%)	7.4%	0.78 (0.70-0.88)	<0.001
CV Death	101 (1.2%)		84 (1.0%)			
MI	481 (5.7%)		387 (4.6%)			
Stroke	89 (1.1%)		61 (0.7%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	72 (0.9%)		39 (0.5%)			
Hemorrhagic Stroke	12 (0.1%)		16 (0.2%)			
Uncertain	5 (0.1%)		6 (0.1%)			

Source: Sponsor's Table 33 of CSR.

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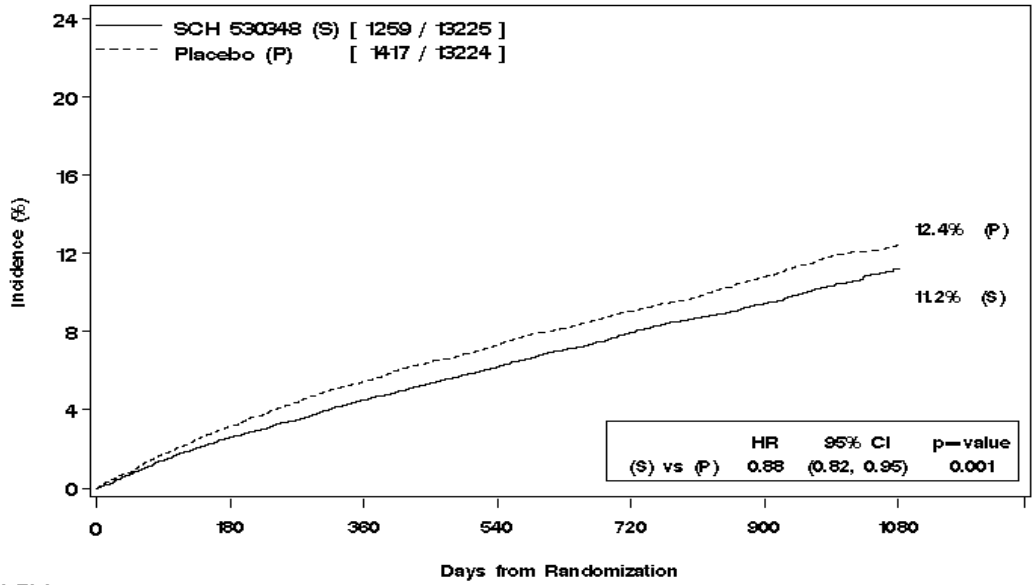
Figure 2 Sponsor's Kaplan-Meier Survival Curves for Overall Patient Population for TRA-2P Study

2A: <u>For Primary Endpoint</u>

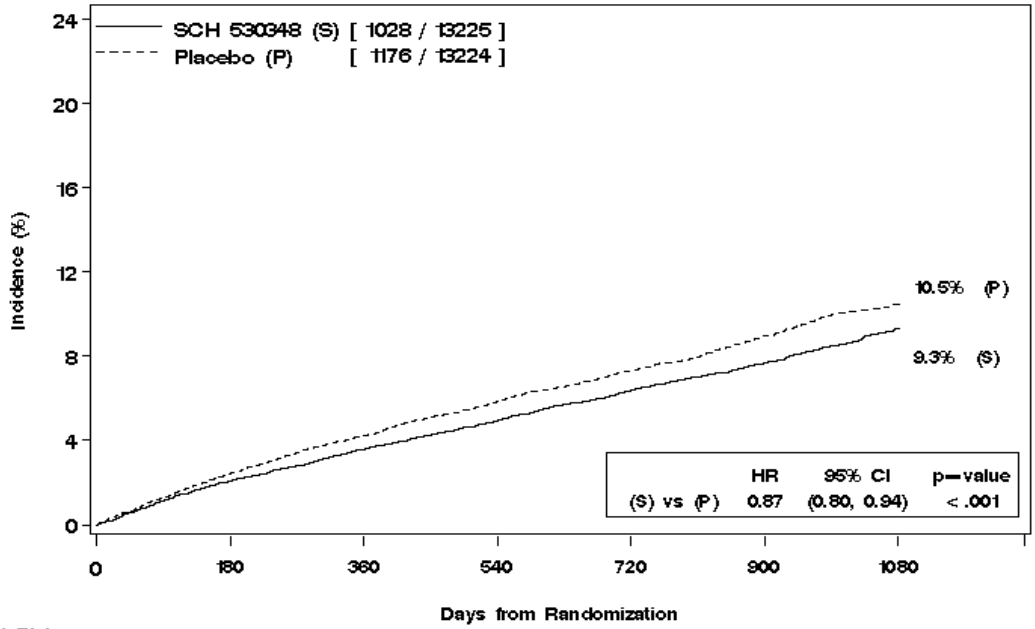


No. at Risk:

SCH 530348 (S)	12720	12364	12003	9295	6147	2706
Placebo (P)	12631	12207	11824	9180	6104	2686

Source: Sponsor's Figure 3 of CSR

2B: <u>For Secondary Endpoint</u>



No. at Risk:

SCH 530348 (S)	12784	12479	12162	9463	6287	2788
Placebo (P)	12727	12364	12013	9366	6239	2751

Source: Sponsor's Figure 4 of CSR

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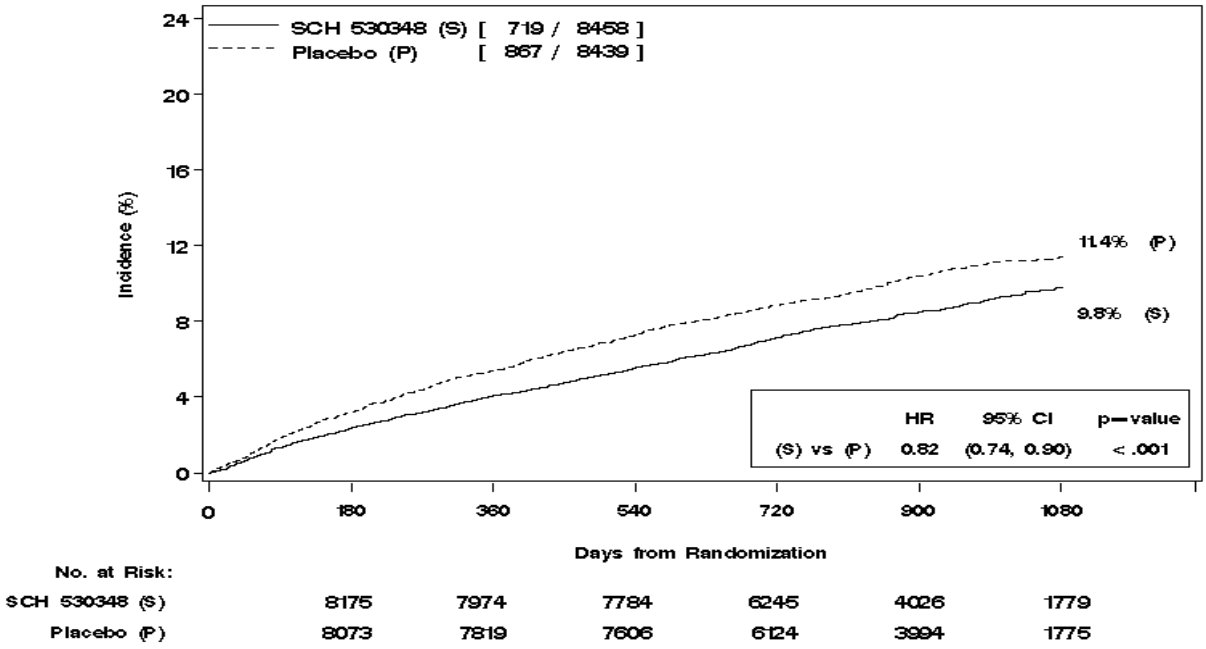
Figure 3 Sponsor's Kaplan-Meier Survival Curves for the Primary Endpoint Based on the Proposed Label Population for TRA-2P Study



Source: Sponsor's Figure 4 of CSR

3.2.4.2 Sponsor's Efficacy Results-Other Secondary Endpoints

The sponsor's analysis results for other secondary endpoints including the time to each component of the primary endpoint for the overall patient population, the CAD patients without stroke history and the proposed label population are shown from Table 10 to Table 12, respectively.

Table 10 Sponsor's Analysis Results for Other Secondary Endpoints for the Overall Patient Population for TRA-2P Study

Endpoints	Placebo (n=13,224)		Vorapaxar (n=13,225)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
All-Cause Death/MI/Stroke/UCR	1,614 (12.2%)	14.2%	1,481 (11.2%)	13.2%	0.91 (0.85-0.98)	0.009
CV Death/MI	913 (6.9%)	8.2%	789 (6.0%)	7.3%	0.86 (0.78-0.94)	0.002
CV Death/MI/Stroke/UCR/UH-VCIN	1,681 (12.7%)	14.7%	1,481 (11.2%)	13.1%	0.87 (0.81-0.93)	<0.001
All-Cause death/MI/Stroke/Any Revascularization	2,594 (19.6%)	22.6%	2,395 (18.1%)	20.7%	0.91 (0.86-0.96)	0.001
CV Death/MI/Stroke/Any Revascularization/UH-VCIN	2,542 (19.2%)	22.1%	2,314 (17.5%)	19.9%	0.90 (0.85-0.95)	<0.001
CV Death	319 (2.4%)	3.0%	285 (2.2%)	2.7%	0.89 (0.76-1.04)	0.151
MI	673 (5.1%)	6.1%	564 (4.3%)	5.2%	0.83 (0.74-0.93)	0.001
UCR	316 (2.4%)	2.6%	279 (2.1%)	2.5%	0.88 (0.75-1.03)	0.108
All-Cause Death	565 (4.3%)	5.3%	540 (4.1%)	5.0%	0.95 (0.85-1.07)	0.411
Stroke	324 (2.5%)	2.8%	315 (2.4%)	2.8%	0.97 (0.83-1.14)	0.733
UH-VCIN	646 (4.9%)	5.5%	539 (4.1%)	4.7%	0.83 (0.74-0.93)	0.001
Any Revascularization	1,768 (13.5%)	15.5%	1,583 (12.0%)	13.6%	0.89 (0.83-0.95)	<0.001

Source: Sponsor's Table 55 of CSR.

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Table 11 Sponsor's Analysis Results for Other Secondary Endpoints for the CAD patients with No History of Stroke for TRA-2P Study

Endpoints	Placebo (n=8,583)		Vorapaxar (n=8,608)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
All-Cause Death/MI/Stroke/UCR	972 (11.3%)	12.7%	854 (9.9%)	11.4%	0.87 (0.79-0.95)	0.002
CV Death/MI	616 (7.2%)	8.2%	510 (5.9%)	7.0%	0.82 (0.73-0.92)	<0.001
CV Death/MI/Stroke/UCR/UH-VCIN	996 (11.6%)	12.9%	877 (10.2%)	11.6%	0.87 (0.79-0.95)	0.002
All-Cause death/MI/Stroke/Any Revascularization	1,456 (17.0%)	18.7%	1,342 (15.6%)	17.5%	0.91 (0.85-0.98)	0.013
CV Death/MI/Stroke/Any Revascularization/UH-VCIN	1,433 (16.7%)	18.4%	1,318 (15.3%)	17.2%	0.91 (0.84-0.98)	0.012
CV Death	163 (1.9%)	2.2%	138 (1.6%)	1.9%	0.84 (0.67-1.05)	0.131
MI	499 (5.8%)	6.6%	408 (4.7%)	5.6%	0.81(0.71-0.92)	0.002
UCR	259 (3.0%)	3.2%	230 (2.7%)	3.1%	0.88 (0.74-1.05)	0.165
All-Cause Death	266 (3.1%)	3.7%	247 (2.9%)	3.4%	0.92 (0.77-1.10)	0.353
Stroke	103 (1.2%)	1.4%	78 (0.9%)	1.1%	0.75 (0.56-1.01)	0.056
UH-VCIN	399 (4.6%)	5.0%	370 (4.3%)	4.9%	0.92 (0.80-1.06)	0.254
Any Revascularization	1,052 (12.3%)	13.6%	963 (11.2%)	12.6%	0.91 (0.83-0.99)	0.029

Source: Sponsor's Table 56 of CSR.

Table 12 Sponsor's Analysis Results for Other Secondary Endpoints for the Proposed Label Population for TRA-2P Study

Endpoints	Placebo (n=8,583)		Vorapaxar (n=8,608)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
All-Cause Death/MI/Stroke/UCR	951 (11.3%)	12.6%	815 (9.6%)	11.1%	0.84 (0.77-0.93)	<0.001
CV Death/MI	601 (7.1%)	8.1%	490 (5.8%)	6.8%	0.81 (0.72-0.91)	<0.001
CV Death/MI/Stroke/UCR/UH-VCIN	972 (11.5%)	12.8%	834 (9.9%)	11.3%	0.85 (0.77-0.93)	<0.001
All-Cause death/MI/Stroke/Any Revascularization	1,424 (16.9%)	18.7%	1,294 (15.3%)	17.2%	0.90 (0.83-0.97)	0.005
CV Death/MI/Stroke/Any Revascularization/UH-VCIN	1,398 (16.6%)	18.2%	1,269 (15.0%)	16.8%	0.90 (0.83-0.97)	0.005
CV Death	159 (1.9%)	2.2%	131 (1.5%)	1.9%	0.82 (0.65-1.03)	0.088
MI	486 (5.8%)	6.6%	393 (4.6%)	5.4%	0.80 (0.70-0.92)	0.001
UCR	253 (3.0%)	3.2%	223 (2.6%)	3.1%	0.88 (0.73-1.05)	0.148
All-Cause Death	259 (3.1%)	3.7%	238 (2.8%)	3.4%	0.91 (0.77-1.09)	0.308
Stroke	101 (1.2%)	1.4%	63 (0.7%)	0.9%	0.62 (0.45-0.85)	0.003
UH-VCIN	387 (4.6%)	4.9%	357 (4.2%)	4.8%	0.92 (0.79-1.06)	0.234
Any Revascularization	1,027 (12.2%)	13.5%	939 (11.1%)	12.5%	0.91 (0.83-0.99)	0.029

Source: Sponsor's Table 56 of CSR.

3.2.4.3 Sponsor's Conclusion

- In the overall population, vorapaxar when added to standard therapy significantly reduced the primary (CV Death/MI/Stroke/UCR) and key secondary efficacy composite endpoints (CV Death/MI/Stroke).

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- In the context of reducing all components of the composite endpoints, the rate of reduction of MI was the major component that contributed to this reduction besides stroke. Importantly, of these MI's most were spontaneous in nature (Type 1), thus defined by associated chest pain, and necessitating emergency hospitalizations.
- Regardless of time from the qualifying MI to randomization, vorapaxar reduced the rate of endpoint MI compared to placebo.
- In the overall population, a statistically significant reduction in the key secondary endpoints including the composite of CV death and MI was observed.
- Based on the composite endpoints, there was little evidence of efficacy observed in subjects with a history of stroke.
- Efficacy in both the primary and key secondary endpoints was evident in the NSH, post MI (CAD) subjects with no history of stroke and in the Proposed Label Population.
- There was a consistency of effect of vorapaxar among subgroups examined that included age, sex, hypertension, use of anti-platelet agents, and diabetes mellitus.
- In both overall and Proposed Label populations, vorapaxar was associated with a reduction in the incidence of recurrent events in the multiple occurrences of adjudicated endpoints in the vorapaxar group was associated with a reduction in the incidence of recurrent events.
- In both overall and Proposed Label populations, a reduction in definite stent thrombosis was observed.

3.2.4.4 Statistical Reviewer's Findings for Efficacy

1. (Unplanned Interim Analyses) Study TRA-2P was initiated on September 26, 2007 and completed on December 23, 2011. Based on the original study protocol dated May 31, 2007, only one formal unblinded interim analysis (IA) for efficacy was planned. It was to be performed by an independent Data and Safety Monitoring Board (DSMB) when approximately 50% of the primary and 50% of the key secondary efficacy endpoint events (either adjudicated or un-adjudicated [i.e., called best available events]) occurred. It was clearly stated in the protocol that the analysis would be based on the CEC-adjudicated events and the O'Brien-Fleming methodology would be implemented to protect the overall Type I error of 0.05. In particular, a nominal alpha level of 0.003 was planned for the interim analysis and 0.049 for the final analysis for both the primary and key secondary efficacy endpoints.

Although only one IA for efficacy was officially planned for Study TRA-2P, due to potential safety concerns, there were 11 DSMB meetings conducted throughout the trial, where the first meeting was held on 2/11/2008 and the last meeting on 1/8/2011. For all 11 meetings, some languages about findings for safety events, either for bleeding or ICH, were recorded in the meeting minutes. In addition to the DSMB meeting of 2/24/2010, when the results for the officially planned IA for TRA-2P study was discussed, the results of efficacy analysis including the p-value of the primary endpoint were also recorded in the minutes of the two other meetings dated 10/20/2010 and 1/8/2011. The exact dates for the sponsor's 11 DSMB meetings are shown on Table 13.

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Table 13 Dates for all DSMB Meetings for both Study TRACER and TRA-2P

Meeting No.	Date
1	2/11/2008
2	5/9/2008
3	9/11/2008
4	2/12/2009
5	5/25/2009
6	9/30/2009
7	2/24/2010 (IA for TRA-2P)
8	6/25/2010 (IA for TRACER)
9	10/20/2010
10	12/15/2010
11	1/8/2011

The reviewers asked the sponsor to explain why those efficacy analyses were conducted and exactly what analyses had been performed in each interim analysis and how these unblinded efficacy analyses would affect the study type I error rate.

The sponsor's response noted: "*The DSMB received periodic aggregated safety reports that were partially blinded – results separated by treatment, but treatment was not identified. At the third meeting on September 11, 2008, the committee requested that the treatment assignment be identified. From that point on, the DSMB received Hazard Ratios for a total of 9 safety evaluations.*"

The sponsor also emphasized that "*Based on the minutes from the open session of the February 12, 2009 meeting [P04737, Section 16.1.9.5.2, volume o] total efficacy event rates were being monitored in accordance with the DSMB charter for an interim analysis at 50% of accrued events, but there is no indication that efficacy endpoint event rates were being monitored by treatment assignment. Importantly, there is no mention of any Hazard Ratios (HR) by treatment assignment or confidence intervals around those HRs for the PEP (Primary Efficacy Endpoint) in the DSMB minutes until February 24, 2010.*"

Regarding how many times that the efficacy results were revealed, they stated: "*Consequently, the DSMB had knowledge of treatment assignment for efficacy data for that meeting, the June 25th meeting, the October 20th meeting of 2010 and the January 8th meeting of 2011. No efficacy results were reported in the minutes of the December 2010 DSMB meeting.*"

Regarding the question about alpha adjustment for these interim looks of the study data, the sponsor acknowledged: "*To our knowledge, after review of the DSMB minutes and a discussion on August 12, 2013 with the DCRI Statisticians who worked with the unblinded DSMB, there were 3 examinations of the efficacy data in an unblinded fashion, in addition to the planned interim analysis. While the charter stated there was no intention of stopping the trial early for efficacy, the DSMB did have safety concerns and therefore requested to see the efficacy and safety information to balance the risk and protect the subjects of the trial. Given these 4 separate examinations of the unblinded efficacy data, a more conservative approach, ignoring the intent in the charter, would be to adjust the alpha for the 4 interim analyses.*" The sponsor further stated that "*However, as stated in the charter, there was no intent of stopping the trial other than at the 50% of accrued events interim analysis, and therefore there*

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was no pre-specified alpha spending function necessary, leading to lack of such a function to provide a basis for a post-hoc adjustment. In lieu of a pre-specified alpha-spending function, a conservative methodology, such as a Bonferonni adjustment, could be utilized. If such an adjustment for 4 interim analyses is applied to the TRA°2P primary and key secondary endpoints, these endpoints would still reach statistical significance. This statement also holds in the most extreme circumstance where FDA believes that an adjustment for 11 interim analyses is appropriate. Utilizing a Bonferonni adjustment by multiplying the final p-values by 11, yields a p-value for the primary endpoint of ≈ 0.01164, and a p-value for the key secondary endpoint of ≈0.01079, both of which are still less than 0.05."

In this reviewer's opinion, it can be argued that the single trial TRAP-2P may need to achieve a p-value of 0.01 or less for vorapaxar's efficacy on atherothrombotic ischemic events, especially that Study TRACER is non-positive. The Bonferroni adjustment for interim analyses, however, is very conservative; thus, by this adjustment, the maximum p-value is about 0.01. Therefore, TRAP-2P seems to have achieved statistical significance at 0.01 level for both the primary and the secondary endpoints.

2. (Sample Size Re-Estimation) According to the sponsor's original protocol for Study TRA-2P, 19,500 subjects (9,750 subjects per treatment group) were to be randomized to observe 2,279 primary efficacy endpoint events and 1,322 Key secondary efficacy endpoint events. This sample size was to provide for detection of a 15% relative risk reduction in the incidence of the key secondary efficacy endpoint with SCH 530348 relative to placebo with approximately 85% power at a two-sided significance level of 0.05. The original protocol was initiated on May 31, 2007 and the study was initiated on Sep. 26, 2007.

About one and half year after Study TRA-2P was initiated, the sponsor amended the protocol, dated Jan. 21, 2009 (i.e., Amendment #1), to perform sample size reassessment for both the primary and key secondary efficacy endpoints using the aggregated, blinded accumulation of events prior to completion of enrollment. On the basis of the estimated event rates for the primary and key secondary efficacy endpoints at one year, as well as adjusting for potential numbers of dropouts for this sample size reassessment, the sponsor decided to increase the sample size to approximately 25,000 subjects (12,500 subjects per treatment group) and an increase in the minimum number of key secondary efficacy endpoint events to approximately 1,400 events. They then amended the protocol the second time to reflect this change (i.e., Amendment #2, dated March 23, 09). In addition to the required number of events for the primary and key secondary efficacy endpoint, each patient must participate for a minimum of one year. The sponsor also left a room for an additional reassessment of sample size up to 27,000 subjects if required to maintain the planned power and overall duration of the trial.

While reviewing Study TRA-2P's results, the reviewer noted that the sponsor's final analysis for Study TRA-2P was based on 2,676 primary endpoint events and 2,204 key secondary observed, which were much larger than what was planned. It is unclear why the sponsor made a decision to amend the protocol for performing the sample size reassessment after one and half year after the study was initiated. Thus, we asked the sponsor to provide us with explanation for why the sample size was increased, information about the exact time(s) of the sample size re-estimation, the overall event rate and dropout rate at the time(s) of the sample

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size re-estimation as well as any observed results that triggered the SSI decision, and who performed the re-estimation.

The sponsor responded: "*The original protocol did not pre-specify for an analysis for sample size adjustment. As part of* ***routine operational procedure*** *the TIMI group monitored the progress of TRA 2ºP - TIMI 50 using TIMI generated operational reports."* They further stated that*" These reports were shared with the Sponsor. Among the parameters captured in these reports were patient enrollment and total events triggered and adjudicated. As all data were blinded as to treatment assignment and all data were reported as total, aggregate values."*

The sponsor noted that there was a communication between TIMI Group and the Sponsor: *"On October 22, 2008, the TIMI Group Study Chair (Eugene Braunwald) issued a letter to the Sponsor noting that* ***the aggregate event rates*** *were lower than the anticipated 8% and that this finding was driven principally by the 3% aggregate event rate in the PAD stratum. The TIMI Group also recommended (although no action was taken) that in the then upcoming amendment (01) , enrollment into the PAD stratus be limited to 3,000 subjects and that sample size be increased by 4,000 subjects to maintain current study timelines."*

After the sponsor received the TIMI Group's Oct. 2008's letter, the sponsor also performed some independent calculations to confirm the TIMI Group's finding. In the sponsor's response, it states that "*Independent calculations by the Sponsor in response to the October 22, 2008 TIMI request confirmed that in the context of lower than anticipated event rates and a more vigorous subject enrollment, there was a need to incorporate into the first amendment to the protocol, a formal re-assessment of sample size and target events."*

It should be noted that TIMI Group's Oct. 2008's letter was sent out a month or so after the 3rd DSMB meeting (September 11, 2008). Recall that the treatment groups had been unblinded since that 3rd DSMB meeting even though the sponsor emphasized that this sample size reassessment was performed as a part of routine operational procedure. Due to the fact of the exact treatment groups had been identified, it is really unclear whether this sample size reassessment could have been influenced by the findings based on the unblinded treatment groups.

3. (Sponsor's Interim Analysis Results) For Study TRA-2P, the only interim efficacy analysis was planned/conducted when 50%/49% of the number of primary endpoint events (from total of adjudicated and un-adjudicated) and 50%/61% of the key secondary endpoint events were observed although the primary analysis would be based on the CEC-adjudicated events and the analyses based upon the best available events would be supportive.

The sponsor's results for IA are shown on Table 14. Note that the interim analysis results based on the best available events suggest stronger efficacy findings than those based on the CEC adjudicated events, which account for only 34% and 43% of the required number of events for the primary and key secondary endpoints, respectively.

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Table 14 Sponsor's Interim Efficacy Analysis for the Primary Endpoint for TRA-2P Study

For Overall Patient Population	Placebo (N=13224)	Vorapaxar (N=13225)	HR	P-Value
Based on the CEC adjudicated events				
Primary Endpoint	405 (3.1%)	363 (2.7%)	0.90	0.133
Key Secondary Endpoint	313 (2.4%)	283 (2.1%)	0.91	0.231
Based on the best available events				
Primary Endpoint	609 (4.6%)	518 (3.9%)	0.85	0.007
Key Secondary Endpoint	464 (3.5%)	395 (3.0%)	0.85	0.022

4. (Modification of Study Population) Due to the safety concern, the DSMB made a recommendation of discontinuing patients who had prior history of stroke while the study was ongoing and the sponsor followed the recommendation. Although the study population was changed, the sponsor performed analyses for the overall patient population and the NSH population (i.e., excluding patients with prior history of stroke) and also the proposed label population. All the analyses in different populations showed that the p-values are less than 0.001; the sponsor concluded that the vorapaxar is effective in reducing patient's events composited in the primary endpoint based on not only the overall population but also the different subsets.

It is worth noting that the mixture of the overall patient population in terms of patients who had prior history of stroke or in CVD stratum was changed. It is unclear whether such a change has any ramification on how to best interpret the positive trial findings.

This reviewer performed an analysis using only data before the final DSMB meeting (i.e., data closed by 1/8/2011); see Table 15. The p-values for both the primary and the secondary endpoints are less than 0.01, suggesting that had the study been closed early before the study population was changed, the study would have shown positive findings.

Table 15 Statistical Reviewer's Analysis Results Using Data Closed by Final IA

Data Closed by 1/8/2011	Placebo (N=13224)	Vorapaxar (N=13225)	HR	P-Value
Primary Endpoint	1186 (9%)	1047 (8%)	0.88	0.002
Key Secondary Endpoint	965 (7.3%)	851 (6.4%)	0.88	0.005

5. (Statistical Reviewer's Sensitivity Analyses) Based on this reviewer's analysis, there seems to be little difference between the treatment arms in terms of discontinued patients' follow-up time (Figure 4) and the time of treatment end (Figure 5).

Figure 6 shows the hazard ratio over time for the overall population, patients with no prior history of stroke (i.e., NSH population) and patients with prior history of stroke, where plots based on calendar date and patients' days after randomization are presented for each population. For the overall patient population and the NSH population, the hazard ratio appears to be stable quickly, way before 200 days and was a bit smaller earlier than later. On the contrary, vorapaxar did not seem to have an effect in the patients with prior history of stroke. Figure 7 is to examine the fluctuation of the p-values over time along with the total number of events. It shows that the p-value was well below 0.05 after 100 days and below 0.01 after 200 days based on patients' day after randomization, but the p-value did not stop

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fluctuating until 2010 based on calendar date. In summary, the vorapaxar appears effective in reducing the risk of ischemic events in atherosclerotic patients although the effect seems small (14-16% hazard reduction).

Figure 4 Censored Patients' Follow-up for TRA-2P Study

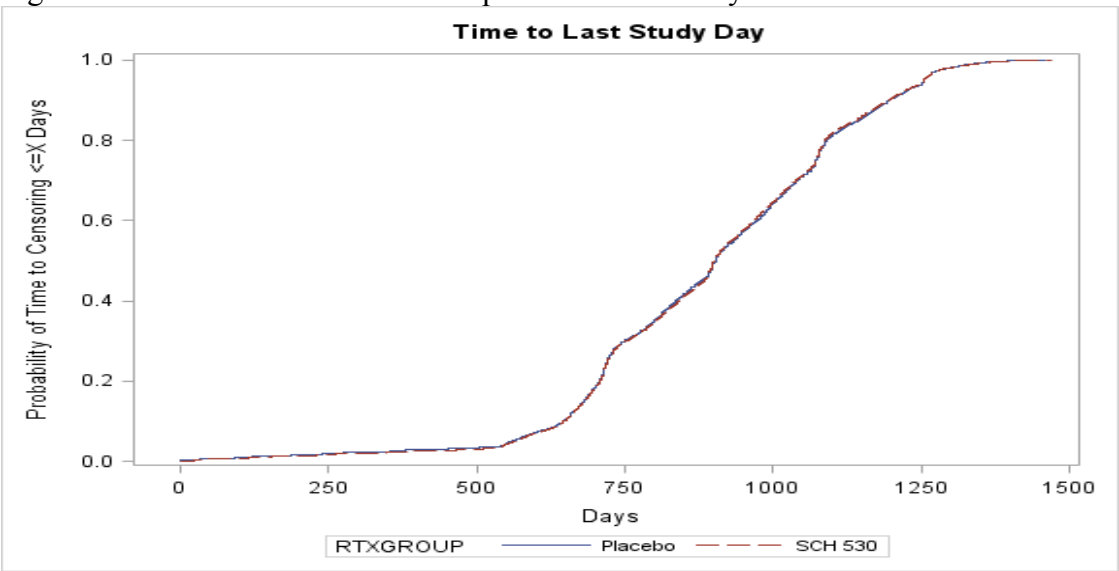

Figure 5 Time to Treatment Discontinuation Over Time for TRA-2P Study

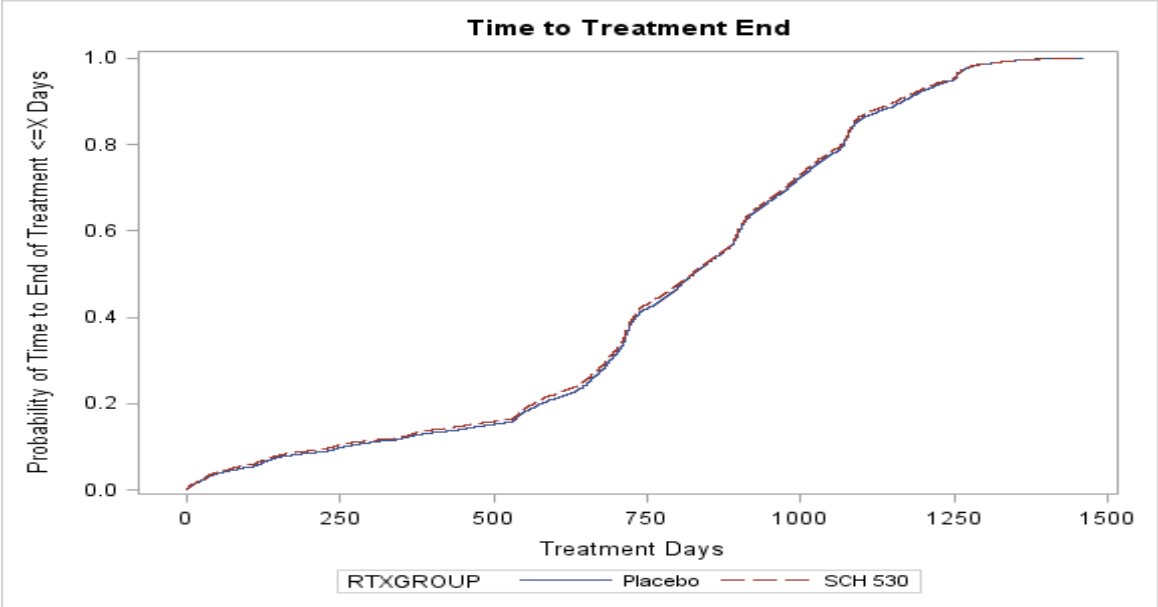

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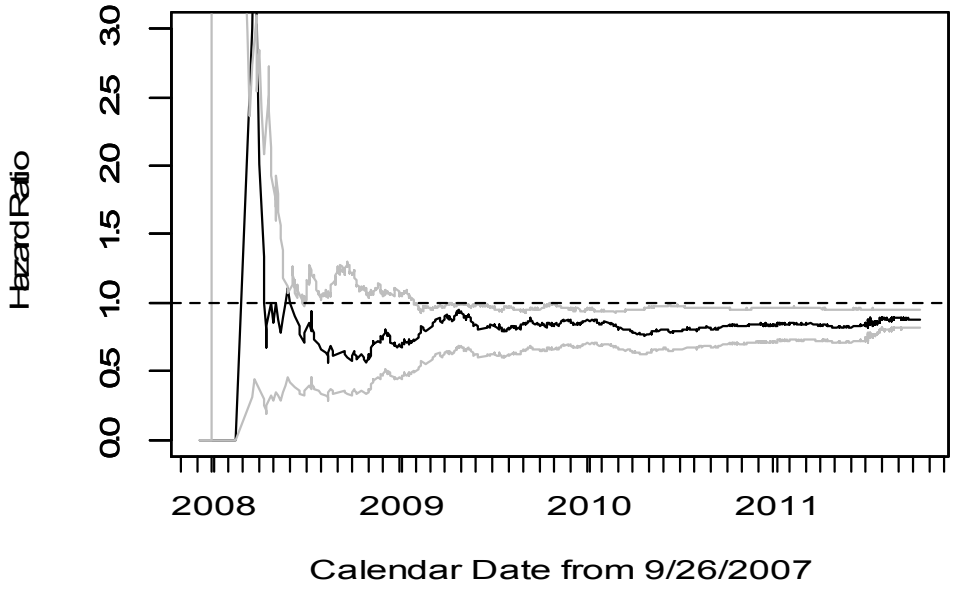
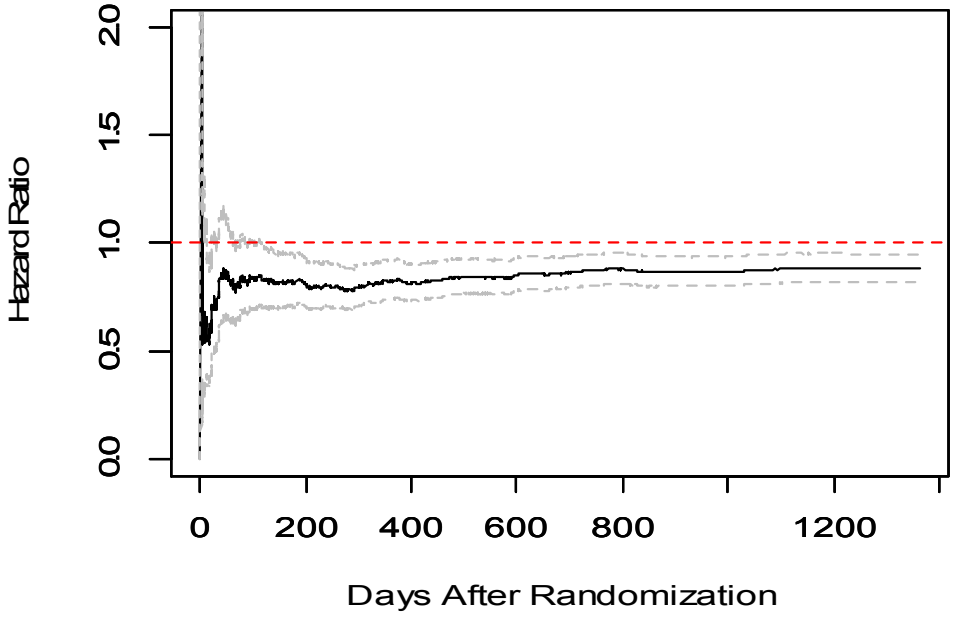
Figure 6 Hazard Ratio Over Time For TRA-2P Study (Based on Calendar Dates and Patients' Days After Randomization)

A. For Overall Population





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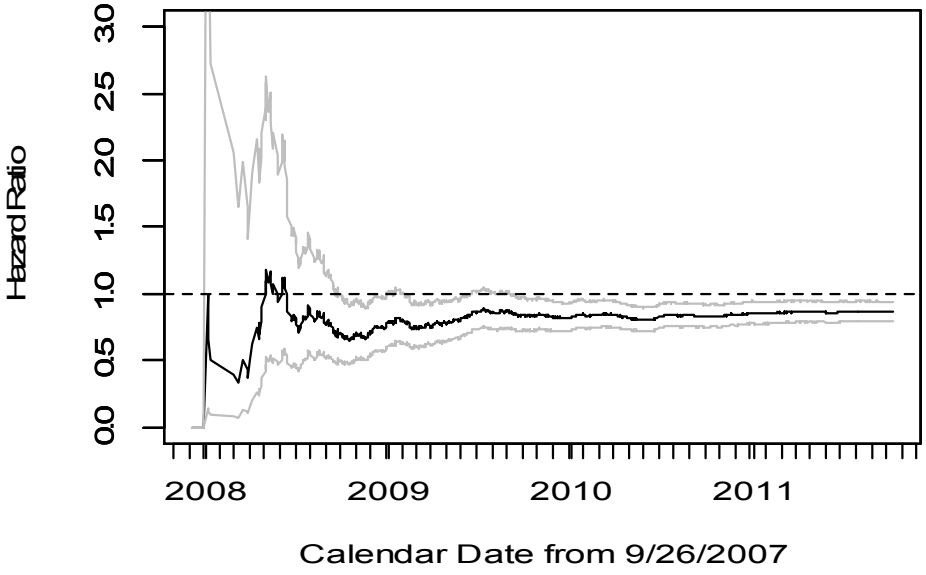
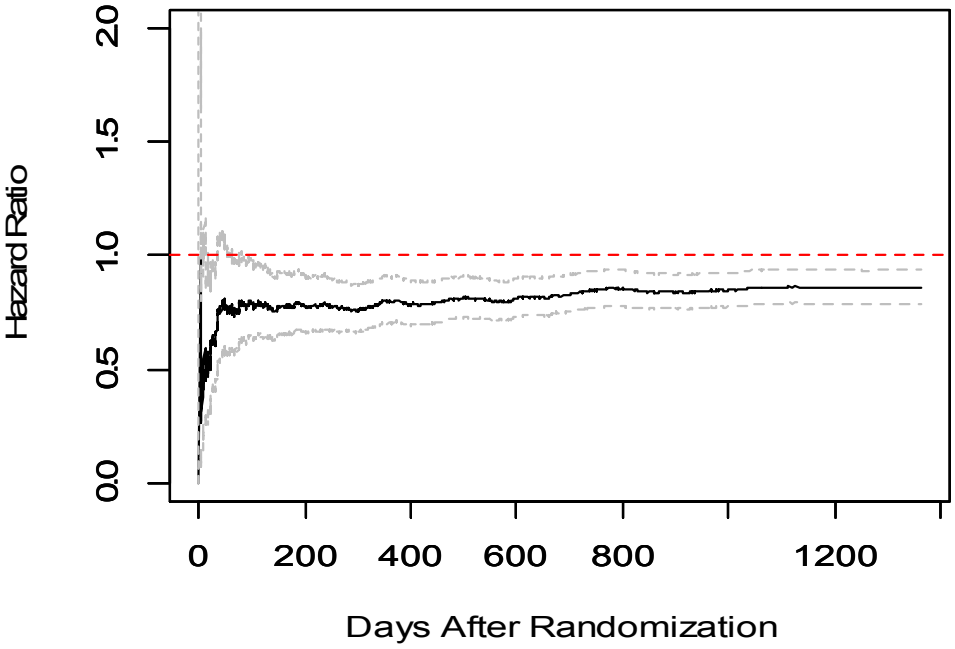
B. For NSH Population





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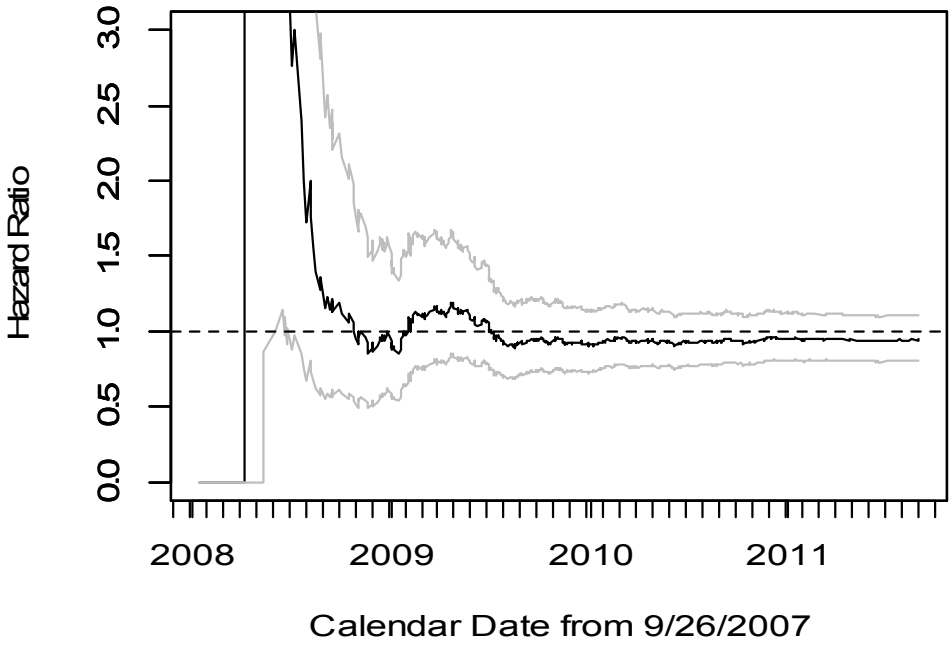
C. For Non-NSH Population



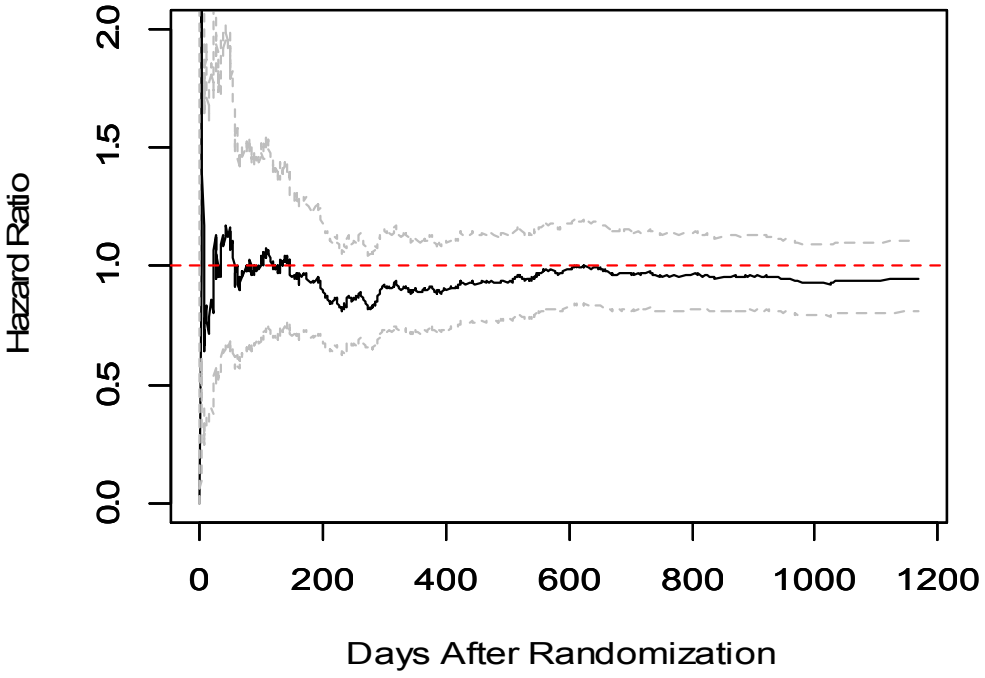


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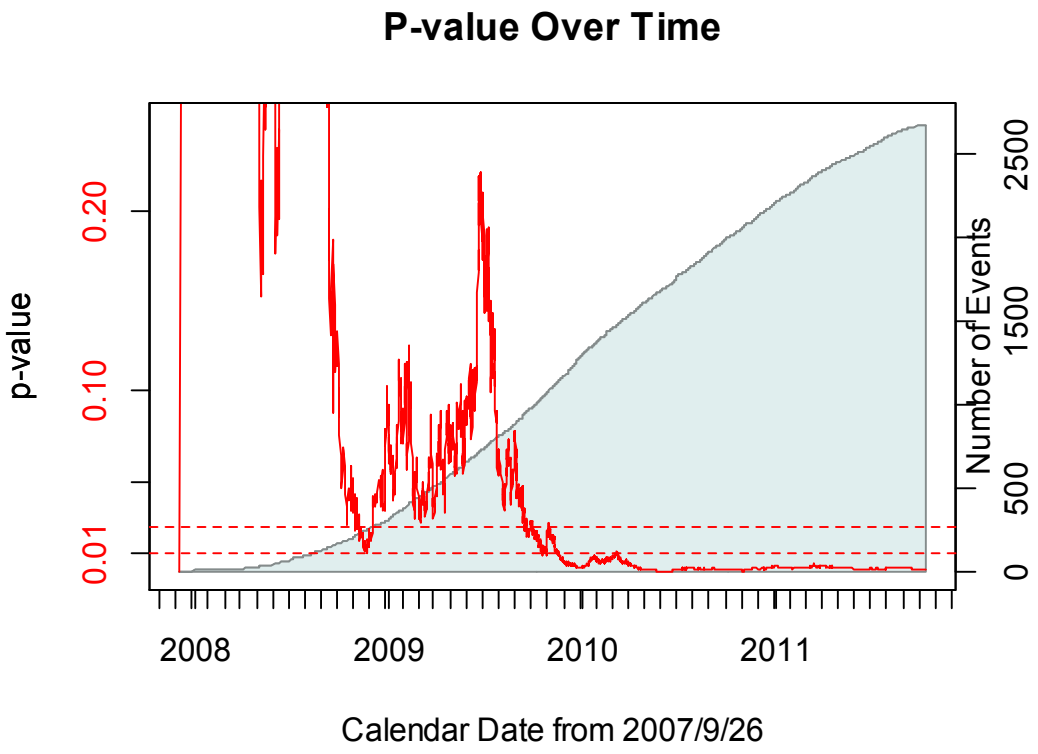
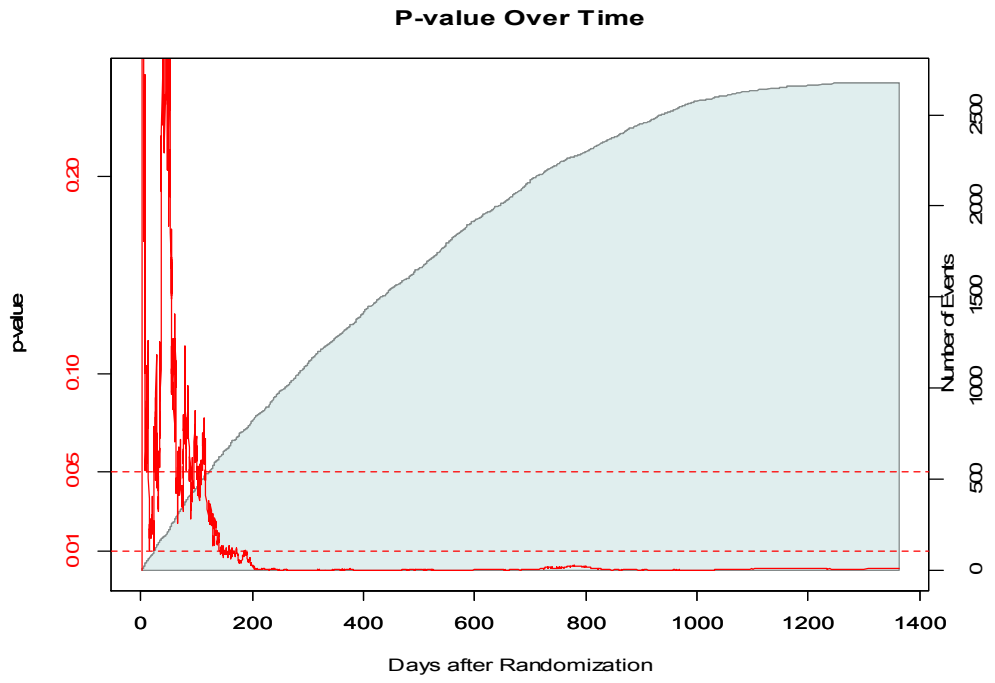
Figure 7 P-Value Over Time for TRA-2P Study (Based on Calendar Dates and Patients' Days After Randomization)





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3.3 EVALUATION OF SAFETY

The evaluation of safety is not performed in this review.

3.4 BENEFIT-RISK ASSESSMENT (OPTIONAL)

The benefit-risk assessment is not performed in this review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

The sponsor's subgroup analysis results for gender, race and age are shown in Table 16. According to the results, vorapaxar seemed to have similar performance in male and female patients, but appeared more effective in younger patients than older patients and non-white patients than white patients.

Table 16 Sponsor's Subgroup Analysis for Gender, Race and Age for TRA-2P Study

Subgroup	Placebo n = 13224		Vorapaxar n = 13225		HR (95% CI)
	Subject with Events m/n (%)	KM %	Subject with Events m/n (%)	KM%	
Sex					
Male	1061/10052 (10.6%)	12.1%	939/10071 (9.3%)	10.9%	0.88 (0.88-0.96)
Female	356/3172 (11.2%)	13.3%	320/3154 (10.1%)	12.4%	0.89 (0.77-1.04)
Age					
<65 years	779/8273 (9.4%)	10.6%	648/8188 (7.9%)	9.3%	0.83 (0.75-0.93)
≥65 years	638/4951 (12.9%)	15.3%	611/5037 (12.1%)	14.3%	0.93 (0.84-1.04)
Age					
<75 years	1181/11718 (10.1%)	11.7%	1042/11711 (8.9%)	10.5%	0.87 (0.81-0.95)
≥75 years	236/1506 (15.7%)	18.0%	217/1514 (14.3%)	17.2%	0.90 (0.75-1.09)
Race					
White	1224/11524 (10.6%)	12.3%	1083/11562 (9.4%)	10.9%	0.96 (0.86-1.08)
Non-white	193/1695 (11.4%)	13.5%	176/1656 (10.6%)	13.5%	0.81 (0.73-0.90)

Source: Sponsor's Display E-2, Page 800 of CSR

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

The sponsor's subgroup analysis results for weight, enrollment stratum and region are shown in Table 17. The patients weighted less than 60 kg or the patients from Asia/Pacific islands seemed to have a large hazard ratio. But their sample sizes are small and thus the opposite trends are difficult to interpret. Interestingly, vorapaxar seemed to have little effect in CVD or PAD stratum. .

To further assess if this reverse findings of vorapaxar comparing with placebo in the light weighted group of patients (<60 kg) needs to be concerned, per the medical reviewer's request, the statistical reviewer performed a more detailed subgroup analysis using more categories for both TRACER and TRA-2P studies and results are shown on Table 18. The vorapaxar's effect

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seems larger as the body weight is larger (Table 18) and seems little or negative in patients with weigh ≤ 60 kg.

Table 17 Sponsor's Other Subgroup Analysis Result for TRA-2P Study

Subgroup	Placebo n = 13224		Vorapaxar n = 13225		HR (95% CI)
	Subject with Events m/n (%)	KM %	Subject with Events m/n (%)	KM%	
Body Weight					
< median	650/6489 (10.0%)	12.0%	634/6574 (9.6%)	11.8%	0.96 (0.86-1.08)
≥ median	765/6703 (11.4%)	12.9%	622/6632 (9.4%)	10.7%	0.81 (0.73-0.90)
Body Weight					
< 60 kg	75/921 (8.1%)	9.6%	96/931 (10.3%)	13.6%	1.28 (0.95-1.73)
≥ 60 kg	1340/12271 (10.9%)	12.6%	1160/12275 (9.5%)	11.1%	0.86 (0.79-0.93)
Stratum					
CAD	956/8881 (10.8%)	12.1%	809/8898 (9.1%)	10.5%	0.83 (0.76-0.92)
CVD	216/2448 (8.8%)	12.1%	217/2435 (8.9%)	12.9%	1.02 (0.84-1.23)
PAD	245/1895 (12.9%)	13.4%	233/1892 (12.3%)	12.7%	0.95 (0.79-1.14)
Region					
North America	535/3920 (13.6%)	15.4%	501/3916 (12.8%)	14.2%	0.93 (0.82-1.05)
Latin America	188/1646 (11.4%)	13.3%	161/1648 (9.8%)	12.4%	0.85 (0.69-1.05)
Europe 1	543/5604 (9.7%)	11.0%	459/5612 (8.2%)	9.7%	0.84 (0.74-0.95)
Europe 2	105/1319 (8.0%)	9.0%	92/1317 (7.0%)	8.3%	0.87 (0.66-1.16)
Asia/Pacific	24/389 (6.2%)	8.7%	26/388 (6.7%)	8.8%	1.10 (0.63-1.92)
Austratia/New Zeland	22/346 (6.4%)	8.5%	20/344 (5.8%)	6.7%	0.90 (0.49-1.66)

Source: Sponsor's Display E-2, Page 800-803 of CSR

Table 18 Statistical Reviewer's Subgroup Analysis Results for Body Weight for both TRACER and TRA-2P Studies (Reported are HR and 95% C.I.)

Primary Endpoint	TRACER	TRA-2P Overall Population	TRA-2P Proposed Label
Baseline Weight<60	1.06 (0.80, 1.42)	1.29 (0.96, 1.74)	1.1 (0.71, 1.70)
60<= Baseline Weight <70	0.99 (0.80, 1.24)	0.90 (0.74, 1.09)	0.91 (0.69, 1.19)
70<= Baseline Weight <80	0.88 (0.73, 1.06)	0.94 (0.81, 1.10)	0.85 (0.69, 1.05)
80<= Baseline Weight <100	0.94 (0.82, 1.08)	0.82 (0.72, 0.92)	0.78 (0.67, 0.91)
100<= Baseline Weight <200	0.80 (0.65, 0.99)	0.81 (0.67, 0.98)	0.75 (0.60, 0.95)
Key2nd Endpoint	**TRACER**	**TRA-2P Overall Population**	**TRA-2P Proposed Label**
Baseline Weight<60	1.01 (0.75, 1.37)	1.24 (0.90, 1.71)	1.1 (0.66, 1.81)
60<= Baseline Weight <70	1.02 (0.8, 1.29)	0.91 (0.74, 1.13)	0.99 (0.72, 1.36)
70<= Baseline Weight <80	0.84 (0.68, 1.03)	0.93 (0.78, 1.10)	0.81 (0.64, 1.03)
80<= Baseline Weight <100	0.91 (0.78, 1.07)	0.81 (0.71, 0.93)	0.74 (0.62, 0.88)
100<= Baseline Weight <200	0.74 (0.58, 0.93)	0.76 (0.61, 0.94)	0.68 (0.51, 0.89)

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5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The statistical reviewer confirmed the sponsor's analysis results for the primary, key secondary and other important secondary endpoints in both TRACER and TRA-2P studies. The efficacy results for vorapaxar demonstrated from TRA-2P appear positive in all different patient populations and the findings appear robust throughout the trial.

This reviewer is concerned with the unplanned interim efficacy analyses conducted, though the trial seems still to achieve significance level of 0.01 for both the primary and the key secondary endpoints (see Section 3.2.4.4). It is unclear whether such unplanned unblinded interim efficacy analyses, sample size re-estimation and change of patient population might have some impact on trial integrity.

Finally, to further examine the reverse finding of the vorapaxar observed for patients' in the light weighted subgroup (i.e., body weight <60 kg) in comparing with placebo, this reviewer performed the more detailed subgroup analyses by different body weight groups for both TRACER and TRA-2P studies. The vorapaxar's effect seems larger as the body weight is larger (Table 18) and seems little or negative in patients with weigh ≤ 60 kg.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The vorapaxar's efficacy in addition to the standard of care for preventing patients' atherothrombotic ischemic events appears to be demonstrated based on TRA 2°P-TIMI 50 trial for the overall study population and also the proposed label population, i.e., post MI patients without history of stroke or TIA. However, we are concerned about several unplanned interim analyses, sample size increase and change of patient population, even though these analyses are performed by an independent statistician through the Data Safety Monitoring Board (DSMB). Whether these analyses might have impacted the trial integrity is uncertain.

_____
Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 204,886
HFD-110/Dr. Stockbridge
HFD-110/Dr. Grant
HFD-110/Dr. Marciniak
HFD-110/Dr. Rose
HFD-110/Ms. Alison
HFD-700/Ms. Patrician
HFD-710/Dr. Hung

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6. APPENDIX

6.1 Brief Description of TRACER Study

Study Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard of Care in Subjects With Acute Coronary Syndrome: Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome

Study Objectives and Efficacy Endpoints

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

Primary Analysis

Analyses of the primary efficacy endpoint and key secondary endpoint were accomplished via the Cox proportional hazards model with covariates of treatment and stratification factors. Treatment differences were tested at 0.049 to account for one interim analysis. P-values and estimates of the hazard ratios and 95% confidence intervals were provided. Similar analyses were performed for other secondary and exploratory efficacy endpoints at α=0.05.

Patient Disposition and Demographics and Baseline Characteristics

Table 19 Subject Disposition for TRACER Study

Number (%) of Subjects	Placebo	SCH 530348	Total
Randomized	n = 6471	n = 6473	n = 12944
Received treatment	6441 (99.5)	6,446 (99.6)	12,887 (99.6)
Never Received Study Drug	30 (0.5)	27 (0.4)	57 (0.4)
Discontinued Study Drug Prematurely	1,726 (26.8)	1,818 (28.2)	3,544 (27.5)
Adverse/Bleeding/Clinical Experience	489 (7.6)	649 (10.1)	1,138 (8.8)
Did not wish to continue	865 (13.4)	858 (13.3)	1,723 (13.4)
Non-compliance	287 (4.5)	232(3.6)	519 (4.0)
Did not have disease of interest	65 (1.0)	56 (0.9)	121 (0.9)
Unknown	20 (0.3)	23 (0.4)	43 (0.3)
Completed Study on Treatment	4,715 (73.2)	4,628 (71.8)	9,343 (72.5)
Died on treatment	156 (2.4)	153 (2.4)	309 (2.4)
Completed treatment	4,559 (70.8)	4,475 (69.4)	9,034 (70.1)

Source: Sponsor's Display A-1.4 on Page 544 of CSR.

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Table 20 Demographic and Other Baseline Characteristics for All Randomized Patients in TRACER Study

Number (%) of Subjects	Placebo N=6,471	Vorapaxar N=6473	Total N=12,944
Age (years), Mean (SD)	64.4 (9.98)	64.4 (9.95)	64.4 (9.96)
Sex, n (%)			
Female	1,822 (28.2)	1,810 (28.0)	3,632 (28.1)
Male	4,649 (71.8)	4,663 (72.0)	9,312 (71.9)
Race, n (%)			
White	5,510 (85.1)	5,529 (85.4)	11,039 (85.3)
Non-White	943 (14.6)	927 (14.3)	1,870 (14.4)
American Indian or Alaskan Native	16 (0.2)	19 (0.3)	35 (0.3)
Asian	533 (8.2)	523(8.1)	1,056 (8.2)
Black or African American	161 (2.5)	151 (2.3)	312 (2.4)
Multiracial	213 (3.3)	222 (3.4)	435 (3.4)
Native Hawaiian or Other Pacific Islander	20 (0.3)	12 (0.2)	32 (0.2)
Missing	18 (0.3)	17 (0.3)	35 (0.3)
Ethnicity, n (%)			
Chinese	136 (2.1)	137 (2.1)	273 (2.1)
Hispanic/Latino	532 (8.2)	557 (8.6)	1,089 (8.4)
Japanese	145 (2.2)	136 (2.1)	281 (2.2)
Korean	65 (1.0)	64 (1.0)	129 (1.0)
Taiwanese	111 (1.7)	107 (1.7)	218 (1.7)
Other	5,336 (82.5)	5,311 (82.0)	10,647 (82.3)
Missing	17 (0.3)	30 (0.5)	47 (0.4)
Weight (kg), Mean (SD)	82.25 (17.66)	82.66 (18.12)	82.45 (17.89)
Height (cm), Mean (SD)	169.74 (9.6)	169.78 (9.64)	169.76 (9.62)
Calculated Body Mass Index (kg/m^2), Mean (SD)	28.44 (5.16)	28.57 (5.34)	28.51(5.25)
Heart Rate (beats/minute), Mean (SD)	70.9 (13.24)	70.8 (13.07)	70.9 (13.15)
Systolic Blood Pressure (mm Hg), Mean (SD)	131.8 (20.83)	132.0 (20.67)	131.9 (20.75)
Diastolic Blood Pressure (mm Hg), Mean (SD)	75.0 (12.48)	74.8 (12.42)	74.9 (12.45)
Waist Circumference (cm), Mean (SD)	100.36 (14.09)	100.61 (14.18)	100.49 (14.13)

Source: Sponsor's Table 16 from Pages 126 to 128 of CSR.

Efficacy Results

Table 21 Sponsor's Results for Primary and Key Secondary Endpoints for the Overall ITT Population for TRACER Study

Endpoint and Contributing Component	Placebo (n=6,471)		Vorapaxar (n=6,473)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Primary Efficacy Endpoint	1,102 (17.0%)	19.9%	1,031 (15.9%)	18.5%	0.92 (0.85-1.01)	0.072
CV Death	122 (1.9%)		115 (1.8%)			
MI	668 (10.3%)		596 (9.2%)			
Stroke	89 (1.4%)		83 (1.3%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	82 (1.3%)		63 (1.0%)			
Hemorrhagic Stroke	6 (0.1%)		19 (0.3%)			
Uncertain	1 (0%)		1 (0.0%)			
RIR	53 (0.8%)		60 (0.9%)			
UCR	170 (2.6%)		177 (2.7%)			

Reference ID: 3421507

Endpoint and Contributing Component	Placebo (n=6,471)		Vorapaxar (n=6,473)		HR (95% C.I.)	P Value
	Events (%)	KM%	Events (%)	KM%		
Key Secondary Efficacy Endpoint	910 (14.1%)	16.4%	822 (12.7%)	14.7%	0.89 (0.81-0.98)	0.018
CV Death	127 (2.0%)		122 (1.9%)			
MI	692 (10.7%)		614 (9.5%)			
Stroke	91 (1.4%)		86 (1.3%)			
Ischemic (Non-hemorrhagic Cerebral Infarction)	84 (1.3%)		66 (1.0%)			
Hemorrhagic Stroke	6 (0.1%)		19 (0.3%)			
Uncertain	1 (0%)		1 (0.0%)			

Source: Sponsor's Table 31 of CSR.

Reference ID: 3421507

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/s/

YEH FONG CHEN
12/13/2013

HSIEN MING J HUNG
12/13/2013

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 204-886/IND 71384
Drug Name:	SCH 530348
Indication(s):	Two Year Rat and Mouse Carcinogenicity Studies
Applicant:	**Sponsor:** Schering-Plough Research Institute Lafayette, NJ 07848 **Testing facility:** Safety Evaluation Center Schering-Plough Research Institute Lafayette, NJ 07848
Documents Reviewed:	**Study report:** Electronic submission submitted on May 10, 2013 **Study data:** Electronic data submitted on May 10, 2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Cardiovascular and Renal Products
Reviewing Pharmacologist:	Patricia Harlow, Ph.D.
Project Manager:	Alison Blaus
Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of SCH 530348 when administered once daily via gavage for about two years. Results of this review have been discussed with the reviewing pharmacologist Dr. Harlow.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and two identical control groups. Two hundred and fifty Crl:CD[SD] (b) (4) rats of each sex were assigned randomly to the treated and control groups in equal size of 50 rats per group. The dose levels for treated groups were 3, 10, or 30 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose groups, respectively. The rats in the control groups received the vehicle (0.4% (w/v) aqueous methylcellulose) once daily via gavage. All animals were dosed for 104 weeks.

All rats were observed for clinical observations once on Day -7; the day of randomization; at least once weekly beginning on the first day of dosing; and the day of sacrifice. The rats were palpated for masses at Week 1; every four weeks from Week 4 through 24; every two weeks from Week 25 through 52; and weekly thereafter. The morbidity and mortality were observed regularly during the whole period of study.

The body weights of all rats were taken on day of randomization; weekly from Week -1 through 24; every two weeks from Week 25 through 36; every four weeks thereafter; prior to the first day of terminal sacrifice; and terminal sacrifice.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor estimated the survival curve of each treatment group using the Kaplan-Meier product limit estimation method and displayed them graphically. The sponsor compared the survival of each treated group with the combined control, and the two control groups using the log rank test.

Sponsor's findings: Sponsor's count showed 25, 21, 28, 22, and 27 male rat mortalities, and 32, 34, 36, 31, and 32 female rat mortalities in control 1, control 2, low, medium and high dose groups, respectively. Sponsor's analysis did not show statistically significant difference in mortality between any treated group and the combined control in either sex.

2.1.2. Tumor data analysis

The sponsor performed statistical analysis of a tumor type if it had a total of two or more animals with the tumor. For the statistical analysis the two identical controls were pooled to form a combined control group. The tumor incidence data were analyzed for dose response relationships using the methods outlined in the paper of Peto et al. (1980). For Peto analysis the sponsor first classified the tumor types as fatal and

incidental, and analyzed them using the death rate and prevalence methods, respectively. For the evaluation of incidental tumors the experimental period was divided into intervals of 1-52, 53-78, 79-103 weeks, and the terminal sacrifice. The ordinal dose values (e.g., 0, 1, 2, and 3) were used as the scores. In general the asymptotic tests were performed, however when the total tumor occurrence across treatment groups was less than 25, the exact permutation test was used.

Adjustment for multiple testing: In order to control the false positive error, the sponsor tested the common and the rare tumor types at 0.005 and 0.025 significance levels, respectively for positive dose response relationship. The tumors with a background rate of > 1% were considered as common and the tumors with a background rate of < 1% were considered as rare.

Sponsor's findings: The sponsor's analyses did not show statistically significant dose response relationship across the treatment groups in any of the observed tumor types in either sex of rats.

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses.

As stated earlier, the rat study had two identical controls. For such study designs the FDA guidance for the carcinogenicity study design and data analysis suggests to combine the two controls and analyze the data using the combined control. This improves the power of the tests. Following the guidance suggestion, this reviewer analyzed both the survival and tumor data using the combined control. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

This reviewer estimated the survival distributions of rats in all five treatment groups using the Kaplan-Meier product limit estimation method. This reviewer tested the positive dose response relationship across combined control, low, medium, and high dose groups using the likelihood ratio test and the homogeneity of survival distributions using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's count showed 25, 21, 28, 22, and 27 mortalities in male rats and 32, 33, 36, 31, and 32 mortalities in female rats in control 1, control 2, low, medium, and high dose groups, respectively. The tests did not show statistically significant dose response relationship in mortality across combined control and treated groups in either sex. The pairwise comparisons also did not show statistically significant difference in mortality in any of the treated dose groups compared to the combined control in either sex.

Reviewer's comment: *This reviewer's count showed 33 mortalities in the female rat control 2 group, while the sponsor's count showed 34 mortalities. This difference is due to the fact that there was one female rat (#613) in control 2 group that died naturally during the terminal sacrifice weeks. This reviewer counted this female rat with the terminally sacrificed animals, while the sponsor counted it with the naturally dead rats.*

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of combined control with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ < 1. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score s_h < 1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female rats, respectively.

Multiple testing adjustment: For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of test levels α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two species, and a significance level α=0.01 for common tumors and α=0.05 for rare tumors for a submission with one species in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control the FDA guidance for the carcinogenicity study design and data analysis the suggested the use of test levels α=0.01 for common tumors and α=0.05 for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

It should be noted that the FDA guidance on multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Lin and Rahman (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship or pairwise comparisons of treated groups and combined control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons of Treated Groups and Combined Control in Rats

							P_Value			
Sex	Organ Name	Tumor Name	Com Cont N=100	Low N=50	Med N=50	High N=50	Dose Resp	L vs Com C	M vs Com C	H vs Com C
Male	ADRENAL GLANDS	ADENOMA [B].	4	5	7	2	0.5290	0.1235	0.0302	0.6259
	LARGE INTESTINE	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
	LIVER	HEPATOCELLULAR ADENOMA [B	0	1	3	1	0.2301	0.3277	0.0352*	0.3220
	LUNGS	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
	PARATHYROID GLA	ADENOMA [B].	1	0	4	1	0.2678	0.3277	0.0418*	0.5499
	PROSTATE GLAND	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
	SEMINAL VESICLE	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
	STOMACH	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
	THYMUS	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
Female	LIVER	HEPATOCELLULAR ADENOMA [B	1	0	1	4	0.0085*	0.3301	0.5620	0.0460*
	PITUITARY GLAND	PARS DISTALIS ADENOMA [B]	55	34	38	33	0.1695	0.0749	0.0084*	0.1652
	UTERUS	ADENOMA [B].	0	0	0	2	0.0419	.	.	0.1154

Based on the criteria of adjustment for multiple testing discussed above, the incidence of hepatocellular adenoma was considered to have statistically significant dose response relationship in female rats. The pairwise comparison showed statistically significant increased incidence of hepatocellular adenoma in the female rat high dose group compared to the combined control. The pairwise comparisons also showed statistically significant increased incidences of hepatocellular adenoma, and parathyroid gland adenoma in male medium dose group, and pituitary gland pars distalis adenoma in female rat medium dose group compared to their respective combined control.

3. Mouse Study

Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups and two identical control groups. Two hundred and fifty Crl:CD1[ICR] (b) (4) mice of each sex were assigned randomly to the treated and control groups in equal size of 50 mice per group. The dose levels for treated groups were 1, 5 or 15 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. The mice in the control groups received the vehicle (0.4% (w/v) aqueous methylcellulose) once daily via gavage. The male and female mice were dosed for 102 and 101 weeks, respectively.

All mice were observed for clinical observations once on Day -7; the day of randomization; at least once weekly beginning on the first day of dosing; and the day of sacrifice. The mice were palpated for masses at Week 1; every four weeks from Week 4 through 24; every two weeks from Week 25 through 52; and weekly thereafter. The morbidity and mortality were observed regularly during the whole period of study.

Body weights of all mice were measured on day of randomization; weekly from Week -1 through 24; every two weeks from Week 25 through 36; every four weeks thereafter; prior to the first day of terminal sacrifice; and terminal sacrifice.

3.1. Sponsor's analyses

3.1.1. Survival analysis

The sponsor used similar statistical methodologies to analyze the mouse survival data as they used to analyze the rat survival data.

Sponsor's findings: The sponsor's count showed 28, 26, 36, 26, and 24 male mouse mortalities, and 26, 32, 35, 34, and 31 female mouse mortalities in control 1, control 2, low, medium and high dose groups, respectively. Sponsor's analysis did not show statistically significant difference in mortality between any of the treated groups and the combined control in either sex.

3.1.2. Tumor data analysis

The sponsor used similar statistical methodologies to analyze the mouse tumor data as they used to analyze the rat tumor data.

Adjustment for multiple testing: The sponsor used similar procedure to adjust the multiple testing in the mouse tumor data analysis as they used to adjust the multiple testing in the rat tumor data analysis.

Sponsor's findings: The sponsor's analyses did not show statistically significant dose response relationship across the treatment groups in any of the observed tumor types in either sex of mice.

3.2. Reviewer's analyses

Similar to the rat study, to verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses of mouse data.

Similar to the rat study the mouse study also had two identical controls. Following the suggestions given in the FDA guidance for the carcinogenicity study design and data analysis, this reviewer analyzed both the survival and tumor data using the combined control. Data used in this reviewer's analyses were provided by the sponsor electronically. For the analysis of both the survival data and the tumor data this reviewer used similar statistical methodologies as he used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for combined control, low, medium, and high dose groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's count showed 28, 26, 36, 26, and 24 mortalities in male mice, and 25, 32, 34, 35, and 31 mortalities in female mice in control 1, control 2, low, medium, and high dose groups, respectively. The tests did not show statistically significant dose response relationship in mortality across combined control and treated groups in either sex. The pairwise comparisons also did not show statistically significant difference in mortality in any of the treated dose groups compared to the combined control in either

sex.

Reviewer's comment: *This reviewer's count showed 25 mortalities in the female mouse control 1 group, and 34 mortalities in the female mouse low dose group, while the sponsor's count showed 26 and 35 mortalities in these two groups. These differences were due to the fact that there was one female mouse (#513) in control 1 group and one female mouse (#1543) in low dose group that died naturally during the terminal sacrifice weeks. This reviewer counted these female mice with the terminally sacrificed animals, while the sponsor counted them with the naturally dead animals.*

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tested tumor types are given in Tables 6A and Table 6B in the appendix, for male and female mice respectively.

Reviewer's findings: Following tumor type showed p-values less than or equal to 0.05 either for dose response relationship or pairwise comparisons of treated groups and combined control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons of Treated Groups and Combined Control in Mice

							P_Value			
Sex	Organ Name	Tumor Name	Com Cont N=100	Low N=50	Med N=50	High N=50	Dose Resp	L vs Com C	M vs Com C	H vs Com C
Male	LUNGS	BRONCHIOLO-ALVEOLAR ADENO	19	16	12	9	0.8335	0.0317	0.3277	0.5541
		BRONCHIOLO-ALVEOLAR CARCI	2	1	1	4	0.0457	0.6725	0.7079	0.1126
		BRONCH-ALVEOLAR ADEN+CARC	21	17	13	13	0.5565	0.0381	0.3192	0.4152
	SKIN	SEBACEOUS CELL ADENOMA [B	0	0	3	1	0.2096	.	0.0381*	0.3486
Female	BONE MARROW	LYMPHOMA [M], metastatic	8	10	4	6	0.4277	0.0349	0.5595	0.2822

Based on the criteria of adjustment for multiple testing discussed in the rat data analysis section, the incidence of none of the observed tumor types was considered to have statistically significant dose response relationship in either sex of mice. The pairwise comparisons showed statistically significant increased incidence of skin sebaceous cell adenoma in the female mice medium dose group compared to the combined control.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of SCH 530348 when administered once daily via gavage.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

Rat Study: Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and two identical control groups. Two hundred and fifty Crl:CD[SD] (b) (4) rats of each sex were assigned randomly to the treated and control groups in equal size of 50 rats per group. The dose levels for treated groups were 3, 10, or 30 mg/kg/day. The rats in the

control groups received the vehicle (0.4% (w/v) aqueous methylcellulose) once daily via gavage. The rats in both sexes were dosed for 104 weeks.

The tests did not show statistically significant dose response relationship in mortality across combined control and treated groups in either sex. The pairwise comparisons also did not show statistically significant difference in mortality in any of the treated groups compared to the combined control in either sex.

The tests showed statistically significant positive dose response relationship in the incidence of hepatocellular adenoma in female rats. The pairwise comparison showed statistically significant increased incidence of hepatocellular adenoma in the female rat high dose group compared to the combined control. The pairwise comparisons also showed statistically significant increased incidences of hepatocellular adenoma, and parathyroid gland adenoma in male rat medium dose group, and pituitary gland pars distalis adenoma in female rat medium dose group compared to their respective combined control.

Mouse Study: Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups and two identical control groups. Two hundred and fifty Crl:CD1[ICR] (b) (4) mice of each sex were assigned randomly to the treated and control groups in equal size of 50 mice per group. The dose levels for treated groups were 1, 5 or 15 mg/kg/day. The mice in the control groups received the vehicle (0.4% (w/v) aqueous methylcellulose) once daily via gavage. The male and female mice were dosed for 102 and 101 weeks, respectively.

The tests did not show statistically significant dose response relationship in mortality across combined control and treated groups in either sex. The pairwise comparisons also did not show statistically significant difference in mortality in any of the treated dose groups compared to the combined control in either sex.

The tests did not show statistically significant dose response relationship in the incidence of any of the observed tumor types in either sex of mice. The pairwise comparisons showed statistically significant increased incidence of skin sebaceous cell adenoma in the female mice medium dose group compared to the combined control.

Mohammad Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, Biometrics-6

cc:
Archival NDA 204-886
Dr. Harlow
Ms. Blaus
Dr. Tsong
Dr. Lin
Dr. Rahman
Ms. Patrician

5. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

	Control 1		Control 2		3 mg|kg|day		10 mg|kg|day		30 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	3	6.00	4	8.00	2	4.00	3	6.00	5	10.00
53 - 78	2	10.00	3	14.00	9	22.00	6	18.00	4	18.00
79 - 91	9	28.00	8	30.00	3	28.00	3	24.00	5	28.00
92 - 104	11	50.00	6	42.00	14	56.00	10	44.00	13	54.00
Ter. Sac.	25	50.00	29	58.00	22	44.00	28	56.00	23	46.00
Total	N=50		N=50		N=50		N=50		N=50	

[#] **Cum. %: Cumulative percentage except for Ter. Sac.**

Table 1B: Intercurrent Mortality Rate
Female Rats

	Control 1		Control 2		3 mg|kg|day		10 mg|kg|day		30 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	1	2.00	1	2.00	3	6.00	3	6.00	2	4.00
53 - 78	13	28.00	12	26.00	8	22.00	13	32.00	10	24.00
79 - 91	8	44.00	9	44.00	12	46.00	3	38.00	8	40.00
92 - 104	10	64.00	11	66.00	13	72.00	12	62.00	12	64.00
Ter. Sac.	18	36.00	17	34.00	14	28.00	19	38.00	18	36.00
Total	N=50		N=50		N=50		N=50		N=50	

[#] **Cum. %: Cumulative percentage except for Ter. Sac.**

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	Statistic	P_Value[#]
Dose-Response	Likelihood Ratio	0.4739
Homogeneity	Log-Rank	0.5460

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.6537
Homogeneity	Log-Rank	0.8351

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Rats

Organ Name	Tumor Name	0 mg Com C N=100	3 mg Low N=50	10 mg Med N=50	30 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
ABDOMINAL CAVIT	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1929	.	.	0.3220
ADRENAL GLANDS	ADENOCARCINOMA [M], corti	1	0	0	0	0.5939	0.3277	0.3333	0.3220
	ADENOMA [B].	4	5	7	2	0.5290	0.1235	0.0302	0.6259
	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1929	.	.	0.3220
	PHEOCHROMOCYTOMA [B].	6	4	6	2	0.6414	0.4248	0.1659	0.5066
	PHEOCHROMOCYTOMA [M].	1	1	2	0	0.6091	0.5499	0.2574	0.3220
BONE	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1929	.	.	0.3220
	LARGE GRANULAR-CELL LYMPH	0	1	0	0	0.3959	0.3277	.	.
BONE MARROW	LARGE GRANULAR-CELL LYMPH	0	1	0	0	0.3959	0.3277	.	.
BRAIN	ASTROCYTOMA [M].	1	0	3	0	0.5348	0.3277	0.1123	0.3220
	GRANULAR CELL TUMOR [B].	0	0	0	1	0.1929	.	.	0.3220
	PARS DISTALIS CARCINOMA [	0	0	1	1	0.1180	.	0.3333	0.3277
EPIDIDYMIDES	MESOTHELIOMA [M], metasta	0	0	1	1	0.1151	.	0.3333	0.3220
ESOPHAGUS	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1929	.	.	0.3220
	SCHWANNOMA [M], metastati	0	1	0	0	0.3959	0.3277	.	.
HEART	BRONCHIOLO-ALVEOLAR CARCI	1	0	0	0	0.5909	0.3250	0.3306	0.3193
	OSTEOSARCOMA [M], metasta	1	0	0	0	0.5939	0.3277	0.3333	0.3220
	SCHWANNOMA [B].	0	0	0	1	0.1929	.	.	0.3220
	SCHWANNOMA [M].	0	1	0	0	0.3959	0.3277	.	.
KIDNEYS	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1929	.	.	0.3220
	LARGE GRANULAR-CELL LYMPH	0	1	0	0	0.3959	0.3277	.	.
LARGE INTESTINE	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
	LARGE GRANULAR-CELL LYMPH	0	1	0	0	0.3959	0.3277	.	.
LARYNX	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1929	.	.	0.3220
	SCHWANNOMA [M], metastati	0	1	0	0	0.3959	0.3277	.	.
LIVER	HEPATOCELLULAR ADENOMA [B	0	1	3	1	0.2301	0.3277	0.0352*	0.3220
	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1970	.	.	0.3277
	LARGE GRANULAR-CELL LYMPH	0	1	0	0	0.3959	0.3277	.	.
LUNGS	ADENOCARCINOMA [M], metas	1	0	0	0	0.5939	0.3277	0.3333	0.3220
	BRONCHIOLO-ALVEOLAR ADENO	0	1	0	0	0.3959	0.3277	.	.
	BRONCHIOLO-ALVEOLAR CARCI	1	0	0	0	0.5909	0.3250	0.3306	0.3193
	FIBROSARCOMA [M], metasta	1	0	0	0	0.5939	0.3277	0.3333	0.3220
	HEMANGIOSARCOMA [M], meta	0	0	1	0	0.3990	.	0.3388	.
	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
	LARGE GRANULAR-CELL LYMPH	0	1	0	0	0.3959	0.3277	.	.
	OSTEOSARCOMA [M], metasta	1	0	0	0	0.5939	0.3277	0.3333	0.3220
	SCHWANNOMA [M], metastati	0	1	0	0	0.3959	0.3277	.	.

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Rats

Organ Name	Tumor Name	0 mg Com C N=100	3 mg Low N=50	10 mg Med N=50	30 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
MAMMARY GLANDS	ADENOCARCINOMA [M].	1	0	0	0	0.5909	0.3250	0.3306	0.3193
	ADENOMA [B].	0	1	0	0	0.3959	0.3277	.	.
	FIBROADENOMA [B].	2	0	0	0	0.8339	0.5462	0.5537	0.5385
	FIBROMA [B].	0	1	2	0	0.4840	0.3277	0.1092	.
MANDIBULAR LYMP	LARGE GRANULAR-CELL LYMPH	0	1	0	0	0.3959	0.3277	.	.
	SQUAMOUS CELL CARCINOMA [	1	0	0	0	0.5939	0.3277	0.3333	0.3220
MESENTERIC LYMP	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1929	.	.	0.3220
	LARGE GRANULAR-CELL LYMPH	0	1	0	0	0.3959	0.3277	.	.
NERVE-PERIPHERA	HISTIOCYTIC SARCOMA [M],	1	0	0	1	0.3494	0.3277	0.3333	0.5422
PANCREAS	ADENOCARCINOMA [M], acina	0	1	0	0	0.3959	0.3277	.	.
	ADENOMA [B], acinar cell.	2	0	2	0	0.6491	0.5499	0.4074	0.5422
	HISTIOCYTIC SARCOMA [M],	1	0	0	2	0.0996	0.3277	0.3333	0.2499
	ISLET CELL ADENOMA [B].	12	6	4	8	0.2249	0.5667	0.6659	0.2957
PARATHYROID GLA	ADENOMA [B].	1	0	4	1	0.2678	0.3277	0.0418*	0.5499
PHARYNX	SCHWANNOMA [M], metastati	0	1	0	0	0.3959	0.3277	.	.
PITUITARY GLAND	ASTROCYTOMA [M], metastat	0	0	1	0	0.3990	.	0.3388	.
	PARS DISTALIS ADENOMA [B]	44	25	20	23	0.3663	0.2659	0.5983	0.3472
	PARS DISTALIS CARCINOMA [	2	0	1	3	0.0596	0.5462	0.7037	0.1934
	PARS INTERMEDIA ADENOMA [	1	0	1	1	0.2626	0.3250	0.5610	0.5385
PRIMARY SITE UN	HISTIOCYTIC SARCOMA [M].	1	1	3	2	0.1492	0.5499	0.1123	0.2499
	LARGE GRANULAR-CELL LYMPH	0	1	0	0	0.3959	0.3277	.	.
	LIPOMA [B].	0	0	1	0	0.3959	.	0.3333	.
	MESOTHELIOMA [M].	0	0	0	1	0.1929	.	.	0.3220
	SQUAMOUS CELL CARCINOMA [	1	0	0	0	0.5939	0.3277	0.3333	0.3220
PROSTATE GLAND	ADENOCARCINOMA [M].	1	0	0	0	0.5939	0.3277	0.3333	0.3220
	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
	LARGE GRANULAR-CELL LYMPH	0	1	0	0	0.3959	0.3277	.	.
SEMINAL VESICLE	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
SKELETAL MUSCLE	HISTIOCYTIC SARCOMA [M],	1	0	1	2	0.0908	0.3277	0.5574	0.2499
	OSTEOSARCOMA [M].	1	0	0	0	0.5939	0.3277	0.3333	0.3220
SKIN	BASAL CELL TUMOR [B].	0	1	1	2	0.0503	0.3277	0.3333	0.1018
	CARCINOMA [M], Zymbal's g	0	1	1	0	0.3898	0.3277	0.3333	.
	FIBROMA [B].	2	0	1	2	0.1666	0.5499	0.7074	0.3871
	FIBROSARCOMA [M].	3	0	1	1	0.4793	0.6962	0.4024	0.3822
	HEMANGIOMA [B].	0	0	0	1	0.1929	.	.	0.3220
	HEMANGIOSARCOMA [M].	0	0	1	0	0.3990	.	0.3388	.
	HISTIOCYTIC SARCOMA [M],	1	0	3	2	0.1036	0.3277	0.1123	0.2499
	KERATOACANTHOMA [B].	4	2	0	0	0.9679	0.6432	0.8075	0.7939

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Rats

Organ Name	Tumor Name	0 mg Com C N=100	3 mg Low N=50	10 mg Med N=50	30 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
SKIN	LIPOMA [B].	0	1	0	0	0.3959	0.3277	.	.
	PAPILLOMA [B].	1	0	0	0	0.5939	0.3277	0.3333	0.3220
	RHABDOMYOSARCOMA [M].	0	0	0	1	0.1970	.	.	0.3277
SMALL INTESTINE	ADENOCARCINOMA [M].	0	0	0	1	0.1929	.	.	0.3220
	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1929	.	.	0.3220
	NEUROENDOCRINE CELL TUMOR	0	1	0	0	0.3959	0.3277	.	.
SPLEEN	HISTIOCYTIC SARCOMA [M],	0	1	0	2	0.0531	0.3277	.	0.1055
	LARGE GRANULAR-CELL LYMPH	0	1	0	0	0.3959	0.3277	.	.
STOMACH	FIBROSARCOMA [M].	1	0	0	0	0.5939	0.3277	0.3333	0.3220
	HEMANGIOSARCOMA [M].	0	0	0	1	0.1929	.	.	0.3220
	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
	PAPILLOMA [B], squamous c	0	0	0	1	0.1929	.	.	0.3220
TESTES	INTERSTITIAL CELL ADENOMA	1	1	1	0	0.5816	0.5499	0.5574	0.3220
	MESOTHELIOMA [M], metasta	0	0	0	1	0.1929	.	.	0.3220
	MESOTHELIOMA [M].	0	0	1	0	0.3959	.	0.3333	.
	SERTOLI CELL TUMOR [B].	1	0	0	0	0.5939	0.3277	0.3333	0.3220
THYMUS	HISTIOCYTIC SARCOMA [M],	0	0	0	2	0.0380	.	.	0.1055
	SCHWANNOMA [M], metastati	0	1	0	0	0.3959	0.3277	.	.
THYROID GLAND	C-CELL ADENOMA [B].	14	6	2	3	0.9432	0.4917	0.9502	0.8619
	FOLLICULAR CELL ADENOMA [	1	3	0	1	0.5395	0.1024	0.3333	0.5422
	SCHWANNOMA [M], metastati	0	1	0	0	0.3959	0.3277	.	.
TRACHEA	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1929	.	.	0.3220
	SCHWANNOMA [M], metastati	0	1	0	0	0.3959	0.3277	.	.
URETERS	HISTIOCYTIC SARCOMA [M],	0	0	1	1	0.1151	.	0.3333	0.3220
URINARY BLADDER	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1929	.	.	0.3220
	TRANSITIONAL CELL PAPILLO	0	0	1	0	0.3959	.	0.3333	.
WHOLE BODY	HISTIOCYTIC SARCOMA [M],	1	1	3	2	0.1492	0.5499	0.1123	0.2499

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Com C N=100	3 mg Low N=50	10 mg Med N=50	30 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
ABDOMINAL CAVIT	FIBROSARCOMA [M], metasta	0	1	0	0	0.4046	0.3301	.	.
ADRENAL GLANDS	ADENOMA [B].	13	5	4	7	0.3770	0.5881	0.7094	0.5143
	PHEOCHROMOCYTOMA [B].	2	1	1	1	0.4222	0.7037	0.2614	0.2614
	PHEOCHROMOCYTOMA [M].	1	2	0	1	0.4701	0.2614	0.3365	0.5620
BONE	OSTEOSARCOMA [M].	0	1	1	0	0.4023	0.3365	0.3365	.
BONE MARROW	HEMANGIOMA [B].	0	0	0	1	0.2023	.	.	0.3365
	HISTIOCYTIC SARCOMA [M],	0	0	1	0	0.4046	.	0.3365	.
BRAIN	GRANULAR CELL TUMOR [B].	1	0	0	0	0.6012	0.3301	0.3365	0.3365
	PARS DISTALIS CARCINOMA [	7	2	1	2	0.7343	0.6230	0.8104	0.6230
HEART	SARCOMA [M], metastatic s	0	1	0	0	0.4023	0.3365	.	.
KIDNEYS	ADENOMA [B], tubular cell	0	1	1	0	0.4046	0.3301	0.3365	.
LARGE INTESTINE	HISTIOCYTIC SARCOMA [M],	1	0	0	1	0.3719	0.3301	0.3365	0.5703
LARYNX	ADENOCARCINOMA [M], metas	1	0	0	0	0.6012	0.3301	0.3365	0.3365
LIVER	HEPATOCELLULAR ADENOMA [B	1	0	1	4	0.0085*	0.3301	0.5620	0.0460*
LUNGS	ADENOCARCINOMA [M], metas	1	1	0	2	0.1497	0.5534	0.3365	0.2700
	ENDOMETRIAL STROMAL SARCO	0	0	0	1	0.2023	.	.	0.3365
	OSTEOSARCOMA [M], metasta	0	1	1	0	0.4023	0.3365	0.3365	.
	PHEOCHROMOCYTOMA [M], met	0	2	0	0	0.6441	0.1111	.	.
	SARCOMA [M], metastatic s	0	1	0	0	0.4023	0.3365	.	.
LYMPH NODES	ENDOMETRIAL STROMAL SARCO	0	0	0	1	0.2023	.	.	0.3365
MAMMARY GLANDS	ADENOCARCINOMA [M].	13	5	7	6	0.5174	0.6000	0.5010	0.4817
	ADENOMA [B].	26	16	10	11	0.8379	0.3787	0.7690	0.7048
	FIBROADENOMA [B].	27	21	18	16	0.4186	0.0504	0.1965	0.3328
	FIBROMA [B].	0	1	2	1	0.2086	0.3301	0.1111	0.3365
MANDIBULAR LYMP	ADENOCARCINOMA [M], metas	1	0	0	0	0.6012	0.3301	0.3365	0.3365
MESENTERIC LYMP	HISTIOCYTIC SARCOMA [M],	1	0	0	0	0.6012	0.3301	0.3365	0.3365
OVARIES	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.2069	.	.	0.3429
	SERTOLI CELL TUMOR [B].	0	1	0	0	0.4023	0.3365	.	.
PANCREAS	ADENOMA [B], acinar cell.	0	1	0	0	0.4046	0.3301	.	.
	ENDOMETRIAL STROMAL SARCO	0	0	1	1	0.1223	.	0.3365	0.3365
	ISLET CELL ADENOMA [B].	3	0	3	0	0.7704	0.7037	0.3228	0.7123
	ISLET CELL CARCINOMA [M].	3	0	0	0	0.9382	0.7037	0.7123	0.7123
PARATHYROID GLA	ADENOMA [B].	2	0	0	0	0.8423	0.5534	0.5620	0.5620

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Com C N=100	3 mg Low N=50	10 mg Med N=50	30 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
PITUITARY GLAND	PARS DISTALIS ADENOMA [B]	55	34	38	33	0.1695	0.0749	0.0084*	0.1652
	PARS DISTALIS CARCINOMA [	14	4	3	5	0.7023	0.7653	0.8734	0.6546
	PARS INTERMEDIA ADENOMA [	1	0	0	0	0.6012	0.3301	0.3365	0.3365
PRIMARY SITE UN	ADENOCARCINOMA [M].	0	1	0	0	0.4046	0.3301	.	.
	FIBROSARCOMA [M].	0	1	0	0	0.4046	0.3301	.	.
	HISTIOCYTIC SARCOMA [M].	1	1	1	1	0.3536	0.5620	0.5620	0.5703
	LYMPHOMA [M].	0	0	1	1	0.1223	.	0.3365	0.3365
SALIVARY GLANDS	ADENOCARCINOMA [M].	1	0	0	0	0.6012	0.3301	0.3365	0.3365
SKELETAL MUSCLE	HEMANGIOSARCOMA [M].	1	0	0	0	0.6012	0.3301	0.3365	0.3365
	OSTEOSARCOMA [M], metasta	0	0	1	0	0.4046	.	0.3365	.
SKIN	CARCINOMA [M], Zymbal's g	1	0	0	0	0.5977	0.3269	0.3333	0.3333
	FIBROSARCOMA [M].	2	1	0	0	0.8414	0.7080	0.5577	0.5577
	HEMANGIOMA [B].	1	0	0	0	0.6012	0.3301	0.3365	0.3365
	KERATOACANTHOMA [B].	2	0	0	1	0.5024	0.5534	0.5620	0.2614
	LIPOMA [B].	0	0	1	0	0.4046	.	0.3365	.
	MALIGNANT FIBROUS HISTIOC	0	2	0	0	0.6441	0.1111	.	.
	MAST CELL TUMOR [B].	1	0	0	0	0.6012	0.3301	0.3365	0.3365
	OSTEOSARCOMA [M].	0	1	0	0	0.4046	0.3301	.	.
	PAPILLOMA [B].	1	0	0	0	0.6012	0.3301	0.3365	0.3365
	SARCOMA [M], not otherwis	1	0	1	0	0.4814	0.3269	0.5577	0.3333
	SCHWANNOMA [B].	1	0	0	0	0.6012	0.3301	0.3365	0.3365
	TRICHOEPITHELIOMA [B].	0	1	0	0	0.4046	0.3301	.	.
SMALL INTESTINE	ENDOMETRIAL STROMAL SARCO	0	0	0	1	0.2023	.	.	0.3365
	HISTIOCYTIC SARCOMA [M],	1	0	0	0	0.6012	0.3301	0.3365	0.3365
	LEIOMYOSARCOMA [M].	0	1	0	0	0.4046	0.3301	.	.
THYMUS	ADENOCARCINOMA [M], metas	1	0	0	0	0.6012	0.3301	0.3365	0.3365
	HISTIOCYTIC SARCOMA [M],	1	0	0	0	0.6012	0.3301	0.3365	0.3365
	LYMPHOMA [M], metastatic	0	0	1	1	0.1223	.	0.3365	0.3365
	SARCOMA [M].	0	1	0	0	0.4023	0.3365	.	.
	THYMOMA [M].	1	0	0	0	0.6012	0.3301	0.3365	0.3365
THYROID GLAND	C-CELL ADENOMA [B].	6	3	7	2	0.6211	0.6230	0.0937	0.5437
	C-CELL CARCINOMA [M].	1	0	1	0	0.4846	0.3301	0.5620	0.3365
	FOLLICULAR CELL ADENOMA [	0	0	0	1	0.2023	.	.	0.3365
	FOLLICULAR CELL CARCINOMA	1	1	0	0	0.6846	0.5534	0.3365	0.3365
URINARY BLADDER	ENDOMETRIAL STROMAL SARCO	0	0	1	1	0.1256	.	0.3365	0.3429
UTERUS	ADENOMA [B].	0	0	0	2	0.0419	.	.	0.1154
	ENDOMETRIAL STROMAL POLYP	5	3	4	4	0.2599	0.5440	0.3700	0.3700
	ENDOMETRIAL STROMAL SARCO	4	0	3	2	0.3504	0.7967	0.4219	0.3227
	GRANULAR CELL TUMOR [B].	0	1	0	0	0.4023	0.3365	.	.
	HEMANGIOMA [B].	1	0	0	0	0.6012	0.3301	0.3365	0.3365
	HISTIOCYTIC SARCOMA [M],	0	1	0	1	0.2069	0.3365	.	0.3429

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Com C N=100	3 mg Low N=50	10 mg Med N=50	30 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
UTERUS	LEIOMYOSARCOMA [M].	0	0	1	0	0.4046	.	0.3365	.
VAGINA	ENDOMETRIAL STROMAL SARCO	1	0	1	0	0.4814	0.3269	0.5577	0.3333
	POLYP [B].	0	1	0	0	0.4023	0.3365	.	.
WHOLE BODY	HISTIOCYTIC SARCOMA [M],	1	1	1	1	0.3536	0.5620	0.5620	0.5703

Table 4A: Intercurrent Mortality Rate in Male Mice

	Control 1		Control 2		1 mg|kg|day		5 mg|kg|day		15 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	5	10.00	3	6.00	4	8.00	8	16.00	3	6.00
53 - 78	7	24.00	8	22.00	14	36.00	5	26.00	6	18.00
79 - 91	10	44.00	7	36.00	7	50.00	4	34.00	11	40.00
92 - 102	6	56.00	8	52.00	11	72.00	9	52.00	4	48.00
Ter. Sac.	22	44.00	24	48.00	14	28.00	24	48.00	26	52.00
Total	N=50		N=50		N=50		N=50		N=50	

Cum. %: Cumulative percentage except for Ter. Sac.

Table 4B: Intercurrent Mortality Rate Female Mice

	Control 1		Control 2		1 mg|kg|day		5 mg|kg|day		15 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	5	10.00	7	14.00	3	6.00	11	22.00	7	14.00
53 - 78	8	26.00	10	34.00	9	24.00	7	36.00	9	32.00
79 - 91	6	38.00	8	50.00	12	48.00	9	54.00	6	44.00
92 - 101	6	50.00	7	64.00	10	68.00	8	70.00	9	62.00
Ter. Sac.	25	50.00	18	36.00	16	32.00	16	32.00	19	38.00
Total	N=50		N=50		N=50		N=51		N=50	

Cum. %: Cumulative percentage except for Ter. Sac.

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.1564
Homogeneity	Log-Rank	0.0841

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.7568
Homogeneity	Log-Rank	0.5250

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Com C N=100	1 mg Low N=50	5 mg Med N=50	15 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
ADRENAL GLANDS	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	LYMPHOMA [M], metastatic	7	4	5	3	0.6222	0.4475	0.3904	0.4656
	SUBCAPSULAR CELL ADENOMA	2	0	0	0	0.8386	0.5176	0.5618	0.5778
AORTA	LYMPHOMA [M], metastatic	6	5	3	2	0.7949	0.2424	0.3533	0.5576
BONE MARROW	LYMPHOMA [M], metastatic	5	3	4	3	0.4433	0.4806	0.3683	0.5576
	MAST CELL TUMOR [M], meta	0	0	1	0	0.4205	.	0.3364	.
BRAIN	LYMPHOMA [M], metastatic	3	2	2	2	0.4197	0.4974	0.5482	0.5601
	OLIGODENDROGLIOMA [M].	1	0	0	0	0.5932	0.3010	0.3333	0.3455
EPIDIDYMIDES	LYMPHOMA [M], metastatic	6	4	3	1	0.8913	0.3798	0.3533	0.7505
EYES	LYMPHOMA [M], metastatic	6	3	4	1	0.8474	0.5748	0.4656	0.7505
GALLBLADDER	LYMPHOMA [M], metastatic	3	0	2	0	0.7903	0.6585	0.5482	0.7196
	PAPILLARY ADENOMA [B].	0	0	0	1	0.2159	.	.	0.3486
HARDERIAN GLAND	ADENOMA [B].	11	7	3	5	0.7292	0.2998	0.7642	0.5093
	LYMPHOMA [M], metastatic	5	4	4	2	0.6603	0.2922	0.3683	0.4363
HEART	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	LYMPHOMA [M], metastatic	5	6	2	1	0.9222	0.0811	0.4223	0.6607
KIDNEYS	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	LYMPHOMA [M], metastatic	11	8	5	4	0.8154	0.2066	0.4529	0.6059
	MAST CELL TUMOR [M], meta	0	0	1	0	0.4205	.	0.3364	.
	RENAL TUBULE ADENOMA [B].	1	0	0	0	0.5966	0.3039	0.3364	0.3486
LARGE INTESTINE	LYMPHOMA [M], metastatic	6	1	1	2	0.6483	0.6829	0.7339	0.5651
LARYNX	LYMPHOMA [M], metastatic	4	2	3	1	0.7076	0.5892	0.4434	0.5540
LIVER	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	HEMANGIOMA [B].	2	2	0	1	0.5947	0.3612	0.5576	0.2736
	HEMANGIOSARCOMA [M], meta	1	1	1	1	0.3672	0.5269	0.5618	0.5778
	HEMANGIOSARCOMA [M].	0	1	0	0	0.4181	0.3107	.	.
	HEPATOCELLULAR ADENOMA [B	11	7	7	3	0.8927	0.3132	0.3851	0.7861
	HEPATOCELLULAR CARCINOMA	2	1	0	2	0.2708	0.6768	0.5618	0.4349
	HISTIOCYTIC SARCOMA [M],	1	0	0	0	0.5932	0.3010	0.3333	0.3455
	LYMPHOMA [M], metastatic	11	7	5	4	0.7841	0.3198	0.4529	0.6059
	MAST CELL TUMOR [M], meta	0	0	1	0	0.4205	.	0.3364	.
LUNGS	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	BRONCHIOLO-ALVEOLAR ADENO	19	16	12	9	0.8335	0.0317	0.3277	0.5541
	BRONCHIOLO-ALVEOLAR CARCI	2	1	1	4	0.0457	0.6725	0.7079	0.1126
	LYMPHOMA [M], metastatic	9	7	5	3	0.8267	0.2060	0.5392	0.6242
	MAST CELL TUMOR [M], meta	0	0	1	0	0.4205	.	0.3364	.
	OLIGODENDROGLIOMA [M], me	1	0	0	0	0.5932	0.3010	0.3333	0.3455

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Com C N=100	1 mg Low N=50	5 mg Med N=50	15 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
LUNGS	RHABDOMYOSARCOMA [M], met	0	0	0	1	0.2159	.	.	0.3486
	BRONCH-ALVEOLAR ADEN+CARC	21	17	13	13	0.5565	0.0381	0.3192	0.4152
LYMPH NODES	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	LYMPHOMA [M], metastatic	4	4	2	3	0.4514	0.2074	0.3226	0.4645
MAMMARY GLANDS	LYMPHOMA [M], metastatic	1	1	0	1	0.4106	0.5228	0.3333	0.5736
MANDIBULAR LYMP	LYMPHOMA [M], metastatic	8	7	5	4	0.6519	0.1454	0.4669	0.3814
MESENTERIC LYMP	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	LYMPHOMA [M], metastatic	12	8	5	4	0.8563	0.2712	0.5388	0.6849
NERVE-PERIPHERA	LYMPHOMA [M], metastatic	1	0	0	0	0.5932	0.3010	0.3333	0.3455
PANCREAS	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	ISLET CELL ADENOMA [B].	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	LYMPHOMA [M], metastatic	7	4	3	3	0.6401	0.4388	0.4407	0.4572
PENIS	LYMPHOMA [M], metastatic	1	0	1	0	0.4963	0.3010	0.5576	0.3455
PITUITARY GLAND	LYMPHOMA [M], metastatic	3	0	2	1	0.4922	0.6585	0.5482	0.4236
PRIMARY SITE UN	HISTIOCYTIC SARCOMA [M].	1	0	0	0	0.5932	0.3010	0.3333	0.3455
	LYMPHOMA [M].	13	8	6	4	0.8736	0.3204	0.4796	0.7369
	MAST CELL TUMOR [M].	0	0	1	0	0.4205	.	0.3364	.
PROSTATE GLAND	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	LYMPHOMA [M], metastatic	7	4	4	2	0.7822	0.4388	0.5491	0.6304
SALIVARY GLANDS	LEIOMYOMA [B].	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	LYMPHOMA [M], metastatic	6	5	4	4	0.4451	0.2205	0.4572	0.4572
SEMINAL VESICLE	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	LYMPHOMA [M], metastatic	3	2	2	0	0.8716	0.4777	0.5421	0.7156
SKELETAL MUSCLE	LYMPHOMA [M], metastatic	3	2	1	1	0.6550	0.4837	0.4019	0.4236
	RHABDOMYOSARCOMA [M].	0	1	0	1	0.2110	0.3107	.	0.3486
SKIN	FIBROMA [B].	0	1	1	1	0.1923	0.3039	0.3364	0.3486
	FIBROSARCOMA [M].	2	2	1	0	0.8271	0.3612	0.7079	0.5736
	LYMPHOMA [M], metastatic	5	4	4	0	0.9493	0.2922	0.3683	0.8770
	SEBACEOUS CELL ADENOMA [B	0	0	3	1	0.2096	.	0.0381*	0.3486
	SQUAMOUS CELL CARCINOMA [	0	0	0	1	0.2159	.	.	0.3486
SMALL INTESTINE	HEMANGIOSARCOMA [M].	0	0	1	0	0.4237	.	0.3426	.
	LYMPHOMA [M], metastatic	5	1	1	2	0.5475	0.5830	0.6489	0.4501
SPINAL CORD	LYMPHOMA [M], metastatic	0	0	0	1	0.2159	.	.	0.3486
SPLEEN	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Com C N=100	1 mg Low N=50	5 mg Med N=50	15 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
SPLEEN	HEMANGIOSARCOMA [M].	2	1	1	1	0.4467	0.6768	0.2613	0.2779
	LYMPHOMA [M], metastatic	12	8	6	4	0.8423	0.2613	0.4074	0.6754
	MAST CELL TUMOR [M], meta	0	0	1	0	0.4205	.	0.3364	.
STOMACH	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	LYMPHOMA [M], metastatic	6	4	4	3	0.5636	0.3619	0.4656	0.3683
	PAPILLARY ADENOMA [B].	1	0	0	0	0.5932	0.3010	0.3333	0.3455
TESTES	HEMANGIOMA [B].	0	1	0	0	0.4181	0.3107	.	.
	INTERSTITIAL CELL ADENOMA	0	0	1	1	0.1345	.	0.3364	0.3486
	LYMPHOMA [M], metastatic	2	1	1	0	0.7623	0.6725	0.2654	0.5736
	SERTOLI CELL TUMOR [B].	1	0	0	1	0.3862	0.3039	0.3364	0.5778
THYMUS	LYMPHOMA [M], metastatic	11	7	2	0	0.9994	0.3076	0.8715	0.9906
THYROID GLAND	LYMPHOMA [M], metastatic	2	1	1	0	0.7584	0.6585	0.7037	0.5695
TRACHEA	LYMPHOMA [M], metastatic	2	0	2	0	0.6867	0.5134	0.4184	0.5736
URETERS	LYMPHOMA [M], metastatic	6	4	3	4	0.4035	0.3798	0.3533	0.4656
URINARY BLADDER	ACINAR CELL ADENOCARCINOM	1	0	0	0	0.5966	0.3039	0.3364	0.3486
	LYMPHOMA [M], metastatic	8	5	3	4	0.5740	0.3598	0.5232	0.3726
	TRANSITIONAL CELL PAPILLO	1	0	0	0	0.5966	0.3039	0.3364	0.3486

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Com C N=100	1 mg Low N=50	5 mg Med N=50	15 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
ABDOMINAL CAVIT	GRANULOSA CELL TUMOR [M],	0	1	0	0	0.3810	0.3365	.	.
	LYMPHOMA [M], metastatic	0	0	2	0	0.3883	.	0.0982	.
ADRENAL GLANDS	LEIOMYOSARCOMA [M], metas	0	0	1	0	0.3810	.	0.3100	.
	LYMPHOMA [M], metastatic	17	11	8	9	0.5182	0.2921	0.4050	0.5256
	PHEOCHROMOCYTOMA [B].	0	1	0	0	0.3810	0.3365	.	.
	SUBCAPSULAR CELL ADENOMA	3	0	1	1	0.4853	0.7123	0.3653	0.4016
	SUBCAPSULAR CELL CARCINOM	1	0	0	0	0.5893	0.3365	0.3100	0.3235
AORTA	GRANULOSA CELL TUMOR [M],	0	0	1	0	0.3810	.	0.3100	.
	LEIOMYOSARCOMA [M], metas	0	0	1	0	0.3810	.	0.3100	.
	LYMPHOMA [M], metastatic	10	9	8	7	0.3609	0.1308	0.1780	0.3254
BONE	FIBROSARCOMA [M].	2	0	0	0	0.8328	0.5620	0.5261	0.5446
	LYMPHOMA [M], metastatic	1	0	0	0	0.5858	0.3333	0.3069	0.3204
	OSTEOSARCOMA [M].	1	0	0	0	0.5893	0.3365	0.3100	0.3235
BONE MARROW	LYMPHOMA [M], metastatic	8	10	4	6	0.4277	0.0349	0.5595	0.2822
BRAIN	BRONCHIOLO-ALVEOLAR CARCI	1	0	0	0	0.5893	0.3365	0.3100	0.3235
	LYMPHOMA [M], metastatic	4	4	2	4	0.2309	0.2585	0.6084	0.2585
CLITORAL GLANDS	LYMPHOMA [M], metastatic	1	0	0	1	0.3628	0.3365	0.3100	0.5534
ESOPHAGUS	LYMPHOMA [M], metastatic	1	1	1	1	0.3337	0.5620	0.5354	0.5534
EYES	LEIOMYOSARCOMA [M], metas	0	0	1	0	0.3810	.	0.3100	.
	LYMPHOMA [M], metastatic	7	8	5	5	0.4418	0.0809	0.3260	0.3636
GALLBLADDER	LYMPHOMA [M], metastatic	6	5	1	4	0.4242	0.3136	0.7079	0.4407
HARDERIAN GLAND	ADENOMA [B].	4	0	1	0	0.8869	0.8120	0.4948	0.7966
	LYMPHOMA [M], metastatic	10	7	5	6	0.4373	0.3254	0.5525	0.4641
HEART	LEIOMYOSARCOMA [M], metas	1	0	1	0	0.4657	0.3365	0.5261	0.3235
	LYMPHOMA [M], metastatic	16	10	4	7	0.6824	0.3153	0.7965	0.4715
KIDNEYS	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1964	.	.	0.3235
	LEIOMYOSARCOMA [M], metas	1	0	1	0	0.4657	0.3365	0.5261	0.3235
	LYMPHOMA [M], metastatic	20	14	9	11	0.5234	0.1854	0.4142	0.4817
LARGE INTESTINE	LYMPHOMA [M], metastatic	3	3	3	3	0.2482	0.3291	0.2904	0.3163
LARYNX	LYMPHOMA [M], metastatic	6	5	2	4	0.4044	0.2806	0.4869	0.4229
LIVER	CARCINOMA [M], metastatic	0	0	1	0	0.3810	.	0.3100	.
	GRANULOSA CELL TUMOR [M],	0	0	1	0	0.3810	.	0.3100	.
	HEMANGIOMA [B].	4	0	0	1	0.6589	0.8120	0.7795	0.5226
	HEPATOCELLULAR ADENOMA [B	0	0	0	1	0.1964	.	.	0.3235
	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1964	.	.	0.3235

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Mice

Organ Name	Tumor Name	0 mg Com C N=100	1 mg Low N=50	5 mg Med N=50	15 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
LIVER	LEIOMYOSARCOMA [M], metas	1	0	2	0	0.5094	0.3365	0.2351	0.3235
	LYMPHOMA [M], metastatic	22	14	8	9	0.8190	0.3052	0.6817	0.6552
	OSTEOSARCOMA [M], metasta	1	0	0	0	0.5893	0.3365	0.3100	0.3235
LUNGS	ADENOCARCINOMA [M], metas	0	0	1	0	0.3846	.	0.3168	.
	BRONCHIOLO-ALVEOLAR ADENO	13	6	7	10	0.0882	0.4567	0.4725	0.1591
	BRONCHIOLO-ALVEOLAR CARCI	4	1	4	0	0.8213	0.5488	0.2178	0.7966
	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1964	.	.	0.3235
	LEIOMYOSARCOMA [M], metas	1	0	1	0	0.4657	0.3365	0.5261	0.3235
	LYMPHOMA [M], metastatic	21	15	10	9	0.7429	0.1442	0.5470	0.5223
	OSTEOSARCOMA [M], metasta	1	0	0	0	0.5893	0.3365	0.3100	0.3235
	SARCOMA [M].	0	0	1	0	0.3846	.	0.3168	.
	BRONCH-ALVEOLAR ADEN+CARC	17	7	10	10	0.2168	0.6198	0.3698	0.3698
LYMPH NODES	BRONCHIOLO-ALVEOLAR CARCI	1	0	0	0	0.5893	0.3365	0.3100	0.3235
	LEIOMYOSARCOMA [M], metas	0	0	1	0	0.3810	.	0.3100	.
	LYMPHOMA [M], metastatic	10	7	8	9	0.1246	0.3362	0.1688	0.1523
MAMMARY GLANDS	ADENOCARCINOMA [M].	0	1	1	0	0.3883	0.3365	0.3168	.
	LYMPHOMA [M], metastatic	11	9	5	6	0.5550	0.1847	0.3827	0.5283
MANDIBULAR LYMP	LYMPHOMA [M], metastatic	20	13	9	10	0.5752	0.2683	0.4142	0.5691
MESENTERIC LYMP	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1964	.	.	0.3235
	LEIOMYOSARCOMA [M], metas	0	0	1	0	0.3810	.	0.3100	.
	LYMPHOMA [M], metastatic	21	14	10	11	0.5286	0.2279	0.5626	0.5085
	OSTEOSARCOMA [M], metasta	1	0	0	0	0.5893	0.3365	0.3100	0.3235
NERVE-PERIPHERA	LYMPHOMA [M], metastatic	0	2	0	1	0.2877	0.1111	.	0.3301
OVARIES	CYSTADENOMA [B].	0	1	1	0	0.3884	0.3365	0.3100	.
	GRANULOSA CELL TUMOR [M].	1	3	1	0	0.7783	0.1096	0.5261	0.3235
	HEMANGIOMA [B].	1	1	0	0	0.6606	0.5620	0.3100	0.3235
	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1964	.	.	0.3235
	LEIOMYOSARCOMA [M], metas	0	0	2	0	0.3883	.	0.0982	.
	LUTEOMA [B].	1	0	0	0	0.5893	0.3365	0.3100	0.3235
	LYMPHOMA [M], metastatic	15	8	7	9	0.3428	0.5127	0.4197	0.4116
	TUBULOSTROMAL ADENOMA [B]	2	1	0	0	0.8267	0.2614	0.5261	0.5446
PANCREAS	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1964	.	.	0.3235
	LYMPHOMA [M], metastatic	11	10	7	7	0.4491	0.1339	0.3486	0.3970
PITUITARY GLAND	LEIOMYOSARCOMA [M], metas	0	0	1	0	0.3810	.	0.3100	.
	LYMPHOMA [M], metastatic	2	2	0	1	0.5473	0.4187	0.5218	0.6994
	PARS DISTALIS ADENOMA [B]	0	1	0	0	0.3810	0.3365	.	.
PRIMARY SITE UN	HISTIOCYTIC SARCOMA [M].	0	0	0	1	0.1964	.	.	0.3235
	LYMPHOMA [M].	24	17	14	13	0.5113	0.1441	0.2925	0.4686
SALIVARY GLANDS	LYMPHOMA [M], metastatic	16	8	5	9	0.3762	0.5768	0.6793	0.4478

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Mice

Organ Name	Tumor Name	0 mg Com C N=100	1 mg Low N=50	5 mg Med N=50	15 mg High N=50	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
SKELETAL MUSCLE	LYMPHOMA [M], metastatic	7	8	5	4	0.5682	0.0809	0.3260	0.5134
SKIN	FIBROSARCOMA [M].	5	2	0	1	0.8203	0.4293	0.8472	0.6290
	LYMPHOMA [M], metastatic	9	2	6	2	0.7297	0.7592	0.3444	0.7446
SMALL INTESTINE	ADENOMA [B].	1	0	0	0	0.5893	0.3365	0.3100	0.3235
	LYMPHOMA [M], metastatic	7	8	7	4	0.5734	0.0852	0.1271	0.5415
SPINAL CORD	LYMPHOMA [M], metastatic	1	1	0	1	0.3916	0.5620	0.3100	0.5534
SPLEEN	LYMPHOMA [M], metastatic	21	14	11	12	0.4378	0.2554	0.4411	0.4261
STOMACH	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1964	.	.	0.3235
	LEIOMYOSARCOMA [M], metas	0	0	1	0	0.3810	.	0.3100	.
	LYMPHOMA [M], metastatic	10	8	6	7	0.3190	0.2222	0.4064	0.3146
THYMUS	LYMPHOMA [M], metastatic	18	11	9	9	0.5233	0.3481	0.4964	0.5579
THYROID GLAND	LYMPHOMA [M], metastatic	4	2	1	4	0.1395	0.6489	0.4961	0.2453
TRACHEA	LYMPHOMA [M], metastatic	3	3	3	1	0.6399	0.3291	0.2904	0.3958
URETERS	LEIOMYOSARCOMA [M], metas	0	0	1	0	0.3810	.	0.3100	.
	LYMPHOMA [M], metastatic	11	8	7	6	0.5083	0.2731	0.3499	0.5398
URINARY BLADDER	FIBROMA [B].	1	0	0	0	0.5893	0.3365	0.3100	0.3235
	HEMANGIOMA [B].	0	0	1	0	0.3810	.	0.3100	.
	LEIOMYOSARCOMA [M], metas	0	0	1	0	0.3810	.	0.3100	.
	LYMPHOMA [M], metastatic	13	10	5	6	0.6977	0.1998	0.5274	0.4567
UTERUS	ADENOCARCINOMA [M].	1	0	0	0	0.5893	0.3365	0.3100	0.3235
	CARCINOMA [M].	0	0	1	0	0.3810	.	0.3100	.
	ENDOMETRIAL STROMAL POLYP	2	1	0	0	0.8238	0.7080	0.5218	0.5403
	FIBROMA [B].	0	0	1	0	0.3846	.	0.3168	.
	GRANULAR CELL TUMOR [M].	1	0	0	0	0.5893	0.3365	0.3100	0.3235
	GRANULOSA CELL TUMOR [M],	0	0	1	0	0.3810	.	0.3100	.
	HEMANGIOMA [B].	2	1	1	1	0.4756	0.2614	0.6760	0.6949
	HISTIOCYTIC SARCOMA [M],	0	0	0	1	0.1964	.	.	0.3235
	LEIOMYOMA [B].	7	3	4	3	0.5281	0.4407	0.4518	0.4407
	LEIOMYOSARCOMA [M].	2	1	2	1	0.4500	0.2614	0.3776	0.7037
	LYMPHOMA [M], metastatic	13	9	6	7	0.4866	0.2861	0.3951	0.4891
VAGINA	FIBROSARCOMA [M].	1	0	0	0	0.5893	0.3365	0.3100	0.3235
	LYMPHOMA [M], metastatic	11	6	3	4	0.7382	0.4936	0.6954	0.5754

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

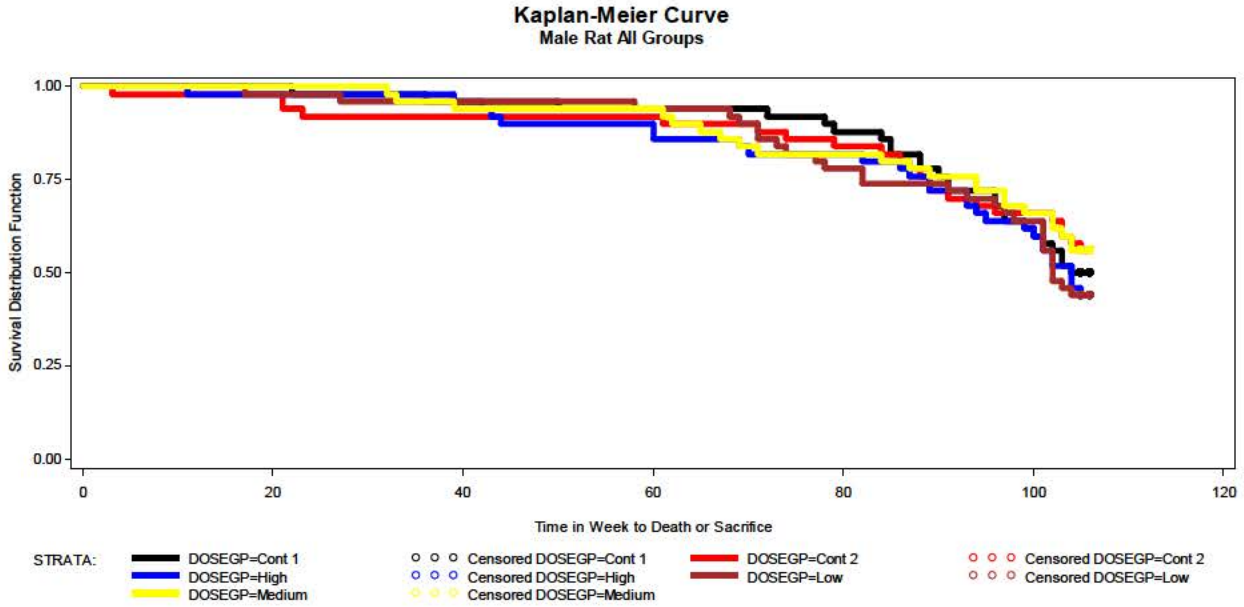


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

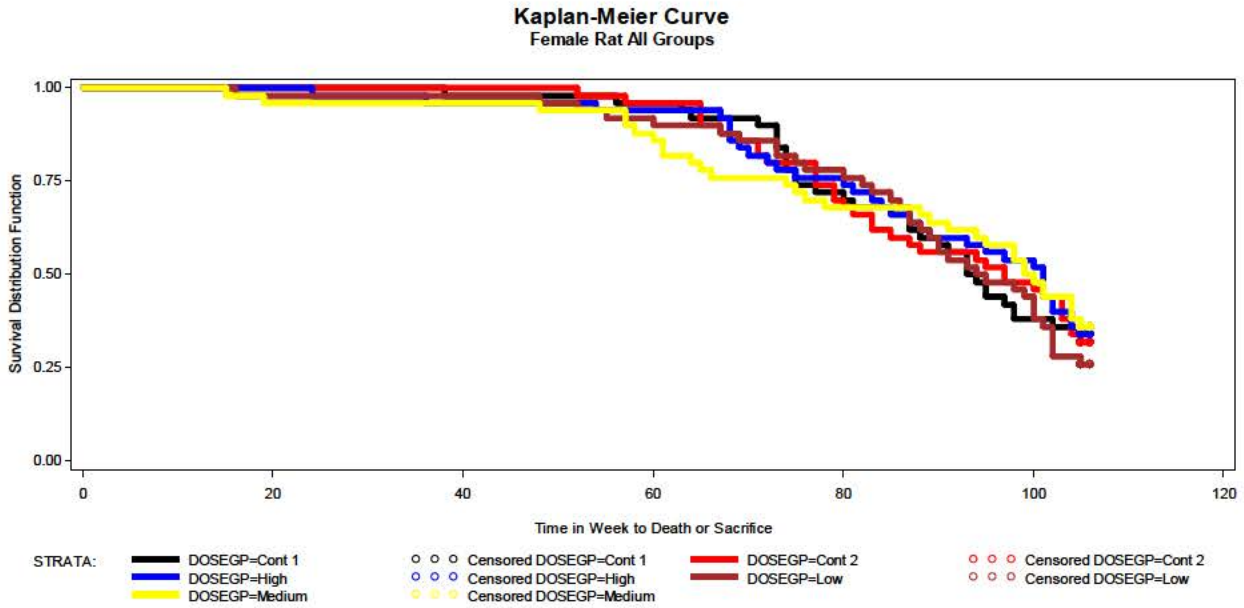


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

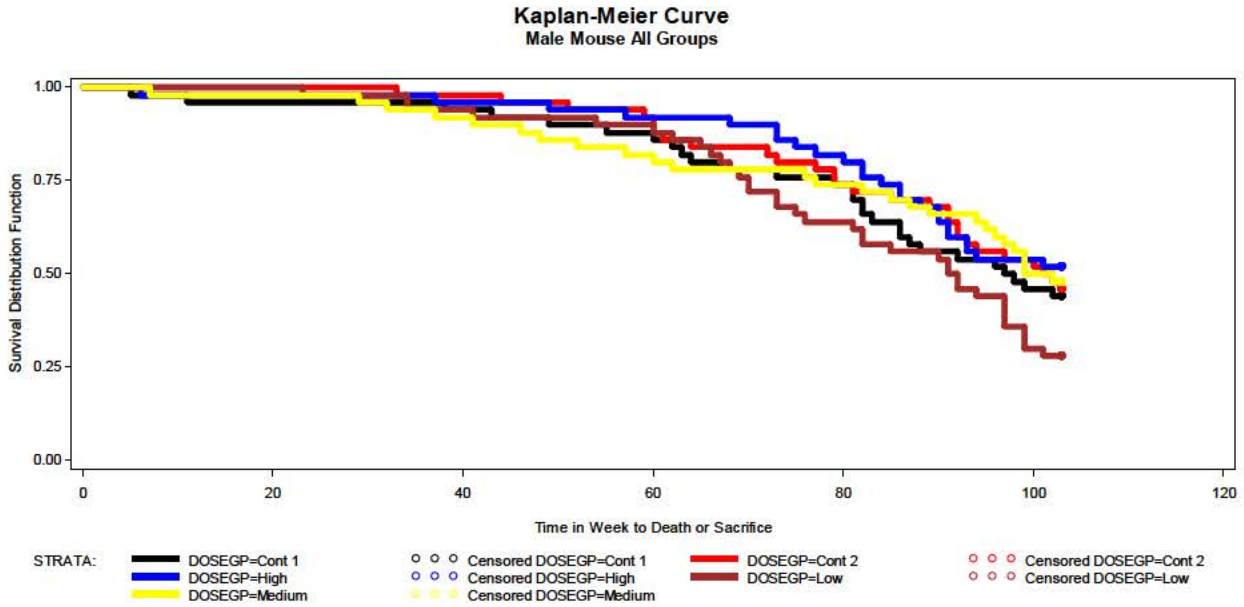
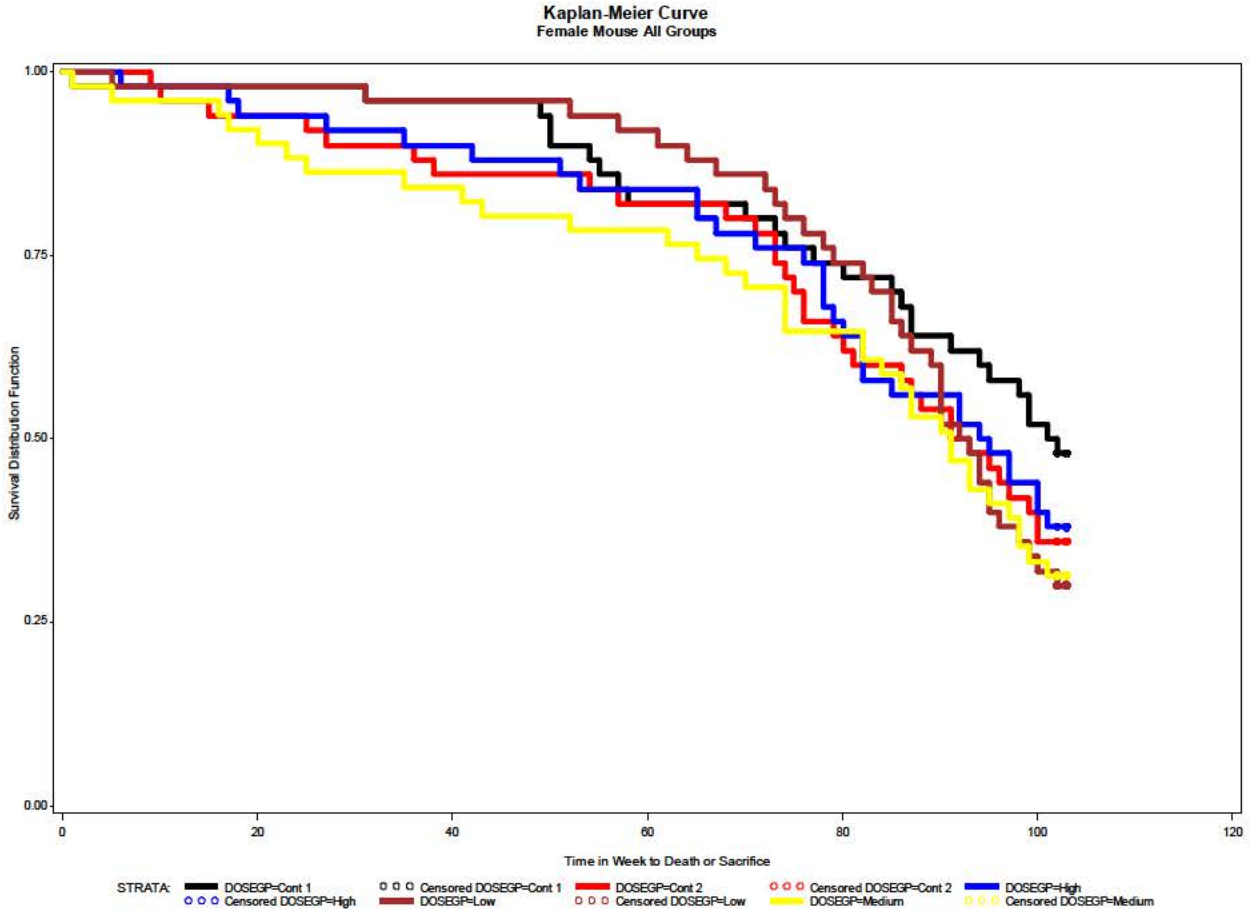


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



6. References

1. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J.Wahrendorf, "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva,* 311-426, 1980.
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7. Guidance for Industry. Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Statues of Pharmaceuticals (Draft Guidance). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), May 2001.

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/s/

MOHAMMAD A RAHMAN
10/21/2013

KARL K LIN
10/21/2013
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204886 **Applicant:** Merck **Stamp Date:** May 10, 2013

Drug Name: Vorapaxar **NDA/BLA Type:** standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	×			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	×			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	×			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	×			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____ Yes**____**

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	×			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	×			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	×			Needs help to identify patient data for interim analysis (See request below).
Appropriate references for novel statistical methodology (if present) are included.			×	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			×	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	×			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

The following requests for both Studies 4736 and 4737 are to be conveyed to sponsor:

- Please provide the detailed algorithm for capturing patient-level data analyzed in the interim analysis from your submitted data sets.
- Please provide detailed interim analysis results including the event rates and hazard ratio in comparing study drug with placebo for the primary endpoint and also for each component endpoint. Please also provide the same type of analysis results for the patients who had history of strokes and those who did not have history of strokes.
- For each component of the primary endpoint, please provide analysis results for time to each component event using the same method for the primary endpoint.
- For Study 4737, we noted that about 7,000 additional patients were randomized and analyzed beyond the originally planned sample size. Please provide your explanation with any document for why the sample size was increased.

Reviewing Statistician Date

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YEH FONG CHEN
06/17/2013

HSIEN MING J HUNG
06/17/2013