

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-291**

**STATISTICAL REVIEW(S)**



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

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/Serial Number:** 22-291/0000

**Drug Name:** Promacta (eltrombopag olamine )

**Indication(s):** Short-term treatment of Idiopathic thrombocytopenic purpura (ITP)

**Applicant:** GlaxoSmithKline

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

The data from two randomized, placebo-controlled, 6-week clinical trials submitted in this New Drug Application (NDA), support applicant's claim of short-term use of eltrombopag for the treatment of previously-treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts. However, the interaction between treatment and each of randomization strata were not statistically significant. Patients responded regardless of splenectomy status, use of ITP medication, baseline platelet count  $\leq 15$  Gi/L. The data on bleeding events in the submission are based on a scale whose clinical interpretation is unclear. In addition, the evidence from the submitted data to support the applicant's claim of using eltrombopag to reduce or prevent bleeding is not statistically robust. This reviewer notes that the data from this submission is limited to short term use. Another study is ongoing to investigate the long term use of eltrombopag in ITP patients. Data from that study was not available at the time of review of this application. This drug was discussed in an advisory committee meeting on May 30, 2008. The overall recommendation from that committee was as follows: during the clinical development of eltrombopag, the "short-term" indication may be reasonable in specified circumstance. However, the sponsor should realize the critical need to evaluate eltrombopag's longer term safety and efficacy data given the likelihood of chronic use regardless if data are only available for short-term use.

### 1.2 Brief Overview of Clinical Studies

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by autoantibody-induced platelet destruction and reduced platelet production, leading to chronically low peripheral blood platelet count ( $< 150$  Gi/L). Persistently low platelet counts of  $< 30$  Gi/L are associated with an increased incidence of spontaneous and induced bleeding, such as bruising, mucosal bleeding and intra-cranial hemorrhage.

Eltrombopag olamine is an orally bioavailable, small molecule thrombopoietin receptor agonist that may be beneficial for subjects with medical disorders associated with thrombocytopenia. This current submission, NDA 22-291 is for the indication of ITP.

One Phase II and one Phase III studies were submitted to support the use of eltrombopag for subjects with medical disorders associated with thrombocytopenia. The Phase II study (TRA 100773A, referred to as Study A) was a double-blind, randomized, placebo-controlled, parallel group study to investigate the efficacy, safety, tolerability,

pharmacokinetics and pharmacodynamics of eltrombopag orally administered at 30, 50 and 75 mg once-daily for 6 weeks to subjects with refractory, chronic ITP. The primary efficacy endpoint was the proportion of subjects with a platelet count of  $\geq 50$  Gi/L after up to 42 days of dosing (compared to a baseline count of  $< 30$  Gi/L). Study A was initiated on 02 February 2005 and ended on 26 August 2006.

The Phase III study (TRA 100773B, referred to as Study B) was a double-blind, randomized, placebo-controlled, parallel group trial. oral administration of eltrombopag 50mg (with dose increase permitted to 75 mg) or matching placebo in subjects with chronic ITP who had either failed or relapsed after at least one prior ITP therapy and had baseline platelet counts  $< 30 \times 10^9$  Gi/L. The primary efficacy endpoint was the same as that of Study A; the proportion of subjects with a platelet count of  $\geq 50$  Gi/L after up to 42 days of dosing (compared to a baseline count of  $< 30$  Gi/L). Study B was initiated on 06 February 2006 and ended on 31 January 2007.

### 1.3 Statistical Issues and Findings

#### Statistical Issues

Several issues arose from the review of this application.

1. One of the conclusions the applicant made was that use of eltrombopag in the treatment of ITP patients decreases the incidence and severity of bleeding in subjects with relapsed or refractory chronic ITP. This conclusion was based on the logistic regression analysis of the bleeding events that the applicant conducted, adjusting for the covariates of use of concomitant medication at randomization, splenectomy status, and baseline platelet count. However, one should note that bleeding events are time dependent with multiple observations per subject. Therefore, it is more appropriate to use survival analysis models to analyze time-to-event data in the multiple event setting. In this review, the Andersen-Gill (AG) formulation of the proportional hazards model as a counting process is used for the assessment of benefit in terms of bleeding. The Schoefeld residuals are used to test the basic assumptions of a Cox model. The findings from the analysis are discussed in details in the Findings section.
2. The applicant did not carry out the subgroup analysis for subjects enrolled in the US sites. It is very important to estimate short-term response rate using eltrombopag in the treatment of US ITP patients. This issue is discussed in detail in the Findings section.
3. The applicant reported that the variables of concomitant medication, splenectomy status and baseline platelet count did not have impact on the treatment efficacy results when comparing eltrobopag group to placebo. This review re-analyzed the data by including interactions between these three variables in the logistic regression model. No significant interaction effects between these three stratification variables and treatment were found. Intuitively, these three variables should have certain level of

impacts on the primary efficacy results. It is essential to have prospective, well-designed, controlled trials to investigate this issue.

4. The applicant concluded that the potential clinical benefit of eltrombopag in this patient population is a significant unmet medical need. Eltrombopag 50 mg (with increases up to 75 mg) once daily for up to 6 weeks of treatment was found to be a well tolerated and effective treatment option for ITP. However, based on Study B's data, 46% patients had received 75 mg dose treatment after the Day 22 visit treatment period. Study B was not designed to investigate the dose titration from 50 mg to 75 mg dosing regimen. It is unknown why it was permitted to increase dose to 75 mg for these 46% of the subjects. One should note that the issue of dose-titration for patients who respond slowly as well as for patients who respond quickly has not been addressed in this NDA submission.
5. Figure 1 shows that the platelet counts of eltrombopag patients were decreasing after discontinuation of the treatment over time. The mean platelet counts of eltrombopag patients became numerically lower than that of placebo patients at the last two follow-up visits. More data with longer follow-up time is necessary for investigating the safety of short-term use of eltrombopag.

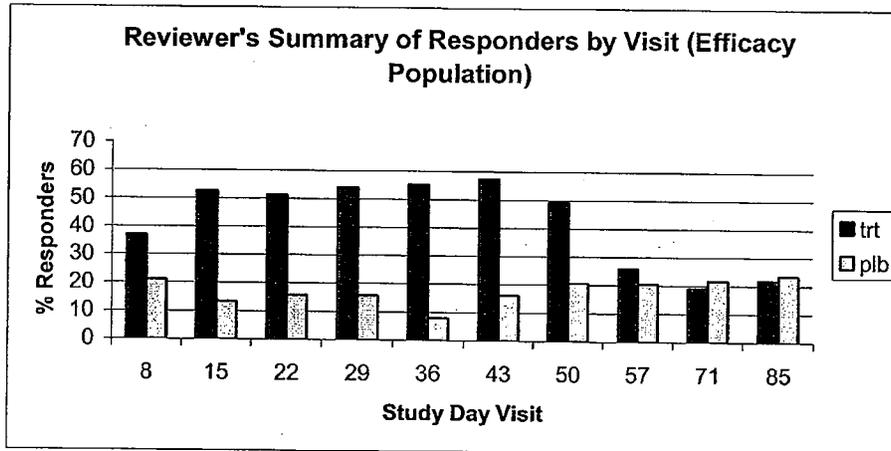


Figure 1 Reviewer's summary of percentages of responders by visit (efficacy population) for TRA 100773B

### Finding

1. The applicant conducted logistic regression analysis of bleeding events, adjusting for the covariates of use of concomitant medication at randomization, splenectomy status and baseline platelet count. The odds of any bleeding in the eltrombopag group were significantly lower than that of placebo group at Day 43. The odds ratio was 0.3 with 95% confidence interval of [0.1, 0.9], and the p-value was 0.03. However, one should note that bleeding events are time dependent with multiple observations per subject. Therefore, it is more appropriate to use survival

analysis models to analyze time-to-event data in the multiple event setting than a logistic regression model.

This reviewer performed this time-to event analysis using the Andersen-Gill model formulation of the proportional hazards model as a counting process in the multiple-event setting. In the Andersen-Gill model (AG model), each subject is represented as a set of rows with time intervals of (entry time, first event], (first event, second event]... (m<sup>th</sup> event, last follow-up]. A subject with zero event would have a single observation, one with one event would have one or two observations (depending on whether there was additional follow-up experience after the first event), and etc. Depending on the time scale, the first observation may or may not begin at zero. This reviewer used R to test the proportional hazard assumption of each covariate by examining the residual plot vs. time (Please see Appendices for discussion). For this purpose, the data generated using SAS is exported to text format which is read by R. The results from AG model are summarized in Tables 1-6 and Figures 1-3.

**Study A:**

The following table shows the results of regression using AG model adjusted for ITP medication use at randomization, splenectomy status (Y/N) and baseline platelet count  $\leq 15$  Gi/L for placebo and eltrombopag 50 arms of study A.

**Table 1 Reviewer's summary of multiple bleeding event analysis during 6 weeks visit (Study A)**

	Exp(coef)	Robust se	P-value
TRTCD	1.928	0.314	0.121
Baseline Platelet	0.821	0.306	0.3800
ITP medication use	0.350	0.276	0.2800
Splenctomy	0.305	0.219	0.0040

P-value of 0.121 suggests that, in Study A, there is no statistically significant difference between 2 groups, placebo and eltrombopag 50 in terms of an effect on bleeding events.

The following table and graphs show the result for testing model assumptions for study A. In this table, p-value great than 0.05 suggests that the use of roportional hazard model is appropriate.

**Table 2 Multiple bleeding event analysis for model assumption (Study A)**

	Rho	chisq	P-value
TRTCD	0.2291	1.495	0.221
Baseline platelet	0.0212	0.014	0.906
ITP medication use	0.0987	0.340	0.560
Splenctomy	0.0705	0.145	0.703
Global		2.128	0.712

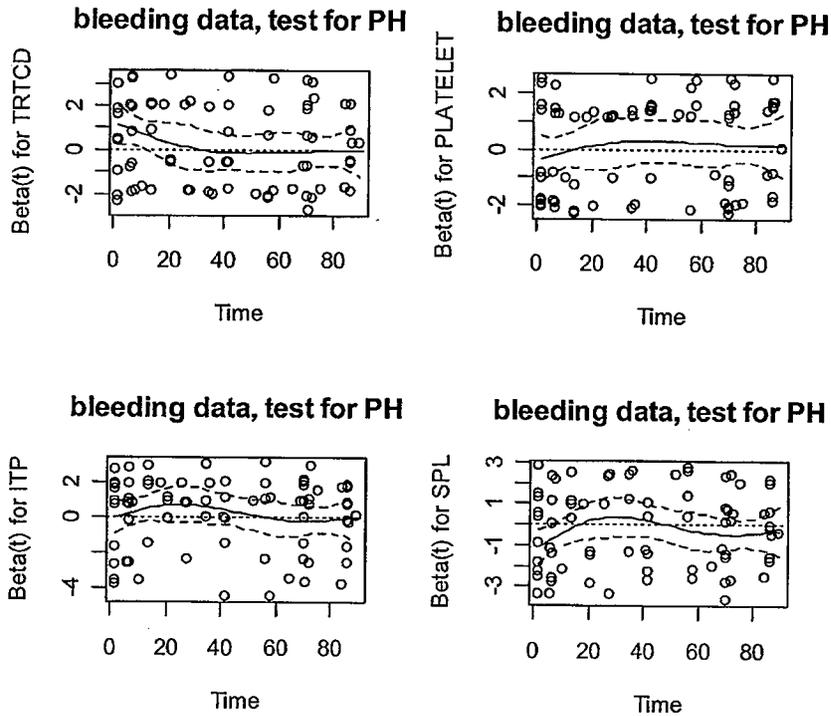


Figure 2 Test assumption of proportion hazard 6 weeks treatment (Study A)

**Study B**

The following table shows the results of regression using AG model adjusted for ITP medication use at randomization, splenectomy status (Y/N) and baseline platelet count  $\leq 15$  Gi/L for study B (Table 3). Note that this study had only two arms, placebo and eltrombopag 50.

Table 3 Reviewer's summary of multiple bleeding event analysis during 6 weeks visit (Study B)

	Exp(coef)	Robust se	P-value
TRTCD	0.792	0.137	0.088
Baseline Platelet	0.865	0.190	0.300
ITP medication use	0.187	0.139	0.230
Splenectomy	1.069	0.139	0.630

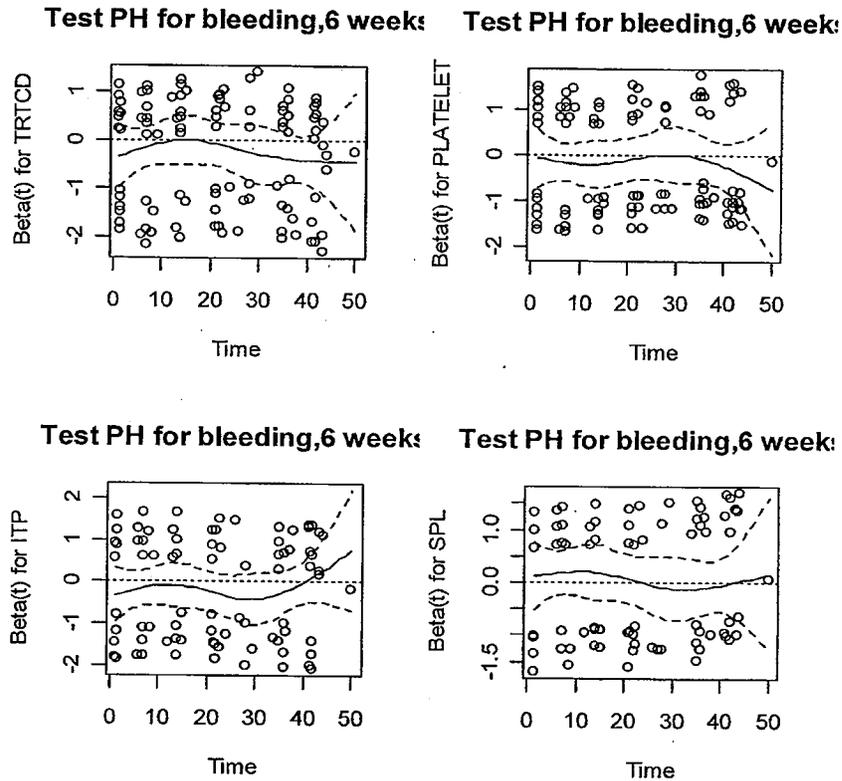
The P-value is 0.088 suggest that, in Study B there is no statistically significant difference between 2 groups, placebo and eltrombopag 50 in terms of an effect on bleeding events.

The following table and graphs show the result for testing model assumptions for study A. In this table, p-value greater than 0.05 suggests that the use of proportional

hazard model is appropriate. The figure shows the residual plot vs. time. The straight lines in the graph suggest that the assumption of proportional hazards is valid.

**Table 4 Multiple bleeding event analysis during 6 weeks for model assumption adjust covariate (Study B)**

	Rho	chisq	P-value
TRTCD	-0.0671	0.308	0.579
Baseline platelet	-0.0439	0.137	0.711
ITP medication use	0.0698	0.377	0.539
Splenctomy	-0.0752	0.378	0.539
Global	NA	1.005	0.909



**Figure 3 Test assumption of proportional hazard adjusting covariate (Study B)**

2. For the analysis of ITP Bleeding Scale data, the bleeding severity was assessed in each of the following ten anatomical locations: Skin: petechiae, Skin: ecchymosis, Oral, Epistaxis, Ocular, Gastrointestinal, Genitourinary, Gynecological, Pulmonary

and Intracerebral Hemorrhage. The results with an ITP Bleeding Scale Grade 1-2 suggested that the decreases from baseline were greater for eltrombopag in the skin ecchymosis and gynecologic categories and similar between eltrombopag and placebo in all other categories (Table 7).

**Table 4 Summary of ITP Bleeding Score Assessment of Subjects**

Assesments	Placebo N=38		EltrombopagN=74	
	Day1	Day43	Day1	Day43
Skin, petechiae,n	37	30	73	51
Grade 0	17(46)	21(70)	48(66)	42(82)
Grade 1	16(43)	8 (27)	20(27)	7 (14)
Grade 2	3 (8)	1 (3)	5 (7)	2 (4)
Skin,ecchymosis,n	37	30	73	51
Grade 0	18(49)	14(47)	29(40)	33(65)
Grade 1	13(35)	12(40)	35 (48)	14 (27)
Grade 2	5 (14)	4 (13)	9 (12)	4 (8)
Oral n	37	30	73	51
Grade 0	28(76)	27(90)	63(86)	47 (92)
Grade 1	7 (19)	3 (10)	9 (12)	4 (8)
Grade 2	1 (3)	0	1 (1)	0
Epistaxis, n	37	30	73	51
Grade 0	32 (86)	30(100)	63 (86)	49(96)
Grade 1	4 (11)	0	9 (12)	1 (2)
Grade 2	0	0	1 (1)	1 (2)
Ocular ,n	37	30	73	51
Grade 0	36(97)	30(100)	73(100)	51(100)
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Gastrointestinal, n	37	30	73	51
Grade 0	36(97)	30(100)	71 (97)	50 (98)
Grade 1	0	0	2 (3)	1 (2)
Grade 2	0	0	0	0
Genitourinary, n	37	30	73	51
Grade 0	34(92)	29 (97)	69 (95)	51
Grade 1	2 (5)	1 (3)	3 (4)	(100) 0
Grade 2	0	0	(1)	0
Gynecologic, n	26	23	41	24
Grade 0	8 (31)	7 (30)	11 (27)	10 (42)
Grade 1	0	0	2 (5)	1 (4)
Grade 2	1 (4)	0	5 (12)	0
Pulmonary, n	37	30	73	51
Grade 0	36(97)	30(100)	71 (97)	51(100)
Grade 1	0	0	2 (3)	0
Grade 2	0	0	0	0
Intracerebralhemorrhage,n	37	30	73	51
Grade 0	36(97)	30(100)	73(100)	51(100)
Grade 1	0	0	0	0

The following graphs show the summary of percentage of ITP Bleed Scale 0-2 for skin ecchymosis.

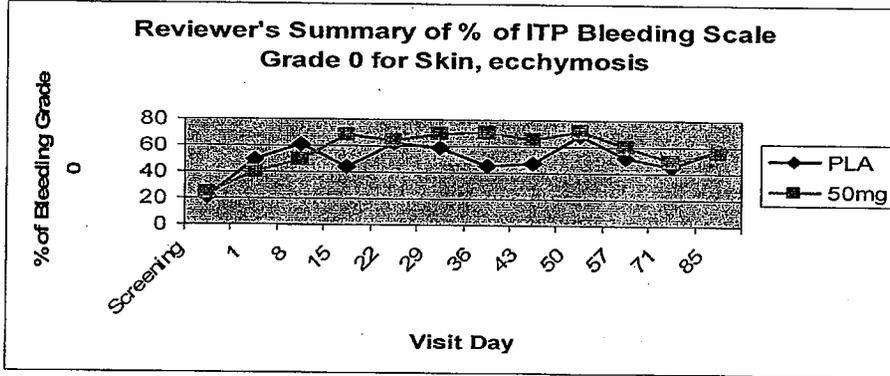


Figure 4 Reviewer's summary of % of ITP bleeding scale grade 0 for skin, ecchymosis.

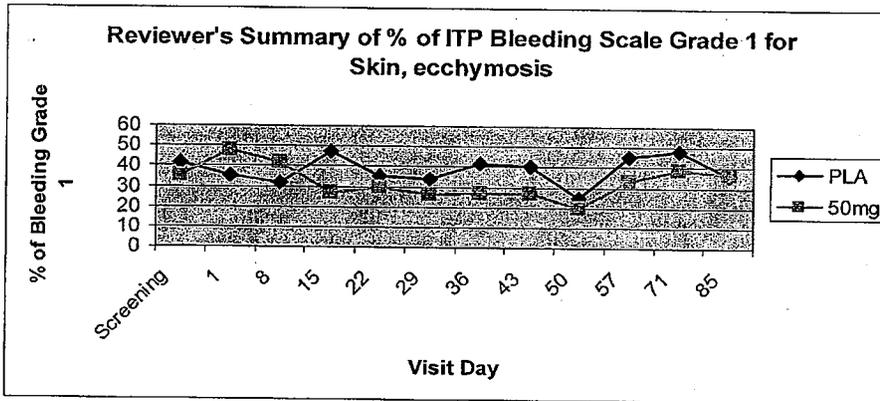


Figure 5 Reviewer's summary of % of ITP bleeding scale grade 1 for skin, ecchymosis

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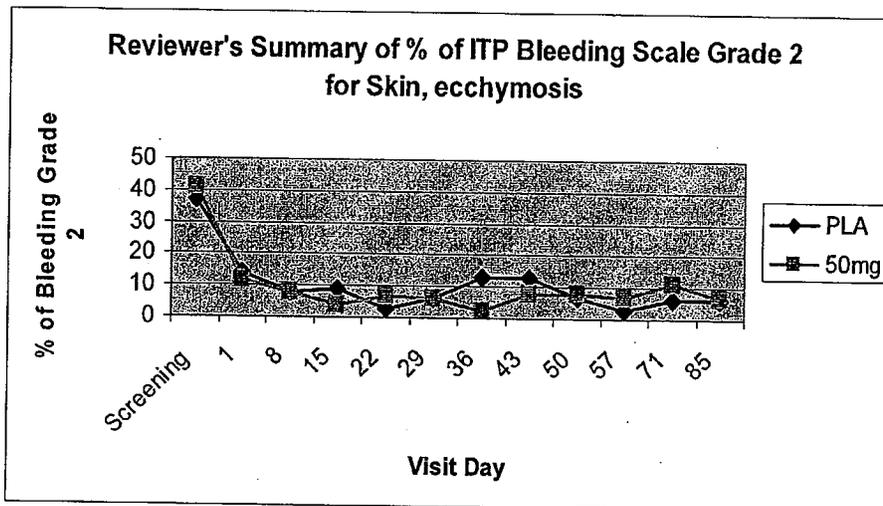


Figure 6 Reviewer's summary of % of ITP bleeding scale grade 2 for skin, ecchymosis

3. For the primary efficacy analysis in the subgroup subjects enrolled in the US sites at Day 43 visit, there were 0/6 (0%) responders in the placebo group and 9/12 (75%) (Table 8) responders in the eltrombopag group. The Fisher's Exact test shows a significantly greater proportion of responders in the eltrombopag group compared to placebo ( $p < 0.01$ ).

Table 5 Reviewer's summary of % responders for us site by visit for study B (Efficacy Population)

Visit Day	Treatment Group	
	Eltrombopag N=12	Placebo N=6
Day 8	41.7 (5/12)	0 (0/6)
Day 15	63.6 (7/11)	0 (0/5)
Day 22	75 (9/12)	0 (0/6)
Day 29	75 (9/12)	0 (0/6)
Day 36	75 (9/12)	0 (0/6)
Day 43	75 (9/12)	0 (0/6)

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## 2. INTRODUCTION

### 2.1 Overview

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by autoantibody-induced platelet destruction and reduced platelet production, leading to chronically low peripheral blood platelet count (<150 Gi/L). Persistently low platelet counts of <30 Gi/L are associated with an increased incidence of spontaneous and induced bleeding, such as bruising, mucosal bleeding and intra-cranial hemorrhage.

A global, randomized, double-blind, placebo-controlled, dose-ranging (eltrombopag 30mg, 50mg, and 75mg) Phase II trial (TRA100773A) was performed in 118 adults with chronic ITP and platelets<30Gi/L. A dose dependent increase in the proportion of responders was observed. The odds-ratio of treatment response to placebo was statistically significant in the 50mg and 75mg arms (p<0.001). A decreased incidence of on-therapy bleeding was observed relative to baseline in subjects who received eltrombopag.

A randomized, double-blind, Phase III trial (TRA 100773B) was designed to assess the efficacy, safety, and tolerability of eltrombopag 50 mg (with dose increases up to 75mg permitted) compared to placebo when administered for up to 6 weeks in adults with chronic ITP and platelet counts <30Gi/L. The up-to-6-week treatment period was chosen to allow 1-2 weeks for platelet count elevation followed by continued platelet elevation for 3-4 weeks, thereby meeting or exceeding the duration of platelet count elevation observed with currently available short-term treatments (intravenous immunoglobulin) with the convenience of oral administration. The study population was comprised of subjects who were refractory to, or had relapsed following standard treatment options, consistent with an ITP patient population with the greatest unmet medical need. The objective of the study was to confirm the efficacy of short-term administration of eltrombopag observed in TRA100773A.

### 2.2 Data Sources

The applicant submitted the results of Phase II and Phase III studies to support the use of eltrombopag for subjects with medical disorders associated with thrombocytopenia. Data sets for the studies were submitted electronically and were used in the review of these studies. The locations of these data sets are as follows:

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All submitted data sets were found to be adequately documented.

### 3. STATISTICAL EVALUATION

This submission contains two pivotal studies. Protocol TRA 100773 used a double-blind, randomized, placebo-controlled adaptive sequential design to allow for two separate and independent studies (TRA 100773A, phase II dose finding and TRA 100773B, phase III) to investigate the efficacy, safety, tolerability, of eltrombopag administered for up to 6 weeks as treatment for subject with chronic ITP.

#### 3.1 Evaluation of Efficacy

##### 3.1.1 Study TRA100773A

###### Study Design

In TRA 100773A, a total of 118 subjects with chronic ITP and platelets <30 Gi/L were randomized to treatment groups (placebo, eltrombopag 30mg, 50mg or 75mg) in a 1:1:1:1 ratio stratified by use of ITP medications (Yes/No), splenectomy status (Yes/No) and baseline platelet count ( $\leq 15$  Gi/L or  $> 15$  Gi/L). The treatment phase of the study involved once-daily dosing with eltrombopag for up to 6 weeks. All subjects were to be assessed every 2 weeks for 6 weeks following the final dose of study medication to assess the durability of the platelet response and safety parameters. Two interim analyses were conducted for the TRA 100773A study.

The applicant defined the following key terms relating to analysis populations or measurements or observations:

**Efficacy population:** Comprised of all subjects randomized and treated with at least one dose of the study treatment, with a baseline platelet count <30,000/uL.

**Intent-to-Treat Population:** Comprised of all subjects randomized who received at least one dose of study medication and with at least one platelet count post-baseline.

**Per-Protocol Population:** Defined as per the Efficacy Population but excluded major protocol violators.

**Safety Population:** comprised of all subjects randomized and who received at least one dose of the study medication. All subjects were to be analyzed under the treatment group to which they were randomized.

**Responders:** A subject who achieved platelet counts of  $\geq 50$  Gi/L after up to 42 days of dosing (Day 43) was considered a responder.

**Baseline Platelet Count:** The baseline platelet count was defined as the platelet counts taken on day 1 or within 72 hours prior to the first dose. Any subjects with a baseline platelet count which was more than 24 hours prior to the first dose was identified and reported in the clinical study report.

## Study Objectives

The primary objective of the study was to determine the efficacy of eltrombopag as a thrombopoietic agent, when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP.

## Definition of Efficacy Endpoints

The primary endpoint for the study was the proportion of subjects with a platelet count of  $\geq 50$  Gi/L after up to 42 days of dosing

## Study Results

### *Disposition of Subjects*

A total of 118 subjects were randomized (Table 9). The Safety Population and the ITT Population were comprised of 117 subjects each. A total of 74 (63%) subjects completed the study. A higher proportion of subjects in the eltrombopag 50mg and 75mg treatment groups discontinued study medication prior to completion of the study, compared to the eltrombopag 30mg and placebo treatment groups. Majority of these discontinuations were due to a platelet count  $>200$ Gi/L. For these patients, treatment discontinuation was mandatory as per the protocol.

**Table 6 Patient disposition (all subjects)**

Disposition Category	Number of Subjects, n (%)				
	Placebo	30mg	50mg	75mg	Total
All randomized subjects	29	30	30	29	118
Safety Population	29	30	30	28	117
ITT Population	29	30	30	28	117
Completed study	22(76)	23(77)	17(57)	12(43)	74 (63)
Completed study or discontinued prematurely due to platelets $\geq 200$ Gi/L	23(79)	27(90)	28(93)	24(86)	102(87)
Discontinued prematurely from study medication	7 (24)	7 (23)	13(43)	16(57)	43 (37)

a. Subjects with platelets  $\geq 200$  Gi/L were required to discontinue.

Data source: Applicant's study report table 5

The following table gives a summary of reasons for treatment discontinuations (Table 10).

**Table 7 Primary reasons for withdrawal from study medication (ITT Population)**

	Number of Subjects, n (%)				
	Placebo N=29	30mg N=30	50mg N=30	75mg N=28	Total N=117
Withdrawn for any reason	7 (24)	7 (23)	13 (43)	16 (57)	43 (37)
Platelets >200Gi/L	1 (3)	4 (13)	11 (37)	12 (43) <sup>b</sup>	28 (24)
Adverse Event	3 (10)	0	2 (7)	1 (4)	6 (5)
Lack of efficacy	0	2 (7)	0	1 (4)	3 (3)
Other	1 (3)	1 (3)	0	1 (4)	3 (3)
Subject decision	2 (7)	0	0	0	2 (2)
Protocol Violation	0	0	0	1 (4)	1 (<1)

Data source: Applicant's study report table 7

**Demographics and Other Baseline Characteristics**

The following table (table 11) shows the distribution of subjects by demographic factors. All four treatment groups had similar demographic profiles. The median ages in the 30mg and 75mg treatment groups were slightly higher than for the placebo and 50 mg.

**Table 8 Summary of demographic characteristics (ITT Population)**

Demographic Characteristic	Treatment Group				Total N=117
	Placebo N=29	30mg N=30	50mg N=30	75mg N=28	
Age, yrs Median	42	51	45	54.5	50.0
Min – Max	18 – 85	23 – 79	23 – 81	18 – 85	18 – 85
Sex, n (%)					
Female	16 (55)	16 (53)	21 (70)	20 (71)	73 (62)
Male	13 (45)	14 (47)	9 (30)	8 (29)	44 (38)
Race, n (%)					
African American/African	1 (3)	1 (3)	0	0	2 (2)
Asian - East Asian	2 (7)	1 (3)	8 (27)	2 (7)	13 (11)
Asian/South-East Asian	0	3 (10)	4 (13)	1 (4)	8 (7)
White - Arabic/North African	5 (17)	1 (3)	3 (10)	5 (18)	14 (12)
White - White/ Caucasian/European	20 (69)	24 (80)	15 (50)	20 (71)	79 (68)
Other/Mixed	1 (3)	0	0	0	1 (<1)
Ethnicity, n (%) Hispanic or Latino	0	0			
Not Hispanic or Latino	29 (100)	30 (100)	2 (7) 28 (93)	2 (7) 26 (93)	4 (3) 113 (97)

Data Source: Applicant's study report table 10

The following table (table 12) shows the summary of baseline stratification variables. In general, subjects in each stratum were evenly distributed across the four treatments groups. Twenty to forty percent of subjects in each treatment group were receiving concomitant ITP medication at randomization. Approximately half of the subjects in each treatment group were refractory following splenectomy. Across all treatment groups approximately one-half of the subjects had baseline platelet counts.

**Table 9 Summary of baseline stratification variables (ITT Population)**

Stratification Variable	Treatment Group, n (%)				Total N=117
	Placebo N=29	30mg N=30	50mg N=30	75mg N=28	
Use of ITP medication at randomization					
Yes	6 (21)	10 (33)	12 (40)	10 (36)	38 (32)
No	23 (79)	20 (67)	18 (60)	18 (64)	79 (68)
Splenectomy status					
Yes	14 (48)	15 (50)	15 (50)	11 (39)	55 (47)
No	15 (52)	15 (50)	15 (50)	17 (61)	62 (53)
Baseline platelet count $\leq 15 \text{Gi/L}$					
Yes	14 (48)	15 (50)	12 (40)	15 (54)	56 (48)
No	15 (52)	15 (50)	17 (57)	13 (46)	60 (51)
Missing	0	0	1 (3)	0	1 (<1)

Data source: Applicant's study report table 11

The following table shows the number of prior ITP therapies by subject (Table 13). Most subjects in each of the treatment groups had >1 prior ITP therapy. Substantial proportions of subjects in each treatment group had  $\geq 3$  prior ITP therapies.

**Table 10 Number of prior ITP therapies by subject (Safety Population)**

Number of Prior ITP Therapies	Treatment Group, n (%)				Total N=117
	Placebo N=29	30 mg N=30	50 mg N=30	75 mg N=28	
No prior therapies	1 (3)	1 (3)	0	2 (7)	4 (3)
$\geq 1$ prior therapy	28 (97)	29 (97)	30 (100)	26 (93)	113 (97)
$\geq 2$ prior therapies	21 (72)	26 (87)	24 (80)	16 (57)	87 (74)
$\geq 3$ prior therapies	14 (48)	17 (57)	18 (60)	11 (39)	60 (51)
$\geq 4$ prior therapies	12 (41)	12 (40)	12 (40)	6 (21)	42 (36)
$\geq 5$ prior therapies	8 (28)	7 (23)	10 (33)	5 (18)	30 (26)

Data Source: Applicant study report table 14

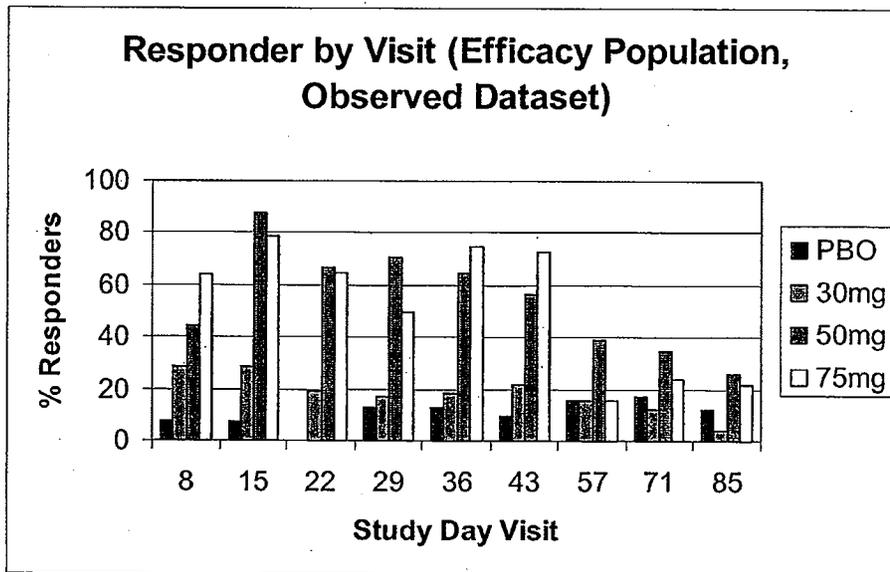
### Efficacy Analyses Results

Analysis of the primary endpoint showed that eltombopag increased the number of subjects achieving platelet counts  $\geq 50 \text{Gi/L}$  in a dose dependent manner (Table 14). After up to 6 weeks of dosing, only 11% of placebo subjects attained a platelet count of  $\geq 50 \text{Gi/L}$  on Day 43, compared to 70-80% of subjects on eltombopag 50mg and 75mg. At each visit during the treatment phase, the percentage of responders was numerically

greater in all eltrombopag treatment groups compared to the placebo treatment group (Figure 7). This reviewer has confirmed applicant's primary efficacy results.

**Table 11 Reviewer's Summary of % Responders by visit (Efficacy Population, observed dataset)**

Visit	Treatment Group			
	Placebo N=27	30 mg N=29	50 mg N=27	75 mg N=26
Day 8 visit	7.4	28.6	44.4	64
Day 15 visit	7.4	28.6	88	79.0
Day 22 visit	0	19.2	66.7	64.3
Day 29 visit	13.0	16.7	70.6	50
Day 36 visit	13.0	18.2	64.7	75
Day 43 visit	9.5	21.7	56.2	72.7
Day 57 visit	15.4	15.4	38.5	15.4
Day 71 visit	16.7	12.0	34.6	24.0
Day 85 visit	12.5	3.8	25.9	21.7



**Figure 7 Reviewer's Summary of % Responders by visit (efficacy population, observed dataset)**

The applicant conducted two interim analyses. Prior to comparing each eltrombopag dose to placebo, an analysis was performed to determine if there were differences among the treatment groups. The results showed significant difference among the treatment group ( $p < 0.001$ ). For comparison of each eltrombopag dose to placebo under the pre-defined closed testing procedure to assess efficacy and futility, both the eltrombopag 50 and 75mg treatment groups achieved a statistically significant treatment effect compared to placebo ( $p < 0.001$ ), the result met the pre-specified p-value ( $p < 0.0113$ ) for stopping the study at the first interim analysis based upon efficacy using a closed testing procedure (Table 15). The odds of responding were greater for each of the eltrombopag treatment groups compared to the placebo treatment group. The primary method of analysis was a logistic regression model adjusted for ITP medication use at

randomization, splenectomy status and baseline platelet count  $\leq 15\text{Gi/L}$ . This reviewer has confirmed applicant's primary efficacy results.

**Table 12 Analysis of responders (Efficacy Population)**

	Treatment Group		
	30mg N=29	50mg N=27	75mg N=26
Odds ratio	3.09	21.96	38.82
95% CI	(0.69,13.75)	(4.72,102.23)	(7.62,197.73)
p-value (one-sided)	0.070	<0.001	<0.001

The applicant conducted additional analyses using different analysis population including Per-Protocol population and Intent-to-Treat population. They all showed results similar to the efficacy population.

This reviewer confirmed these analyses.

#### **Assessment of Bleeding**

The following plot (Figure 8) shows the proportion of subjects with bleeding (WHO Grade 1 to Grade 3) during the on-therapy (Day 1 to 43 Visits) and post-therapy (Day 57 to Day 85 Visit). During the on-therapy period, there was a decrease in the proportion of subjects with bleeding for the 30mg, 50mg and 75mg treatment groups compared to baseline. The proportion of subjects with bleeding was lower in all the eltrombopag treatment groups compared to placebo for the Day 15 to Day43 Visits. However, the statistical significance of these observed trends was not reached. Also, the reviewer recommends caution when interpreting these observed trends since these are based on observed data when the proportion of treatment discontinuations ranged from 23% to 57% in the eltrombopag groups. In addition, this reviewer notes that almost all the bleeding events in all the groups at all time-points including baseline were of WHO grades 1 and 2. The decrease in WHO Grades 1 and 2 bleeding events is not considered to be clinically important at this time. At the first post-therapy assessment, within 2-weeks after discontinuation of study medication (Day 57 Visit), the proportion of subjects with bleeding in the 50mg and 75mg treatment groups rose to near baseline values and remained similar for the remainder of the post therapy assessments.

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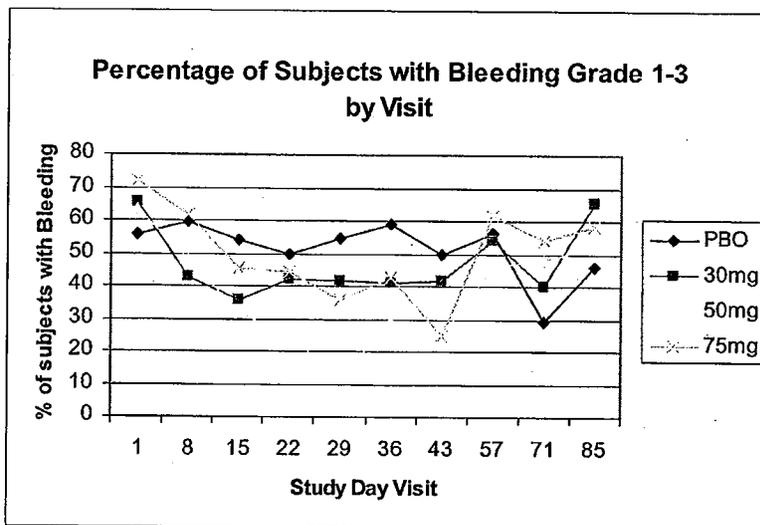


Figure 8 Percentage of subjects with bleeding grade 1-3 by visit (Efficacy Population)

### 3.1.2 Study TRA100773B

#### 3.1.2.1 Study Design

In TRA100773B, a total of 114 subjects with chronic ITP were randomized to one of two treatment arms in a 2:1 ratio stratified by use of ITP medications (Yes/No), splenectomy status(Yes/No) and baseline platelet count ( $\leq 15\text{Gi/L}$  or  $>15\text{Gi/L}$ ). In total 76 subjects were randomized to receive eltrombopag 50mg and 38 subjects were randomized to receive placebo. The treatment phase of the study involved once-daily dosing with study medication for up to 6 weeks. Subjects who attained a platelet count  $>200\text{Gi/L}$  discontinued treatment with study medication to minimize the risk of developing further increase in platelet counts. After the dosing period, subjects were assessed at 1, 2, 4, and 6 weeks following the final dose of study medication to assess the durability of the platelet response and safety parameters. Subjects were also to complete an ocular examination at 6 weeks and 6 months following the final dose of study medication.

#### 3.1.2.2 Study Objectives

The primary objective of the study was to determine the efficacy of eltrombopag as a thrombopoietic agent when administered once daily for up to 6 weeks to previously treated adult subjects with chronic immune thrombocytopenic purpura (ITP).

#### 3.1.2.3 Definition of Efficacy Endpoints

The primary endpoint for the study was the proportion of subjects with a platelet count of  $\geq 50\text{Gi/L}$  after up to 42 days of dosing (compared to a baseline count of  $<30\text{Gi/L}$ ). Subjects who meet this criterion will be referred to as treatment responders.

The secondary efficacy endpoints were:

- Platelet counts;
- Proportion of subjects responding to treatment during weeks 2 to 6 of the study
- Proportion of subjects with platelet counts  $\geq 50$  Gi/L and at least twice their baseline
- Incidence and severity of symptoms associated with chronic ITP, including bleeding, bruising, and petechiae, where using WHO Bleeding Scale and the ITP Bleeding Score.

All primary and secondary efficacy analyses were conducted using the efficacy population. The primary efficacy analysis was repeated using the Per-Protocol population.

The study was designed to assess the null hypothesis  $H_0: \gamma = 1$  (no difference) versus the alternative hypothesis  $H_1: \gamma \neq 1$  (two-sided at 5% level) where  $\gamma$  is the odds of being a responder in the eltrombopag 50mg treatment group relative to placebo.

#### **3.1.2.4 Primary Efficacy Analysis**

The primary analysis of the endpoint was performed with a dataset which classified all subjects as either responders or non-responders. A logistic regression model adjusting for the stratification variables of use of ITP medication at baseline (Yes/No), splenectomy status (Yes/No) and baseline platelet count  $\leq 15$  Gi/L (Yes/No) was used to test the global null hypothesis that the odds of response were equal in both treatment arms. In this analysis, the subjects who discontinued study medication for reasons other than for platelet count  $> 200$  Gi/L were considered as non-responders. Treatment by strata interactions were included in this analysis. A sensitivity analysis of the primary endpoint was performed at the Day 43 Visit for observed data without including subjects who withdrew prematurely for any reason. The applicant also performed primary analysis for different populations.

#### **3.1.2.5 Secondary Efficacy Analyses**

The applicant conducted GEE model for odds of responding at each assessment during Weeks 2-6 of the 6 week treatment period between eltrombopag 50mg relative to placebo. A logistic regression analysis allowing for use of concomitant ITP medication at randomization (Yes/No), splenectomy (Yes/No), baseline platelet count  $\leq 15$  Gi/L (Yes/No) and treatment was used to compare the odds of achieving a platelet count  $\geq 50$  Gi/L at Day 43 between treatment groups using the imputed dataset using the imputation model of "last observation carry forward". The odds of no bleeding in the treated group relative to placebo utilizing information at each assessment during weeks 2-6 of the 6 week treatment period were compared using GEEs for the observed dataset, adjusting for baseline WHO Bleeding Grade, use of concomitant ITP medication at

randomization (Yes/No), splenectomy (Yes/No), baseline platelet count. Ninety-five percent confidence intervals of the overall odds ratio of no bleeding during this time period, for subjects on eltrombopag 50mg relative to placebo, are provided.

The logistic regression model, and ordinal logistic regression analysis were repeated for the odds of bleeding.

### 3.1.2.6 Study Population Results

#### *Disposition of Subjects*

A total of 114 subjects were enrolled in the study. With 76 randomized to the eltrombopag treatment group, and 38 randomized to placebo. A total of 52 (68%) subjects in the eltrombopag treatment group and 30 (79%) subjects in the placebo treatment group completed the study (Table 16).

Thirty-two (28%) subjects withdrew from treatment prior to completion of the full 6 week treatment period. The most common reason for withdrawal from study medication in the eltombopag treatment group was a platelet count >200Gi/L, which occurred in 17(22%) subjects. In contrast, 1 (3%) subject in the placebo treatment group withdrew from study medication because of a platelet count >200 Gi/L. Two subjects (5%) in the placebo treatment group withdrew due to lack of efficacy in contrast with none withdrawing due to the lack of efficacy in the eltrombopag group. AEs leading to withdrawal occurred in a total of 5 subject; 2 subjects (5%) in the placebo treatment group and 3 subjects (4%) in the eltrombopag treatment group (Table 17).

**Table 13 Subject disposition (All Subjects)**

Disposition Category	Number of subjects, n (%)		
	Placebo	Eltrombopag	Total
All randomized subjects	38	76	114
Safety Population	38 (100)	76 (100)	114 (100)
ITT Population	38 (100)	76 (100)	114(100)
PP Population	37 (97)	71 (93)	108 (95)
Efficacy Population	38 (100)	74 (97)	112 (98)
Completed <sup>a</sup>	30 (79)	52 (68)	82(72)
Discontinued prematurely from study medication	8 (21)	24 (32)	32(28)

a. Completed 6 weeks of treatment. Subject with platelet count >200Gi/L were required to discontinue treatment.

**Table 14 Primary reasons for withdrawal from study medication (ITT Population)**

	Number of subjects, n (%)		
	Placebo N=38	Eltrombopag N=76	Total N=114
Withdrawn for any reason	8 (21)	24 (32)	32 (28)
Platelet>200Gi/L	1 (3)	18 (24)	19 (17)
Adverse Event	2 (5)	3 (4)	5 (4)
Protocol Violation	1 (3)	2 (3)	3 (3)
Lack of efficacy	2 (5)	0	2 (2)
Subject decision	0	1 (1)	1 (<1)
Other <sup>a</sup>	2 (5)	0	2 (2)

***Demographics and Other Baseline Characteristics***

The following table shows the summary of demographic characteristics. Subjects had a median age of 48 years and 70 subjects (61%) were female. Most subjects (76 subjects, 67%) were of White-White/Caucasian/European heritage. In the eltrombopag treatment group, approximately half of the subjects were female, whereas in the placebo treatment group, there was nearly a 2:1 ratio of females to males. The treatment arms were well balanced with respect to race. (Table 18)

**Table 15 Summary of demographic characteristics (ITT Population)**

Demographic Characteristic	Treatment Group		
	Placebo N=38	Eltrombopag N=76	Total N=114
Age, yrs Median	51.0	47.0	48.0
Min – Max	21-79	19-84	19-84
Sex, n (%)			
Female	27 (71)	43 (57)	70 (61)
Male	11 (29)	33 (43)	44 (39)
Race, n (%)			
African American/African	0	1 (1)	1 (<1)
American Indian/Alaskan Native	2 (5)	4 (5)	6 (5)
Asian - East Asian	1 (3)	0	1 (<1)
Asian - South-East Asian	3 (8)	7 (9)	10 (9)
Asian – Central/South Asian	4 (11)	5 (7)	9 (8)
White - Arabic/North African	3 (8)	5 (7)	8 (7)
White - White/ Caucasian/European	23 (61)	53 (70)	76 (67)
Mixed Race	2 (5)	1 (1)	3 (3)
Ethnicity, n (%)			
Hispanic or Latino	6 (16)	10 (13)	16 (14)
Not Hispanic or Latino	32 (84)	66 (87)	98 (86)

Data source: Applicant's study report table 10.

The following table shows the summary of baseline stratification variables. Randomization was stratified by use of ITP medication at randomization (Yes/No), splenectomy status (Yes/No) and baseline platelet count ( $\leq 15\text{Gi/L}$ ,  $\geq 15\text{Gi/L}$ ). Overall, 49 subjects (43%) were receiving ITP medication at randomization, 45 subject (39%) had a prior splenectomy and 55 subjects (48%) had baseline platelet counts of  $\leq 15\text{Gi/L}$  (Table 19).

**Table 16 Summary of baseline stratification variables (ITT Population)**

Stratification Variable	Treatment Group, n (%)		Total N=114
	Placebo N=38	Eltrombopag N=76	
Use of ITP medication at randomization			
Yes	17 (45)	32 (42)	49 (43)
No	21 (55)	44 (58)	65 (57)
Splenectomy status			
Yes	14 (37)	31 (41)	45 (39)
No	24 (63)	45 (59)	69 (61)
Baseline platelet count $\leq 15\text{Gi/L}$			
Yes	17 (45)	38 (50)	55 (48)
No	21 (55)	38 (50)	59 (52)

Source: Applicant's study report table 11

The following table shows the current medical conditions reported.

**Table 17 Current medical conditions reported in 4% or more of subjects in any treatment group (ITT Population)**

Preferred Term	Treatment Group, n (%)		Total N=114
	Placebo N=38	Eltrombopag N=76	
Any condition	24 (63)	52 (58)	76 (67)
Hypertension	5 (13)	22 (29)	27 (24)
Diabetes mellitus	3 (8)	5 (7)	8 (7)
Hypercholesterolemia	0	6 (8)	6 (5)
Hypothyroidism	0	4 (5)	4 (4)
Menorrhagia	1 (3)	3 (4)	4 (4)
Hepatic steatosis	0	3 (4)	3 (3)
Sarcoidosis	2 (5)	0	2 (2)

Source: Applicant's study report table 12

The following table shows the summary of number of prior ITP therapies by subjects. All subjects in both treatment groups had  $\geq 1$  prior ITP therapy. Approximately 50% of subjects had received at least 3 prior treatments. A higher percentage of subjects in the eltrombopag arm had  $\geq 3$  and  $\geq 4$  prior therapies compared to placebo (Table 21).

**Table 18 Number of prior ITP therapies by subject (Safety Population)**

Number of Prior ITP Therapies	Treatment Group, n (%)		Total
	Placebo N=38	Eltrombopag N=76	N=114
No prior therapies	0	0	0
≥1 prior therapy	38 (100)	76 (100)	114 (100)
≥2 prior therapy	26 (68)	56 (74)	82 (72)
≥3 prior therapies	16 (42)	42 (55)	58 (51)
≥4 prior therapies	9 (24)	30 (39)	39 (34)
≥5 prior therapies	7 (18)	16 (21)	23 (20)

Source Applicant's study report table 14

### 3.1.2.7 Primary Efficacy Results

The analysis of the primary endpoint showed that that the eltrombopag increased the number of subjects achieving platelet counts  $\geq 50\text{Gi/L}$  after up to 6 weeks of dosing compared to placebo and this increase was statistically significant. Fifty-nine percent of subjects on eltrombopag attained a platelet count of  $\geq 50\text{Gi/L}$  on Day 43 compared to 16% of subjects on placebo (Table 22). At each visit, the percentage of responders was greater in the eltrombopag treatment group compared to the placebo treatment group (Figure9).

**Table 19 Reviewer's summary of responders at the Day 43 Visit (Efficacy Population)**

Visit Day	Treatment Group	
	Eltrombopag N=76	Placebo N=38
Day 8	36.84	21.05
Day 15	52.7	13.51
Day 22	51.32	15.79
Day 29	53.95	15.79
Day 36	55.26	7.89
Day 43	57.33	16.22
Day 50	49.28	20.69
Day 57	26.03	20.59
Day 71	19.18	21.88
Day 85	21.92	23.53

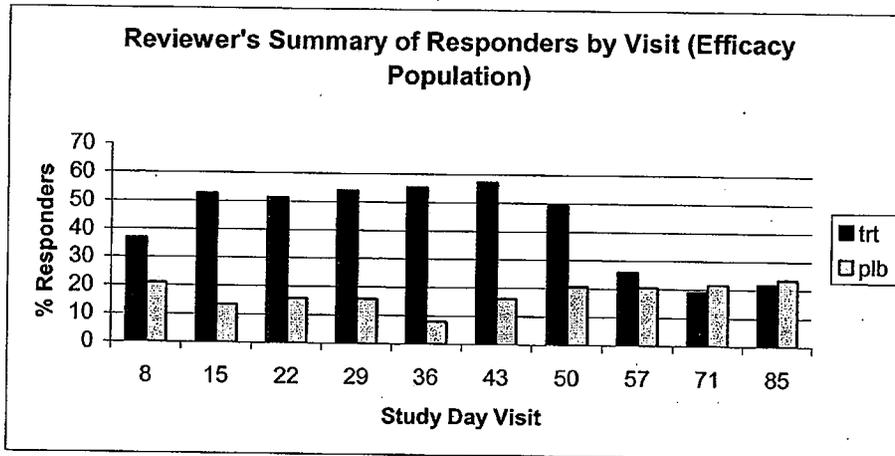


Figure 9 Reviewer's summary of percentages of responders by visit (Efficacy Population)

The odds of responding using logistic regression model for the primary efficacy analysis were significantly greater for the eltrombopag treatment group compared to the placebo treatment group ( $p < 0.0001$ ) adjusted for ITP medication use at randomization, splenectomy status and baseline platelet count. The odds ratio of responding in the eltrombopag-treated group compared to placebo group was 9.61, with the 95% confidence interval of (3.3, 27.9) (Table 23).

Table 20 Reviewer's Summary of Analysis of Responders (Efficacy Population)

	Eltrombopag N=74
Odds ratio for Active/Placebo Treatments	9.6
95% CI	(3.3, 27.9)
p-value (two-sided)	<0.001

The result of the primary endpoint analysis for PP population and ITT population were consistent with those for the Efficacy Population.

### Median Platelet Counts

The following table shows the median platelet counts for all subjects by visit (Table 24). Baseline median platelet counts were similar in the 2 treatment groups. From the Day 8 to Day 43 visits, the median platelet counts for the eltrombopag treatment group were higher than that in the placebo treatment group and the increase in the median platelet count was maintained throughout the on-therapy period of the study. During the follow-up (off-therapy) period, after Day 50 visit, the median platelet count was decreased for eltrombopag (Figure 10).

Table 21 Reviewer's summary of median platelet counts for all subjects by visit

Assessment Visit	Treatment Group	
	placebo (N=38)	Eltrombopag (N=74)
Day 1 Visit	17	18
Day 8 Visit	26	29.5
Day 15 Visit	18	53
Day 22 Visit	20.5	47
Day 29 Visit	19	49
Day 36 Visit	18.5	50.5
Day 43 Visit	20	53
Day 50 Visit	21	51
Day 57 Visit	21	24
Day 71 Visit	19	18
Day 85 Visit	25.5	23

Reviewer's Summary of Median Platelet Counts for all subjects by visit

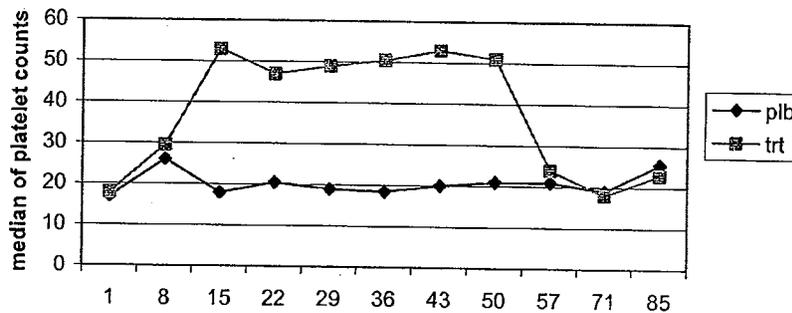


Figure 10 Reviewer's Summary of Median Platelet Counts (Gi/L) for all subjects by visit

#### Assessment of Bleeding

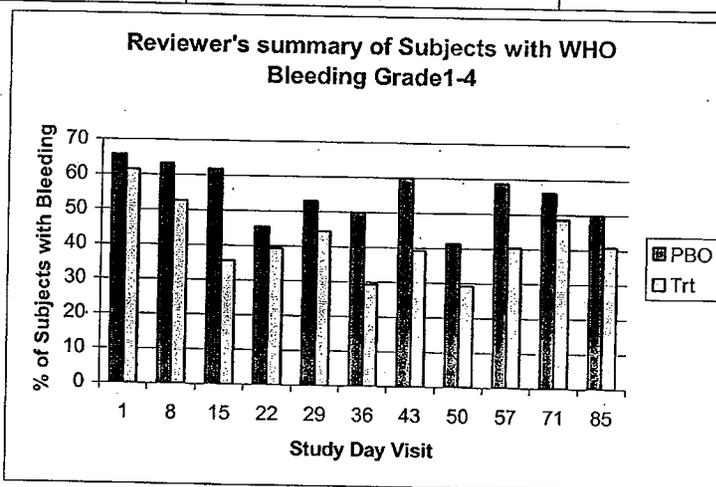
A review of subjects with a WHO Bleeding Scale Grade of 1 to 4 showed a decreased incidence of bleeding on treatment relative to baseline in subjects who received eltrombopag (Figure 8). At the baseline visit, 61% of subjects in the eltrombopag treatment group and 66% of subjects in the placebo treatment group reported any bleeding (Grade 1-4). At the Day 43 Visit, 39% of subjects in the eltrombopag treatment group had bleeding compared with 60% in the placebo treatment group (Table 25). The results of the logistic regression analysis, adjusting for the covariates of use of concomitant medication at randomization, splenectomy and platelets  $\leq 15$  Gi/L and dichotomized baseline WHO Bleeding Grade indicated that the odds of any bleeding in the eltrombopag were significantly lower than that of placebo at Day 43 (OR=0.27, 95% CI=[0.09,0.88],  $p=0.029$ )

At the first off-treatment assessment, 1-week after discontinuation of study medication (Day 50 Visit), the proportion of subjects with bleeding remained lower in the eltrombopag treatment arm

compared to placebo, and continued to be slightly lower than placebo for the remainder of the post-therapy visits

**Table 22 Reviewer's summary of percentages of subjects with WHO bleeding grade 1-4**

Assessment Visit	Treatment Group, n (%)	
	Placebo N=38	Eltrombopag N=74
Day 1	65.7	61.4
Day 8	63.2	52.7
Day 15	61.8	35.6
Day 22	45.5	39.3
Day 29	53.1	44.4
Day 36	50	29.4
Day 43	60	39.2
Day 50	41.4	29.2
Day 57	58.8	40.3
Day 71	56.3	48.6
Day 85	50	40.8



**Figure 11 Reviewer's Summary of Subjects with WHO Bleeding Grade 1-4**

### 3.1.3 Reviewer's Detailed Analysis of assessment of incidence of Bleeding

This section provides statistical reviewer's analyses of the data on bleeding events submitted by the applicant in their NDA 022291. These analyses were conducted to assess if the data presented in this NDA at the time of initial submission provide statistically significant evidence to support a proposed labeling claim that eltrombopag in the treatment of ITP patients significantly decreases the incidence and severity of bleeding in subjects with relapsed or refractory chronic ITP.

The overall conclusion of the statistical reviewer's analyses is that although a trend toward reduced incidence of bleeding is observed in the eltrombopag group compared to placebo, this trend is not statistically significant and does not provide robust evidence to support the proposed labeling claim of a decrease in the incidence and severity of bleeding in subjects with relapsed or refractory chronic ITP when treated with eltrombopag.

To capture the full picture of bleeding events for two pivotal studies (Phase II 773A and Phase III 773B), the protocol-specified assessment included incidence and severity of bleeding using the WHO Bleeding Scale and ITP Bleeding Scale (Study 773B only)

WHO Bleeding Scale has 5 grades:

- Grade 0- no bleeding
- Grade 1- mild blood loss
- Grade 2- mild blood loss
- Grade 3- gross blood loss
- Grade 4- debilitating blood

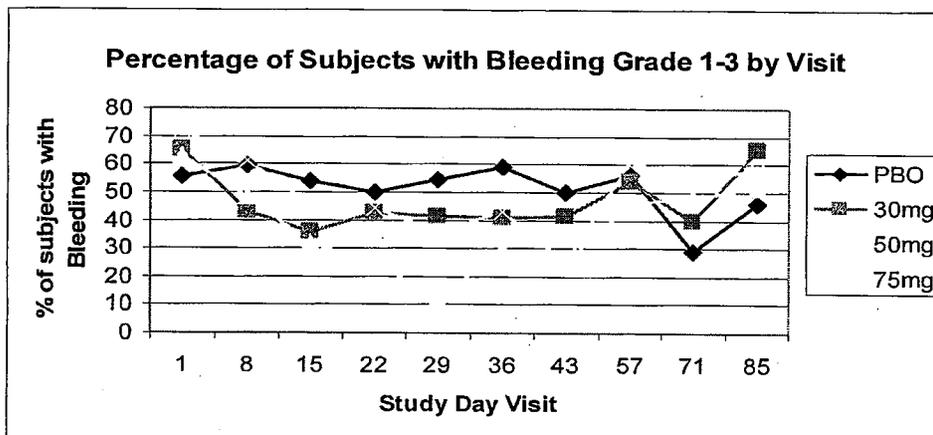
ITP Bleeding Score is an assessment of the bleeding severity in each of ten anatomical locations: Skin: Petechiae, Skin: ecchymosis, Oral, Epistaxis, Ocular, Gastrointestinal, Genitourinary, Gynecological, Pulmonary and intracerebral Hemorrhage. Severity was graded using scores 0, 1 and 2.

#### Assessment of WHO Bleeding Scale

##### **Study 773A**

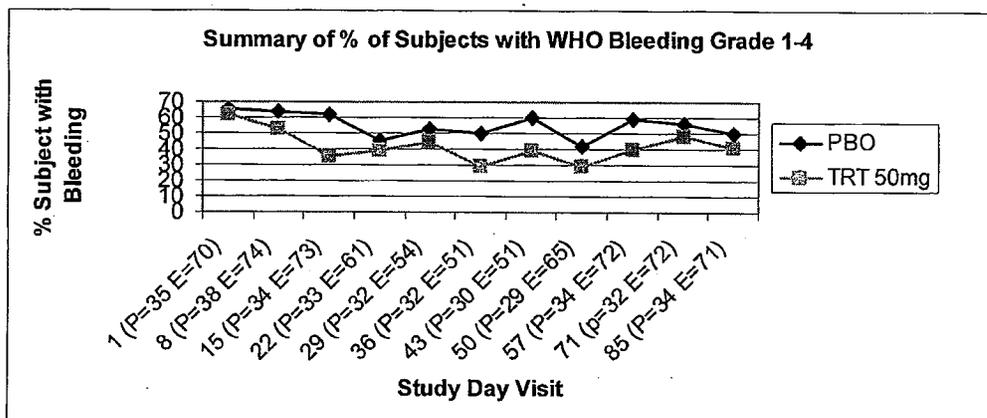
The following plot shows the observed proportion of subjects with bleeding (WHO Grade 1 to Grade 3, no subject on Grade 4) during the on-therapy as well as post-therapy period. A decrease was observed in the proportion of subjects with bleeding for the 30mg, 50mg and 75mg treatment groups compared to baseline. The proportion of subjects with bleeding was observed to be lower in all the eltrombopag treatment groups compared to placebo for the Day 15 to Day 43 Visits. However, the sample-sizes in this study are not large enough to conduct a formal statistical hypotheses testing procedure to assess the significance of the observed decrease. At the first post-therapy assessment, within 2-weeks after discontinuation of study medication (Day 57 Visit), the proportion of subjects with bleeding in the 50mg and 75mg treatment groups increased to near baseline values and remained similar for the remainder of the post therapy assessments.

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**Study 773B**

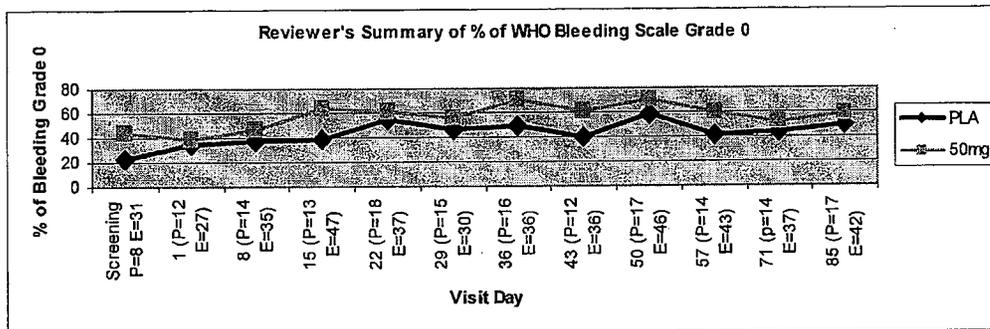
The following plot shows the observed proportion of subjects with bleeding (WHO Grade 1 to Grade 4) during the on-therapy as well as post-therapy period. As in Study 773A, a decreased incidence of bleeding on treatment relative to baseline in subjects who received eltrombopag was observed. At the baseline visit, 61% of the subjects in the eltrombopag treatment group and 66% of subjects in the placebo group reported any bleeding (Grade 1-4). At the Day 43 Visit, 39% of subjects in the eltrombopag treatment group had bleeding compared with 60% in the placebo group.

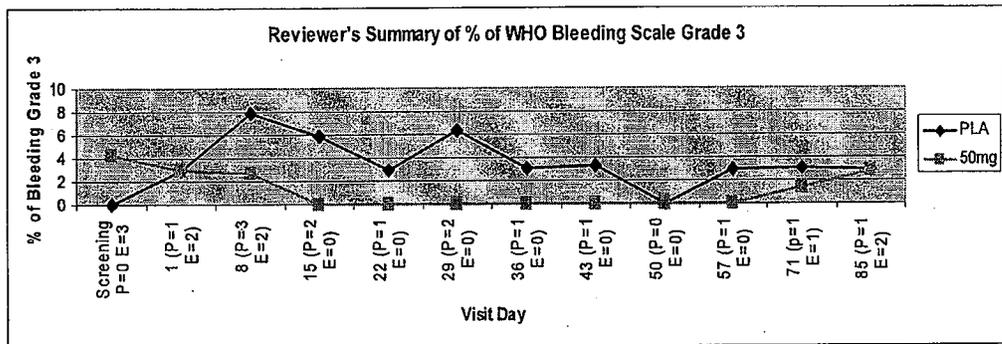
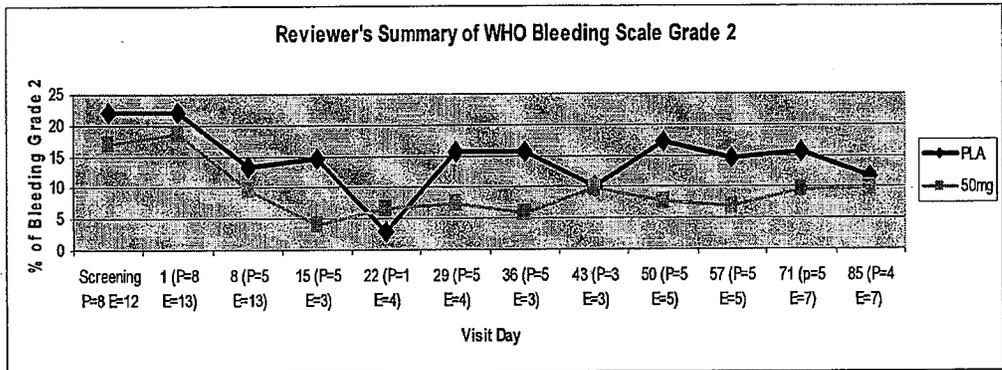
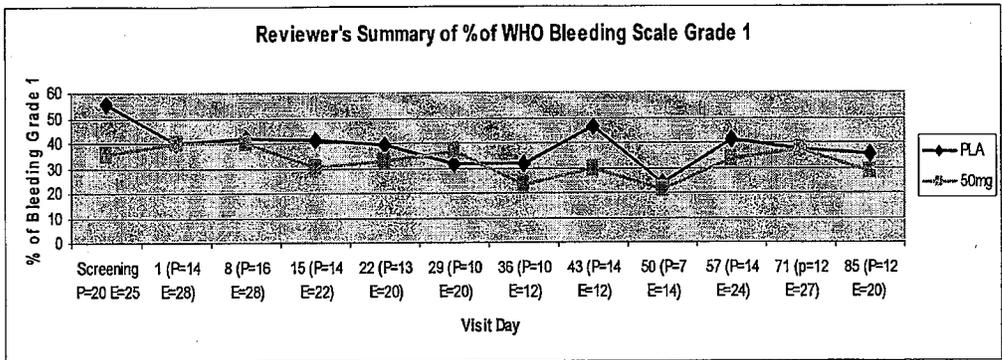


The applicant conducted the logistic regression analysis, adjusting for the covariates of using concomitant medication at randomization, splenectomy and dichotomized baseline platelets. Results indicated that the odds of any bleeding in the eltrombopag were significantly lower than that of placebo at Day 43 (OR=0.27, 95% CI= [0.09, 0.88], p=0.029). However, the applicant's analysis does not account for the time-dependant nature of bleeding and is subject to erroneous conclusion. Since, for the patient population in this study, the bleeding event is time dependent with multiple observations per subject, it is more appropriate to use survival analysis models based on time-to-event in multiple event setting. This statistical reviewer used the Andersen-Gill

(AG) proportional hazards model and the results showed that the decrease in the incidence of bleeding for the eltrombopag group is not statistically significant (hazard ratio =0.781, p-value = 0.067). The following table and figures show the observed % of patients with bleeding at Grade 0, 1, 2, and 3

Visit Day	WHO Bleeding	PLA N=38	50mg N=74
Day 1	n	35	70
	Grade 0	34.3% (12)	38.6% (27)
	Grade 1	40% (14)	40.0% (28)
	Grade 2	22.9% (8)	18.6% (13)
	Grade 3	2.9% (1)	2.9% (2)
Day 15	n	34	73
	Grade 0	38.2% (13)	64.4% (47)
	Grade 1	41.2% (14)	30.1% (22)
	Grade 2	14.7% (5)	4.1% (3)
	Grade 3	5.9% (2)	0
Day 43	n	30	51
	Grade 0	40% (12)	70.6% (36)
	Grade 1	46.7% (14)	23.5% (12)
	Grade 2	10% (3)	5.9% (3)
	Grade 3	3.3% (1)	0
Day 85	n	34	71
	Grade 0	50%	59.2% (42)
	Grade 1	35.3% (12)	28.2% (20)
	Grade 2	11.8% (4)	9.9% (7)
	Grade 3	2.9% (1)	2.8% (2)





**Assessment of ITP Bleeding Scale**  
**Study 773B**

The following table shows the summary of results using ITP Bleeding Score Assessment. Note that in 4 of the 10 categories, no or very few patients reported bleeding at baseline in both placebo and eltrombopag groups. A review of subjects with Grade 1-2 on ITP Bleeding Scale in the 6 categories in which the bleeding was reported, shows that in the skin ecchymosis and gynecologic categories, the observed decreases from baseline were greater for eltrombopag compared to placebo and for the remaining four categories, the observed decreases from baseline were similar between eltrombopag and placebo.

Assesments	Placebo N=38		EltrombopagN=74	
	Day1	Day43	Day1	Day43
Skin, petechiae,n	37	30	73	51
Grade 0	17(46)	21(70)	48(66)	42(82)
Grade 1	16(43)	8 (27)	20(27)	7 (14)
Grade 2	3 (8)	1 (3)	5 (7)	2 (4)
Skin, ecchymosis,n	37	30	73	51
Grade 0	18(49)	14(47)	29(40)	33(65)
Grade 1	13(35)	12(40)	35 (48)	14 (27)
Grade 2	5 (14)	4 (13)	9 (12)	4 (8)
Oral n	37	30	73	51
Grade 0	28(76)	27(90)	63(86)	47 92)
Grade 1	7 (19)	3 (10)	9 (12)	4 (8)
Grade 2	1 (3)	0	1 (1)	0
Epistaxis, n	37	30	73	51
Grade 0	32 86)	30(100)	63 86)	49(96)
Grade 1	4 (11)	0	9 (12)	1 (2)
Grade 2	0	0	1 (1)	1 (2)
Ocular ,n	37	30	73	51
Grade 0	36(97)	30(100)	73(100)	51(100)
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Gastrointestinal, n	37	30	73	51
Grade 0	36(97)	30(100)	71 (97)	50 (98)
Grade 1	0	0	2 (3)	1 (2)
Grade 2	0	0	0	0
Genitourinary, n	37	30	73	51
Grade 0	34(92)	29 (97)	69 (95)	51(100)
Grade 1	2 (5)	1 (3)	3 (4)	0
Grade 2	0	0	(1)	0
Gynecologic, n	26	23	41	24
Grade 0	8 (31)	7 (30)	11 (27)	10 (42)
Grade 1	0	0	2 (5)	1 (4)
Grade 2	1 (4)	0	5 (12)	0
Pulmonary, n	37	30	73	51
Grade 0	36(97)	30(100)	71 (97)	51(100)
Grade 1	0	0	2 (3)	0
Grade 2	0	0	0	0
Intracerebralhemorrhage,n	37	30	73	51
Grade 0	36(97)	30(100)	73(100)	51(100)
Grade 1	0	0	0	0

### 3.2 Evaluation of Safety

#### Study TRA100773A

The following tables show the reviewers summary of subjects with adverse event during the treatment period (Table 26) and during the entire study (Table 27).

**Table 23 Reviewer's Summary of Subjects with adverse event during the treatment from study A**

During Treatment	Treatment Group, n (%)			
	Placebo N=29	30mgN=30	50mgN=30	75mgN=28
Any AE	17 (59)	14 (47)	14 (47)	17 (61)
Any SAE	2 (7)	0	2 (7)	0
AEs related to study medication	9 (31)	9 (30)	8 (27)	10 (36)
AEs leading to withdrawal	2 (7)	0	2 (7)	1 (4)

**Table 24 Reviewer's Summary of Subjects with adverse event during the entire**

During Entire Study	Treatment Group, n (%)			
	Placebo N=29	30mgN=30	50mgN=30	75mgN=28
Any AE	18 (62)	20 (67)	17 (57)	19 (68)
Any SAE	4 (14)	1 (3)	6 (20)	2 (7)
AEs related to study medication	11 (38)	10 (33)	8 (27)	10 (36)
AEs leading to withdrawal	3 (10)	0	2 (7)	1 (4)

The incidence of on therapy AEs regardless of causality was between 47% and 61%, and was similar across treatment groups. The incidence of AEs regardless of causality was similar across treatment groups over the course of the entire study. There is no dose-dependent pattern of AEs.

#### Study TRA 100773B

The following tables show the reviewer's summary of subjects with adverse event during on therapy period (Table 28) and entire study period (Table 28).

**Table 25 Reviewer's Summary of Subjects with Adverse Event During on Therapy Period**

AEs During on-therapy	Treatment Group, n (%)	
	Placebo N=38	Eltombopag N=76
Any AE	14 (37)	45 (59)
Any SAE	2 (5)	2 (3)
AEs related to study medication	4 (11)	20 (26)
AEs leading to withdrawal	2 (5)	3 (4)

**Table 26 Reviewer's Summary of Subjects with Adverse Event During entire study**

AEs during entire study	Treatment Group, n (%)	
	Placebo N=38	Eltrombopag N=76
Any AE	17 (45)	53 (70)
Any SAE	4 (11)	6 (8)
AEs related to study medication	5 (13)	23 (30)
AEs leading to withdrawal	2 (5)	3 (4)

On therapy SAEs occurred in 2 subjects each in both treatment groups. AEs leading to withdrawal occurred in 2 subjects in the placebo treatment group, and in 3 subjects in the eltrombopag treatment group. The overall incidence of AEs and treatment-related AEs with onset during the treatment phase and entire study was greater in the eltrombopag treatment group compared to the placebo treatment group.

**Assessment of Bleeding** (please see Section 3.1.3)

#### 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

##### 4.1 Gender, Race and Age

##### 4.1.1 Study TRA100773A

The following table shows the subgroup analysis for Gender, Age, and Race for analysis of responder at the Day 43 (Table 30). For all three subgroups, the percentages of responders in the eltrombopag treatment groups were greater than the placebo treatment group, and the percentages of responders were higher in the 50mg and 75mg treatment groups than in 30mg treatment group. Logistic regression showed that there was no statistically significant treatment by sex interaction (the p-value is 0.9).

**Table 27 Reviewer's summary of responders by Age Gender Race at the Day 43 Visit**

Subgroup Category Responders	Treatment Group			
	Placebo N=27	30mg N=29	50mg N=27	75mg N=26
<b>Age</b>				
18 to ≤49	10% (2/10)	18.2% (2/11)	66.7% (10/15)	77.8% (7/9)
50 to ≤64	16.7% (1/6)	50.0% (5/10)	66.7% (6/9)	81.8% (9/11)
≥65	0% (0/1)	12.5% (1/8)	100% (3/3)	83.3% (5/6)
<b>Gender</b>				
Female	12.5%(2/16)	33.3% (5/15)	73.7% (14/19)	79% (15/19)
Male	9.1% (1/11)	21.4% (3/14)	62.5% (5/8)	85.7% (6/7)
<b>Race</b>				
Arabic/North African	25.0% (1/4)	0 (0/1)	100% (3/3)	80% (4/5)
East Asian	0 (0/2)	100% (1/1)	42.9% (3/7)	100% (2/2)
South- East Asian	0 (0)	66.7% (2/3)	75% (3/4)	100% (1/1)
White/Caucasian	10.5%(2/19)	21.7% (5/23)	76.9% (10/13)	77.8%(14/18)

#### 4.1.2 Study TRA100773B

The following table shows the subgroup analysis for Gender, Age, and Race for analysis of responder at the Day 43 (Table 31). For all three subgroups, the percentages of responders in the eltrombopag treatment groups were greater than the placebo treatment group. Logistic regression showed that there was no statistically significant treatment by age interaction. This result is consistent with the result from TRA100773A.

**Table 28 Reviewer's summary of responders by Age Gender Race at the Day 43 Visit**

Subgroup Category Responders	Treatment Group	
	Placebo N=38	Eltombopag N=74
Age		
18 to ≤49	22.2% (4/18)	50% (20/40)
50 to ≤64	7.7% (1/3)	64.3% (9/14)
≥65	16.7% (1/6)	73.7% (14/19)
Gender		
Female	23.1% (6/26)	67.5% (27/40)
Male	0 (0/11)	48.5% (16/33)
Race		
Arabic/North African	33.3% (1/3)	43.9% (3/7)
Asian-Southeast Asian	33.3% (1/3)	42.9% (3/7)
Asian-Central/South	25% (1/4)	40% (2/5)
White/Caucasian	13.6% (3/22)	62.8% (32/51)
American Indian	0 (0/2)	75% (3/4)

#### 4.2 Other Special/Subgroup Populations

##### 4.2.1 Study TRA100773A

The following table shows the subgroup analyses for using of ITP medication at randomization, splenectomy status and baseline platelet counts of 15Gi/L. The result shows that number of responders increased in a dose dependent manner. However, number of responders has a lower percentage among subjects using ITP medication at randomization for 75 mg treatment group compared to the proportion of responders in the 50 mg group. There is a higher percentage of responders in the 50mg and 75mg treatment groups who were not splenectomized compared to subjects who were refractory following splenectomy. There is a higher percentage of responders in the placebo, 50mg and 75mg treatment groups with baseline platelet counts >15Gi/l compared to subjects with baseline platelet count ≤15Gi/L. However, in the 30mg treatment group, there is a lower percentage of responder with a baseline platelet count >15Gi/L compared to subjects with a baseline platelet ≤15Gi/L (Table 32).

**Table 29 Responders for using ITP Medication at Randomization, Splenectomy Status, Baseline Platelet Count of 15 Gi/L at Day 43 Visit**

Day 43 Visit	Treatment Group							
	Placebo N=27		30mg N=29		50mg N=27		75mg N=26	
Use of ITP medication Responders	Yes 16.7% (1/6)	No 9.5% (2/21)	Yes 44.4% (4/9)	No 20% (4/20)	Yes 72.7% (8/11)	No 68.8% (11/16)	Yes 60% (6/10)	No 93.8% (15/16)
Splenectomy Status Responders	Yes 14.3% (2/14)	No 7.7% (1/13)	Yes 21.4% (3/14)	No 33.3% (5/15)	Yes 53.3% (8/15)	No 91/7% (11/12)	Yes 70% (7/10)	No 87.5% (14/16)
Baseline Platelet Count Responders	≤15 7.1% (1/14)	>15 15.4% (2/13)	≤15 33.3% (5/15)	>15 21.4% (3/14)	≤15 54.6% (6/11)	>15 81.2% (13/16)	≤15 64% (9/14)	>15 100% (12/12)

The following table shows the analysis of responders using logistic regression analysis adjusted for using ITP medication at randomization, splenectomy status, and baseline platelet counts (Table 33). The p-value for the interaction between treatment group and use of ITP medication at randomization is 0.09. This result may be due to the different pattern of dose response in subjects who reported use of ITP medication at randomization compared to those who did not. The p-value for the interaction between treatment group and baseline platelet counts is 0.04. The p-value for the interaction between treatment group and splenectomy status is 0.3. There is no significant interaction between treatment group and splenectomy status, indicating that the proportion of responders increases with increasing dose in both subgroups.

**Table 30 Reviewer's Subgroup analysis of responder at Day 43 Visit**

	Treatment Group		
	30mg N=29	50mg N=27	75mg N=26
Use of ITP Medication: Yes Odds Ratio (95% CI) p-value (one-sided vs placebo)	2.78 (0.2, 38.9) 0.22	13.92 (0.97, 198.87) 0.03	7.09 (0.52, 96.36) 0.07
Use of ITP Medication: No Odds Ratio (95% CI) p-value (one-sided vs placebo)	2.62 (0.4, 17.3) 0.16	26.41 (3.8, 185.5) <0.001	274.2 (17.6, 4268.7) <0.001
Baseline Platelet Counts: ≤15 Odds Ratio (95% CI) p-value (one-sided vs placebo)	6.6 (0.7, 67.5) 0.056	15.1 (1.4, 164.1) 0.013	22 (2.2, 224.93) 0.005
Baseline Platelet Counts: >15 Odds Ratio (95% CI) p-value (one-sided vs placebo)	1.5 (0.2, 12.13) 0.35	67.52 (4.7, 981.4) 0.001	

#### 4.2.2 Study TRA100773B

The following table shows the subgroup analyses for use of ITP medication at randomization, splenectomy status and baseline platelet counts ≤ 15Gi/L (Table 29). The

result shows a higher percentage of responders at Day 43 in the eltrombopag group compared to placebo, regardless of whether subjects used ITP medication at randomization, splenectomy status, or baseline platelet counts  $\leq 15\text{Gi/L}$  (Yes/No). There is no statistical significant interaction between response and the use of ITP medication at randomization (P-value is 0.77). No interaction between response and splenectomy status (p-value is 0.75), No interaction between response and baseline platelet count status (p-value is 0.45).

**Table 31 Reviewer's summary of responders for ITP Medication used at Randomization, Splenectomy Status, and Baseline Platelet Count at Day 43 Visit**

Day 43 Visit	Treatment Group			
	Placebo N=38		Eltrombopag N=74	
Use of ITP medication Responders	Yes 12.5% (2/16)	No 19.1% (4/21)	Yes 54.8% (17/31)	No 61.9% (26/42)
Splenectomy Status Responders	Yes 15.4% (2/13)	No 16.7% (4/24)	Yes 62.1% (18/29)	No 56.8% (25/44)
Baseline Platelet Count Responders	$\leq 15\text{Gi/L}$ 12.5% (2/16)	$> 15\text{Gi/L}$ 19.1% (4/21)	$\leq 15\text{Gi/L}$ 43.2% (16/37)	$> 15\text{Gi/L}$ 75% (27/36)

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

1. One of the conclusions the applicant made was that eltrombopag in the treatment of ITP patients decrease the incidence and severity of bleeding in subjects with relapsed or refractory chronic ITP. The applicant conducted logistic regression analysis of the bleeding events, adjusting for the covariates of use of concomitant medication at randomization, splenectomy status, and baseline platelet count. However, it is obvious that the bleeding event is time dependent with multiple observations per subject. It is more appropriate to use survival analysis models based on time-to-event in multiple event setting. In this review, the Andersen-Gill (AG) formulation of proportional hazards model as a counting process are performed for assessment of bleeding, using the Schoefeld residuals to test the basic assumptions of a Cox model. The proportional hazard and the functional form of the covariates are also included in the review. This issue is discussed in details in the sections 1.3 and 3.1.3.

2. No subgroup analysis was carried out for subjects enrolled in the US sites. It is very important to have short-term response rate using eltrombopag in the treatment of US ITP patients. This issue is discussed in detail in section 1.3.

3. The applicant reported that the variables of concomitant medication, splenectomy status and baseline platelet count did not have impact on the treatment efficacy results when comparing eltrobopag group to placebo. This review re-analyzed the data by including interactions between these three variables in the logistic regression model. No significant interaction effects between the three stratification variables and treatment

were found. Intuitively, those three variables should have certain level of impacts on the primary efficacy results. It is essential to have prospective, well-designed, controlled trials to investigate this issue.

4. The applicant concluded that the potential clinical benefit of eltrombopag in this patient population is a significant unmet medical need. Eltrombopag 50 mg (with increases up to 75 mg) once daily for up to 6 weeks of treatment was found to be a well tolerated and effective treatment option for ITP. However, based on Study B's data, only 46% patients had ever received 75 mg dose treatment after the Day 22 visit treatment period. Study B was not designed to investigate the dose titration from 50 mg to 75 mg dosing regiment. It is unknown why subjects permitted to increase dose to 75 mg.

5. Platelet counts of eltrombopag patients were decreasing after tape-off the treatment over time. The mean platelet counts of eltrombopag patients became numerically lower than that of placebo patients at the last two follow-up visits. More data with longer follow-up time is necessary for investigating the safety of using eltrombopag in a short-term purpose.

## **5.2 Conclusions and Recommendations**

1. Analysis of the primary endpoint showed that treatment increased platelet counts in subject with chronic ITP in a dose dependent manner. The primary endpoint was achieved. Subjects treated with treatment had statistically significant greater odds of responding at the Day 43 Visit compared to subjects treated with placebo.

2. The interaction between treatment and each of randomization strata were not statistically significant. Patients responded regardless of splenectomy status, use of ITP medication, baseline platelet count  $\leq 15$  Gi/L. (Intuitively, those three variables should have certain level of impacts on the primary efficacy results. It is essential to have prospective, well-designed, controlled trails to investigate this issue.)

3. Assessment WHO bleeding Scale showed treatment can decrease in the percentage of subject of any bleeding during on-therapy period of the trial. It is not robust statistically significant ( $p=0.067$ ). However, the clinical meaningfulness of this scoring system is unclear, especially with respect to incremental changes. Additionally, the scores could have been biased by knowledge of patients' platelet counts.

## **SIGNATURES/DISTRIBUTION LIST (Optional)**

An example of this optional documentation is as follows:

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Date: 6/01/08

Concurring Reviewer(s):

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Biometrics Deputy Division Director: Aloka Chakravarty

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**Statistical Review and Evaluation**  
**(Carcinogenicity Studies)**

**NDA Number:** 22-291

**Drug Name:** Promacta

**Sponsor:** GlaxoSmithKline

**Pharm/tox Reviewer:** Yash Chopra, Ph.D.  
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**Supervisory Pharmacologist:** Adebayo A. Lanionu, Ph.D.  
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**Project Manager:** Hyon-Zu Lee,  
Division of Medical Imaging and Hematology Products

**Statistical Reviewers:** Steven F. Thomson and Karl K. Lin, Ph.D.  
Division of Biometrics 6

**Document Reviewed:** " SB-497115-GR: 2-Year Oral Gavage Carcinogenicity Study in CD<sup>TM</sup>IGS Rats", — Study Number 7274-638, GSK Document Number CD2007/00923/00, Report Issued 28 September 2007

"SB-497115-GR: 2-Year Oral Gavage Carcinogenicity Study in CD-1<sup>®</sup> Mice", — Study Number 7274-666, GSK Document Number CD2006/00751/02, Report Issued 09 October 2007

Electronic tumor datasets in FDA format submitted by the sponsor on April 11, 2008

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**APPEARS THIS WAY  
ON ORIGINAL**

## 1. Summary

Based on the Agency's decision rules for adjustment of multiple testing, the reviewers' analysis results show that there was no statistically significant positive trend among all treatment groups or positive pairwise increase in incidence in individual treated groups over the control in both males and females in both the rat and the mouse studies for all the tumor types tested. The reviewer's analysis results are consistent with the results of the sponsor's analysis of the neoplastic lesions data of the rat and the mouse studies.

The above negative findings of the two studies do not necessarily mean that the drug is truly not animal carcinogenic. One can always conduct a carcinogenicity study of a compound using an invalid design to get a negative result by either killing the animals early and/or using doses that are not high enough to present tumor challenges to the tested animals. The pharm/tox reviewers should address this important issue before drawing their final conclusion of the carcinogenicity effect of the drug.

## 2. Introduction

There were two carcinogenicity studies, one in rats and one in mice, included in this submission. The purpose of conducting the carcinogenicity studies was to evaluate the carcinogenicity potential of Promacta when it was administered to the animals for two years. Both the rat and mouse studies were conducted at \_\_\_\_\_

\_\_\_\_\_ The study initiation and completion dates of the rat study were December 2, 2004 and September 28, 2007, respectively. The study initiation and completion dates of the mouse study were November 15, 2004 and October 9, 2007, respectively. The sponsor submitted the tumor datasets of the two studies in FDA format for the Agency to perform statistical review and evaluation on April 11, 2008.

b(4)

Yash Chopra, Ph.D. of Division of Medical Imaging and Hematology Products who is the reviewing pharmacologist of this submission has requested that the Pharm/Tox Statistics Team of the Office of Biostatistics (OB) conducts a statistical review and evaluation of the carcinogenicity studies of this submission. The statistical reviewers have met and discussed the preliminary results with Dr. Chopra.

## 3. Rat Study

### 3.1. Study Design

Groups of rats (60/sex/group) were given 0 (vehicle), 10, 20, or 40 mg/kg/day SB-497115 (Batch Nos. TPO-E-02C. — F076633; and F083255) in aqueous 2% hydroxypropyl methylcellulose (HPMC) with 0.2% sodium lauryl sulfate (SLS) in reverse osmosis (RO) water (dose volume of 10 mL/kg) once daily for at least 104 weeks by oral gavage. An additional six rats/sex were included at each dose level for toxicokinetic evaluation. The design of the rat study is summarized in the following table (Table 1) from the sponsor's report.

b(4)

Table: 1 The Design of the Rat Study

Group Number	Dose <sup>a, b</sup> (mg/kg/day)	Dose Concentration <sup>a, b</sup> (mg/mL)	Number/Sex
<b>Toxicology Animals</b>			
1 <sup>c</sup>	0	0	60
2	10	1	60
3	20	2	60
4	40	4	60
<b>Toxicokinetic Animals</b>			
5 <sup>c</sup>	0	0	6
6	10	1	6
7	20	2	6
8	40	4	6

a. The dose volume was 10 mL/kg.

b. Dose concentrations were adjusted for salt form and purity using a correction factor specific to each batch of test article.

c. Animals in the control groups received the control article (2% aqueous HPMC with 0.2% SLS in RO water) only.

### 3.2. Sponsor's Analyses and Results

#### 3.2.1. Sponsor's Methods of Analysis of Survival Data and Results

Evaluations of trend and heterogeneity of survival data were performed using the Cox-Tarone binary regression on life tables and Gehan-Breslow nonparametric methods using the National Cancer Institute (NCI) Life Table Package (Thomas et al., 1977). Those animals sacrificed at the scheduled interval and animals sacrificed for other reasons (gavage-related or aggressive behavior) were censored in the analyses. Continuity-corrected, one-sided tail probabilities for trend and group comparisons were evaluated at the 5% significance level. The Kaplan-Meier product-limit survival curves from the sponsor's report are presented in Figure 1 and Figure 2 for males and females, respectively. Sponsor's analysis results of survival data are presented in Tables 2 and 3 for males and females, respectively.

Survival As indicated in Text Table 1, no significant positive trend in mortality was observed in the males. The significantly increased mortality in the males given 10 mg of SB-497115-GR/kg of body weight/day (mg/kg/day) ( $p = 0.0318$  for Cox – Tarone test and  $p = 0.0197$  for Gehan-Breslow test) when compared to the males given 0 mg/kg/day is probably due to background variation because no other treated groups in the males showed any significant increase when compared with males given 0 mg/kg/day.

Figure 1: Kaplan-Meier Product Limit Estimates of Survival Curves of Male Rats

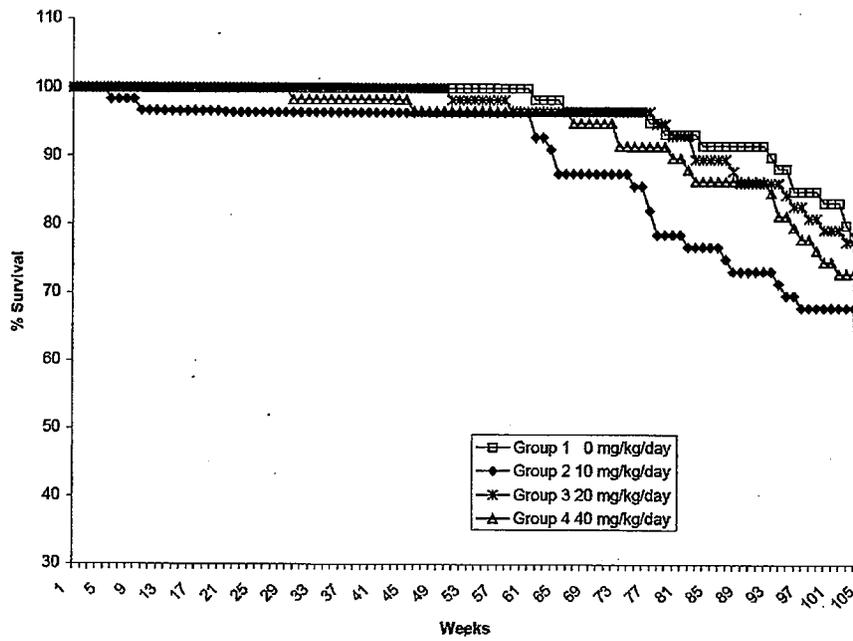


Figure 2: Kaplan-Meier Product Limit Estimates of Survival Curves of Female Rats

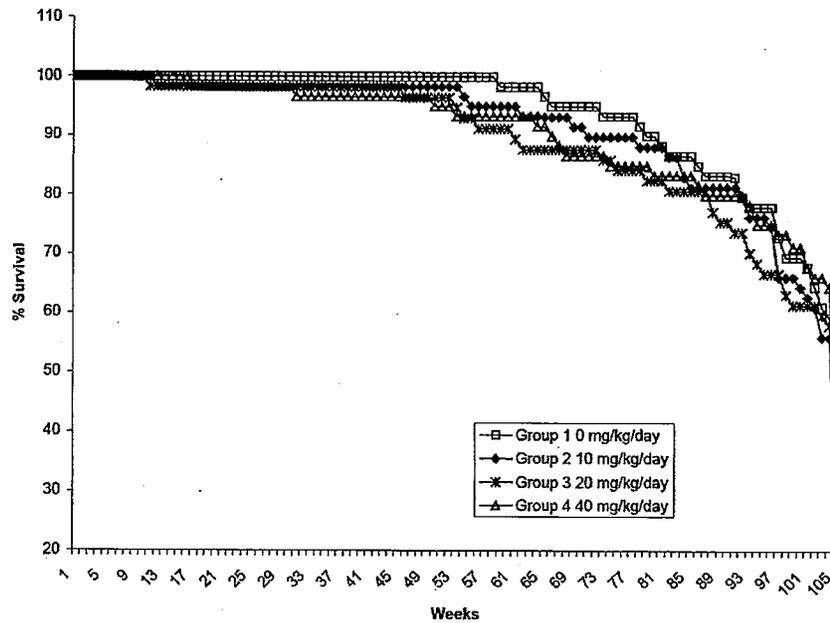


Table 2: Results of Statistical Analyses of Survival Data – Male Rats

Group	1	2	3	4
Dose (mg/kg/day)	0	10	20	40
Unadjusted Mortality (Rate)	13/60 (0.217)	21/60 (0.350)	14/60 (0.233)	16/60 (0.267)
Adjusted Mortality				
Kaplan-Meier Estimate (Final)	0.217	0.409	0.263	0.271
Standard Error	0.053	0.078	0.064	0.058

	Cox-Tarone Test	Gehan-Breslow Test
1 vs 2-4 p-value (one-sided)	0.4535 +	0.4266 +
1 vs 2 p-value (one-sided)	0.0318 + *	0.0197 + *
1 vs 3 p-value (one-sided)	0.4370 +	0.3886 +
1 vs 4 p-value (one-sided)	0.2797 +	0.2020 +

+ = Effect in the increased direction.

\* = Significant at 5.0% level.

Table 3: Results of Statistical Analyses of Survival Data – Female Rats

Group	1	2	3	4
Dose (mg/kg/day)	0	10	20	40
Unadjusted Mortality (Rate)	25/60 (0.417)	26/60 (0.433)	24/60 (0.400)	22/60 (0.367)
Adjusted Mortality				
Kaplan-Meier Estimate (Final)	0.422	0.440	0.421	0.369
Standard Error	0.064	0.065	0.065	0.063

	Cox-Tarone Test	Gehan-Breslow Test
1 vs 2-4 p-value (one-sided)	0.3813 -	0.4670 -
1 vs 2 p-value (one-sided)	0.4333 +	0.3357 +
1 vs 3 p-value (one-sided)	0.4436 +	0.2876 +
1 vs 4 p-value (one-sided)	0.4041 -	0.4292 -

+ = Effect in the increased direction.

- = Effect in the decreased direction.

As the results in Table 2 indicated, no significant positive trend in mortality was observed in the males. The significantly increased mortality in the males given 10 mg of SB-497115-GR/kg of body weight/day (mg/kg/day) ( $p = 0.0318$  for Cox – Tarone test and  $p = 0.0197$  for Gehan-Breslow test) when compared to the males given 0 mg/kg/day is probably due to background variation because no other treated groups in the males showed any significant increase when compared with males given 0 mg/kg/day.

Results in Table 3 indicated that there was no significant positive trend or increase in any of the treated groups when compared with the animals given 0 mg/kg/day in female mortality.

### **3.2.2. Sponsor's Methods of Analysis of Data of Neoplastic Lesions and Results**

Neoplastic Lesions Neoplastic lesions were chosen for statistical analyses if the incidence in at least one treated group for each sex was increased or decreased by at least two occurrences over that of the control group. The occult tumors (incidental alone or incidental and fatal combined) were analyzed by asymptotic fixed interval-based prevalence test (Peto et al., 1980). The cutoff points for the interval-based test were Weeks 0 through 52, 53 through 78, 79 through 92, 93 up to before terminal euthanasia and terminal euthanasia. The test was implemented using PROC MULTTEST in the SAS system (2003). In the case of sparse tables (<5), the exact form of the previously listed analysis was used. Palpable (superficial) tumors were analyzed by the Cox-Tarone binary regression method using the death time or the first palpation time (as applicable) as a surrogate for the tumor onset time. Because of variable end-of-study for various groups in some cases, the interval-based method may be biased.

One-sided positive trends in common (background incidence rate of >1%) and rare (background incidence of <1%) tumors (if applicable) defined by the study pathologist were evaluated at the 0.005 and 0.025 significance levels, respectively. High-dose group comparisons in common and rare tumors were evaluated at the 0.01 and 0.05 significance levels [Food and Drug Administration (FDA) Draft Guidance for Industry, 2001]. Other intermediate pairwise one-sided group comparisons were evaluated at the 5.0% significance level. The benign and malignant neoplastic incidences were evaluated separately and combined, where appropriate. The criteria for combination were based on the work of McConnell et al (1986). The incidences of multiple-organ and combined neoplastic findings such as hemangioma, hemangiosarcoma, leiomyoma, leiomyosarcoma, endometrial stromal polyp, and endometrial stromal sarcoma were counted by animal not by tissue type. They were evaluated statistically if they met the

selection criterion for the analysis. The statistical results for these cases may be biased because not all animals may have been examined for every tissue.

Appendixes A.1 and A.2 include the tumor incidence rates by group and the statistical results in the form of one-sided tail probabilities for the males and females, respectively.

Results in Appendix A.1 show that there was no statistically significant positive trend among all treatment groups or positive pairwise increase in incidence in individual treated groups over the control in male rats for all the tumor types tested.

Results in Appendix A.2 also show that there was no statistically significant positive trend among all treatment groups or positive pairwise increase in incidence in individual treated groups over the control in female rats for all the tumor types tested. The sponsor reported in the analysis results of neoplastic lesions that, in female rats, there were a close to statistically significant NEGATIVE trend among all treatment groups ( $p=0.0027 > 0.0025$ ) and a statistically

significant pairwise DECREASE in the 40 mg/kg group over the control group ( $p=0.0020 < 0.01$ ) in incidence in adenoma combined with carcinoma in the pituitary,

### **3.3. Reviewers' Methods of Analysis of Data of Neoplastic Lesions and Results**

#### **3.3.1. Reviewers' Methods of Analysis**

The sponsor performed a complete analysis of the survival data of the rat and mouse studies using the same methods routinely used by FDA statistical reviewers. The results of the sponsor's analysis are included in this report. For this reason, the FDA reviewers of this submission did not repeat the sponsor's analysis.

The FDA reviewers performed an independent analysis of the data of neoplastic lesions electronically submitted by the sponsor. The FDA reviewers used the poly-3 trend test and pairwise comparison test described in Bailer and Portier (1988), and Bieler and Williams (1993) in their analysis of the neoplastic lesions data while, as mentioned above, the sponsor used the Peto trend test and pairwise comparison test. Both the Peto and the poly-3 methods that adjust for differences in mortality among treatment groups have been widely used in the analysis of neoplastic lesions data. However, the Peto method relies on good information on cause of death of tumors. There have been debates among pathologists if the cause of death information of tumors can be determined accurately. There are consequences in misclassifying tumors as fatal or as incidental in survival adjusted statistical tests. The prevalence method will reject the null hypothesis of no positive trend less frequently than it should as the lethality of a tumor increases (Peto et al. 1980; Dinse 1994). This will increase the probability of failing to detect true carcinogens.

The poly-3 method was developed as an alternative method to the Peto method to overcome the problem of having to determine if a tumor caused an animal's death or not while adjusting the differences in mortality among treatment groups in the test of trend or pairwise increase in tumor incidence. The poly-3 method has been used more widely than the Peto method recently because of the advantage of not having to rely on the questionable cause of death information of tumors.

Because of the large number of comparisons involved (usually 2 species, 2 sexes, and 30 or more tissues examined), a great potential exists for finding statistically significant positive trends or treatment-placebo differences due to chance alone (i.e., a false positive). Therefore, it is important that an overall evaluation of the carcinogenic potential of a drug take into account the multiplicity of statistical tests of significance for both trends and pairwise comparisons. The sponsor used the multiplicity adjustment method developed by Lin and Rahman (1998), and recommended in the 2001 FDA draft guidance for industry document in their analysis of neoplastic lesions data. The multiplicity adjustment methods recommended in the FDA guidance document are as follows: For a two-year-two-species-two-sex submission, one-sided positive trends in incidence in common (background incidence rate of  $> \text{ or } = 1\%$ ) and rare (background incidence of  $< 1\%$ ) tumors are tested at the 0.005 and 0.025 significance levels, respectively; and pairwise increase in incidence of individual treated groups over the control group are tested at the 0.01 and 0.05 significance levels, respectively, for common and rare tumors.

Originally, the above multiplicity adjustment methods for controlling the overall false positive rate was developed for tumor data analysis using the Peto method. However, some later simulation results also Lin and Rahman (unpublished manuscript presented in 2006 BASS meeting in Savanna, Georgia) indicated the multiplicity adjustment methods described above are also applicable to the tumor data analysis using the poly-3 method.

### **3.3.2. Reviewers' Analysis Results**

The reviewers' analysis results of individual tumor types of the rat study using the survival-adjusted poly-3 method are presented in Appendices B.1 and B.2 for male rats and female rats, respectively.

Based on the Agency's decision rules for adjustment of multiple testing, the reviewers' analysis results show that there was no statistically significant positive trend among all treatment groups or positive pairwise increase in incidence in individual treated groups over the control in both male and female rats for all the tumor types tested. The reviewer's analysis results are consistent with the results of the sponsor's analysis of the neoplastic lesions data of the rat study.

The sponsor reported in the analysis results of neoplastic lesions that, in female rats, there was a statistically significant pairwise DECREASE in the 40 mg/kg group over the control group ( $p=0.0020 < 0.01$ ) in incidence in adenoma combined with carcinoma in the pituitary. However, the reviewers treat a negative trend in incidence among treatment groups or a pairwise decrease in incidence in a treated group over the control group as not statistically significant.

## **4. Mouse Study**

### **4.1. Study Design**

A 104-week oral carcinogenicity study with SB-497115 was conducted in male and female CD-1 mice (60/sex/group) at doses of 25, 75, 150 and 300 mg/kg/day. SB-497115 (Batch Numbers TPO-E-01C and TPO-E-07) was formulated in aqueous 2% hydroxypropyl methylcellulose with 0.2% sodium lauryl sulfate in reverse osmosis water and administered at a volume of 10 mL/kg/day. Due to treatment-related morbidity and mortality, mice given 300 mg/kg/day were terminated during Week 3, while the 150 mg/kg/day dose level was reduced to 115 mg/kg/day in females during Week 21 and was discontinued in males and females during Week 43. This dose group was terminated in Week 64. All surviving mice in the 25 and 75 mg/kg/day treatment groups were euthanized at the end of the 104-week treatment period. Additional groups of mice were used for the purposes of toxicokinetic evaluation.

Table 4: The Design of the Mouse Study

Group Number	Dose Level <sup>1</sup> (mg/kg/day)	Dose Concentration (mg/mL)	Number/Sex
Toxicology Animals			
1	0	0	60
2	25	2.5	60
3	75	7.5	60
4 <sup>3,4</sup>	150/115	15/11.5	60
5 <sup>2</sup>	300	30	60
Toxicokinetic Animals			
6	0	0	48
7	25	2.5	48
8	75	7.5	48
9 <sup>3,4</sup>	150/115	15/11.5	48
10 <sup>2</sup>	300	30	48

1. Doses are expressed in terms of the parent compound.
2. Groups 5 and 10 were last dosed on Day 15 for males and Day 14 for females and terminated on Day 17 for males and Day 16 for females.
3. Dose Levels for Groups 4 and 9 Females were decreased on Day 143 (Week 21)
4. Groups 4 and 9 mice were not dosed after 22 September 2005 (study Day 298 for males and study Day 297 for females).

## 4.2. Sponsor's Analyses and Results

### 4.2.1. Sponsor's Methods of Analysis of Survival Data and Results

The methods of analysis of survival data of the mouse study by the sponsor are the same as those used in the rat study. The Kaplan-Meier product-limit survival curves are presented in Figure 3 and Figure 4 for males and females, respectively. Continuity-corrected, 1-sided tail probabilities for trend and group comparisons were evaluated at the 5% significance level and are reported in Table 5 and Table 6, respectively.

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Figure 3: Kaplan-Meier Product Limit Estimates of Survival Curves of Male Mice

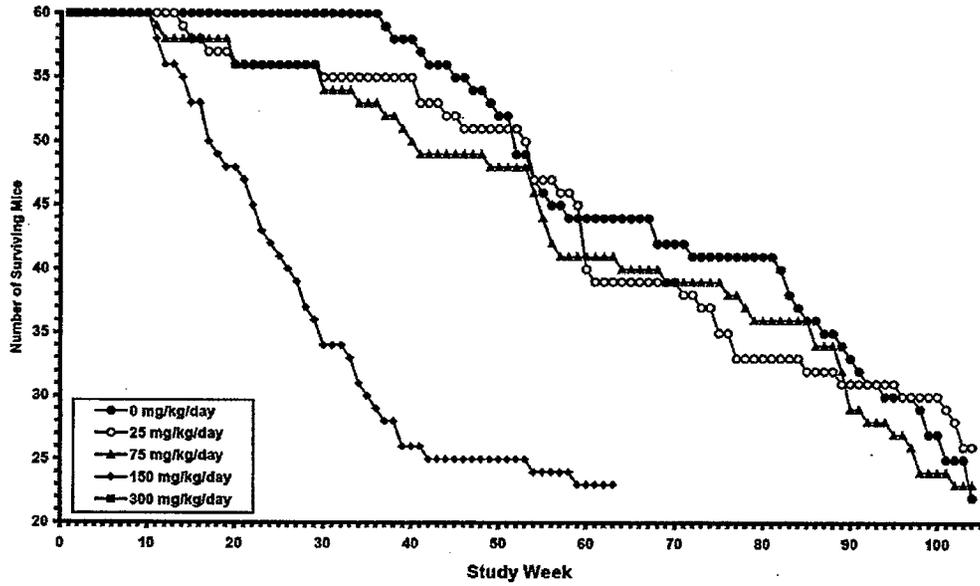


Figure 4: Kaplan-Meier Product Limit Estimates of Survival Curves of Female Mice

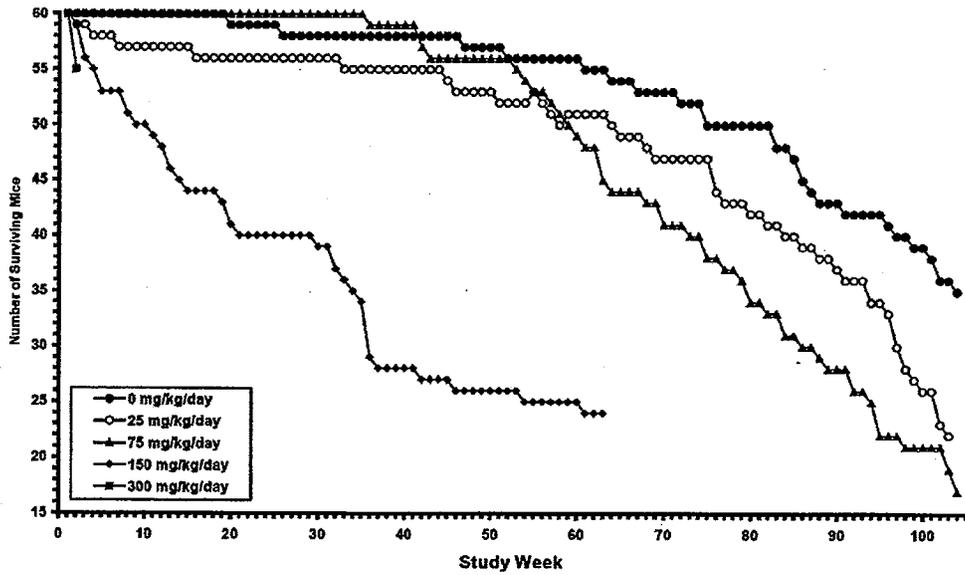


Table 5: Results of Statistical Analyses of Survival Data – Male Mice

Group	1	2	3
Dose (mg/kg/day)	0	25	75
Unadjusted Mortality (Rate)	37/60 (0.617)	34/60 (0.567)	37/60 (0.617)
Adjusted Mortality			
Kaplan-Meier Estimate (Final)	0.627	0.567	0.617
Standard Error	0.063	0.064	0.063

	Cox-Tarone Test	Gehan-Breslow Test
1 vs 2-3 p-value (one-sided)	0.3978 +	0.2434 +
1 vs 2 p-value (one-sided)	0.4564 -	0.4277 +
1 vs 3 p-value (one-sided)	0.4116 +	0.2315 +

+ = Effect in the increased direction. - = Effect in the decreased direction.

Table 6: Results of Statistical Analyses of Survival Data – Female Mice

Group	1	2	3
Dose (mg/kg/day)	0	25	75
Unadjusted Mortality (Rate)	25/60 (0.417)	38/60 (0.633)	43/60 (0.717)
Adjusted Mortality			
Kaplan-Meier Estimate (Final)	0.417	0.633	0.717
Standard Error	0.064	0.062	0.058

	Cox-Tarone Test	Gehan-Breslow Test
1 vs 2-3 p-value (one-sided)	0.0003 + **	0.0003 + **
1 vs 2 p-value (one-sided)	0.0153 + *	0.0155 + *
1 vs 3 p-value (one-sided)	0.0004 + **	0.0003 + **

+ = Effect in the increased direction.

\* = Significant at 5.0% level. \*\* = Significant at 1.0% level.

The sponsor used the survival data of only the control, 25 mg/kg, and 75 mg/kg groups in its analysis. The sponsor's results show that no statistically significant positive trend or increase over the control group was observed in mortality in any of the treated groups for the males.

However, a statistically significant positive trend ( $p = 0.0003$  for both Cox-Tarone and Gehan-Breslow tests) was observed in mortality in the females given 0, 25, or 75 mg/kg/day of the test compound. The trend was associated with significantly increased mortality in the females given 25 ( $p=0.0153$  for Cox-Tarone test and  $p=0.0155$  for Gehan-Breslow test) or 75 ( $p=0.0004$  for Cox-Tarone test and  $p=0.0003$  for Gehan-Breslow test) mg/kg/day as compared to the control group.

#### **4.2.2. Sponsor's Methods of Analysis of Data of Neoplastic Lesions and Results**

The methods of analysis of data of neoplastic lesions of the mouse study by the sponsor are the same as those used in the rat study. Appendix A.3 and Appendix A.4 show the tumor incidence rates by group and the statistical results in the form of one-sided tail probabilities for the males and females, respectively.

Results of the sponsor's analysis show that there was no statistically significant positive trend among all treatment groups or positive pairwise increase in incidence in individual treated groups over the control in males and females for all the tumor types tested except the bronchiolar-alveolar adenoma combined with carcinoma in the females noted below.

For bronchiolar-alveolar adenoma combined with carcinoma in the females, a statistically significant increase was observed in the animals given 25 mg/kg/day compared with animals given 0 mg/kg/day ( $p = 0.0049 < 0.01$ ). No corresponding significant trend was noted.

#### **4.3. Reviewers' Methods of Analysis of Data of Neoplastic Lesions and Results**

##### **4.3.1. Reviewers' Methods of Analysis**

The reviewers' methods of analysis of the neoplastic lesions data of the mouse study are the same as those used in the rat study.

##### **4.3.2. Reviewers' Analysis Results**

The reviewers' analysis results of individual tumor types of the mouse study using the survival-adjusted poly-3 method are presented in Appendices B.3 and B.4 for male rats and female rats, respectively.

Based on the Agency's decision rules for adjustment of multiple testing, the reviewers' analysis results show that there was no statistically significant positive trend among all treatment groups or positive pairwise increase in incidence in individual treated groups over the control in both male and female rats for all the tumor types tested. The reviewer's analysis results are consistent with the results of the sponsor's analysis of the neoplastic lesions data of the mouse study except the lung bronchiolar-alveolar carcinoma.

The sponsor reported that for bronchiolar-alveolar carcinoma in the females, a statistically significant increase was observed in the animals given 25 mg/kg/day compared with animals

given 0 mg/kg/day ( $p = 0.0049 < 0.01$ ). The incidence rates of the tumor type in the two groups are 5/60 and 12/58, respectively. However, the reviewer's pairwise comparison test using the poly-3 method for this tumor type yielded a p-value of 0.0337, and did not reach the statistically significance level of 0.01.

### 5. Evaluation of Validity of Designs of Negative Studies

A negative finding of a carcinogenicity study of a drug can be either that the drug is truly not carcinogenic or that the design of the study is not valid either because there were not sufficient numbers of animals living long enough to provide adequate exposure to the chemical and to be at risk of forming late-developing tumors, or because the doses used were not adequate to present a reasonable tumor challenge to the tested animals (Haseman 1985).

As a rule of thumb, a 50 percent survival rate of the 50 initial animals in any treatment group between weeks 80 to 90 of a 2-year study would be considered to yield a sufficient number of animals with adequate exposure. The percentage can be lower or higher if the number of animals used in each treatment/sex group is larger or smaller than 50, but between 20 to 30 animals should be still alive during these weeks.

The adequacy of doses selected and of the animal tumor challenge in long-term carcinogenicity experiments is evaluated by pharmacologists and the CDER Carcinogenicity Assessment Committee (CAC) based on the previously described ICH approaches as well as on the results of the long-term carcinogenicity experiments. To assist the evaluation, CDER statistical reviewers are often asked to provide analyses of body weight and mortality differences between treated and control groups.

The following reviewers' additional analyses of survival and body weight data are intended for the pharm/tox reviewers and ECAC members to use along with their pharm/tox expertise to determine if the study designs of the rat and mouse studies are valid so that the negative finding is true indication of lack of carcinogenic potential of the drug.

In the rat study, the survival rates at week 104 are at least 56% for all treatment groups of both sexes. The survival rates at week 104 for the 0, 10, 20, and 40 mg/kg groups are 78%, 68%, 78%, and 73%, respectively, for males, and 59%, 56%, 58%, and 64%, respective, for females.

In the mouse study, the survival rates at week 90 and at week 104 are presented in the table below (Table 7)

Table 7: Survival Rates at Week 90 and 104 in the Mouse Study

Treatment Group	Males		Females	
	Week 90	Week 104	Week 90	Week 104
0 mg/kg	56%	37%	72%	58%
25 mg/kg	52%	43%	63%	37%
75 mg/kg	48%	38%	47%	28%

The following two tables (Tables 8, and 9) contain the summary body weight data of the rat and the mouse studies, respectively.

Table 8: Group Mean Body Weight Changes (in G) of the Rat Study

Treatment Group	Mean Weight at Week 1	Mean Weight at Week 104	Mean Weight Gain	% Gain of the Control Group
Males				
0 mg/kg	196	436	240	
10 mg/kg	194	440	246	102.5%
20 mg/kg	197	453	256	106.7%
40 mg/kg	196	453	257	107.1%
Females				
0 mg/kg	173	246	73	
10 mg/kg	172	262	90	123.3%
20 mg/kg	169	278	109	149.3%
40 mg/kg	170	270	100	137.0%

Table 9: Group Mean Body Weight Changes (in G) of the Mouse Study  
(Included Data of 0, 25, and 75 mg/kg Groups Only)

Treatment Group	Mean Weight at Week 1	Mean Weight at Week 102	Mean Weight Gain	% Gain of the Control Group
Males				
0 mg/kg	29.9	38.4	8.5	
25 mg/kg	29.6	37.9	8.3	97.6%
75 mg/kg	29.5	38.4	8.9	104.7%
Females				
0 mg/kg	24.0	33.5	9.5	
25 mg/kg	24.0	33.1	9.1	95.6%
75 mg/kg	23.6	32.8	9.2	96.8%

## 6. Concluding Remarks

Based on the Agency's decision rules for adjustment of multiple testing, the reviewers' analysis results show that there was no statistically significant positive trend among all treatment groups or positive pairwise increase in incidence in individual treated groups over the control in both males and females in both the rat and the mouse studies for all the tumor types tested.

The reviewer's analysis results are consistent with the results of the sponsor's analysis of the neoplastic lesions data of the rat and the mouse studies.

The above negative findings of the two studies do not necessarily mean that the drug is truly not animal carcinogenic. One can always conduct a carcinogenicity study of a compound using an invalid design to get a negative result by either killing the animals early and/or using doses that are not high enough to present tumor challenges to the tested animals. The pharm/tox reviewers should address this important issue before drawing their final conclusion about the carcinogenicity effect of the drug.

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Appendix A.1

Sponsor's Statistical Analysis of Data of Neoplastic Lesions  
Using Peto Trend and Pairwise Comparison Tests

Male Rats

Results of Statistical Analyses of Neoplastic Lesions - Males

Tissue and Lesion	Group Dose level (mg/kg/day)	Unadjusted Lifetime Incidence Rate			
		1	2	3	4
Pituitary, B-Adenoma (I/F)		0	10	20	40
1 vs 2-4 p (one-sided)		0.1462 -	0.1475 +	0.2788 -	0.2902 -
Pituitary, M-Carcinoma (I/F)		0/60	0/60	0/60	1/60
1 vs 2-4 p (one-sided)		Incidences across groups do not meet selection criterion.			
Pituitary, Adenoma/Carcinoma (I/F)		18/60	20/60	14/60	15/60
1 vs 2-4 p (one-sided)		0.1935 -	0.1475 +	0.2788 -	0.3665 -
Adrenal, Medulla, B-Pheochromocytoma (I)		3/60	1/60	1/60	5/60
1 vs 2-4 p (one-sided)		0.1950 +	0.4272 - (E)	0.3572 - (E)	0.2042 +
Adrenal, Medulla, M-Pheochromocytoma (I/F)		0/60	0/60	1/60	0/60
1 vs 2-4 p (one-sided)		Incidences across groups do not meet selection criterion.			
Adrenal, Medulla, B/M-Pheochromocytoma (I/F)		3/60	1/60	2/60	5/60
1 vs 2-4 p (one-sided)		0.1684 +	0.4272 - (E)	NA	0.2042 +
Thyroid, B-C-Cell Adenoma (I)		4/60	1/60	3/60	3/60
1 vs 2-4 p (one-sided)		0.4552 -	0.2874 - (E)	NA	NA
Thyroid, M-C-Cell Carcinoma (I)		0/60	0/60	4/60	1/60
1 vs 2-4 p (one-sided)		0.1180 + (E)	NA	0.0508 + (E)	NA
Thyroid, C-Cell Adenoma/Carcinoma (I)		4/60	1/60	7/60	4/60
1 vs 2-4 p (one-sided)		0.2406 +	0.2874 - (E)	0.1357 +	NA

I = Incidental tumor; F = Fatal tumor.  
+/- = Effect in the increased/decreased direction.  
(E) = Exact test.  
NA = Not Analyzed.

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### Results of Statistical Analyses of Neoplastic Lesions - Males

Tissue and Lesion	Group Dose level (mg/kg/day)	Unadjusted Lifetime Incidence Rate			
		1	2	3	4
Thyroid, B-Adenoma, Follicular Cell Adenoma (I)	0	2/60	3/60	1/60	0/60
1 vs 2-4 p (one-sided)		0.0785 -	NA	NA	0.2611 - (E)
Heart, M-Endocardial Schwannoma (I/F)	0	2/60	0/60	2/60	2/60
1 vs 2-4 p (one-sided)		0.3875 +	0.2292 - (E)	NA	NA
Liver, B-Adenoma, Hepatocellular (I)	0	0/60	3/60	1/60	0/60
1 vs 2-4 p (one-sided)		0.4207 - (E)	0.0739 + (E)	NA	NA
Liver, M-Carcinoma, Hepatocellular (I)	0	1/60	0/60	0/60	0/60
1 vs 2-4 p (one-sided)		Incidences across groups do not meet selection criterion.			
Liver, Adenoma/Carcinoma, Hepatocellular (I)	0	1/60	3/60	1/60	0/60
1 vs 2-4 p (one-sided)		0.2250 - (E)	0.2058 + (E)	NA	NA
Pancreas, B-Adenoma, Islet Cell (I)	0	6/60	4/60	1/60	1/60
1 vs 2-4 p (one-sided)		0.0119 - @	0.3402 -	0.0381 - *	0.0332 - @
Pancreas, M-Carcinoma, Islet Cell (I)	0	1/60	1/60	1/60	0/60
1 vs 2-4 p (one-sided)		Incidences across groups do not meet selection criterion.			
Pancreas, Adenoma/Carcinoma, Islet Cell (I)	0	7/60	5/60	2/60	1/60
1 vs 2-4 p (one-sided)		0.0087 - @	0.3862 -	0.0502 -	0.0190 - @

I = Incidental tumor; F = Fatal tumor.

+/- = Effect in the increased/decreased direction.

@ = Not a significant trend at 0.005 level or a significant high-dose group comparison at 0.01 for a common tumor.

\* = Significant at 5.0% level.

(E) = Exact test. NA = Not Analyzed.

### Results of Statistical Analyses of Neoplastic Lesions - Males

Tissue and Lesion	Group Dose level (mg/kg/day)	Unadjusted Lifetime Incidence Rate			
		1	2	3	4
Testis, B-Benign Interstitial Cell Tumor (I)	0	2/60	1/60	0/60	2/60
1 vs 2-4 p (one-sided)		0.5057 - (E)	NA	0.2640 - (E)	NA
Hemato Neoplasia, M-Lymphoma/Leukemia (I/F)	0	3/60	2/60	0/60	1/60
1 vs 2-4 p (one-sided)		0.0776 -	NA	0.1335 - (E)	0.3409 - (E)
Hemato Neoplasia, M-Sarcoma, Histiocytic (I/F)	0	1/60	3/60	3/60	2/60
1 vs 2-4 p (one-sided)		0.3258 +	0.2115 + (E)	0.2942 + (E)	NA

I = Incidental tumor; F = Fatal tumor.

+/- = Effect in the increased/decreased direction.

(E) = Exact test. NA = Not Analyzed.

## Appendix A.2

### Sponsor's Statistical Analysis of Data of Neoplastic Lesions Using Peto Trend and Pairwise Comparison Tests

#### Female Rats

#### Results of Statistical Analyses of Neoplastic Lesions - Females

Tissue and Lesion	Group Dose level (mg/kg/day)	Unadjusted Lifetime Incidence Rate			
		1	2	3	4
Pituitary, B-Adenoma (I/F)		39/60	34/60	26/60	26/60
1 vs 2-4 p (one-sided)		0.0051 - @	0.2233 -	0.0332 - *	0.0117 - @
Pituitary, M-Carcinoma (I/F)		5/60	1/60	7/60	3/60
1 vs 2-4 p (one-sided)		0.4728 -	0.0528 -	0.2370 +	0.2143 -
Pituitary, Adenoma/Carcinoma (I/F)		44/60	35/60	33/60	29/60
1 vs 2-4 p (one-sided)		0.0027 - &	0.0467 - *	0.0539 -	0.0020 - &
Adrenal, Cortex, B-Adenoma (I/F)		0/60	2/60	3/60	1/60
1 vs 2-4 p (one-sided)		0.2225 +	0.2873 + (E)	0.0768 + (E)	NA
Adrenal, Cortex, M-Carcinoma (I/F)		0/60	1/60	0/60	0/60
1 vs 2-4 p (one-sided)		Incidences across groups do not meet selection criterion.			
Adrenal, Cortex, Adenoma/Carcinoma (I/F)		0/60	3/60	3/60	1/60
1 vs 2-4 p (one-sided)		0.2996 +	0.1393 + (E)	0.0768 + (E)	NA
Adrenal, Medulla, B-Pheochromocytoma (I)		2/60	0/59	0/59	0/60
1 vs 2-4 p (one-sided)		0.0620 - (E)	0.2615 - (E)	0.2615 - (E)	0.2258 - (E)

I = Incidental tumor; F = Fatal tumor.

+/- = Effect in the increased/decreased direction.

@ = Not a significant trend at 0.005 level or a significant high-dose group comparison at 0.01 for a common tumor.

& = Significant trend at 0.005 level or a significant high-dose group comparison at 0.01 for a common tumor.

\* = Significant at 5.0% level.

(E) = Exact test. NA = Not Analyzed.

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**Results of Statistical Analyses of Neoplastic Lesions - Females**

Tissue and Lesion	Group Dose level (mg/kg/day)	Unadjusted Lifetime Incidence Rate			
		1	2	3	4
Thyroid, B-C-Cell Adenoma (I)	0	6/60	10	20	40
1 vs 2-4 p (one-sided)		0.0725 -	0.1938 -	0.1029 -	0.0878 -
Thyroid, M-C-Cell Carcinoma (I)	0/60	0/60	1/60	0/59	
1 vs 2-4 p (one-sided)		Incidences across groups do not meet selection criterion.			
Thyroid, C-Cell Adenoma/Carcinoma (I)	6/60	3/60	3/60	2/59	
1 vs 2-4 p (one-sided)		0.1068 -	0.1938 -	0.2154 -	0.0878 -
Kidney, B-Adenoma, Tubular Cell (I)	0/60	0/60	1/60	0/60	
1 vs 2-4 p (one-sided)		Incidences across groups do not meet selection criterion.			
Kidney, M-Carcinoma, Tubular Cell (I)	0/60	0/60	1/60	0/60	
1 vs 2-4 p (one-sided)		Incidences across groups do not meet selection criterion.			
Kidney, Adenoma/Carcinoma, Tubular Cell (I)	0/60	0/60	2/60	0/60	
1 vs 2-4 p (one-sided)		0.3903 + (E)	NA	0.2388 + (E)	NA
Mammary, B-Fibroadenoma (P)	14/60	12/59	12/59	13/60	
1 vs 2-4 p (one-sided)		0.4696 -	0.4219 -	0.4424 -	NA
Mammary, B-Adenoma (P)	2/60	0/59	0/59	1/60	
1 vs 2-4 p (one-sided)		0.2863 -	0.2462 -	0.2569 -	NA
Mammary, M-Carcinoma (P)	13/60	13/59	9/59	10/60	
1 vs 2-4 p (one-sided)		0.2235 -	NA	0.3579 -	0.3242 -

I = Incidental tumor; F = Fatal tumor; P = Palpable tumor.

+/- = Effect in the increased/decreased direction.

(E) = Exact test. NA = Not Analyzed.

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**Results of Statistical Analyses of Neoplastic Lesions - Females**

Tissue and Lesion	Group Dose level (mg/kg/day)	Unadjusted Lifetime Incidence Rate			
		1	2	3	4
Mammary, Fibroadenoma/Carcinoma (P)	0	25/60 <sup>a</sup>	23/59 <sup>a</sup>	20/59 <sup>a</sup>	19/60 <sup>a</sup>
1 vs 2-4 p (one-sided)		0.1497 -	0.4524 -	0.3586 -	0.1900 -
Mammary, Adenoma/Fibroadenoma/Carcinoma (P)	25/60 <sup>a</sup>	23/59 <sup>a</sup>	20/59 <sup>a</sup>	19/60 <sup>a</sup>	
1 vs 2-4 p (one-sided)		0.1497 -	0.4524 -	0.3586 -	0.1900 -
Uterus, B-Endometrial Stromal Polyp (I)	2/60	5/60	4/60	3/59	
1 vs 2-4 p (one-sided)		0.4357 +	0.1092 +	0.1874 +	NA
Uterus, M-Endometrial Stromal Sarcoma (I)	0/60	0/60	1/60	0/59	
1 vs 2-4 p (one-sided)		Incidences across groups do not meet selection criterion.			
Uterus, Endometrial Stromal Polyp/Sarcoma (I)	2/60	5/60	5/60	3/59	
1 vs 2-4 p (one-sided)		0.3929 +	0.1092 +	0.1092 +	NA
Hemato Neoplasia, M-Lymphoma/Leukemia (I/F)	0/60	1/60	3/60	0/60	
1 vs 2-4 p (one-sided)		0.3817 + (E)	NA	0.0978 + (E)	NA
Hemato Neoplasia, M-Sarcoma, Histiocytic (I/F)	1/60	2/60	2/60	3/60	
1 vs 2-4 p (one-sided)		0.1070 +	NA	NA	0.2758 + (E)

I = Incidental tumor; F = Fatal tumor; P = Palpable tumor.

+/- = Effect in the increased/decreased direction.

(E) = Exact test. NA = Not Analyzed.

<sup>a</sup> The following animals had a combination of fibroadenoma, carcinoma or adenoma: B87583, B87607, B87612, and B87622 (Group 1); B87673 and B87674 (Group 2); B87713 (Group 3); and B87771, B87776, B87781, and B87789 (Group 4). For the purpose of statistical analysis, each animal was counted once.

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### Appendix A.3

#### Sponsor's Statistical Analysis of Data of Neoplastic Lesions Using Peto Trend and Pairwise Comparison Tests

##### Male Mice

##### Results of Statistical Analyses of Neoplastic Lesions - Males

Tissue and Lesion	Group Dose level (mg/kg/day)	Unadjusted Lifetime Incidence Rate		
		1	2	3
Adrenal, Cortex, B-Adenoma (I)	0/60	1/60	2/60	
1 vs 2-3 p (one-sided)	0.1461+ (E)	NA	0.2556 + (E)	
Adrenal, Cortex, B-Adenoma, Subcapsular Cell (I)	2/60	0/60	0/60	
1 vs 2-3 p (one-sided)	0.1468 - (E)	0.2946 - (E)	0.3143 - (E)	
Liver, B-Adenoma, Hepatocellular (I)	4/60	6/60	3/60	
1 vs 2-3 p (one-sided)	0.3765 -	0.2398 +	NA	
Liver, M-Carcinoma, Hepatocellular (I/F)	4/60	4/60	2/60	
1 vs 2-3 p (one-sided)	0.2642 -	NA	0.2501 -	
Liver, Adenoma/Carcinoma, Hepatocellular (I/F)	8/60	9/60 <sup>a</sup>	5/60	
1 vs 2-3 p (one-sided)	0.2488 -	NA	0.2233 -	
Lung, B-Adenoma, Bronchiolar-Alveolar (I)	2/60	4/60	4/60	
1 vs 2-3 p (one-sided)	0.1825 +	0.2930 +	0.1316 +	
Lung, M-Carcinoma, Bronchiolar-Alveolar (I/F)	11/60	4/60	7/60	
1 vs 2-3 p (one-sided)	0.1902 -	0.0235 - *	0.2299 -	
Lung, Adenoma/Carcinoma, Bronchiolar-Alveolar (I/F)	12/60 <sup>b</sup>	8/60	11/60	
1 vs 2-3 p (one-sided)	0.4727 +	0.1221 -	NA	
Harderian Gland, B-Adenoma (I)	5/60	4/59	0/60	
1 vs 2-3 p (one-sided)	0.0194 - @	NA	0.0367 - (E) @	
Harderian Gland, M-Carcinoma (I)	1/60	1/59	0/60	
1 vs 2-3 p (one-sided)	Incidences across groups do not meet selection criterion.			
Harderian Gland, Adenoma/Carcinoma (I)	6/60	5/59	0/60	
1 vs 2-3 p (one-sided)	0.0131 - @	NA	0.0085 - **	
Hemato Neoplasia, M-Lymphoma (I/F)	8/60	3/60	3/60	
1 vs 2-3 p (one-sided)	0.0474 - @	0.0793 -	0.0577 -	

I = Incidental tumor; F = Fatal tumor.

+/- = Effect in the increased/decreased direction.

@ = Not a significant trend at 0.005 level or a significant high-dose group comparison at 0.01 for a common tumor.

\* = Significant at 5.0% level. \*\* = Significant at 1.0% level.

(E) = Exact test. NA = Not Analyzed.

a Animal No. A84290 had both adenoma and carcinoma. For the purpose of statistical analysis, the animal was counted once.

b Animal No. A84228 had both adenoma and carcinoma. For the purpose of statistical analysis, the animal was counted once.

## Appendix A.4

### Sponsor's Statistical Analysis of Data of Neoplastic Lesions Using Peto Trend and Pairwise Comparison Tests

#### Female Mice

#### Results of Statistical Analyses of Neoplastic Lesions - Females

Tissue and Lesion	Group Dose level (mg/kg/day)	Unadjusted Lifetime Incidence Rate		
		1	2	3
Adrenal, Medulla, B-Pheochromocytoma (I)	0	1/60	1/60	0/59
1 vs 2-3 p (one-sided)		Incidences across groups do not meet selection criterion.		
Adrenal, Medulla, M-Malignant Pheochromocytoma (I)	0	1/60	0/60	0/59
1 vs 2-3 p (one-sided)		Incidences across groups do not meet selection criterion.		
Adrenal, Medulla, B/M-Pheochromocytoma (I)	2/60	1/60	0/59	
1 vs 2-3 p (one-sided)		0.2148 - (E)	NA	0.4487 - (E)
Liver, M-Carcinoma, Hepatocellular (I)	2/60	0/60	0/59	
1 vs 2-3 p (one-sided)		0.2203 - (E)	0.3728 - (E)	0.4487 - (E)
Lung, B-Adenoma, Bronchiolar-Alveolar (I)	5/60	2/58	3/59	
1 vs 2-3 p (one-sided)		0.3670 -	0.1982 -	0.4066 -
Lung, M-Carcinoma, Bronchiolar-Alveolar (I/F)	5/60	12/58	2/59	
1 vs 2-3 p (one-sided)		0.4786 +	0.0049 + **	0.3259 -
Lung, Adenoma/Carcinoma, Bronchiolar-Alveolar (I/F)	8/60 <sup>a</sup>	13/58 <sup>a</sup>	5/59	
1 vs 2-3 p (one-sided)		0.4366 +	0.0236 + *	0.4525 -
Ovary, B-Adenoma (I)	3/60	0/60	1/58	
1 vs 2-3 p (one-sided)		0.3868 - (E)	0.2237 - (E)	0.6044 - (E)
Ovary, M-Carcinoma (I)	1/60	0/60	0/58	
1 vs 2-3 p (one-sided)		Incidences across groups do not meet selection criterion.		
Ovary, Adenoma/Carcinoma (I)	4/60	0/60	1/58	
1 vs 2-3 p (one-sided)		0.1842 - (E)	0.1193 - (E)	0.3665 - (E)
Hemato Neoplasia, M-Lymphoma (I/F)	12/60	14/60	8/59	
1 vs 2-3 p (one-sided)		0.4641 -	0.2821 +	0.3520 -
Hemato Neoplasia, M-Sarcoma, Histiocytic (I/F)	1/60	3/60	4/59	
1 vs 2-3 p (one-sided)		0.0432 + @	0.3359 + (E)	0.0825 + (E)
Multiple Organs, B-Leiomyoma (I)	1/59	2/54	0/57	
1 vs 2-3 p (one-sided)		Incidences across groups do not meet selection criterion.		
Multiple Organs, M-Leiomyosarcoma (I/F)	1/60	2/60	2/59	
1 vs 2-3 p (one-sided)		Incidences across groups do not meet selection criterion.		
Multiple Organs, Leiomyoma/Leiomyosarcoma (I/F)	2/60	4/60	2/59	
1 vs 2-3 p (one-sided)		0.2039 +	0.0694 +	NA

I = Incidental tumor; F = Fatal tumor.

+/- = Effect in the increased/decreased direction.

@ = Not a significant trend at 0.005 level or a significant high-dose group comparison at 0.01 for a common tumor.

\* = Significant at 5.0% level. \*\* = Significant at 1.0% level.

(E) = Exact test. NA = Not Analyzed.

a Animal Nos. A84780 and A84798 (Group 1) and A84836 (Group 2) had both bronchiolar-alveolar adenoma and carcinoma. For the purpose of statistical analysis, each animal was counted once.

Appendix B.1

Results of Reviewers' Statistical Analysis of Data of Neoplastic Lesions  
Using Poly-3 Trend and Pairwise Comparison Tests

Male Rats

sex=M	Organ/Tumor Name	Cntrl	Low	Med	High	Trend	C vs H	C vs M	C vs L
	ADRENAL, CORTEX								
	B-ADENOMA	0	0	1	0	0.5122	.	0.4907	.
	ADRENAL, MEDULLA								
	B-PHEOCHROMOCYTOMA	3	1	1	5	0.1397	0.3171	0.3375	0.3955
	M-MALIGNANT PHEOCHROMOCYTOMA	0	0	1	0	0.5122	.	0.4907	.
	BRAIN								
	B-GRANULAR CELL TUMOR	1	0	0	0	0.2696	0.5140	0.5140	0.5500
	M-ASTROCYTOMA	1	0	1	0	0.3761	0.5140	0.7430	0.5500
	M-OLIGODENDROGLIOMA	0	0	1	0	0.5122	.	0.4907	.
	CAVITY, ABDOM								
	B-FIBROMA	0	1	0	0	0.4902	.	.	0.4500
	M-FIBROSARCOMA	0	0	1	0	0.5122	.	0.4907	.
	M-MESOTHELIOMA	0	0	1	0	0.5122	.	0.4907	.
	CORD, CERVICAL								
	B-GRANULAR CELL TUMOR	1	0	0	0	0.2696	0.5140	0.5140	0.5500
	EPIDIDYMS								
	M-MALIGNANT MESOTHELIOMA	0	0	0	1	0.2549	0.4860	.	.
	GLAND, ZYMBAL'S								
	M-CARCINOMA	0	0	1	0	0.5122	.	0.4907	.
	HEART								
	M-ENDOCARDIAL SCHWANNOMA	2	0	2	2	0.3803	0.6625	0.6625	0.3050
	HEMATO NEOPLASIA								
	M-LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.2549	0.4860	.	.
	M-LYMPHOMA/LEUKEMIA	3	2	0	1	0.1382	0.3304	0.1322	0.5950
	M-SARCOMA, HISTIOCYTIC	1	3	3	2	0.4294	0.4792	0.2954	0.2311
	KIDNEY								
	M-CARCINOMA, TUBULAR CELL	1	0	0	1	0.5073	0.7335	0.5185	0.5545
	LIVER								
	B-ADENOMA, HEPATOCELLULAR	0	3	1	0	0.3200	.	0.4860	0.0878
	M-CARCINOMA, HEPATOCELLULAR	1	0	0	0	0.2696	0.5140	0.5140	0.5500
	MAMMARY, MALE								
	B-FIBROADENOMA	0	1	0	0	0.4902	.	.	0.4500
	MULTIPLE ORGANS								
	M-HEMANGIOSARCOMA	0	1	1	1	0.2973	0.4860	0.4907	0.4500
	PANCREAS								
	B-ADENOMA, ISLET CELL	6	4	1	1	0.0160	0.0689	0.0655	0.5011
	M-CARCINOMA, ISLET CELL	1	1	1	0	0.2637	0.5140	0.7381	0.7000
	PARATHYROID								
	B-ADENOMA	0	1	2	1	0.2998	0.4860	0.2338	0.4554
	PITUITARY								
	B-ADENOMA	18	20	14	14	0.1765	0.3741	0.3277	0.1927
	M-CARCINOMA	0	0	0	1	0.2549	0.4860	.	.
	SALIV GL, MANDIB								
	M-SCHWANNOMA	0	1	1	0	0.4902	.	0.4860	0.4500
	SKIN, OTHER								
	B-FIBROMA	1	0	0	0	0.2696	0.5140	0.5140	0.5500
	B-KERATOACANTHOMA	1	0	0	0	0.2696	0.5140	0.5140	0.5500
	B-SEBACEOUS CELL ADENOMA	1	0	0	0	0.2696	0.5140	0.5140	0.5500
	B-SQUAMOUS CELL PAPILLOMA	1	1	1	1	0.5462	0.7381	0.7381	0.7000
	SUBCUTANEOUS TIS								
	B-BASAL CELL TUMOR	0	1	1	0	0.4902	.	0.4860	0.4500
	B-FIBROMA	0	0	3	0	0.4566	.	0.1113	.
	B-LIPOMA	0	0	0	1	0.2549	0.4860	.	.
	M-FIBROSARCOMA	1	3	0	1	0.3693	0.7381	0.5140	0.2445
	M-MYXOSARCOMA	1	0	0	0	0.2732	0.5185	0.5185	0.5545
	M-SCHWANNOMA	0	1	1	0	0.4902	.	0.4907	0.4500
	TESTIS								
	B-INTERSTITIAL CELL TUMOR	2	1	0	2	0.5155	0.6696	0.2619	0.5755
	THYMUS								
	M-THYMOMA	1	0	0	0	0.2696	0.5140	0.5140	0.5500

Organ/Tumor Name	Cntrl	Low	Med	High	Trend	C vs H	C vs M	C vs L
THYROID								
B-"C" CELL ADENOMA	4	1	3	3	0.5354	0.5416	0.5416	0.2569
B-FOLLICULAR CELL ADENOMA	2	3	1	0	0.0844	0.2665	0.5280	0.3966
M-"C" CELL CARCINOMA	0	0	4	1	0.2087	0.4860	0.0525	.
M-FOLLICULAR CELL CARCINOMA	0	0	0	1	0.2549	0.4860	.	.

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Appendix B.2

Results of Reviewers' Statistical Analysis of Data of Neoplastic Lesions  
Using Poly-3 Trend and Pairwise Comparison Tests

Female Rats

NDA 22291 Rats 12:10 Tuesday, May 27, 2008 2

All neoplasms

sex=F	Organ/Tumor Name	Cntrl	Low	Med	High	Trend	C vs H	C vs M	C vs L
	ADRENAL, CORTEX								
	B-ADENOMA	0	2	3	1	0.3673	0.4900	0.1030	0.2426
	M-CARCINOMA	0	1	0	0	0.5155	1.0000	1.0000	0.4900
	ADRENAL, MEDULLA								
	B-PHEOCHROMOCYTOMA	2	0	0	0	0.0681	0.2576	0.2796	0.2576
	BRAIN								
	M-ASTROCYTOMA	0	1	1	1	0.2934	0.4950	0.4687	0.4900
	CAVITY, ABDOM								
	M-LIPOSARCOMA	0	0	0	1	0.2526	0.4900	1.0000	1.0000
	M-SCHWANNOMA	0	0	0	1	0.2564	0.4950	1.0000	1.0000
	CAVITY, ORAL								
	M-CARCINOMA, SQUAMOUS CELL	0	0	1	0	0.4845	1.0000	0.4687	1.0000
	CAVITY, THORACIC								
	M-HIBERNOMA	0	1	0	0	0.5155	1.0000	1.0000	0.4900
	CERVIX								
	M-CARCINOMA, SQUAMOUS CELL	0	1	0	0	0.5155	1.0000	1.0000	0.4900
	CLITORAL GLAND								
	B-ADENOMA	0	0	0	1	0.2526	0.4900	1.0000	1.0000
	HEART								
	M-CHEMODECTOMA	0	0	0	1	0.2526	0.4900	1.0000	1.0000
	M-ENDOCARDIAL SCHWANNOMA	0	0	1	0	0.4845	1.0000	0.4687	1.0000
	HEMATO NEOPLASIA								
	M-LEUKEMIA, GRANULOCYTIC	0	1	0	0	0.5179	1.0000	1.0000	0.4950
	M-LYMPHOMA/LEUKEMIA	0	1	3	0	0.5362	1.0000	0.1066	0.4900
	M-SARCOMA, HISTIOCYTIC	1	2	2	3	0.1919	0.2940	0.4537	0.4775
	KIDNEY								
	B-ADENOMA, TUBULAR CELL	0	0	1	0	0.4845	1.0000	0.4687	1.0000
	M-CARCINOMA, TUBULAR CELL	0	0	1	0	0.4845	1.0000	0.4687	1.0000
	LIVER								
	B-ADENOMA, HEPATOCELLULAR	0	0	1	0	0.4845	1.0000	0.4687	1.0000
	MAMMARY, FEMALE								
	B-ADENOMA	2	0	0	1	0.4098	0.5075	0.2796	0.2576
	B-FIBROADENOMA	14	12	12	13	0.4773	0.5845	0.5821	0.4773
	M-CARCINOMA	13	13	9	10	0.2538	0.3763	0.3416	0.5227
	OVARY								
	B-GRANULOSA/THECA CELL TUMOR	0	1	0	0	0.5155	1.0000	1.0000	0.4900
	B-SERTOLIFORM TUBULAR ADENOM	1	0	0	0	0.2629	0.5100	0.5312	0.5100
	M-TUBULOSTROMAL CARCINOMA	0	0	0	1	0.2526	0.4900	1.0000	1.0000
	PANCREAS								
	B-ADENOMA, ISLET CELL	1	0	0	1	0.4952	0.7424	0.5312	0.5100
	M-CARCINOMA, ISLET CELL	0	1	1	0	0.5048	1.0000	0.4687	0.4900
	PARATHYROID								
	B-ADENOMA	1	0	0	0	0.2629	0.5100	0.5312	0.5100
	PITUITARY								
	B-ADENOMA	39	34	26	26	0.0181	0.0409	0.1189	0.4925

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All neoplasms

sex=F	Organ/Tumor Name	Cntrl	Low	Med	High	Trend	C vs H	C vs M	C vs L
	M-CARCINOMA	5	1	7	3	0.5060	0.3916	0.2957	0.1165
	SALIV GL, MANDIB								
	B-GANGLIONEUROMA	0	0	1	0	0.4845	1.0000	0.4687	1.0000
	M-SCHWANNOMA	0	0	0	1	0.2526	0.4900	1.0000	1.0000
	SKIN, OTHER								

B-KERATOACANTHOMA	0	0	0	1	0.2526	0.4900	1.0000	1.0000
B-SEBACEOUS CELL ADENOMA	1	0	0	0	0.2629	0.5100	0.5312	0.5100
SUBCUTANEOUS TIS								
B-FIBROMA	0	0	1	0	0.4872	1.0000	0.4742	1.0000
M-FIBROSARCOMA	1	0	0	1	0.5004	0.7475	0.5312	0.5100
THYROID								
B-"C" CELL ADENOMA	6	3	2	2	0.0931	0.1546	0.1778	0.2744
B-FOLLICULAR CELL ADENOMA	1	1	0	0	0.2016	0.5100	0.5312	0.7424
M-"C" CELL CARCINOMA	0	0	1	0	0.4845	1.0000	0.4687	1.0000
TONGUE								
M-SQUAMOUS CELL CARCINOMA	0	0	1	0	0.4845	1.0000	0.4687	1.0000
UTERUS								
B-ENDOMETRIAL STROMAL POLYP	2	5	4	3	0.4812	0.4905	0.2809	0.2018
M-ENDOMETRIAL STROMAL SARCOM	0	0	1	0	0.4845	1.0000	0.4687	1.0000

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### Appendix B.3

#### Results of Reviewers' Statistical Analysis of Data of Neoplastic Lesions Using Poly-3 Trend and Pairwise Comparison Tests

##### Male Mice

sex=M									
ADRENAL, CORTEX									
B-ADENOMA	0	1	2	0	0	0.1332	0.2264	0.4865	
B-ADENOMA, SUBCAPSULAR CELL	2	0	0	0	0	0.1194	0.2675	0.2603	
HARDERIAN GLAND									
B-ADENOMA	5	4	0	0	0	0.0151	0.0357	0.5342	
M-CARCINOMA	1	1	0	0	0	0.3519	0.5205	0.7397	
HEAD, CORONAL									
M-HEMANGIOSARCOMA	0	1	0	0	0	0.6789	.	0.4865	
HEMATO NEOPLASIA									
M-LEUKEMIA, GRANULOCYTIC	1	0	0	0	0	0.3486	0.5205	0.5135	
M-LYMPHOMA	8	3	3	0	0	0.1390	0.1416	0.1215	
M-SARCOMA, HISTIOCYTIC	1	0	0	0	0	0.3486	0.5205	0.5135	
KIDNEY									
B-ADENOMA, TUBULAR CELL	0	1	0	0	0	0.6789	.	0.4865	
LIVER									
B-ADENOMA, HEPATOCELLULAR	4	6	3	0	0	0.3216	0.5456	0.3343	
M-CARCINOMA, HEPATOCELLULAR	4	4	2	0	0	0.2620	0.3906	0.6141	
M-HEMANGIOSARCOMA	0	0	1	0	0	0.3273	0.4865	.	
M-HEPATOBLASTOMA	0	1	0	0	0	0.6818	.	0.4933	
LUNG									
B-ADENOMA, BRONCHIOLAR-ALVEO	2	4	4	1	0	0.2560	0.3114	0.3372	
M-CARCINOMA, BRONCHIOLAR-ALV	11	4	7	0	0	0.3488	0.2483	0.0518	
PITUITARY									
B-ADENOMA	0	0	1	0	0	0.3211	0.4795	.	
SALIV GL, SUBLING									
M-SCHWANNOMA	0	0	1	0	0	0.3211	0.4795	.	
SKIN									

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##### All neoplasms

sex=M	Organ/Tumor Name	Cntrl	Low	Med	High	Max	Trend	C vs M	C vs L
	M-CARCINOMA, ADNEXAL	0	0	0	1	0	.	.	.
	SKIN, OTHER								
	B-PAPILLOMA	0	0	1	0	0	0.3211	0.4795	.
	M-SARCOMA (ASSOC W BIOMED IM	0	2	0	0	0	0.4629	.	0.2400
	SPLEEN								
	M-HEMANGIOSARCOMA	2	0	0	0	0	0.1194	0.2675	0.2603
	STOMACH, GL								
	M-SARCOMA (NOS)	0	0	1	0	0	0.3273	0.4865	.
	STOMACH, NONGL								
	B-SQUAMOUS CELL PAPILOMA	0	1	0	0	0	0.6789	.	0.4865
	TESTIS								
	B-HEMANGIOMA	0	1	0	0	0	0.6789	.	0.4865

B-INTERSTITIAL CELL TUMOR	0	1	0	0	0	0.6789	.	0.4865
M-HEMANGIOSARCOMA, PAMPINIFO	0	0	1	0	0	0.3273	0.4865	.
THYROID								
B-FOLLICULAR CELL ADENOMA	0	1	0	0	0	0.6789	.	0.4865

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## Appendix B.4

### Results of Reviewers' Statistical Analysis of Data of Neoplastic Lesions Using Poly-3 Trend and Pairwise Comparison Tests

#### Female Mice

NDA 22291 Mice

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#### All neoplasms

sex=F Organ/Tumor Name	Cntrl	Low	Med	High	Max	Trend	C vs M	C vs L
sex=F								
ADRENAL, CORTEX								
B-ADENOMA	0	0	1	0	0	0.2903	0.4337	.
ADRENAL, MEDULLA								
B-PHEOCHROMOCYTOMA	1	1	0	0	0	0.4009	0.5732	0.7176
M-MALIGNANT PHEOCHROMOCYTOMA	1	0	0	0	0	0.3821	0.5732	0.5341
BONE, FEMUR								
B-OSTEOMA	0	0	1	0	0	0.2903	0.4337	.
CERVIX								
B-LEIOMYOMA	1	2	0	0	0	0.3274	0.5732	0.4483
M-HEMANGIOSARCOMA	1	1	0	0	0	0.4060	0.5783	0.7120
M-LEIOMYOSARCOMA	0	2	1	0	0	0.2895	0.4268	0.2142
M-STROMAL SARCOMA	0	0	1	0	0	0.2903	0.4337	.
CLITORAL GLAND								
M-CARCINOMA, SQUAMOUS CELL	0	1	0	0	0	0.7154	.	0.4659
EYE								
M-CARCINOMA, SQUAMOUS CELL	0	0	0	1	0	.	.	.
HARDERIAN GLAND								
B-ADENOMA	1	2	1	0	0	0.6388	0.6745	0.4483
M-CARCINOMA	0	0	1	0	0	0.2846	0.4268	.
HEMATO NEOPLASIA								
M-LYMPHOMA	12	14	8	2	0	0.3355	0.5335	0.1958
M-SARCOMA, HISTIOCYTIC	1	3	4	0	0	0.0732	0.1038	0.2595
LIVER								
M-CARCINOMA, HEPATOCELLULAR	2	0	0	0	0	0.1441	0.3255	0.2824
M-HEMANGIOSARCOMA	0	0	1	0	0	0.2846	0.4268	.
LUNG								
B-ADENOMA, BRONCHIOLAR-ALVEO	5	2	3	0	0	0.4879	0.5272	0.2875
M-CARCINOMA, BRONCHIOLAR-ALV	5	12	2	0	0	0.0920	0.3410	0.0337
MAMMARY, FEMALE								
M-CARCINOMA	1	1	0	0	0	0.4060	0.5783	0.7120
OVARY								
B-ADENOMA	3	0	1	0	0	0.3194	0.4265	0.1478
B-GRANULOSA/THECA CELL TUMOR	1	0	1	0	0	0.4898	0.6745	0.5341
B-LUTEOMA	1	0	0	0	0	0.3821	0.5732	0.5341
B-SERTOLI CELL TUMOR	1	0	0	0	0	0.3821	0.5732	0.5341
M-CARCINOMA	1	0	0	0	0	0.3871	0.5783	0.5393
M-HEMANGIOSARCOMA	1	1	1	0	0	0.5065	0.6685	0.7120
M-YOLK SAC CARCINOMA	0	0	1	0	0	0.2903	0.4337	.
PANCREAS								
B-ADENOMA, ISLET CELL	0	1	0	0	0	0.7154	.	0.4659
PITUITARY								
B-ADENOMA	1	1	0	0	0	0.4009	0.5732	0.7176
SKIN, OTHER								

## All neoplasms

sex=F	Organ/Tumor Name	Cntrl	Low	Med	High	Max	Trend	C vs M	C vs L
	M-CARCINOMA, ADNEXAL	1	0	0	0	0	0.3821	0.5732	0.5341
	SPLEEN								
	M-HEMANGIOSARCOMA	0	1	0	0	0	0.7154	.	0.4659
	STOMACH, GL								
	B-POLYP	0	1	0	0	0	0.7154	.	0.4659
	SUBCUTANEOUS TIS								
	M-FIBROSARCOMA	3	0	0	0	0	0.0558	0.1882	0.1523
	M-MYXOSARCOMA	0	0	1	0	0	0.2903	0.4337	.
	M-SARCOMA (ASSOCIATED WITH B	0	0	2	0	0	0.0826	0.1851	.
	THYROID								
	B-FOLLICULAR CELL ADENOMA	1	0	1	0	0	0.4980	0.6823	0.5341
	URINARY BLADDER								
	M-LEIOMYOSARCOMA	0	0	1	0	0	0.2903	0.4337	.
	UTERUS								
	B-ENDOMETRIAL STROMAL POLYP	1	0	1	0	0	0.4898	0.6745	0.5341
	M-LEIOMYOSARCOMA	1	0	0	0	0	0.3821	0.5732	0.5341

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