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RESEARCH**

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STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

SHIFT was an international, randomized, double-blind, parallel-arm, event-driven morbidity/mortality study, that investigated the effects of Ivabradine versus Placebo in patients with moderate to severe, Chronic Heart Failure (CHF) and Left Ventricular Systolic Dysfunction (LVSD), who were in sinus rhythm with Heart Rate (HR) ≥ 70 bpm at rest and received recommended background therapy for CHF based on current guidelines.

The main objective of this study was to demonstrate the superiority of Ivabradine over Placebo, using an intent-to-treat analysis, on the reduction of the number of primary composite endpoints (first event of hospitalization for worsening HF or CV mortality). The results of SHIFT demonstrated that treatment with Ivabradine significantly reduces the risk of Primary Composite Endpoint (PCE) compared with Placebo. The estimate of the hazard ratio was 0.82 [95% CI: (0.75, 0.90); p-value < 0.0001], corresponding to a relative risk reduction of 18% in the primary composite endpoint, a result that is statistically significant.

SHIFT also appeared to be a favorable study with a lean on mortality. However, the findings of the two other large(r) cardiovascular outcome trials (BEAUTIFUL, SIGNIFY) are highly inconsistent with the findings of SHIFT. Both of these two trials failed their respective primary composite endpoints, which are very similar to the primary endpoint of SHIFT. From Table 3-10 (page 19), there seemed to be some differences in design features among the three trials, but it is unclear whether these differences cause the inconsistency. Ideally we need to understand the reasons for these different trial results to understand for which patients' Ivabradine is useful and to determine if there is a heart failure benefit. The issue of the inconsistent findings among the three large outcome trials of Ivabradine needs to be addressed.

2 INTRODUCTION

Heart failure affects more than 5 million adults in the United States (US), or 2.1% of the adult population, and despite currently available therapy, results in approximately 56,000 deaths annually; US patients with heart failure have 1-year and 5-year adjusted mortality rates estimated at approximately 30% and 48%, respectively. The development program for Ivabradine in the treatment of CHF was designed to address the clear unmet medical need in this condition.

Ivabradine reduces heart rate by interacting with the hyperpolarization-activated, cyclic nucleotide-gated channel, selectively inhibiting the cardiac f-current (If) and thereby modulating pacemaker activity in the sinus node. The cardiac effects are specific to the sinus node, therefore resulting in decreased heart rate without negative effects on myocardial contractility or ventricular repolarization. Ivabradine is formulated as an immediate-release tablet in 5 mg and 7.5 mg strengths for twice daily (BID) oral dosing.

Ivabradine was developed by Les Laboratoires Servier and is approved for use in 102 countries for the treatment of angina and 88 countries for the treatment of CHF as of 31 December 2013. Amgen acquired US commercial rights to Ivabradine in 2013. Ivabradine has not previously been marketed in the US for any indication.

2.1 Overview

The benefit of Ivabradine in the treatment of CHF is supported primarily by the improvement in clinical outcomes observed in a single large, multi-center, randomized, double-blind, Placebo-controlled, pivotal phase 3 outcomes study, CL3-063 (Systolic Heart failure treatment with the If inhibitor Ivabradine Trial, or SHIFT (Section 3.2.1).

SHIFT randomized 6,558 subjects with symptomatic CHF (NYHA class II, III, or IV) in stable clinical condition and LVSD, with baseline HR ≥ 70 bpm and normal sinus rhythm. Subjects were randomized to receive Ivabradine or Placebo at a starting dose of 5 mg BID; after 2 weeks the dose could be up-titrated to 7.5 mg, maintained at 5 mg BID, or down-titrated to 2.5 mg BID. The study duration ranged from 12 to 41 months. The study was conducted in Europe, Australia, Canada, Asia, Africa, and South America. There were no US sites. As SHIFT was conducted entirely outside the US, Les Laboratoires Servier did not consult the FDA for advice and guidance during the development of the clinical program. Hence, there was never an IND application associated with this program.

The primary composite endpoint for SHIFT was time to first event of cardiovascular death (including death from unknown cause) or hospitalization for Worsening Heart Failure (WHF). SHIFT was initiated in 2006 and completed in 2010. SHIFT demonstrated the treatment with Ivabradine significantly reduced cardiovascular mortality or hospitalization for worsening heart failure, compared to Placebo.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: <\\CDSESUB1\evsprod\NDA206143\0017>.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There are following statistical issues with the data and analysis quality.

- The last patient visit was on 19 April 2010. However, the final and only version of the Statistical Analysis Plan was not finalized until 28 May 2010. Les Laboratoires Servier claimed that it was finalized prior to study unblinding.
- The entire clinical development program was conducted entirely outside of the US. There was not an IND associated with this application during the development. Hence, FDA did not provide any consultations to the program.

3.2 Evaluation of Efficacy

3.2.1 STUDY DESIGN AND ENDPOINTS

SHIFT was conducted in subjects with symptomatic CHF with systolic dysfunction receiving maximally tolerated doses of beta-blockers and other guideline-based heart failure therapies. The study enrolled patients across 677 study centers in 37 countries and included 6558 randomized subjects (of which 6505 subjects were evaluable).

Study Objectives

The primary objective was to demonstrate the superiority of Ivabradine over Placebo in the reduction of cardiovascular mortality or hospitalizations for worsening heart failure, in patients with moderate to severe symptoms of CHF, a reduced left ventricular ejection fraction (LVEF), currently receiving recommended therapy for this disease.

The secondary objectives were to assess the effects of Ivabradine compared with Placebo on:

- the PCE among subjects receiving at least half of the target daily dose of beta-blockers at randomization
- Death from heart failure, cardiovascular death and overall mortality, morbidity (including hospitalization for any cause, cardiovascular reason, or worsening heart failure), functional capacity, and clinical symptoms of heart failure for subjects overall and the subset of subjects receiving at least half of the target daily dose of beta-blockers at randomization.

Treatment

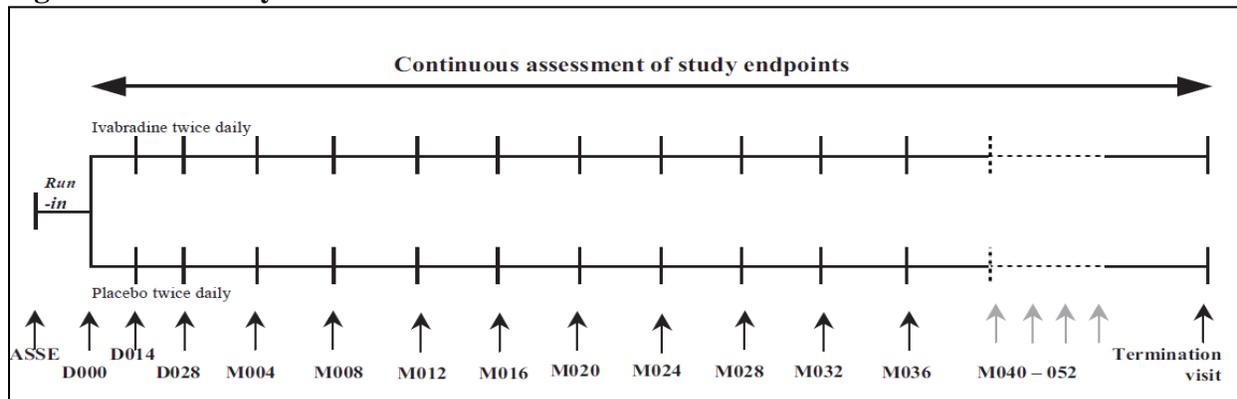
Subjects were randomized 1:1 to receive Placebo or Ivabradine; randomization was stratified by beta-blocker intake and center. Subjects received Ivabradine at an initial dose of 5 mg BID, then up-titrated to 7.5 mg BID, maintained at 5 mg BID, or down-titrated to 2.5 mg BID at any time during the study, depending on resting heart rate and tolerability.

Study Periods

The study was divided into two periods, which is described in Figure 3-1:

- A run-in period of two weeks (from selection visit [ASSE] to inclusion visit [D000]; 7 to 30 days was accepted) dedicated to confirm the eligibility of patients and their clinical stability. No study treatment was dispensed.
- A post-randomization period included:
 - A titration period with visits at the following scheduled time-points: 2 weeks (D014) and 4 weeks (D028).
 - A follow-up period, starting after the D028 visit, with a first visit at 4 months (M004) and then every 4 months thereafter until the end-of-study (TERM) visit (patient follow-up was extended by Amendment Nos. 5 and 6 up to a theoretical 52 months).

Figure 3-1 Study Plan



[Source: Study Report Figure (9.1) 1]

Efficacy Endpoints

The primary composite endpoint is the first event of cardiovascular death (including death from unknown cause) or hospitalization for worsening HF.

The secondary endpoints are:

- Hospitalization for worsening HF.
- Cardiovascular death (including death from unknown cause).
- Death from any cause.
- Death from heart failure.
- Hospitalization for any cause.
- Unplanned hospitalization for any cause.
- Hospitalization for cardiovascular reason (including hospitalization for undetermined cause).
- Unplanned hospitalization for cardiovascular reason.
- Secondary composite endpoint: First event among cardiovascular death (including death from unknown cause), hospitalization for non-fatal MI or hospitalization for worsening HF

All criteria above are expressed as the time to first event.

3.2.2 STATISTICAL METHODOLOGIES

The initial SHIFT protocol was written on April 18, 2006. There were six amendments in the following three years. The original protocol proposed a sample size of 5,500 patients for the detection of a 17% relative risk reduction of the PCE (90% power and 1220 events) and an expected mean follow-up of 2 years, assuming an annual incidence rate of the PCE of 14% in Placebo group and an incidence of non-cardiovascular death of 1% in both groups.

According to Amendment 5, in September 2008, the sample size was increase to 7,000 patients and the study will continue until at least 1600 composite endpoints had occurred. Per the Amendment, the changes were caused by the unfavorable results of another study, BEAUTIFUL, which suggested a possible lower treatment effect of Ivabradine on heart failure endpoints than expected.

Per Amendment 6, in June 2009, SHIFT was to be stopped when 6,500 patients have been randomized due to lower than expected recruitment rate.

SHIFT had only one version of the Statistical Analysis Plan, which was finalized prior to study unblinding, per the study report. However, the SAP completion date was 28 May 2010, which is later than the study completion date of 19 April 2010.

Definition of the Analysis Sets

Two analysis sets were defined according to the intention-to-treat principle.

The Randomized Set (RS) was defined as all included patients with a randomization number allocated by Interactive Response System (IRS) and to whom a therapeutic unit has been dispensed.

The RS_{BBdose} was defined as all patients of the RS receiving at least half of target daily dose of beta-blockers at randomization. “At least half target daily dose” was attained if the dose was equal to or superior to the following dose for each beta-blocker:

- Carvedilol: 25 mg.
- Metoprolol succinate: 95 mg.
- Bisoprolol: 5 mg.
- Nebivolol: 5 mg.
- Metoprolol tartrate: 75 mg.

All analyses were carried out both on the RS and RS_{BBdose} (hierarchical procedure).

Efficacy Analysis Methods

The primary composite endpoint was tested using a survival analysis conducted on a time-to-first event basis using the intention-to-treat principle. A Cox’s proportional hazards model adjusted for previous beta-blocker intake at randomization was used to estimate the treatment effect and calculate the associated two-sided p-value (significance level: 5%).

For other efficacy endpoints, the analyses were performed as for the primary composite endpoint.

Interim Analyses and Multiplicity

Three interim analyses were performed by the Data Monitoring Committee: the first one (20% of the expected events) dedicated only to prematurely detect an eventual harmful effect, the two other ones (40% and 70% of the expected events) were to investigate both premature efficacy and harmful effects. The alpha spending for the latter two interim analyses were based on the Peto group sequential procedure, the type I error rates used for interim efficacy analyses were fixed at 0.1% and have no significant impact on the type I error rate used for the final analysis.

The study would have been stopped for efficacy if Ivabradine was better than Placebo with a p-value on the primary composite endpoint lower than or equal to 0.1%.

The study would have been stopped for harmful effect if Ivabradine was worse than Placebo with a p-value on the primary composite endpoint or on deaths of any cause lower than or equal to 1%.

3.2.3 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A total of 7,411 patients were screened, 7,106 were selected and 6,558 were randomized. Of these 6,558, 7 who did not meet the inclusion criteria and did not take the study drug were not included (2 in the Ivabradine and 5 in the Placebo group). A further 46 patients, all of those recruited in two Polish centers No.’s. 1142 and 1121, were excluded from all analysis sets for concerns over invalid data due to misconduct. The total number of patients retained in the RS was therefore 6,505 (91.5% of selected patients): 3,241 patients randomized to Ivabradine and 3,264 to Placebo.

The disposition of patients by treatment group in the RS is listed in Table 3-1. There are slightly more Ivabradine patients withdrew from the study.

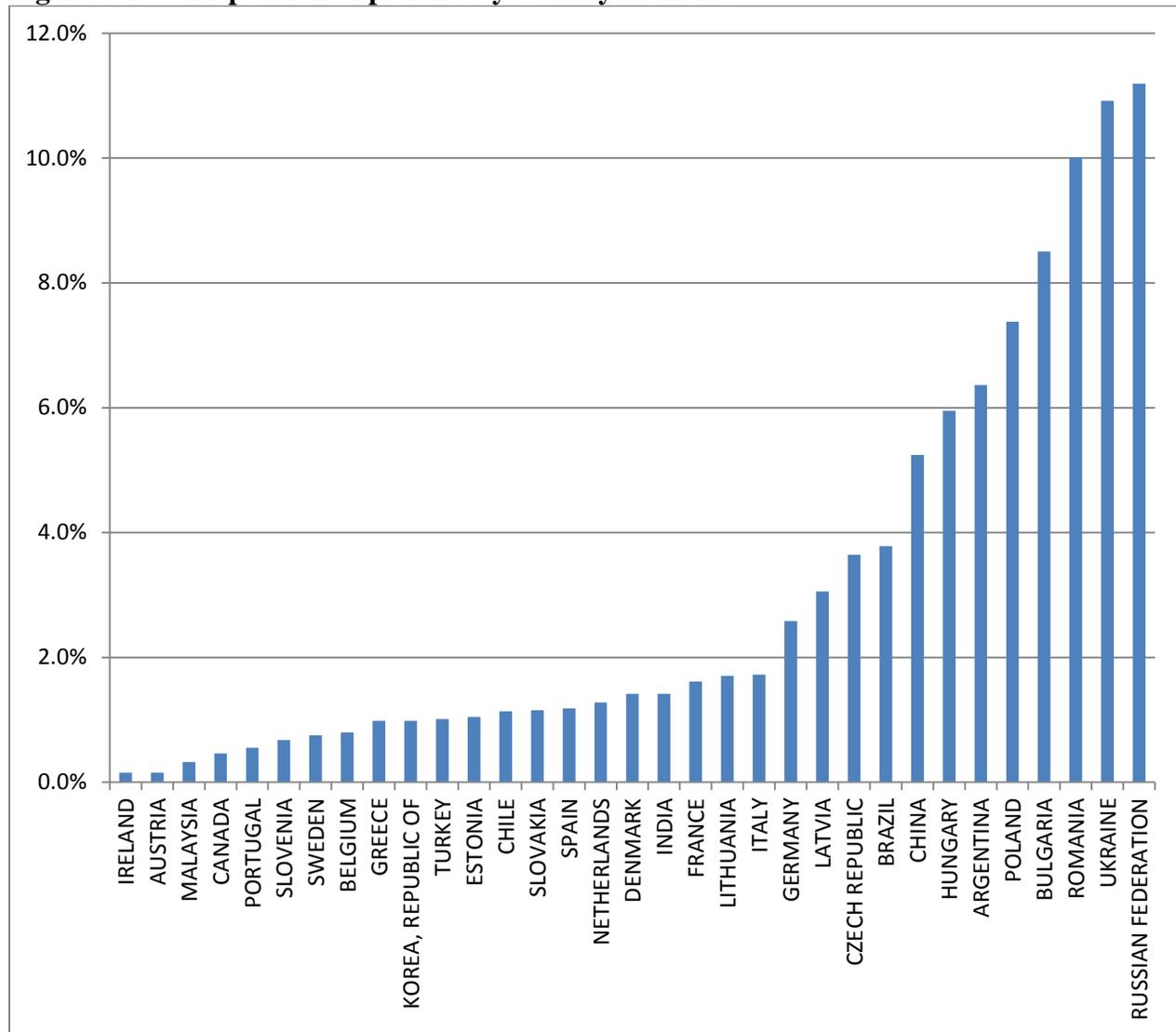
Table 3-1 Disposition of patients by treatment group in the RS

Status	Ivabradine (N=3241)	Placebo (N=3264)	Total (N=6505)
	n (%)	n (%)	n (%)
Consent Withdrawal	73 (2.3)	58 (1.8)	131 (2.0)
Death	503 (15.5)	553 (16.9)	1056 (16.2)
Lost to Follow-up	2 (<0.1)	1 (<0.1)	3 (<0.1)
Study Completed	2663 (82.2)	2652 (81.3)	5315 (81.7)

[Source: Reviewer’s result]

Thirty seven countries enrolled patients and the number of patients ranged from 10 (Ireland) to 728 (Russian Federation). The detailed percentage distributions among all the enrolling countries are list in Figure 3-2.

Figure 3-2 Disposition of patients by country in the RS



[Source: Reviewer’s Results]

The demographic data are summarized in Table 3-2. There were no major discrepancies between treatment groups. Most patients were Males and Caucasians.

Table 3-2 Main demographic characteristics in the RS

	Parameters	Ivabradine	Placebo
Age	Mean (SD)	60.7 (11.2)	60.1 (11.5)
Gender	Male (%)	2462 (76.0)	2508 (76.8)
	Female (%)	779 (24.0)	756 (23.2)
Ethnic	Caucasian (%)	2879 (88.8)	2892 (88.6)
	Asian (%)	268 (8.3)	264 (8.1)
	Black (%)	32 (1.0)	43 (1.3)
	Other (%)	62 (1.9)	54 (2.0)
Weight (kg)	Mean (SD)	80.9 (17.2)	80.7 (17.1)
Heart Rate (bpm)	Mean (SD)	79.7 (9.5)	80.1 (9.8)
Sitting SBP	Mean (SD)	122.0 (16.1)	121.4 (15.9)
Sitting DBP	Mean (SD)	75.7 (9.6)	75.6 (9.4)
Smoking Habits	Yes (%)	541 (16.7)	577 (17.7)
	Stopped (%)	1355 (41.8)	1364 (41.8)
	Never (%)	1345 (41.5)	1323 (40.5)

[Source: Reviewer's Results]

3.2.4 RESULTS AND EXPLORATORY ANALYSES

The efficacy analyses were based on the intent-to-treat principle and took account of all endpoints (on treatment or not) that occurred before, or at, the patients' TERM visit and before or on the 31 March 2010. The same statistical analyses were carried out on patients of the RS (Randomised Set) then on patients of the RS_{BBdose} based on a hierarchical procedure.

3.2.4.1 Primary Efficacy Results

The primary composite endpoint (PCE) was the first event among cardiovascular death (including death of unknown cause) or hospitalization for worsening heart failure.

In the RS, a total of 793 patients reached the primary composite endpoint in the Ivabradine group versus 937 patients in the Placebo group. The superiority of Ivabradine over Placebo in the reduction of the incidence of the primary endpoint was demonstrated, using a Cox proportional hazards model adjusted for beta-blocker intake at randomization, with an estimate of the hazard ratio of 0.82 (95% CI [0.75; 0.90], $p < 0.0001$).

In the RS_{BBdose} over the study period, a total of 330 patients reached the primary composite endpoint in the Ivabradine group versus 362 patients in the Placebo group. The estimate of the hazard ratio of the primary endpoint in this analysis set was 0.90 (95% CI [0.77; 1.04]), indicating a 10% RRR, but statistical significance was not reached ($p = 0.155$).

The results of primary composite endpoint are provided in the Table 3-3.

Table 3-3 Results of Incidence of the primary composite endpoint

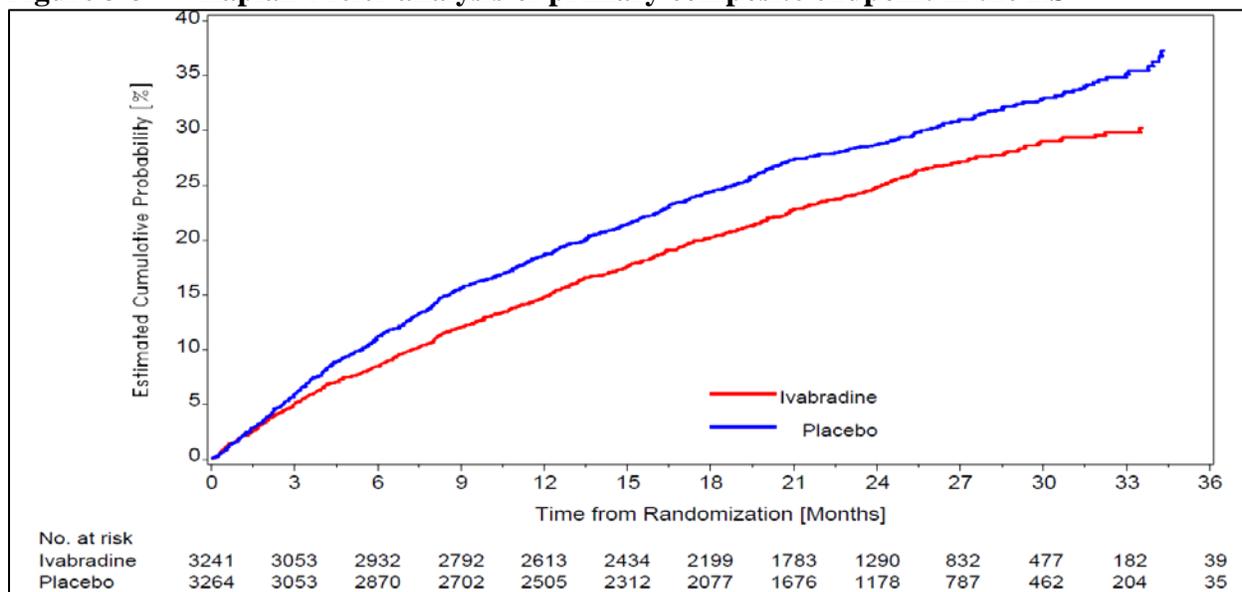
Analysis Sets	Ivabradine		Placebo		HR (95% CI)	p-value
	n/N	%	n/N	%		
RS					0.82	
PCE	793/3241	24.5	937/3264	28.7	(0.75, 0.90)	<0.0001
Cardiovascular Death	449/3241	13.9	491/3264	15.0	0.91 (0.80, 1.03)	0.128
Hospitalization for WHF	514/3241	15.9	672/3264	20.6	0.74 (0.66, 0.83)	<0.0001
RS_{BBdose}					0.90	
PCE	330/1581	20.9	362/1600	22.6	(0.77, 1.04)	0.155

[Source: Reviewer’s results]

Upon further inspection of the components of the primary composite endpoint, it is noticed that the primary composite endpoint was mostly driven by the rate of hospitalization for WHF than by the rate of CV death, see Table 3-3.

The Kaplan-Meier curves of the time to first event of primary composite endpoint in the RS are presented in Figure 3-3. The early separation between the two curves indicated a rapid treatment effect in favor of Ivabradine in the patient population.

Figure 3-3 Kaplan-Meier analysis of primary composite endpoint in the RS



[Source: Reviewer’s Results]

Recall a total of 46 patients from two Polish centers #1142 and #1121 were excluded from all analyses sets for concerns over invalid data due to misconduct. A sensitivity analysis, which included these patients, showed these patients did not affect the efficacy results and provided the exact same results as Table 3-3.

The slight imbalance in the rate of consent withdrawals between two treatment groups, which involved only very small number of patients (131), also did not affect the overall efficacy results. The analyses of completely remove these 131 patients or reclassify them all as primary event/censure are identical to primary analysis results.

3.2.4.2 Secondary Efficacy Analysis

This section examined Ivabradine treatment effect over Placebo in various causes of deaths and hospitalizations.

Analyses of Deaths

There were 1055 adjudicated deaths in the RS. The detailed breakdowns of the causes of deaths are provided in Table 3-4.

Table 3-4 Causes of deaths by treatment group in the RS

	Ivabradine (N=3241)		Placebo (N=3264)	
	n	%	n	%
Death from any cause	503	15.5	552	16.9
Cardiovascular death	449	13.9	491	15.0
Sudden cardiac death	232	7.2	220	6.7
Death from heart failure	113	3.5	151	4.6
Non-cardiovascular death	54	1.7	61	1.9

[Source: Reviewer's Results]

The estimates of the effect of Ivabradine in comparison to Placebo in reduction of death from any cause, cardiovascular death, sudden cardiac death, death from heart failure, and non-cardiovascular death are presented in Table 3-5. Ivabradine had favorable treatment effects in the most types of death, except sudden cardiac deaths.

Table 3-5 Estimates of treatment effect on causes of death in the RS

	Hazard Ratio (95% CI)	p-value
Death from any cause	0.90 (0.80, 1.02)	0.092
Cardiovascular death	0.91 (0.80, 1.03)	0.128
Sudden cardiac death	1.05 (0.87, 1.26)	0.630
Death from heart failure	0.74 (0.58, 0.94)	0.014
Non-cardiovascular death	0.87 (0.60, 1.25)	0.455

[Source: Reviewer's results]

Analyses of hospitalizations

A total 2587 patients were hospitalized at least once for any cause during the study (planned or unplanned). The detailed breakdown of the causes of hospitalizations is provided in Table 3-6.

Table 3-6 Causes of hospitalizations by treatment group in the RS

Number of patients with at least one:	Ivabradine (N=3241)		Placebo (N=3264)	
	n	%	n	%
Hospitalization from any cause	1231	38.0	1356	41.5
Hospitalization from CV reason	577	17.8	635	19.5
Hospitalization from WHF	514	15.9	672	20.6
Unplanned hospitalization for any cause	1137	35.1	1264	38.7
Unplanned hospitalization for CV reason	909	28.1	1047	32.1

[Source: Reviewer's results]

The treatment effect (Ivabradine versus Placebo) in the reduction of hospitalizations for any cause, hospitalizations for CV reason and hospitalizations for WHF were specifically analyzed and all were statistically significant in favor of Ivabradine (see Table 3-7).

Table 3-7 Estimates of treatment effect on causes of hospitalization in the RS

	Hazard Ratio (95% CI)	p-value
Hospitalization from any cause	0.89 [0.82, 0.96]	0.0027
Hospitalization from CV reason	0.85 [0.78, 0.92]	0.0002
Hospitalization from WHF	0.74 [0.66, 0.83]	<0.0001
Unplanned hospitalization for any cause	0.88 [0.81, 0.95]	0.0013
Unplanned hospitalization for CV reason	0.84 [0.77, 0.92]	0.0002

[Source: Reviewer's results]

3.2.4.3 Reviewer's Results

This section presents some exploratory analyses that seem to provide support for the efficacy findings of SHIFT, and some analyses which may raise some questions to the findings.

3.2.4.3.1 Analyses of Supportive Evidence

Test based on Weighted Observations

The trial sample size and number of primary events were modified in Amendments 5 and 6. The total number of primary events is increased from 1220 to 1600, specifically. Hence, there are concerns regarding possible inflation of the Type I error probability if such sample size adjustments are influenced by the internal trial data. To address this potential concern (noting that there is no document that can be used to check if the adjustments of sample size or number of pre-planned number of events was ever influenced by the internal trial data), this reviewer performed an analysis to adjust p-value using the valid statistical test method of Cui, Hung, and Wang (1999, Biometrics).

The CHW statistic is formed by combining the incremental Z statistics. Suppose $\hat{\delta}_j^*$ be the Cox model estimate of $-\ln(\text{HR})$, $I_j^* = [\text{se}(\hat{\delta}_j^*)]^{-2}$ be the corresponding Fisher information through look j , and define

$$Z^{*(j)} = \frac{\sqrt{I_j^* \hat{\delta}_j^*} - \sqrt{I_{j-1}^* \hat{\delta}_{j-1}^*}}{\sqrt{I_j^* - I_{j-1}^*}}, \quad j = 1, 2, \dots, K,$$

with the prespecified weights

$$w^{(j)} = \frac{D_j}{D^K}, \quad j = 1, 2, \dots, K,$$

where D_j is the number of events in the initial design at look j and $K=2$.

The Amendment No. 5 was dated on September 10, 2008, and a total of 655 primary events have been accumulated by the date. If we assume this is the trial end date, then we would observe the estimated Hazard Ratio, $\widehat{HR} = 0.77$. Thus, the corresponding Z statistic is

$$Z^{(1)} = \frac{\hat{\delta}_{(1)}^*}{SE(\hat{\delta}_{(1)}^*)} = -\frac{\ln(0.77)}{\left(\frac{2}{\sqrt{655}}\right)} = 3.33.$$

The final analysis is taken at 1730 cumulative events and $\widehat{HR}=0.82$. Therefore, the cumulative Z statistics is

$$Z_2^* = \frac{\hat{\delta}_2^*}{SE(\hat{\delta}_2^*)} = -\frac{\ln(0.82)}{\left(\frac{2}{\sqrt{1730}}\right)} = 4.13$$

Hence, the incremental Z statistic is

$$Z^{*(2)} = \frac{\sqrt{D_2^* Z_2^*} - \sqrt{D_1^* Z_1^*}}{\sqrt{D_2^* - D_1^*}} = \frac{\sqrt{1730} * 4.13 - \sqrt{655} * 3.33}{\sqrt{1730 - 655}} = 2.64$$

Lastly, the final weighted Z statistic would be

$$Z_{2,CHW}^* = \frac{\sqrt{w^{(1)}} Z^{(1)} + \sqrt{w^{(2)}} Z^{*(2)}}{\sqrt{w^{(1)} + w^{(2)}}} = \frac{\sqrt{0.54} * 3.33 + \sqrt{0.46} * 2.64}{\sqrt{0.54 + 0.46}} = 4.24$$

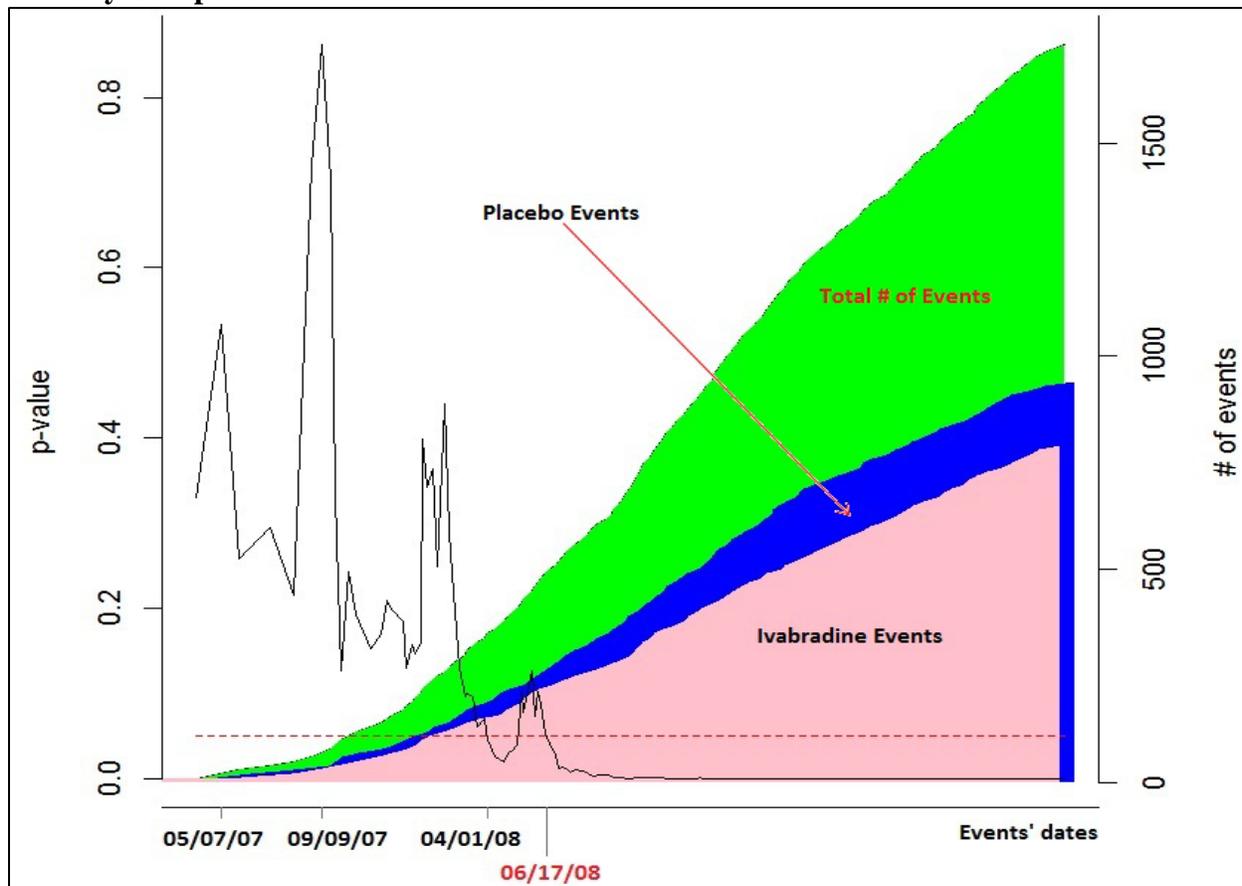
where $w^{(1)} = \frac{655}{1220} = 0.54$ and $w^{(2)} = 1 - w^{(1)}$. Furthermore, the corresponding p-value of $Z_{2,CHW}^*$ is <0.0001 , which supports the sponsor's unweighted test.

Analysis on the Different End of Trial Dates

It would be very useful to find out how early the statistical significant findings were established during the course of the trial. Figure 3-4 shows the P-values of Cox proportional hazards model for the primary endpoint as a function of calendar date of the study. In this analysis, the ascending event dates (regardless the treatment assignments) are assumed to be the artificial new end of trial dates, and the subjects' event/censor statuses are modified accordingly. The Cox proportional hazards models were repeated to each new modified analysis dataset. The red dash line is the reference line for the p-value of 0.05. We can see that the trial result reached a nominal p-value < 0.05 in favor of Ivabradine as early as of June 17, 2008. The colorful shaded areas are the cumulative number of events of Total, Placebo and Ivabradine as indicated in the

Figure 3-4. The Placebo group consistently has more primary events than Ivabradine group through the course of the trial.

Figure 3-4 The Distribution of Cox PH model P-values Along with the Accumulation of Primary Composite Events across the Calendar Date



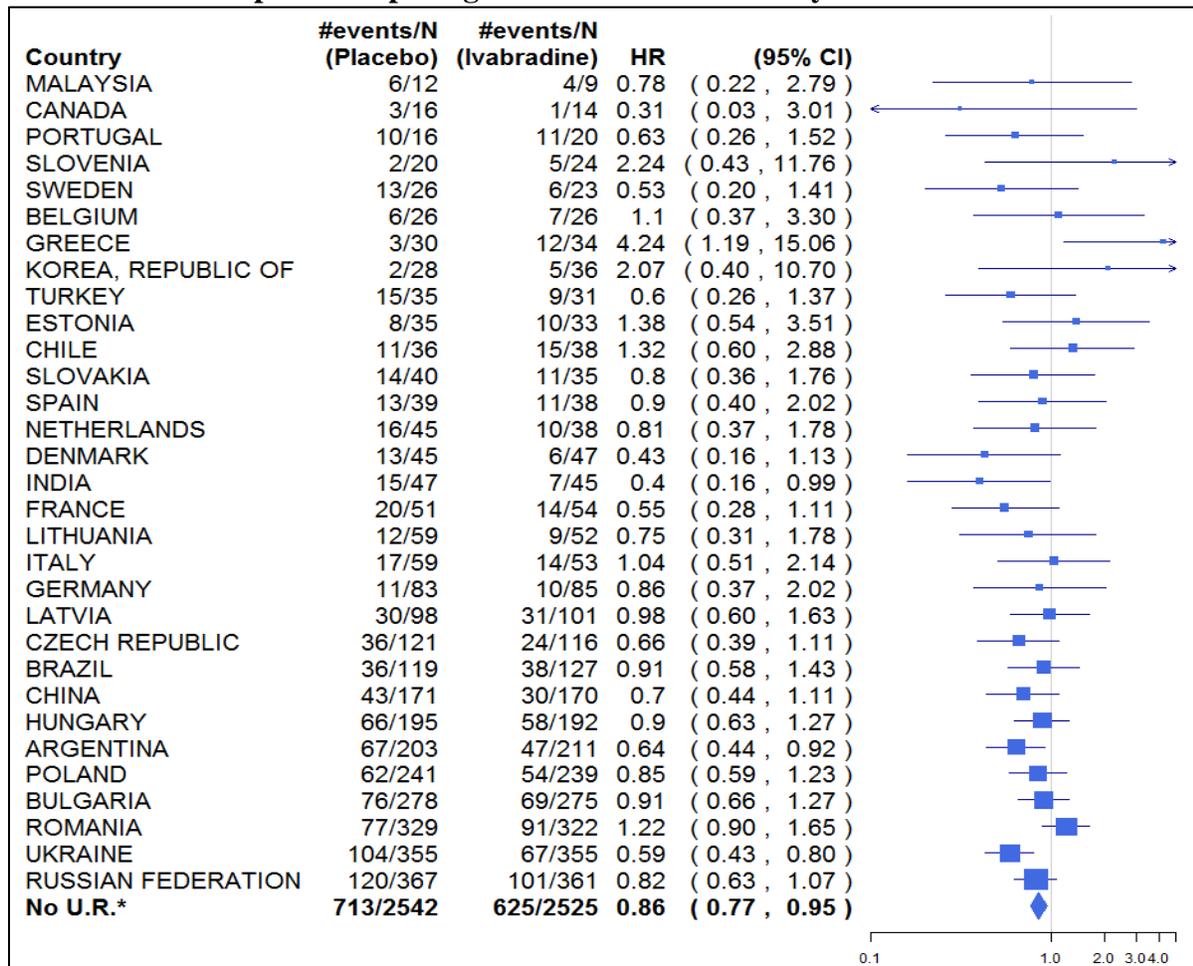
[Source: Reviewer's Results]

Analysis on the Impact of Individual Country

The study was conducted in 37 countries. Among these countries, Ivabradine were numerically superior to Placebo in the vast majority of countries (see Figure 3-5). This figure excluded six countries which had very low enrollments and zero events observed in either treatment group.

In the bottom row of this figure, it is noted that the statistical significant finding is maintained even if the entire countries of Russia and Ukraine (about 40% of trial population) are both removed from the analysis set. This subgroup provided an estimate of the hazard ratio of 0.86 (95% CI [0.77, 0.95], $p=0.0046$).

Figure 3-5 The Forest Plots of Hazard ratio and 95% CI for Primary Composite Endpoint comparing Ivabradine to Placebo by countries



[Source: Reviewer’s Results,

*No U.R. represents the analysis result when Ukraine and Russian are both removed]

3.2.4.3.2 Analyses of Questionable Findings

Analysis on Financial Disclosure

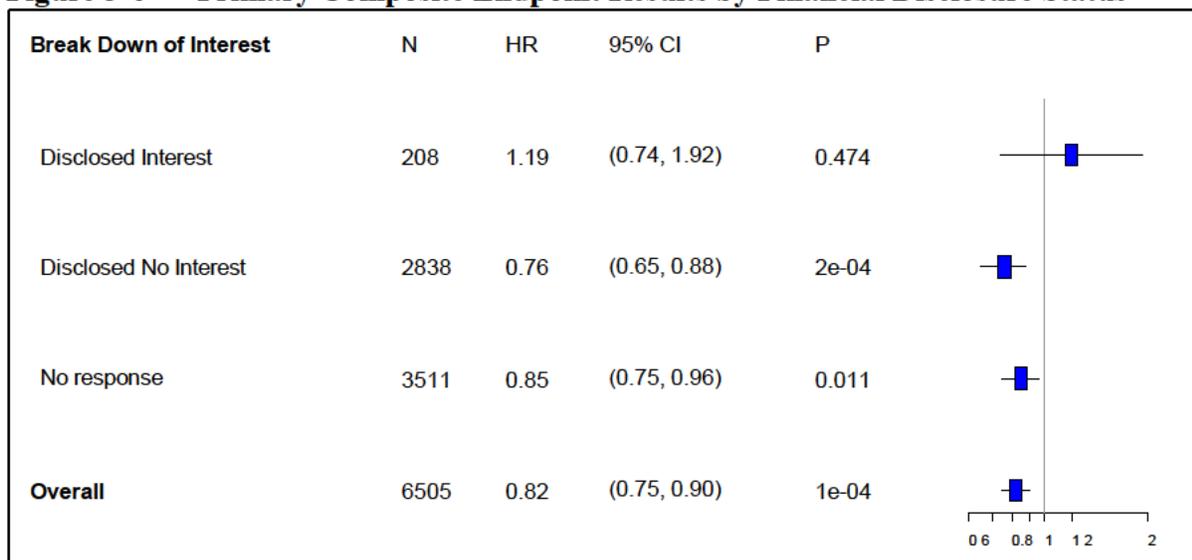
SHIFT was conducted entirely outside of US and FDA had no prior involvement with the planning, design, and conduct of SHIFT. During the NDA review, the agency noticed that a large number of investigational sites and/or sub-investigators had various issues with the request for financial disclosures as well as conflicts of interest. The study investigators can be classified into three categories: a) Responded to the disclosure request and reported a disclosable relationship, b) Responded to the request and reported no disclosable relationship, and c) Did not respond to the request for financial disclosure. SHIFT had a total of 667 study sites and the detailed breakdown of these three categories is presented in Table 3-8.

Table 3-8 Study Sites Disclosure Category

	Number of Sites (%)	Number of patients in the corresponding Sites
Disclosed Interest	14 (2.1)	208
Disclosed No Interest	314 (46.4)	2838
Did not Respond	349 (51.6)	3511
Total	667	6505

[Source: Reviewer's results]

Over half (51.6%) of the sites did not respond to the request and almost other half (46.4%) of the sites disclosed no disclosable relationship in the study. The results of these two categories are consistent with the overall population. However, the sites who reported disclosable financial relationship observed a favorable treatment effect towards Placebo with a hazard ratio of 1.19, see Figure 3-6.

Figure 3-6 Primary Composite Endpoint Results by Financial Disclosure Status

[Source: Reviewer's Analysis]

Interim Analyses

The DMC reviewed efficacy and safety data at regular intervals during the study, thus ensuring the safety of the patients. They carried out 3 formal interim analyses, the first one dedicated only to prematurely detect an eventual harmful effect and the two other ones to investigate both efficacy and harmful effects. Based on the Peto group sequential procedure, the nominal type I error rate used for interim efficacy analyses was fixed at 0.1% and had no significant impact on the global type I error rate used for the final analysis. These three interim analyses took place when approximately 20%, 40% and 70% of the expected events for the primary composite endpoint had been observed.

Amendment No. 5 increased the total number of events from 1220 to at least 1600 composite endpoints on September 10, 2008. The 488th primary event, which is 40% of 1220, occurred on June 6, 2008. Since the Amendment No.5 was dated 3 months after, the first two interim

analyses were based on the information time of the original number of events. However, the third analysis was conducted when 70% of 1600 events had occurred.

Table 3-9 Results of Interim Analyses on Primary Endpoint

Interim Analysis	Date	Ivabradine		Placebo		HR (95% CI)	p-value
		n/N	%	n/N	%		
IA1	3/13/2008	145/1751	8.3	176/1735	10.1	0.82 (0.66, 1.03)	0.08
IA2	6/9/2008	223/2419	9.2	265/2418	10.9	0.83 (0.70, 0.997)	0.0458
IA3	3/16/2009	494/3128	15.8	629/3161	19.9	0.77 (0.68, 0.87)	<0.0001

[Source: Reviewer's Results]

Table 3-9 listed the result of each interim analysis. There are two interesting observations from the following results:

1. The poor Ivabradine efficacy results from BEAUTIFUL trial prompted the sample size/event increase with SHIFT Amendment No. 5 in September of 2008 (see Table 3-11), but the second interim analysis on the SHIFT's primary endpoint provided a very promising result ($p=0.0458$) just three months prior to the amendment.
2. According to the stopping rule of the 3rd interim analysis, SHIFT had crossed the early stopping boundary for the overwhelming efficacy ($p<0.0001$) in March of 2009. This interim analysis was conducted, again, three months prior to the Amendment No. 6, which stopped SHIFT recruitment when 6500 patients were randomized. The amendment did not stop the trial for the reason of overwhelming efficacy, but stated that the sample size change was made due to the lower than expected recruitment rate.

3.2.4.4 Inconsistent Findings of External Trials

The benefit of Ivabradine in the treatment of chronic heart failure is supported primarily by the results of SHIFT. BEAUTIFUL, a large outcome trial in subjects with coronary artery disease (CAD), did not meet its primary endpoint (risk reduction for first event among cardiovascular death, hospital admission for acute myocardial infarction, or hospital admission for new onset or worsening heart failure).

BEAUTIFUL results inspired another even larger outcome trial in patients who had stable CAD without clinical heart failure and a heart rate of 70 beats per minute or more, SIGNIFY. However, SIGNIFY again failed to demonstrate the addition of Ivabradine to standard background therapy to reduce the risk of cardiovascular events.

Table 3-10 summarized the key design features of these three large outcome trials.

Table 3-10 Comparisons in key design features among three outcome trials

	SHIFT (pivotal)	BEAUTIFUL (support)	SIGNIFY
N	6,558 (efficacy - benefit)	10,917 (efficacy – none)	19102 (efficacy - ? none)
Duration	09/2006 – 04/2010	12/2004 – 02/2008	9/2009 – 1/2014
Population	Mean Iva Age 60.7 yrs CHF in SR LVEF \leq 35% NYHA CHF Class II-IV rHR > 70	Mean Iva Age 65.3 yrs Documented CAD in SR LVEF < 39% Stable CAD/CHF Sx rHR > 60	Mean Iva Age 65.0 yrs Stable CAD in SR LVEF > 40% NYHA CHF Class 1 rHR \geq 70
Ivabradine Treatments	2.5, 5 or 7.5 mg BID	PBO vs. Ivabradine (5 or 7.5 mg BID)	PBO vs. Ivabradine (5, 7.5 , or 10 mg BID)
Mean Dose	6.4±1.4 mg BID (Iva) 7.8±0.7 mg BID (Pla)	6.18±1.25 mg b.i.d. RS 6.64±1.25 mg b.i.d. RS-HR70	8.2±1.7 mg BID (Iva) 9.5±0.9 mg BID (Pla)
HR Target	50 – 60	50 – 60	55-60
Mean HR	~65 bpm @ 3 mos (Iva) ~75 bpm @ 3 mos (Pl)	~ 61 bpm @ 3 mos (Iva) ~ 70 bpm @ 3 mos (Pl)	60.7±9.0 bpm (Iva-all) ~62 bpm (Iva-angina) 70.6±10.1 bpm (Pl-all)
Endpoint	Time To CV death or hospitalization for WHF	CV death/hosp for acute MI/hosp for new onset or WHF	CV Death or non-fatal MI

BEAUTIFUL

This was a phase 3 study in 10,946 subjects with CAD and left ventricular systolic dysfunction (LVSD) and heart rate \geq 60 bpm. The study was specifically designed to evaluate CAD outcomes: the reduction of cardiovascular morbidity and mortality, defined as first event among cardiovascular death, hospital admission for acute myocardial infarction, or hospital admission for new onset or worsening heart failure. BEAUTIFUL was initiated in 2004 and completed in 2008. The study was conducted at 757 centers in 33 countries, including Canada, Australia, and countries in Western Europe, Eastern Europe, Asia, and South America. Subjects received Ivabradine at an initial dose of 5 mg BID, which could be uptitrated to 7.5 mg BID depending on resting heart rate and tolerability.

In Table 3-11, BEAUTIFUL did not demonstrate an overall treatment benefit with Ivabradine as measured by the primary efficacy endpoint in the overall patient population (HR: 1.00, 95% CI: 0.91, 1.10; p-value = 0.945).

Table 3-11 Incidence of the primary endpoint and components -BEAUTIFUL

	Ivabradine (N=5479) n (%)	Placebo (N=5438) n (%)	HR (95% CI)	p-value
Primary Composite Endpoint	844 (15.4)	832 (15.3)	1.00 (0.91, 1.10)	0.945
Secondary Endpoints				
Cardiovascular Death	469 (8.6)	435 (8.0)	1.07 (0.94, 1.22)	0.316
Hospitalization for acute MI	199 (3.6)	226 (4.2)	0.87 (0.72, 1.06)	0.159
Hospitalization for new onset or Worsening Heart Failure	426 (7.8)	427 (7.9)	0.99 (0.86, 1.13)	0.850
	N=2699	N=2693		
Hospitalization for acute MI in RS-HR70*	85 (3.2)	131 (4.9)	0.64 (0.49, 0.84)	0.001

[Source: Sponsor's CSR np27426-01 Table (11.1.1) 1, confirmed by the reviewer

* **RS-HR70** is randomized set of patients with baseline heart rate 70 bpm or more]

In a post hoc analysis, the subgroup of subjects with baseline heart rate \geq 70 bpm appeared to suggest a potential signal of a reduced risk on hospitalization for acute myocardial infarction (0.64 [0.49, 0.84]) by Ivabradine.

SIGNIFY

The results of the BEAUTIFUL shed new light on the role of heart rate control in cardiovascular disease and lead to a series of stimulating hypotheses that constitute the rationale for another trial called SIGNIFY (Study assessInG the morbidity-mortality beNefits of the If inhibitor Ivabradine in patients with coronarY artery disease).

This is a randomized, double-blind, Placebo-controlled trial of Ivabradine, added to standard background therapy, in 19,102 patients who had both stable coronary artery disease without clinical heart failure and a heart rate of 70 beats per minute or more. SIGNIFY was initiated in 2009 and completed in 2013. The study was conducted at 1139 centers in 51 countries, not including United States. Subjects received Ivabradine at starting dose of 7.5 mg bid and then 5,

7.5. 10 mg to reach target heart rate of 60 bpm. The primary composite endpoint of SIGNIFY was a composite of death from cardiovascular causes or nonfatal myocardial infarction. The secondary endpoints included the components of the primary endpoint as well as death from any cause.

Results with respect to study endpoints are presented in Table 3-12. There was no significant difference in the incidence of the primary endpoint between the Ivabradine group and the Placebo group (6.8% vs. 6.4%, respectively; hazard ratio, 1.08; 95% confidence interval, 0.96 to 1.20; P=0.20). There were also no significant differences between the two groups in the incidences of the components of the primary endpoint. The rate of death from any cause also did not differ significantly between the two groups (hazard ratio, 1.06; 95% CI, 0.94 to 1.21; P = 0.35).

Table 3-12 Incidence of the primary endpoint and components -SIGNIFY

	Ivabradine (N=9550) n (%)	Placebo (N=9552) n (%)	HR (95% CI)	p-value
Primary Composite Endpoint	COPYRIGHT MATERIAL WITHHELD			
Secondary Endpoints	COPYRIGHT MATERIAL WITHHELD			
Cardiovascular Death	COPYRIGHT MATERIAL WITHHELD			
Nonfatal MI	COPYRIGHT MATERIAL WITHHELD			
Death from Any Cause	COPYRIGHT MATERIAL WITHHELD			

[Source: Fox K et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1406430]

3.3 Evaluation of Safety

Safety is not evaluated in this review. Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

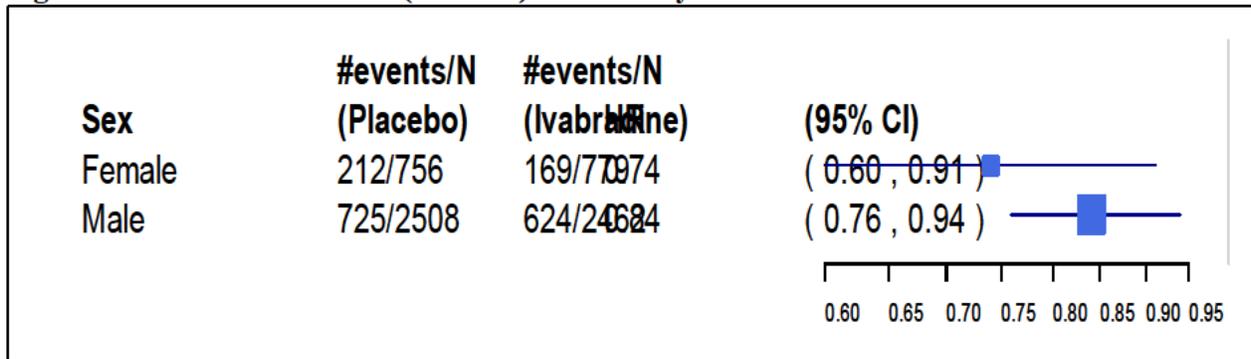
4.1 Gender, Age and Race group

The following subsections present the incidence of the primary composite endpoint and the estimate of treatment effect in the subgroups of the gender, age and race.

4.1.1 GENDER

There were no obvious differences in hazard ratios for the primary endpoint across either Gender group. Ivabradine demonstrated statistical significant effects over Placebo in both gender groups, see Figure 4-1.

Figure 4-1 Hazard Ratios (95% CI) for PCE by Gender

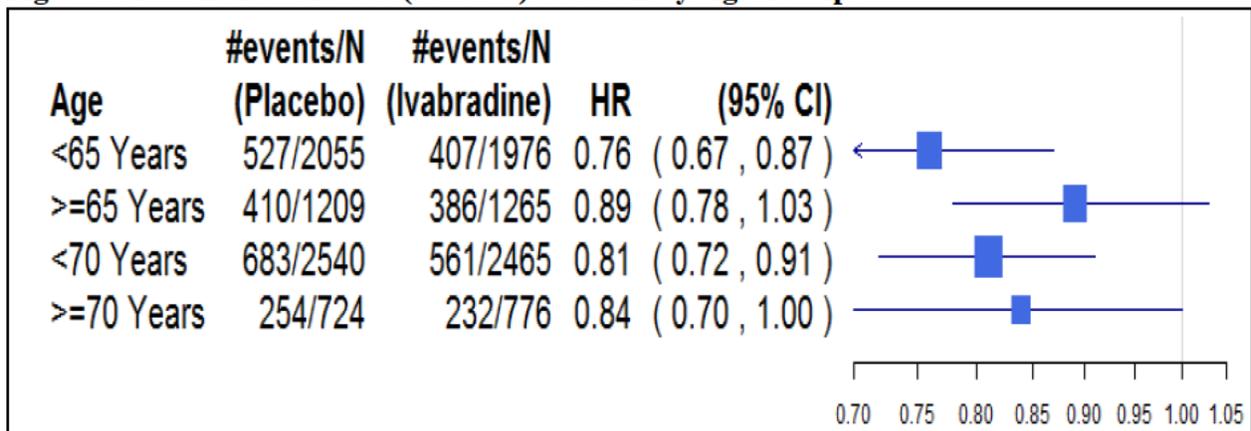


[Source: Reviewer’s results]

4.1.2 AGE

The age is categorized into the following two subgroups: younger or older than 65 and 70 years of age. The hazard ratios in all four subgroups are consistent with the primary analysis results. It seemed that there are better numerical Ivabradine treatment effects in younger populations, see Figure 4-2.

Figure 4-2 Hazard Ratios (95% CI) for PCE by Age Groups

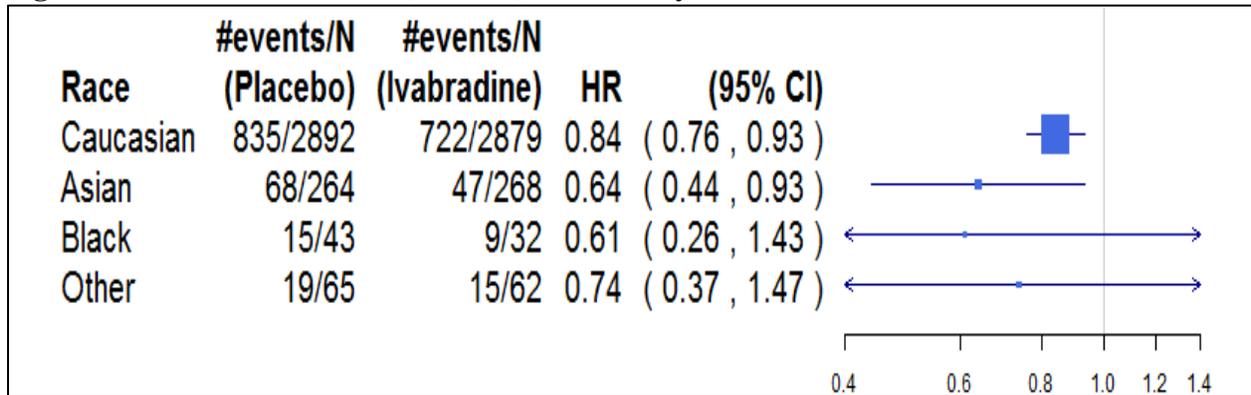


[Source: Reviewer’s results]

4.1.3 RACE

The majority of subjects are Caucasians. All races numerically confirmed the primary analysis results, see Figure 4-3

Figure 4-3 Hazard Ratios (95% CI) for PCE by Race



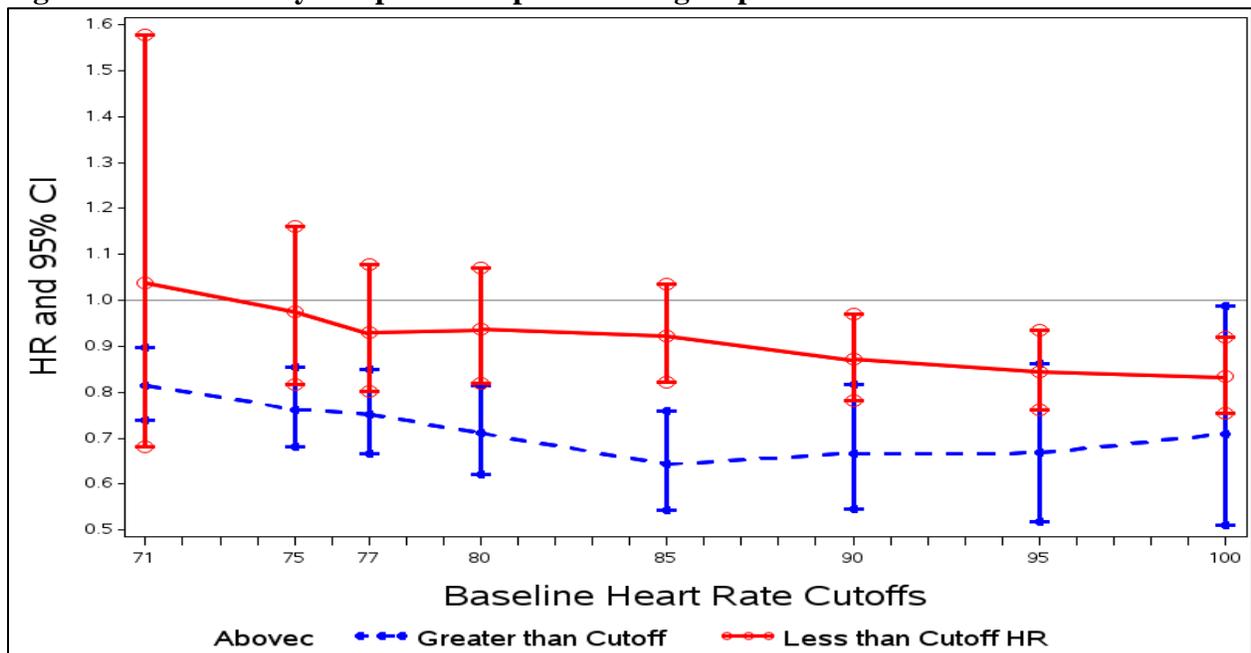
[Source: Reviewer’s results]

4.2 Other Subgroup Populations

4.2.1 BASELINE HEART RATE

Sponsor’s CSR observed significant interaction between treatment and baseline heart rate \leq/\geq 77 bpm (median HR in RS) with $p=0.0288$, which indicating a great effect of Ivabradine in patients with higher HR at baseline. Figure 4-4 expended sponsor’s analysis to multiple cutoff points of HR at baseline.

Figure 4-4 Primary composite endpoint in subgroups of the HR at baseline



[Source: Reviewer’s results]

Above figure confirmed the sponsor's claim that patients with higher baseline HR would have greater benefit of Ivabradine.

4.2.2 BASELINE BETA-BLOCKER INTAKE

The subjects in SHIFT received different percentages of the target daily beta-blocker dose at randomization. Figure 4-5 suggested a numeric reduction in the magnitude of treatment effect of Ivabradine on the primary endpoint with increasing background beta-blocker dose.

Figure 4-5 Estimates of the effect of randomized treatment by category of baseline beta-blocker treatment status

	Ivabradine	Placebo	HR (95% CI)	P-value
	n (%)	n (%)		
Primary Endpoint				
No BB	101 (29.4)	134 (39.3)	0.68 (0.52, 0.88)	0.003
BB < 25%	148 (30.8)	171 (40.0)	0.74 (0.60, 0.93)	0.008
BB 25% to 50%	204 (26.2)	260 (30.8)	0.81 (0.68, 0.98)	0.029
BB 50% to 100%	181 (21.6)	212 (24.8)	0.84 (0.69, 1.02)	0.077
BB >= 100%	149 (20.1)	150 (20.1)	0.99 (0.79, 1.24)	0.904

[Source: Reviewer's results
BB stands for Beta-Blocker]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

SHIFT demonstrated the superiority of Ivabradine over Placebo in the reduction of cardiovascular mortality or hospitalization for worsening heart failure. In the pre-specified randomized set (N=6505), the primary endpoint was attained by 793 patients in the Ivabradine group vs. 937 patients in the Placebo group. The estimate of the hazard ratio was 0.82 (95% CI was [0.75, 0.90]; p<0.0001). However, we need to note that the majority of the benefit of Ivabradine in the study was a reduction in heart failure hospitalizations.

Although SHIFT as one study appears to show a benefit of Ivabradine, the two other Cardiovascular outcome trials, BEAUTIFUL and SIGNIFY, appear to be highly inconsistent with SHIFT. BEAUTIFUL failed to demonstrate the treatment benefit of Ivabradine in the time to first event among cardiovascular death, hospitalization for acute myocardial infarction, or hospitalization for new onset or worsening heart failure, whereas SIGNIFY was at best neutral--leaning negatively--for CV and all-cause mortality in the study as a whole and worse than Placebo for the primary endpoint of CV death or nonfatal MI. There seemed to be some differences in design features among the three trials (Table 3-10, page 19), but it is unclear whether these differences cause the inconsistency.

5.2 Conclusions and Recommendations

The primary objective of the SHIFT study was reached, i.e., the demonstration of the superiority of Ivabradine over Placebo in the reduction of cardiovascular mortality or hospitalizations for

worsening heart failure, in patients with moderate to severe symptoms of CHF, reduced LVEF and receiving currently recommended therapy for this disease.

SHIFT also appeared to be a favorable study with a lean on mortality. However, the findings of the two other large(r) cardiovascular outcome trials (BEAUTIFUL, SIGNIFY) are highly inconsistent with the findings of SHIFT. Both of these two trials failed their respective primary composite endpoints, which are very similar to the primary endpoint of SHIFT. From Table 3-10 (page 19), there seemed to be some differences in design features among the three trials, but it is unclear whether these differences cause the inconsistency. Ideally we need to understand the reasons for these different trial results to understand for which patients' Ivabradine is useful and to determine if there is a heart failure benefit. The issue of the inconsistent findings among the three large outcome trials of Ivabradine needs to be addressed.

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/s/

STEVE G BAI
11/16/2014

HSIEN MING J HUNG
11/17/2014



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

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number: NDA 206-143

Drug Name: Ivabradine (S 16257-2)

Indication(s): 104 Week Rat and Mouse Carcinogenicity Studies

Applicant: **Sponsor:** Amgen Inc.
One Amgen Center Drive, Thousand Oaks, CA 91320-1799

Performing laboratory: [REDACTED] (b) (4)

Documents Reviewed: **Electronic submission:** Submitted on April 30, 2014
Electronic data: Submitted on April 30, 2014

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Biometrics Division: Division of Biometrics -6

Statistical Reviewer: Mohammad Atiar Rahman, Ph.D.

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Project Manager: Alexis Childers

Keywords: Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of Ivabradine (S 16257-2) when administered orally daily through dietary admixture at appropriate drug levels for 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Wu.

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

2. Rat Study

Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and two identical control groups. Two hundred and fifty Hanibm Wistar rats of each sex were assigned randomly to the treated and control groups in equal size of 50 rats per group. The dose levels for treated groups were 7.5, 30, or 120 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose groups, respectively. Due to excessive toxicity as characterized by lower body weight and food intake, as well as complementary information, from Week 53 the high dosage level was lowered to 60 mg base/kg/day. The rats in the control groups remained untreated and received normal basal diet.

During the administration period all rats were observed twice daily for morbidity and mortality. Individual animals were observed at least once weekly for any signs of behavioral changes, reaction to treatment or ill health. A detailed palpation of each rat was performed once weekly in order to record the date of appearance, location and dimension, of all new palpable masses. Body weights of all rats were measured once before the beginning of the study and weekly thereafter up to the scheduled necropsy.

2.1. Sponsor's analyses

For both mortality and tumor data analyses the sponsor pooled the two control groups to form one combined control group.

2.1.1. Survival analysis

The sponsor estimated the proportion of mortalities in all five treated groups using the Kaplan and Meier product limit method and presented them graphically for male and female rats separately. The sponsor analyzed the mortality data using the logrank test for dose response relationship across the combined control and the three treated groups and performed pairwise comparisons of each treated group with the combined control. Both the dose response relationship and pairwise comparison were two-tailed.

Sponsor's findings: The sponsor analysis showed 78%, 80%, 82%, 80%, and 82% survival of male rats and 60%, 80%, 68%, 82%, and 68% survival of female rats in Control 1, Control 2, low,

medium and high dose groups, respectively. The sponsor's analysis did not show any statistically significant dose response relationship or treatment related effects on mortality between the combined control and any of treated groups.

2.1.2. Tumor data analysis

The sponsor analyzed the tumor data using the methods outlined in the paper of Peto et al. (1980) for dose response relationships and the Fisher Exact test for pairwise comparisons of the treated groups with combined control. For Peto analysis the sponsor first classified the tumor types as fatal and incidental, and analyzed them using the death rate and prevalence methods, respectively. For the evaluation of non-incidental tumors, the strata were defined as those weeks during which there were deaths; and for incidental tumors, the strata were calculated using the method suggested by Peto et al. (1980) i.e. maximum likelihood method such that the overall prevalence is non-decreasing over the course of the study

In general the sponsor's analyses of tumor data were carried out using the combined control. However, for some tumor types e.g. uterine epithelial tumors in females, two additional analyses were conducted to include all treated groups and Control 1 or Control 2.

Adjustment for multiple testing: No method for the adjustment for multiple comparisons was mentioned in the report.

Sponsor's findings: The sponsor's analyses did not show statistically significant dose response relationship among the treatment groups in any of the observed tumor types. Pairwise comparisons also did not show increased incidence in any of the observed tumors in either sex.

2.2. Reviewer's analyses

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

For animal carcinogenicity experiments with two identical controls, the FDA guidance for statistical design and analysis of carcinogenicity studies suggests to combine the control groups for statistical analysis of the data. Such combination of control increases the power of the test. Following the guidance, this reviewer analyzed both the mortality and tumor data using the combined control.

2.2.1. Survival analysis

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

response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed 78%, 80%, 82%, 80%, 82% survival male rats and 60%, 80%, 68%, 82%, 68% female rats of survival in female rats in Control 1, Control 2, low, medium, and high dose groups, respectively. The tests did not show statistically significant dose response relationship in mortality across the combined control and treated groups in either sex. The pairwise comparisons showed statistically significant increased mortality in Control 2 compared to Control 1 in the female rats.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across the combined control and treated groups, and pairwise comparisons of combined control with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period (w_{\max}) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of $s_h = 1$. An animal that dies at week w_h without a tumor before

the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted group size is then defined as $\sum s_h$.

As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal, while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used, using 0, 7.5, 30, and 90 as the scores for combined control, low, medium, and high dose groups, respectively, where 90 is the weighted average of 120 and 60 for 94 weeks i.e. $(120 \times 52 + 60 \times 52) / 104$.

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

Multiple testing adjustment: For the adjustment of multiple testing this reviewer used the methodologies suggested in the FDA guidance for statistical design and analysis of carcinogenicity studies. For dose response relationship tests, the guidance suggests the use of test levels of $\alpha=0.005$ for common tumors and $\alpha=0.025$ for rare tumors for a submission with two species, and a significance level $\alpha=0.01$ for common tumors and $\alpha=0.05$ for rare tumors for a submission with one species in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor

is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control the guidance suggests the use of test levels of $\alpha=0.01$ for common tumors and $\alpha=0.05$ for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

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

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

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

Sex	Organ Name	Tumor Name	Comb				P_Value			
			Cont	Low	Med	High	Dose Resp	C vs. L	C vs. M	C vs. H
Female	OVARIES	TUBULOSTROMAL ADENOMA	0	1	3	0	0.4617	0.3409	0.0396*	.

Based on the criteria of adjustment for multiple testing discussed above, none of the observed tumors was considered to have statistically significant dose response relationship in either sex. The pairwise comparison showed statistically significant increased incidence of tubulostromal adenoma in ovaries in female rat medium dose group compared to their combined control.

3. Mouse Study

Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups and two identical control groups. Two hundred and fifty Crl:CD-1(ICR)BR mice of each sex was assigned randomly to the treated and control groups in equal size of 50 mice per group. The target dosage levels were initially set at 20, 90 and 405 mg/kg/day. However, due to the high mortality in both sexes receiving 405 mg/kg/day, it was lowered to 180 mg/kg/day from Week 81. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. The mice in the control groups remained untreated and received normal basal diet.

During the administration period all mice were observed regularly for morbidity and mortality. Individual animals were observed at least once weekly for any signs of behavioral changes, reaction to treatment or ill health. A detailed palpation of each mouse was performed once weekly in order to record the date of appearance, location and dimension, of all new palpable masses. Body weights of all mice were measured once before the beginning of the study and weekly thereafter up to the scheduled necropsy.

Even after lowering the dose level of the high dose group there were continued mortality in the high dose group. Due to this high mortality the male high dose group was terminated early in Week 94, when survival reached 20%.

3.1. Sponsor's analyses

3.1.1. Survival analysis

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

Sponsor's findings: The sponsor analysis showed 46%, 44%, 42%, 40%, and 20% (on week 94) survival of male mice, and 40%, 58%, 44%, 46%, and 24% survival of female mice in their Control 1, Control 2, low, medium, and high dose groups, respectively. The sponsor's analysis showed statistically significant dose response relationship in both sexes across combined control and all treated groups ($p < 0.001$). Upon exclusion of the high dose group, no significant dose response relationship was detected. The pairwise comparisons showed statistically significant increased mortality in the high dose group compared to the combined control ($p < 0.001$) in both sexes.

3.1.2. Tumor data analysis

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

Adjustment for multiple testing: No method for the adjustment for multiple comparisons was mentioned in the report.

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

3.2. Reviewer's analyses

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

For the analysis of both the survival data and the tumor data this reviewer used similar methodologies as he used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively. Results

of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer’s findings: This reviewer’s analysis showed 46%, 44%, 42%, 40%, and 20% survival of male mice, and 40%, 58%, 44%, 46%, and 24% survival of female mice in their Control 1, Control 2, low, medium, and high dose groups, respectively. The survival for male mice high dose group was calculated at Week 94. The tests showed statistically significant dose response relationship in mortality across the combined control and treated groups in both sexes of mice. The pairwise comparison show statistically significant increased mortality in the high dose group in both sexes compared to their respective combined control.

3.2.2. Tumor data analysis

For tumor data analysis this reviewer used 0, 20, 90 and 371 as the scores for male mice combined control, low, medium, and high dose groups, respectively, where 371 is the weighted average of 405 and 180 for 94 weeks i.e. $(405 \times 80 + 180 \times 14) / 94$. Also for female mice this reviewer used 0, 20, 90 and 353 as the scores for female mice combined control, low, medium, and high dose groups, respectively, where 353 is the weighted average of 405 and 180 for 104 weeks i.e. $(405 \times 80 + 180 \times 24) / 104$.

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

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

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

Sex	Organ Name	Tumor Name	Comb				P_Value			
			Cont	Low	Med	High	Dose Resp	C vs. L	C vs. M	C vs. H
fff										
Female	HARDERIAN GLAND	ADENOMA	4	2	3	5	0.0131	0.6550	0.4150	0.0373
	LYMPHOID/ MULTICENTRIC	HISTIOCYTIC SARCOMA	3	8	2	3	0.3182	0.0090*	0.5299	0.1795

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

4. Evaluation of the validity of design of rat and mouse studies

As has been noted, except for the significant increased incidences of tubulostromal adenoma in ovaries of female rats in medium dose group and multicentric lymphoid histiocytic sarcoma of female mice in the low dose group compared their respective combined control. However, before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the study compound in rats and mice, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with about fifty to sixty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field.

Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be consider as a sufficient number and adequate exposure.

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

(i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the riocignat rat and mouse carcinogenicity study, in the light of the above guidelines.

4.1. Rat Study

The following is the summary of survival data of rats in the high dose groups:

Percentage of Survival in the High Dose Group at the End of Weeks 52, 78, and 91 in Rats

Percentage of survival			
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	100%	98%	94%
Female	94%	88%	86%

Based on the survival criterion Haseman proposed, it may be concluded that enough rats were exposed to the high dose for a sufficient amount of time in both sexes.

The following table shows the percent difference in mean body weight gain in rats from the combined control, calculated as

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain from Combined Control in Rats

Male			Female		
Low	Medium	High	Low	Medium	High
-7.80	-18.58	-28.44	-18.28	-26.02	-41.94

Source: TABLE 2 “Bodyweights – Main group mean values (g)” of sponsor’s rat study report

Therefore, relative to combined control the male rats in high dose group had about 28% and the female rats had about 42% decrements in their body weight gains.

The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End of the Experiment in Rats

	Comb Cont	Low	Medium	High
Male	21%	18%	20%	18%
Female	30%	32%	18%	32%

This shows that the mortality rates in the male rats high dose group was 3% lower, while that in female rat high dose group was 2% higher than their respective combined control.

Thus, from the body weight gain data it can be concluded that the used high dose level might have exceeded the MTD in both sexes, however the mortality data do not support it. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

4.2. Mouse Study

The following is the summary of survival data of mice in the high dose groups:

Percentage of Survival in the High Dose Group at the End of Weeks 52, 78, and 91 in Mice

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	80%	42%	22%
Female	88%	44%	30%

Based on the survival criterion Haseman proposed, it may be concluded that not enough mice were exposed to the high dose for a sufficient amount of time in either sex.

The following table shows the percent difference in mean body weight gain in mice from the combined control,

Percent Difference in Mean body Weight Gain from Combined Control in Mice

Male			Female		
Low	Medium	High	Low	Medium	High
Using data up to Week 104*			Using data up to Week 104		
0.00	0.00	-26.32	-12.82	-23.08	-12.82
Using data up to Week 93					
-15.56	-15.56	-37.78			

Source: TABLE 2 "Bodyweights – Main group mean values (g)" of sponsor's mouse study report

* Since the body weight of male mouse high dose group was taken up to Week 93, the final weight for high dose group in this calculation was the body weight taken at Week 93.

Therefore, relative to the combined control the male mice in high dose group had about 26% at week 104 and about 38% at Week 93, and the female mice in the high dose group also had about 13% decrements in their body weight gains.

The mortality rates at the end of the experiment were as follows:

Mortality Rates End of the Experiment

	Control	Low	Medium	High
Male	55%	58%	60%	80%
Female	51%	56%	54%	76%

This shows that the mortality rates were 25% higher in the high dose group in both sexes than their respective combined control.

Thus, from the body weight gain and mortality data it can be concluded that the used high dose level

might have exceeded the MTD in both sexes of mice. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

5. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of Ivabradine (S 16257-2) when administered orally daily through dietary admixture at appropriate drug levels for 104 weeks.

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

Rat Study: Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and two identical control groups. Two hundred and fifty Hanibm Wistar rats of each sex were assigned randomly to the treated and control groups in equal size of 50 rats per group. The dose levels for treated groups were 7.5, 30, or 120 mg/kg/day. The rats in the control groups remained untreated and received normal basal diet. Due to excessive toxicity as characterized by lower body weight and food intake, as well as complementary information, from Week 53 the high dosage level was lowered to 60 mg base/kg/day.

During the administration period all rats were observed twice daily for morbidity and mortality. Individual animals were observed at least once weekly for any signs of behavioral changes, reaction to treatment or ill health. A detailed palpation of each rat was performed once weekly in order to record the date of appearance, location and dimension, of all new palpable masses. Body weights of all rats were measured once before the beginning of the study and weekly thereafter up to the scheduled necropsy.

The tests did not show statistically significant dose response relationship in mortality across the combined control and treated groups in either sex. The pairwise comparisons showed statistically significant increased mortality in Control 2 compared to Control 1 in the female rats.

The tests did not show statistically significant dose response relationship in any of the observed tumor types in either sex. The pairwise comparison showed statistically significant increased incidence of tubulostromal adenoma in ovaries in female rat medium dose group compared to their combined control.

The body weight gain data indicated that the used high dose level might have exceeded the MTD in both sexes, however the mortality data did not support it. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

Mouse Study: Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups and two identical control groups. Two hundred and fifty Crl:CD-1(ICR)BR mice of each sex was assigned randomly to the treated and

control groups in equal size of 50 mice per group. The target dosage levels were initially set at 20, 90 and 405 mg/kg/day. However, due to the high mortality in both sexes receiving 405 mg/kg/day, it was lowered to 180 mg/kg/day from Week 81. The mice in the control groups remained untreated and received normal basal diet.

During the administration period all mice were observed regularly for morbidity and mortality. Individual animals were observed at least once weekly for any signs of behavioral changes, reaction to treatment or ill health. A detailed palpation of each mouse was performed once weekly in order to record the date of appearance, location and dimension, of all new palpable masses. Body weights of all mice were measured once before the beginning of the study and weekly thereafter up to the scheduled necropsy.

Even after lowering the dose level of the high dose group there were continued mortality in the high dose group. Due to this high mortality the male high dose group was terminated early in Week 94, when survival reached 20%.

The tests showed statistically significant dose response relationship in mortality across the combined control and treated groups in both sexes of mice. The pairwise comparison show statistically significant increased mortality in the high dose group in both sexes compared to their respective combined control.

The tests did not show statistically significant dose response relationship in any of the observed tumor types in either sex. The pairwise comparisons showed statistically significant increased incidence of multicentric lymphoid histiocytic sarcoma in the female mice low dose group compared the combined control.

The body weight gain and mortality data indicate that the used high dose level might have exceeded the MTD in both sexes of mice. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

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6. Appendix

**Table 1A: Intercurrent Mortality Rate
Male Rats**

Week	Control 1		Control 2		7.5 mg kg day		30 mg kg day		120/60 mg kg day	
	No. of Death	Cum. % [#]	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52 53 - 78 79 - 91 92 - 104 Ter. Sac.										
Total	N=50		N=50		N=50		N=50		N=50	

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

**Table 1B: Intercurrent Mortality Rate
Female Rats**

Week	Control 1		Control 2		7.5 mg kg day		30 mg kg day		120/60 mg kg day	
	No. of Death	Cum. % [#]	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52 53 - 78 79 - 91 92 - 104 Ter. Sac.										
Total	N=50		N=50		N=50		N=50		N=50	

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

**Table 2A: Intercurrent Mortality Comparison
Male Rats**

Test	Statistic	P_Value [#]
Dose-Response Homogeneity		
Likelihood Ratio		0.6562
Log-Rank		0.9368

Pvalues were calculated using the combined control, low, medium, and high dose groups

**Table 2B: Intercurrent Mortality Comparison
Female Rats**

Test	Statistic	P_Value [#]
Dose-Response Homogeneity		
Likelihood Ratio		0.9317
Log-Rank		0.3834

Pvalues were calculated using the combined control, low, medium, and high dose groups

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

Organ Name	Tumor Name	0 mg	7.5 mg	30 mg	120/60mg	P_Value	P_Value	P_Value	P_Value
		Com C N=100	Low N=50	Med N=50	High N=50	Dose Resp	L vs Com C	M vs Com C	H vs Com C
fff									
ADIPOSE TISSUE	HAEMANGIOMA	0	2	0	0	0.6463	0.1160	.	.
	MALIGNANT SCHWANNOMA	0	0	1	0	0.4043	.	0.3382	.
ADRENAL GLANDS	CORTICAL ADENOMA	0	0	0	1	0.2043	.	.	0.3431
	CORTICAL CARCINOMA	0	0	1	0	0.4043	.	0.3382	.
	PHAECHROMOCYTOMA	2	2	1	2	0.3087	0.4249	0.2642	0.4249
BONE	FIBROSARCOMA	0	0	0	1	0.2078	.	.	0.3478
BRAIN	ASTROCYTOMA	3	0	0	0	0.9413	0.7198	0.7135	0.7198
CAECUM	FIBROMA	1	0	0	0	0.6087	0.3431	0.3382	0.3431
HEAD	MALIGNANT SCHWANNOMA	1	0	0	0	0.6061	0.3406	0.3358	0.3406
JEJUNUM	LEIOMYOMA	0	0	1	0	0.4043	.	0.3382	.
KIDNEYS	LIPOMA	0	0	0	1	0.2043	.	.	0.3431
LIMBS	FIBROMA	1	0	0	0	0.6061	0.3406	0.3358	0.3406
	HAEMANGIOSARCOMA	0	1	0	1	0.2070	0.3431	.	0.3431
LIVER	HEPATOCELLULAR CARCINOMA	0	1	0	0	0.4043	0.3431	.	.
LUNGS	BRONCHIOLAR-ALVEOLAR ADEN	1	1	1	0	0.6013	0.5701	0.5637	0.3431
LYMPH NODES - M	HAEMANGIOMA	13	4	3	6	0.5354	0.7626	0.8599	0.5146
	HAEMANGIOSARCOMA	2	0	0	0	0.8479	0.5701	0.5637	0.5701
LYMPHOID/MULTIC	LYMPHOBLASTIC/LYMPHOCYTIC	2	1	1	1	0.4280	0.2641	0.7070	0.2705
	MYELOID LEUKAEMIA	1	0	0	0	0.6087	0.3431	0.3382	0.3431
	PLEOMORPHIC LYMPHOMA	0	0	1	0	0.4069	.	0.3431	.
MAMMARY GLANDS	FIBROADENOMA	0	0	0	1	0.2043	.	.	0.3431
ORAL CAVITY	SQUAMOUS CELL CARCINOMA	0	0	1	0	0.4043	.	0.3382	.
PANCREAS	ISLET CELL ADENOMA	2	2	1	1	0.5211	0.4249	0.2642	0.2708
	ISLET CELL CARCINOMA	1	0	0	2	0.1103	0.3431	0.3382	0.2773
	MIXED ACINAR-ISLET CELL A	1	0	0	0	0.6087	0.3431	0.3382	0.3431
PITUITARY	ADENOCARCINOMA - PARS DIS	0	1	0	0	0.4043	0.3431	.	.
	ADENOMA - PARS DISTALIS	25	7	8	11	0.5622	0.9181	0.8470	0.6157
SALIVARY GLANDS	FIBROSARCOMA	1	0	0	0	0.6087	0.3431	0.3382	0.3431
SEMINAL VESICLE	ADENOCARCINOMA	1	0	0	0	0.6087	0.3431	0.3382	0.3431
SKELETAL MUSCLE	SQUAMOUS CELL CARCINOMA	0	0	1	0	0.4043	.	0.3382	.

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

Organ Name	Tumor Name	0 mg	7.5 mg	30 mg	120/60mg	P_Value	P_Value	P_Value	P_Value
		Com C N=100	Low N=50	Med N=50	High N=50	Dose Resp	L vs Com C	M vs Com C	H vs Com C
fff									
SKIN	BASAL CELL CARCINOMA	1	0	0	0	0.6087	0.3431	0.3382	0.3431
	KERATOACANTHOMA	5	1	4	4	0.1656	0.6680	0.3650	0.3650
	SEBACEOUS CELL ADENOMA	0	1	0	0	0.4043	0.3431	.	.
	SQUAMOUS CELL PAPILLOMA	0	0	1	1	0.1231	.	0.3382	0.3431
STOMACH	SQUAMOUS CELL PAPILLOMA	0	1	0	0	0.4043	0.3431	.	.
SUBCUTIS	FIBROMA	6	0	4	1	0.7384	0.9224	0.4612	0.7567
	FIBROSARCOMA	0	1	0	0	0.4043	0.3431	.	.
	HAEMANGIOMA	0	0	0	1	0.2043	.	.	0.3431
	LIPOMA	1	0	0	0	0.6087	0.3431	0.3382	0.3431
	LIPOSARCOMA	1	0	0	0	0.6061	0.3406	0.3358	0.3406
TESTES	INTERSTITIAL CELL ADENOMA	5	0	0	1	0.7711	0.8800	0.8755	0.6680
THORACIC CAVITY	HAEMANGIOSARCOMA	1	0	0	0	0.6061	0.3406	0.3358	0.3406
THYMUS	LYMPHOCYTIC THYMOMA	2	2	4	0	0.7395	0.4249	0.1001	0.5701
	THYMIC ADENOMA	1	0	0	0	0.6087	0.3431	0.3382	0.3431
THYROIDS	C-CELL ADENOMA	4	0	1	4	0.0789	0.8181	0.5513	0.2741
	C-CELL CARCINOMA	5	1	0	2	0.5431	0.6729	0.8779	0.4523
	FOLLICULAR CELL ADENOMA	8	2	1	5	0.2838	0.7266	0.8690	0.4867
	FOLLICULAR CELL CARCINOMA	2	0	1	1	0.4273	0.5668	0.2609	0.2674

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

Organ Name	Tumor Name	0 mg	7.5 mg	30 mg	120/60mg	P_Value	P_Value	P_Value	P_Value
		Com C N=100	Low N=50	Med N=50	High N=50	Dose Resp	L vs Com C	M vs Com C	H vs Com C
fff									
ADRENAL GLANDS	CORTICAL ADENOMA	2	1	0	1	0.4617	0.2678	0.5738	0.7037
	CORTICAL CARCINOMA	1	0	0	1	0.3520	0.3409	0.3459	0.5538
	PHAEOCHROMOCYTOMA	2	0	0	2	0.1778	0.5673	0.5738	0.4028
BRAIN	ASTROCYTOMA	1	0	0	1	0.3520	0.3409	0.3459	0.5538
	MIXED GLIOMA	0	0	0	1	0.1982	.	.	0.3359
CAECUM	FIBROSARCOMA	0	1	0	0	0.4027	0.3409	.	.
CERVIX	FIBROMA	0	0	1	0	0.4027	.	0.3459	.
	MALIGNANT SCHWANNOMA	0	0	0	1	0.1946	.	.	0.3308
	PROLAPSED ENDOMETRIAL POL	1	0	0	0	0.6063	0.3409	0.3459	0.3308
DUODENUM	LEIOMYOMA	0	0	1	0	0.4027	.	0.3459	.
EYES	MALIGNANT SCHWANNOMA	0	1	0	0	0.4027	0.3409	.	.
HEAD	SUBCUTANEOUS FIBROSARCOMA	0	0	1	0	0.4027	.	0.3459	.
KIDNEYS	PELVIC TRANSITIONAL CELL	0	0	0	1	0.1946	.	.	0.3308
LIVER	CHOLANGIOMA	0	0	1	0	0.4027	.	0.3459	.
	HEPATOCELLULAR ADENOMA	0	0	2	0	0.3946	.	0.1179	.
LYMPH NODES - M	HAEMANGIOMA	4	1	0	0	0.9673	0.5567	0.8213	0.8040
LYMPHOID/MULTIC	LYMPHOBLASTIC/LYMPHOCYTIC	0	0	1	0	0.4054	.	0.3507	.
MAMMARY GLANDS	ADENOCARCINOMA	4	4	3	0	0.9299	0.2638	0.4528	0.8010
	ADENOMA	0	2	1	0	0.5648	0.1145	0.3459	.
	FIBROADENOMA	32	13	4	2	1.0000	0.7307	0.9995	0.9999
	FIBROADENOMA WITH ATYPIA	6	1	0	0	0.9938	0.7576	0.9264	0.9153
OVARIES	FIBROMA	2	0	0	0	0.8461	0.5673	0.5738	0.5538
	GRANULOSA CELL TUMOUR	1	1	0	0	0.6851	0.5673	0.3459	0.3308
PANCREAS	TUBULOSTROMAL ADENOMA	0	1	3	0	0.4617	0.3409	0.0396*	.
	ISLET CELL ADENOMA	2	0	1	0	0.6919	0.5673	0.2745	0.5538
PITUITARY	ADENOCARCINOMA - PARS DIS	3	0	1	0	0.8262	0.7171	0.4299	0.7037
	ADENOMA - PARS DISTALIS	51	19	20	16	0.9621	0.9049	0.8811	0.9664
SKIN	FIBROMA	1	0	0	0	0.6063	0.3409	0.3459	0.3308
	SQUAMOUS CELL PAPILLOMA	1	0	0	0	0.6063	0.3409	0.3459	0.3308
STOMACH	FIBROSARCOMA	1	0	0	0	0.6063	0.3409	0.3459	0.3308
	LEIOMYOSARCOMA	1	0	0	0	0.6063	0.3409	0.3459	0.3308
SUBCUTIS	FIBROMA	0	0	1	1	0.1185	.	0.3459	0.3308
	FIBROSARCOMA	0	1	0	0	0.4027	0.3409	.	.

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

Organ Name	Tumor Name	0 mg	7.5 mg	30 mg	120/60mg	P_Value	P_Value	P_Value	P_Value
		Com C N=100	Low N=50	Med N=50	High N=50	Dose Resp	L vs Com C	M vs Com C	H vs Com C
fff									
SUBCUTIS	LIPOMA	1	0	0	0	0.6063	0.3409	0.3459	0.3308
	MALIGNANT SCHWANNOMA (MIC	0	0	0	1	0.1946	.	.	0.3308
THORACIC CAVITY	THYMIC ADENOCARCINOMA	0	1	0	0	0.4027	0.3409	.	.
THYMUS	LYMPHOCYTIC THYMOMA	10	1	3	2	0.8354	0.9399	0.7230	0.8267
THYROIDIS	C-CELL ADENOMA	6	2	1	5	0.1365	0.5540	0.7663	0.2755
	C-CELL CARCINOMA	7	1	1	4	0.2839	0.8255	0.8330	0.5237
	FOLLICULAR CELL ADENOMA	4	2	1	1	0.7248	0.3323	0.5665	0.5365
UTERUS	ENDOMETRIAL ADENOCARCINOM	8	6	4	8	0.0907	0.3176	0.3945	0.1117
	ENDOMETRIAL ADENOMA	0	1	0	1	0.1981	0.3409	.	0.3308
	ENDOMETRIAL POLYP	9	3	2	5	0.3704	0.6368	0.8031	0.5374
	ENDOMETRIAL STROMAL CELL	1	0	0	0	0.6063	0.3409	0.3459	0.3308
	FIBROSARCOMA	1	0	0	0	0.6063	0.3409	0.3459	0.3308
	LEIOMYOSARCOMA	1	0	0	0	0.6063	0.3409	0.3459	0.3308
	MALIGNANT SCHWANNOMA (MIC	1	1	0	1	0.3886	0.5673	0.3459	0.5538
	UTERINE CARCINOMA (ANAPLA	1	0	0	0	0.6063	0.3409	0.3459	0.3308
UTERINE EPITHELIAL TUMORS*	9	7	4	9	0.0806	0.2659	0.4802	0.0913	

 *UTERINE EPITHELIAL TUMORS = Endometrial adenoma+endometrialadenocarcinoma+
 Uterine carcinoma

Table 4A: Intercurrent Mortality Rate in Male Mice

Week	Control 1		Control 2		20 mg kg day		90 mg kg day		405/180 mg kg day	
	No. of Death	Cum. % [#]	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	3	6.00	4	8.00	5	10.00	8	16.00	10	20.00
53 - 78	4	14.00	7	22.00	7	24.00	4	24.00	19	58.00
79 - 91	11	36.00	6	34.00	9	42.00	7	38.00	10	78.00
92 - 104	9	54.00	11	56.00	8	58.00	11	60.00	1	80.00
Ter. Sac.	23	46.00	22	44.00	21	42.00	20	40.00	10 [@]	20.00
Total	N=50		N=50		N=50		N=50		N=50	

All Cum. %: Cumulative percentage except for Ter. Sac. @Terminal sacrifice of high dose group was Week 94

Table 4B: Intercurrent Mortality Rate Female Mice

Week	Control 1		Control 2		20 mg kg day		90 mg kg day		405/180 mg kg day	
	No. of Death	Cum. % [#]	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	3	6.00	2	4.00	2	4.00	7	14.00	6	12.00
53 - 78	11	28.00	3	10.00	8	20.00	5	24.00	22	56.00
79 - 91	8	44.00	12	34.00	11	42.00	9	42.00	7	70.00
92 - 104	8	60.00	4	42.00	7	56.00	6	54.00	3	76.00
Ter. Sac.	20	40.00	29	58.00	22	44.00	23	46.00	12	24.00
Total	N=50		N=50		N=50		N=50		N=50	

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

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	Statistic	P_Value [#]
Dose-Response	Likelihood Ratio	<.0001
Homogeneity	Log-Rank	<.0001

Pvalues were calculated using the combined control, low, medium, and high dose groups

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	Statistic	P_Value [#]
Dose-Response	Likelihood Ratio	0.0067
Homogeneity	Log-Rank	0.0003

Pvalues were calculated using the combined control, low, medium, and high dose groups

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

Organ Name	Tumor Name	0 mg	20 mg	90 mg	405/180mg	P_Value	P_Value	P_Value	P_Value
		Com C N=100	Low N=50	Med N=50	High N=50	Dose Resp	L vs Com C	M vs Com C	H vs Com C
fff									
ADRENAL GLANDS	CORTICAL ADENOMA	2	3	2	1	0.3342	0.1915	0.3793	0.4880
BONE	OSTEOMA	1	0	0	0	0.5375	0.3148	0.3148	0.1957
BRAIN	MALIGNANT SCHWANNOMA	0	1	0	0	0.3250	0.3241	.	.
COLON	ADENOCARCINOMA	0	0	1	0	0.3270	.	0.3178	.
DUODENUM	OSTEOSARCOMA	1	0	0	0	0.5375	0.3148	0.3148	0.1957
HARDERIAN GLAND	ADENOMA	11	2	6	3	0.3153	0.8563	0.4568	0.5822
HEAD	OSTEOSARCOMA	1	0	0	0	0.5375	0.3148	0.3148	0.1957
HIBERNATING GLA	HIBERNOMA	5	4	4	1	0.5484	0.3222	0.3064	0.3390
KIDNEYS	MESENCHYMAL TUMOUR	0	0	0	1	0.1132	.	.	0.1978
	TUBULAR CELL ADENOMA	0	1	1	0	0.2589	0.3178	0.3178	.
	TUBULAR CELL CARCINOMA	2	1	0	0	0.7695	0.6866	0.5366	0.3582
LIVER	CHOLANGIOCARCINOMA	1	0	0	0	0.5375	0.3148	0.3148	0.1957
	HAEMANGIOMA	2	2	1	1	0.3298	0.3793	0.6866	0.4880
	HEPATOCELLULAR ADENOMA	29	15	10	1	0.9987	0.3991	0.7488	0.9940
	HEPATOCELLULAR CARCINOMA	15	2	1	1	0.9491	0.9482	0.9846	0.8650
LUNGS	BRONCHIOLAR-ALVEOLAR ADEN	23	7	10	10	0.0732	0.8458	0.4586	0.1872
	BRONCHIOLAR-ALVEOLAR CARC	10	6	4	0	0.9671	0.4306	0.4876	0.9004
LYMPHOID/MULTIC	HISTIOCYTIC SARCOMA	6	0	0	2	0.2365	0.9006	0.9006	0.4835
	IMMUNOBLASTIC LYMPHOMA	2	0	0	0	0.7908	0.5366	0.5366	0.3582
	LYMPHOBLASTIC/LYMPHOCYTIC	7	2	2	3	0.1905	0.5999	0.5838	0.3452
	MAST CELL TUMOUR	0	0	0	1	0.1132	.	.	0.1978
	MYELOID LEUKAEMIA	1	0	0	0	0.5375	0.3148	0.3148	0.1957
	PLEOMORPHIC LYMPHOMA	4	2	2	1	0.4616	0.6301	0.6170	0.6724
PANCREAS	ISLET CELL ADENOMA	2	0	0	0	0.7908	0.5366	0.5366	0.3582
PITUITARY	ADENOMA - PARS DISTALIS	1	0	1	0	0.3509	0.3178	0.5366	0.1978
	ADENOMA - PARS INTERMEDIA	1	0	0	0	0.5409	0.3178	0.3178	0.1978
PREPUTIAL GLAND	HAEMANGIOMA	0	2	0	0	0.5485	0.0989	.	.
SKELETAL MUSCLE	HAEMANGIOSARCOMA	0	0	1	0	0.3270	.	0.3178	.
SKIN	FIBROMA	1	0	0	0	0.5409	0.3178	0.3178	0.1978
	FIBROSARCOMA	1	0	0	0	0.5409	0.3178	0.3178	0.1978
	SQUAMOUS CELL CARCINOMA	0	0	0	1	0.1132	.	.	0.1978
SPLEEN	HAEMANGIOSARCOMA	0	0	2	0	0.2589	.	0.0989	.

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

Organ Name	Tumor Name	0 mg	20 mg	90 mg	405/180mg	P_Value	P_Value	P_Value	P_Value
		Com C N=100	Low N=50	Med N=50	High N=50	Dose Resp	L vs Com C	M vs Com C	H vs Com C
fff									
STOMACH	SQUAMOUS CELL CARCINOMA	1	0	0	0	0.5409	0.3178	0.3178	0.1978
	SQUAMOUS CELL PAPILLOMA	1	0	0	0	0.5409	0.3178	0.3178	0.1978
SUBCUTIS	FIBROSARCOMA	0	2	2	1	0.1201	0.1030	0.0989	0.1978
	OSTEOSARCOMA	1	0	0	0	0.5375	0.3148	0.3148	0.1957
	RHABDOMYOSARCOMA	0	1	0	0	0.3270	0.3178	.	.
TAIL	FIBROMA	1	0	0	0	0.5409	0.3178	0.3178	0.1978
	FIBROSARCOMA	0	0	1	0	0.3270	.	0.3178	.
TESTES	HAEMANGIOMA	1	0	1	0	0.3480	0.3148	0.5325	0.1957
	INTERSTITIAL CELL ADENOMA	3	1	1	0	0.7292	0.3793	0.3793	0.4880
	SCHWANNOMA	0	0	0	1	0.1132	.	.	0.1978

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

Organ Name	Tumor Name	0 mg	20 mg	90 mg	353 mg	P_Value	P_Value	P_Value	P_Value
		Com C N=100	Low N=50	Med N=50	High N=50	Dose Resp	L vs Com C	M vs Com C	H vs Com C
fff									
ADRENAL GLANDS	MALIGNANT PHAEOCHROMOCYTO	0	1	0	0	0.3491	0.3273	.	.
	PHAEOCHROMOCYTOMA	1	1	0	0	0.6214	0.5576	0.3211	0.2449
BONE	OSTEOMA	0	2	0	0	0.5750	0.1091	.	.
BRAIN	MIXED GLIOMA	0	0	1	0	0.3529	.	0.3273	.
CERVIX	CERVICAL POLYP	2	0	2	0	0.5414	0.5455	0.3801	0.4280
	FIBROMA	1	0	0	0	0.5621	0.3273	0.3211	0.2449
	GRANULAR CELL TUMOUR	1	0	0	0	0.5621	0.3273	0.3211	0.2449
	MALIGNANT GRANULAR CELL T	0	1	0	0	0.3471	0.3333	.	.
	SCHWANNOMA	1	0	0	0	0.5588	0.3243	0.3182	0.2424
FEMUR/JOINT	MARROW - HAEMANGIOMA	0	0	1	0	0.3491	.	0.3211	.
	MARROW - HAEMANGIOSARCOMA	1	0	0	0	0.5621	0.3273	0.3211	0.2449
	OSTEOSARCOMA	1	0	0	0	0.5621	0.3273	0.3211	0.2449
HARDERIAN GLAND	ADENOCARCINOMA	0	1	0	0	0.3491	0.3273	.	.
	ADENOMA	4	2	3	5	0.0131	0.6550	0.4150	0.0373
HEAD	FIBROSARCOMA	1	0	0	0	0.5588	0.3243	0.3182	0.2424
	ZYMBAL'S GLAND - SEBACEOU	0	0	0	1	0.1420	.	.	0.2449
LIVER	HAEMANGIOMA	0	2	1	0	0.4614	0.1051	0.3211	.
	HEPATOCELLULAR ADENOMA	6	1	1	1	0.6973	0.7339	0.7220	0.5485
LUNGS	BRONCHIOLAR-ALVEOLAR ADEN	13	7	9	6	0.2536	0.5027	0.1919	0.3513
	BRONCHIOLAR-ALVEOLAR CARC	4	1	5	1	0.4631	0.5421	0.1352	0.3562
LYMPHOID/MULTIC	HISTIOCYTIC SARCOMA	3	8	2	3	0.3182	0.0090*	0.5299	0.1795
	LYMPHOBLASTIC/LYMPHOCYTIC	16	9	8	6	0.3915	0.4354	0.5103	0.4658
	PLEOMORPHIC LYMPHOMA	9	2	2	5	0.1073	0.7662	0.7526	0.2617
MAMMARY GLANDS	ADENOCARCINOMA	4	4	1	0	0.9288	0.2335	0.5239	0.6771
	ADENOMA	0	1	0	0	0.3471	0.3333	.	.
OVARIES	CYSTADENOMA	2	2	1	1	0.4088	0.3965	0.6912	0.5738
	GRANULOSA CELL TUMOUR	1	0	0	1	0.2646	0.3273	0.3211	0.4317
	LEIOMYOMA - FALLOPIAN TUB	1	1	0	0	0.6214	0.5576	0.3211	0.2449
	LEIOMYOSARCOMA - FALLOPIA	0	0	0	1	0.1471	.	.	0.2525
	LUTEOMA	2	2	1	0	0.7192	0.3965	0.6912	0.4317
	MALIGNANT GRANULOSA CELL	1	0	0	0	0.5621	0.3273	0.3211	0.2449
PANCREAS	LEIOMYOMA	1	0	0	0	0.5621	0.3273	0.3211	0.2449
PITUITARY	ADENOMA - PARS DISTALIS	2	0	4	0	0.6011	0.5495	0.0825	0.4317
SKELETAL MUSCLE	OSTEOSARCOMA	1	0	0	0	0.5588	0.3243	0.3182	0.2424
SPLEEN	HAEMANGIOMA	1	0	1	0	0.3953	0.3273	0.5411	0.2449

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

Organ Name	Tumor Name	0 mg	20 mg	90 mg	353 mg	P_Value	P_Value	P_Value	P_Value
		Com C N=100	Low N=50	Med N=50	High N=50	Dose Resp	L vs Com C	M vs Com C	H vs Com C
fff									
SPLEEN	HAEMANGIOSARCOMA	2	0	0	0	0.8068	0.5455	0.5371	0.4280
STERNUM/BONE MA	OSTEOMA	1	0	0	0	0.5621	0.3273	0.3211	0.2449
STOMACH	OSTEOSARCOMA	0	0	0	1	0.1471	.	.	0.2525
	SQUAMOUS CELL CARCINOMA	0	0	1	0	0.3491	.	0.3211	.
SUBCUTIS	FIBROSARCOMA	4	0	1	0	0.8444	0.7934	0.5055	0.6728
	RHABDOMYOSARCOMA	0	1	0	0	0.3471	0.3333	.	.
TAIL	FIBROSARCOMA	0	0	1	0	0.3529	.	0.3273	.
THYROIDS	FOLLICULAR CELL CARCINOMA	0	1	0	0	0.3491	0.3273	.	.
TIBIA	HAEMANGIOSARCOMA	1	0	0	0	0.5621	0.3273	0.3211	0.2449
UTERUS	ENDOMETRIAL POLYP	8	4	5	2	0.6081	0.5888	0.3982	0.4783
	ENDOMETRIAL STROMAL CELL	1	0	0	0	0.5621	0.3273	0.3211	0.2449
	HAEMANGIOMA	5	2	0	0	0.9721	0.4223	0.8590	0.7587
	LEIOMYOMA	5	4	1	0	0.9518	0.3457	0.6301	0.7628
	LEIOMYOSARCOMA	4	0	1	0	0.8500	0.8007	0.5174	0.6815
VAGINA	FIBROSARCOMA	0	0	0	1	0.1471	.	.	0.2525

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

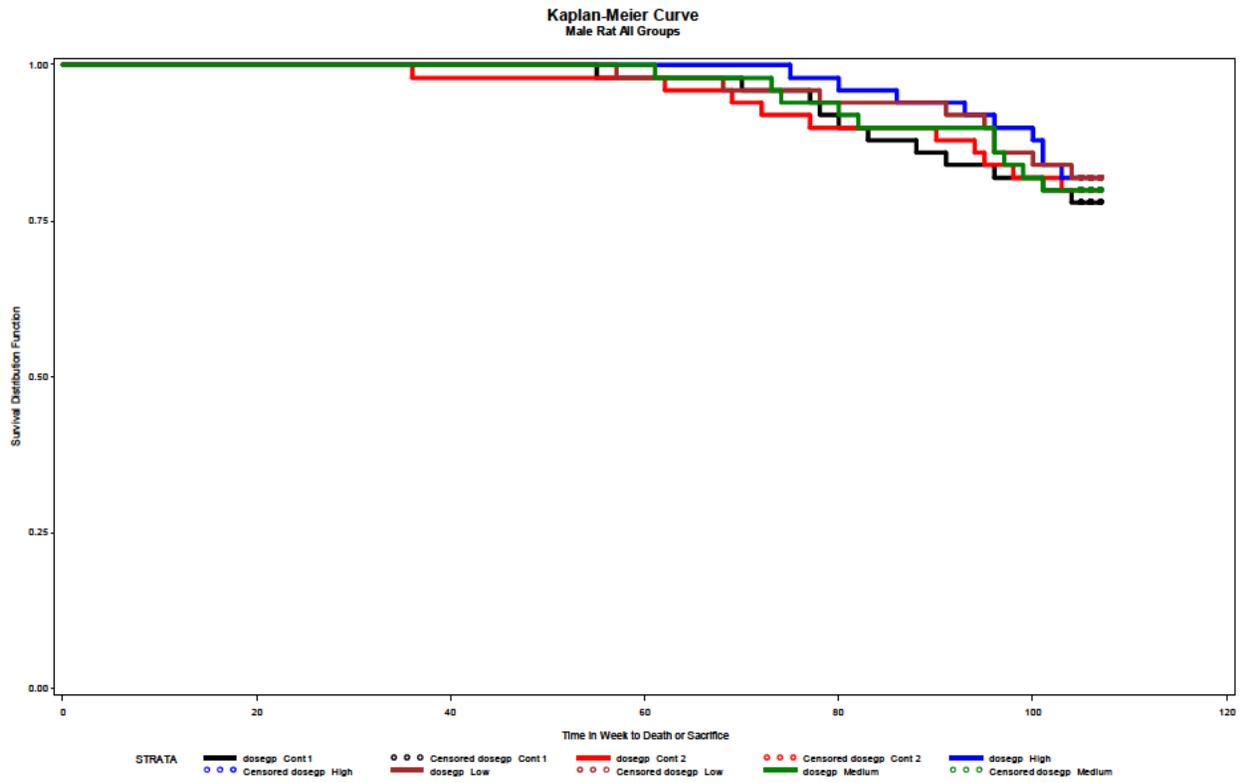


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

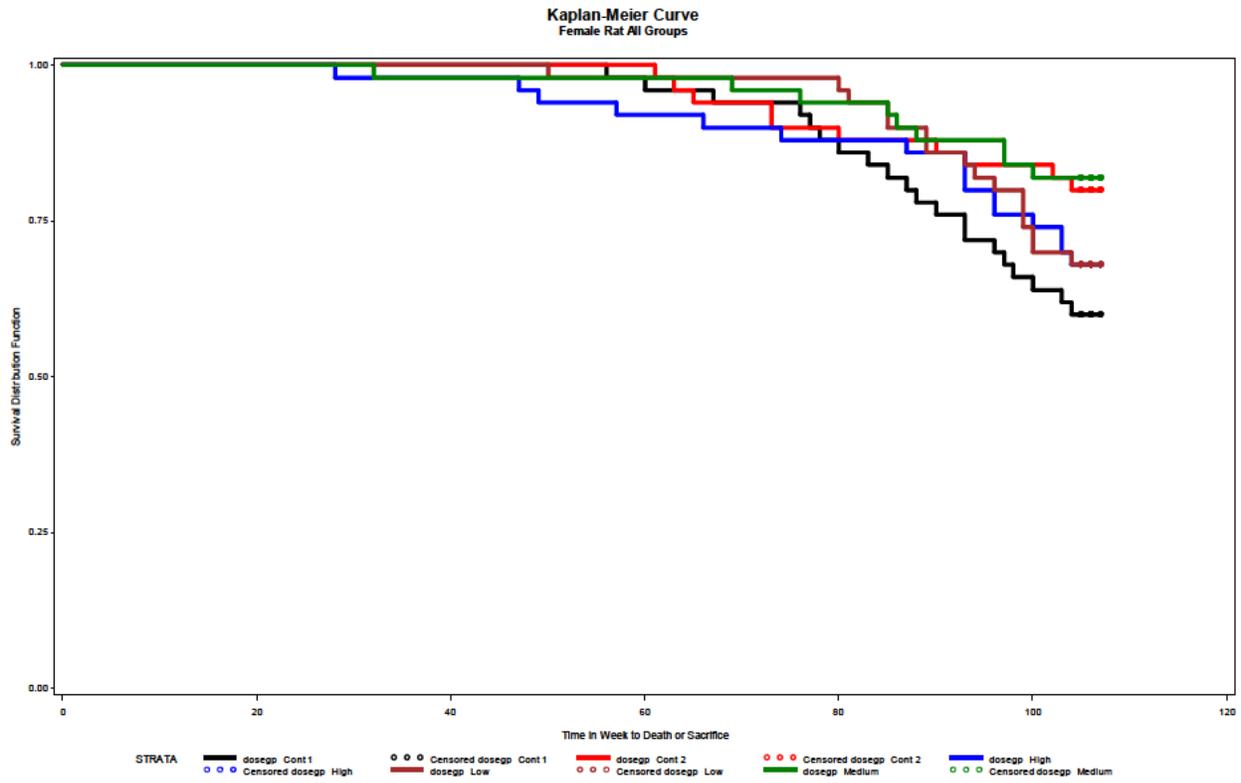


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

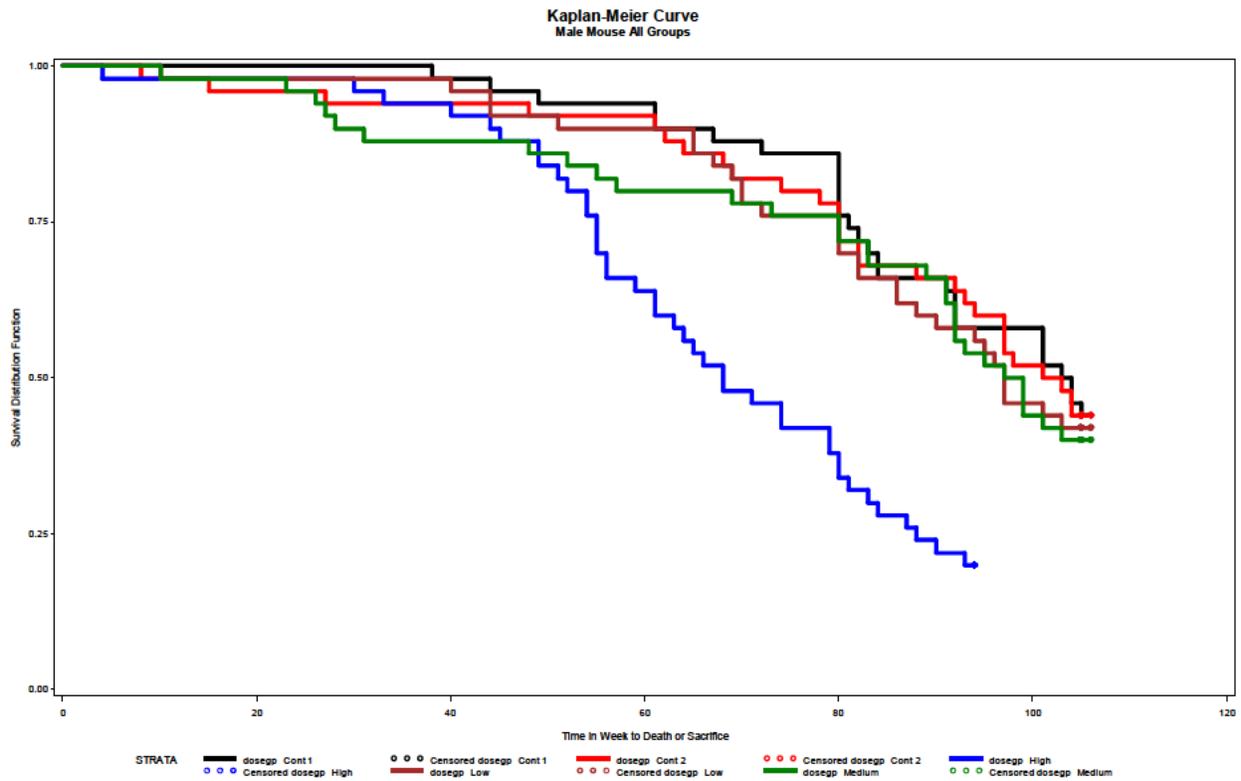
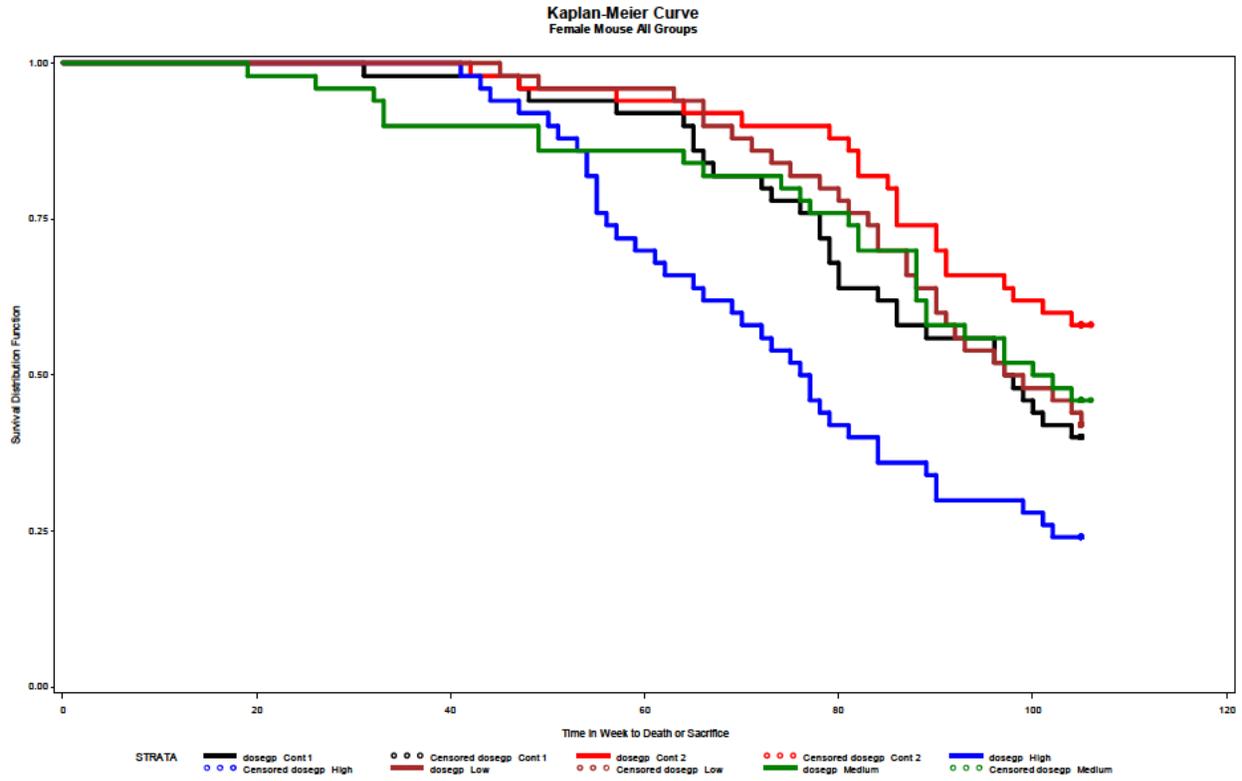


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



7. References

1. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J. Wahrendorf, "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva*, 311-426, 1980.
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6. Haseman, J, "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339, 1983.
7. Guidance for Industry. Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (Draft Guidance). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), May 2001.

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/s/

MOHAMMAD A RAHMAN
09/29/2014

KARL K LIN
10/05/2014
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 206143

Applicant: Amgen

Stamp Date: 6/27/2014

Drug Name: Ivabradine

NDA/BLA Type: 505(b)(1)

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

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

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

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

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

Steve Bai

8/1/2014

Reviewing Statistician

Date

Hsien Ming Hung

8/1/2014

Supervisor/Team Leader

Date

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/s/

STEVE G BAI
08/05/2014

HSIEN MING J HUNG
08/05/2014