

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022529Orig1s000

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

NDA/Serial Number: 022529/0

Drug Name: Lorcaserin tablets

Indication(s): Weight management

Applicant: Arena Pharmaceuticals Inc

Dates: Submission date: December 23, 2011 (Complete Response resubmission)
PDUFA Goal Date: June 23, 2012
Advisory Committee Date: May 10, 2012
This review: May 22, 2012

Review Priority: Standard

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Keywords: clinical studies, NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Efficacy Conclusions for Study 010 (Bloom-DM):

Study 010 was a 52-week randomized, double-blind, placebo-controlled study in adult subjects who were overweight or obese and who also had Type 2 diabetes. Study 010 had three arms: placebo, lorcaserin 10 mg qd and lorcaserin 10 mg bid.

Continuous endpoint: After one year of treatment with lorcaserin 10 mg bid, subjects in Study 010 lost a statistically significant amount of weight. The placebo-adjusted average weight loss was a 3.1% change from baseline (TABLE 1; $p < 0.0001$). This result was consistent across different versions of the analysis population and different methods of analysis. Subjects in the lorcaserin 10 mg qd arm also lost an average of 3.1% of baseline body weight, adjusted for placebo (TABLE 1; $p < 0.0001$). The lorcaserin qd arm was included only in the first part of the enrollment in Study 010, and there were some differences in retention and overall weight loss between the first part and the second part of enrollment.

Categorical endpoints: After one year of treatment with lorcaserin 10 mg bid, 37.5% of subjects in the lorcaserin 10 mg bid arm lost at least 5% of their baseline body weight, compared to the placebo arm (16.1%; TABLE 1; $p < 0.0001$). In the lorcaserin 10 mg qd arm, 44.7% were 5% responders, compared to 21.3% in the subgroup of the placebo arm that was used for this comparison. The longitudinal profile of 5% responders suggests that weight loss takes place up to about week 28, at which point the percentage of responders stays fairly constant, and then declines somewhat in the final months leading up to week 52 (FIGURE 1).

Key secondary efficacy endpoints: In general, the results from the secondary efficacy endpoints supported the efficacy of lorcaserin compared to placebo. The placebo-adjusted effect of lorcaserin 10 mg bid on HbA1c was a change of -0.5 (% units) from baseline at week 52 ($p < 0.0001$). Subjects with baseline HbA1c ≥ 8.0 had a greater placebo-adjusted mean decrease in HbA1c at week 52, compared to subjects with baseline HbA1c < 8.0 (treatment arm by baseline HbA1c subgroup $p = 0.0603$). This relationship between baseline HbA1c and change from baseline in HbA1c at study endpoint has also been identified in several anti-diabetic drugs.

Key subgroups: The placebo-adjusted effect of lorcaserin was fairly similar across sex and race. Subjects over 65 years old were not enrolled in Study 010. Subjects with baseline HbA1c < 8.0 had a greater placebo-adjusted mean weight loss with lorcaserin 10 mg bid than subjects with baseline HbA1c ≥ 8.0 (treatment arm by baseline HbA1c subgroup $p = 0.0209$). Subjects with metformin but no sulfonylureas (SFU) as diabetes medication had more weight loss on average with the lorcaserin 10 mg bid dose than subjects with SFUs (treatment arm by baseline diabetes medication subgroup $p = 0.0430$).

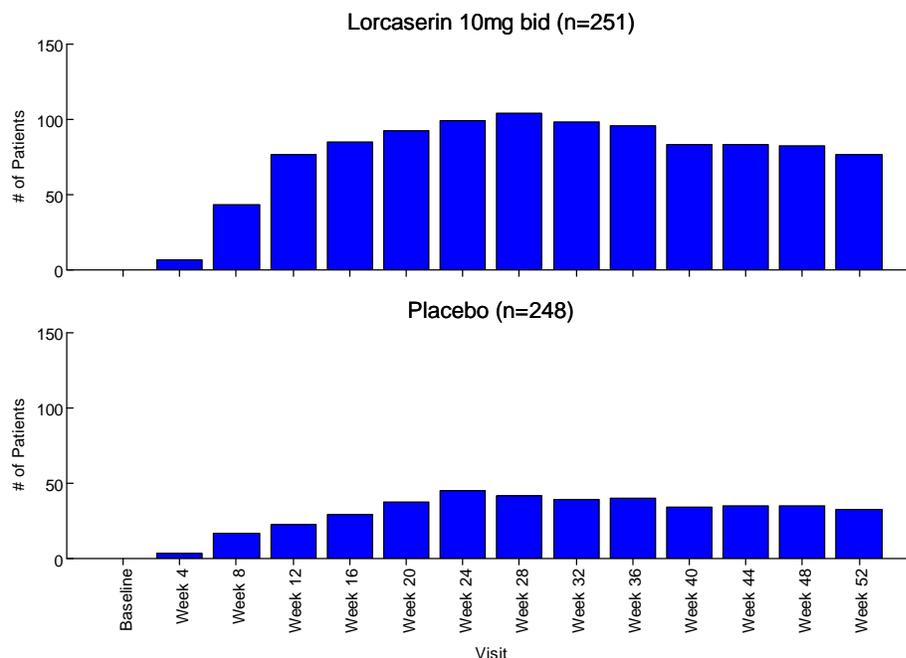
TABLE 1 Weight as a percent change from baseline at week 52 in Study 009, Study 011 and Study 010

Study Treatment arms	N	Baseline mean (kg) ± SE	Adjusted mean % change from baseline at Week 52 ± SE ¹	Difference in adjusted mean % change, Lorcaserin - placebo (95% CI)	P-value vs. placebo
Weight as percent change from baseline (%); MITT/LOCF, primary ANCOVA model¹					
1. Study 009 “Bloom”					
Lorcaserin 10 mg bid	1538	100.4 ± 0.4	-5.9 ± 0.2	-3.7 (-4.1, -3.3)	<0.0001
Placebo	1499	99.7 ± 0.4	-2.2 ± 0.1		
2. Study 011 “Blossom”					
Lorcaserin 10 mg bid	1561	100.3 ± 0.4	-5.8 ± 0.2	-3.0 (-3.4, -2.6)	<0.0001
Lorcaserin 10 mg qd	771	100.1 ± 0.6	-4.7 ± 0.2	-1.9 (-2.5, -1.4)	<0.0001
Placebo	1541	100.8 ± 0.4	-2.8 ± 0.2		
3. Study 010 “Bloom-DM”					
Lorcaserin 10 mg bid	251	103.5 ± 1.1	-4.7 ± 0.4	-3.1 (-4.0, -2.2)	<0.0001
Lorcaserin 10 mg qd	94	106.5 ± 2.0	-5.3 ± 0.5	-3.1 (-4.5, -1.7)	<0.0001
Placebo for bid comparison	248	102.3 ± 1.1	-1.6 ± 0.4		
Placebo for qd comparison*	94	102.8 ± 1.8	-2.2 ± 0.2		
*from the subgroup that enrolled prior to Protocol Amendment 3. This amendment discontinued enrollment into the lorcaserin qd arm					

TABLE 2 5% weight loss responders at Week 52 in Study 009, Study 011 and Study 010

Study Treatment arms	N	Number of responders (%)	Difference in proportions ¹ (95% CI)	Odds ratio (95% CI)	p-value vs. placebo
% of subjects achieving ≥ 5% weight loss at week 52 (MITT/LOCF)					
1. Study 009 “Bloom”					
Lorcaserin 10 mg bid	1538	731 (47.5%)	27.2 (24.0, 30.5)	3.6 (3.1, 4.2)	<0.0001
Placebo	1499	304 (20.3%)			
2. Study 011 “Blossom”					
Lorcaserin 10 mg bid	1561	737 (47.2%)	22.2 (18.9, 25.5)	2.7 (2.3, 3.1)	<0.0001
Lorcaserin 10 mg qd	771	310 (40.2%)	15.2 (11.1, 19.3)	2.0 (1.7, 2.4)	<0.0001
Placebo	1541	385 (25.0%)			
3. Study 010 “Bloom-DM”					
Lorcaserin 10 mg bid	251	94 (37.5%)	27.3 (13.8, 28.9)	3.1 (2.1, 4.8)	<0.0001
Lorcaserin 10 mg qd	94	42 (44.7%)	23.4 (10.1, 36.0)	3.1 (1.6, 6.0)	0.0006
Placebo for the bid comparison	248	40 (16.1%)			
Placebo for the qd comparison*	94	20 (21.3%)			
*from the subgroup that enrolled prior to Protocol Amendment 3. This amendment discontinued enrollment into the lorcaserin qd arm					

FIGURE 1 Study 010; 5% non-responders by study visit, MITT with non-responder imputation for dropouts; lorcaserin 10 mg bid and placebo



Efficacy Comparisons between Study 010 (Bloom-DM), Study 009 (Bloom) and Study 011 (Blossom):

The original NDA 022529 submission for lorcaserin included the results from two large Phase 3 studies, APD356-009 (Bloom) and APD356-011 (Blossom). Both studies enrolled adults either obese or overweight with at least one weight related co-morbid condition. Diabetes was an exclusion from both of these studies. On average, the diabetic subjects in Study 010 were about 10 years older than the subjects in Study 009 and Study 011. Study 010 enrolled approximately equal numbers of men and women, while approximately 80% of the subjects in Study 009 and Study 011 were women. The distribution of subjects across racial and ethnic subgroups was similar in all three studies. The average baseline BMI was fairly similar across the three studies.

All three studies had similar estimates of the placebo-adjusted effect of lorcaserin 10 mg bid at 52 weeks (TABLE 1). The consistency of the efficacy results across Studies 010, 009 and 011 supports the collective evidence for the efficacy of lorcaserin 10 mg bid. However, the efficacy endpoints, while statistically significant, do not fully meet the benchmarks for clinical significance that are described in the Agency’s Weight Management Guidance (2007):

- For the continuous endpoint, the guidance states that the difference in mean weight loss between the active product and placebo-treated groups should be at least 5% and the difference should be statistically significant. For all three studies, the placebo-adjusted percentage change from baseline at week 52 was statistically significant. However, in

each of the three studies, the placebo-adjusted effect of lorcaserin was statistically significantly less than 5%.

- For the categorical endpoint, at least 5% of weight loss at week 52, the guidance states that the observed percentage of responders should be at least 35% and at least double the percentage in the placebo-treated group. These criteria are met in all three studies, when the last observation carried forward (LOCF) method was used to impute the 52-week results from subjects who discontinued early. However, these results are somewhat sensitive to the imputation method. When early dropouts are classified as non-responders, Studies 009 and 011 meet the criteria for the categorical endpoint but Study 010 does not.

In my opinion, the 5% responder endpoint is a key endpoint because of the substantial percentage of early withdrawals in all three studies. Because of the relationship between dropping out and being less successful at weight loss in these studies, I believe it is reasonable to classify dropouts as non-responders. I described this relationship in the statistical review of Studies 009 and 011. On average, subjects in these studies who withdrew early had lost less weight at the time of withdrawal, compared to the weight loss at the corresponding time period in subjects who completed the study. For this reason, I believe that classifying dropouts as non-responders is a reasonable way to extend the study results to the intended target population.

This review focuses on the lorcaserin 10 mg bid dose, because it was evaluated in all three studies. The results for the lorcaserin 10 mg qd dose were consistent with a dose-response relationship in Study 011 (non-diabetic subjects). The two dose arms were fairly similar in Study 010 (diabetic subjects). Neither study was powered for a statistical comparison between the two lorcaserin dose arms.

1.2 Brief Overview of Clinical Studies

The December 22, 2011 re-submission of NDA 022529/0 includes the study report for Study APD356-010, (Bloom-DM). Study 010 was a 52-week randomized, double-blind, placebo-controlled study in subjects who were overweight or obese and who also had Type 2 diabetes. Study 010 had three arms: placebo, lorcaserin 10 mg once a day (qd) and lorcaserin 10 mg twice a day (bid). Due to slow enrollment, the total enrollment target was reduced from 750 subjects to 600 subjects by discontinuing randomization to the low dose group, about halfway through enrollment. Eligible subjects were randomized to receive study medication for 52 weeks, with periodic follow-up visits to assess efficacy and safety endpoints.

As part of my review, I compared the results from Study 010 to the results from Study APD-356-009 (Bloom) and Study APD-356-011 (Blossom). The reports for these two studies were submitted in the original NDA submission. Both studies enrolled adults between ages 18 and 65 years who were either obese ($BMI \geq 30 \text{ kg/m}^2$), or overweight with at least one weight related co-morbid condition ($BMI 27-30 \text{ kg/m}^2$). Diabetes was an exclusion from both of these studies. Study 009 enrolled approximately 3200 subjects, randomized to lorcaserin 10 mg bid or placebo. The primary weight endpoints were evaluated after 52 weeks. Study 009 was continued for a second year, with a re-randomization of lorcaserin subjects to either continue with lorcaserin or

to switch to placebo. Subjects in the first year were continued on placebo. Study 011 enrolled approximately 4000 subjects, and randomized to three arms, lorcaserin 10 mg bid, lorcaserin 10 mg qd or placebo. The primary weight endpoints were evaluated after 52 weeks.

1.3 Statistical Issues and Findings

Study 010: A substantial percentage of early withdrawals affected the best way to estimate weight loss in the intended population for lorcaserin: A substantial percentage of randomized subjects, 34%, withdrew from Study 010 prior to week 52 (TABLE 4). This is not unexpected in weight loss studies. Subjects who discontinued early were less likely to have achieved a target weight loss of at least 5% of their baseline body weight at the time of discontinuation than subjects who completed the study (FIGURE 10). I believe that the percentage of 5% weight loss responders is a key endpoint. In my opinion, a reasonable approach involves looking at three estimates of the categorical 5% responder endpoint: (1) the percentage of subjects who completed the study who were 5% responders; (2) the percentage of subjects in the MITT population who were 5% responders, with LOCF imputation; and (3) the percentage of subjects in the MITT population who were 5% responders, with non-response imputation for subjects who discontinued. Taken together, the three approaches provide a useful range for understanding the efficacy of lorcaserin in the intended target population. All three approaches are reported in TABLE 11, and the longitudinal profile of the percentage of 5% responders over time is depicted side by side for each approach in FIGURE 12.

Study 010: The discontinuation of enrollment into the lorcaserin qd arm affected the analysis plan for this arm. The implementation of Protocol Amendment 3 (discontinuing the lorcaserin qd arm) created two enrollment subgroups. In my opinion, the lorcaserin qd arm should be compared against the subgroup of the placebo arm that was also enrolled prior to Protocol Amendment 3. I also believe that the assessment of the lorcaserin qd arm should be separated from the gate-keeping sequence, and viewed as exploratory. This separation of the lorcaserin qd arm from the gate-keeping sequence did not affect the evaluation of the lorcaserin bid arm, because none of the evaluations of the bid arm depended on outcomes from the qd arm.

2. INTRODUCTION

2.1 Overview

Lorcaserin hydrochloride in tablet form is intended for weight management, including weight loss and maintenance of weight loss in obese subjects ($BMI \geq 30 \text{ kg/m}^2$), or overweight subjects ($BMI \geq 27\text{-}30 \text{ kg/m}^2$) who have one or more weight-related co-morbid medical conditions. The dosage is 10 mg twice a day. In response to the initial submission to NDA 022529/0, the Division issued a Complete Response letter (dated 10/22/10). One of the items in the complete response letter was a request for the clinical study report for Study APD356-010, "Behavior modification and lorcaserin for overweight and obesity management in diabetes mellitus (Bloom-DM)." The December 22, 2011 re-submission includes the study report for the Bloom-DM study.

2.1.1 Class and Indication

Lorcaserin is a selective serotonin 2C receptor agonist. Serotonin and certain serotonin agonists decrease food intake and reduce body weight through activation of centrally located 5-HT_{2C} receptors. The applicant developed lorcaserin with the intention of activating t-HT_{2C} receptors without initiating the heart valve toxicity seen in the historical weight management products fenfluramine and dexfenfluramine. These products enhanced serotonin release and blocked its reuptake, leading to activation of multiple serotonin receptor subtypes with toxicity that included cardiac valvular regurgitation. The manufacturers of fenfluramine and dexfenfluramine voluntarily withdrew these drugs from the marketplace in 1997 after numerous reports revealed that subjects who had taken the drugs experienced serious adverse cardiovascular effects. The applicant also developed lorcaserin with the intent to minimize its effect on mood and perception.

2.1.2 Specific Studies Reviewed

The applicant's response to the Division's Complete Response letter includes the results from the Phase 3 Study APD356-010 (Bloom-DM), a 52-week randomized, double-blind, placebo-controlled study in subjects who were overweight or obese and who also had Type 2 diabetes. This statistical review evaluates the evidence for efficacy of lorcaserin 10 mg bid and lorcaserin 10 mg qd from Study 010, and compares the results from this study to the results from Study APD356-009 (Bloom) and Study APD356-011 (Blossom) that were reviewed in the original NDA submission.

2.1.3 Major Statistical Issues

A substantial percentage of early withdrawals affected the best way to estimate weight loss in the intended population for lorcaserin: A substantial percentage of randomized subjects, 34%, withdrew from Study 010 prior to week 52 (TABLE 4). This is not unexpected in weight loss studies. Subjects who discontinued early were less likely to have achieved a target weight loss of at least 5% of their baseline body weight at the time of discontinuation than subjects who completed the study (FIGURE 10). A smaller percentage of subjects withdrew early from the lorcaserin arms than from the placebo arm (TABLE 4). These findings make it challenging to extend the study results to the target population. The average weight loss of the subset of completers is likely to overestimate the average weight loss in the intended population. The average weight loss of the full analysis set with last observation carried forward (LOCF) imputation is also likely to overestimate the average weight loss in the intended population. Moreover, the use of LOCF as an imputation method has recently been criticized for its poor inferential properties.¹

¹ See the 2010 report from the National Academy of Sciences (NAS), *The Prevention and Treatment of Missing Data in Clinical Trials*. This report was commissioned by the FDA. The report states "The panel believes that in nearly all cases, there are better alternatives to [LOCF]...which are based on more reasonable assumptions and hence result in more reliable inferences about treatment effects". A version of the NAS report can be found online at http://www.nap.edu/catalog.php?record_id=12955.

This is why I believe that the percentage of 5% weight loss responders is a key endpoint. The categorical endpoint lends itself to a third approach, which is to classify subjects who discontinued as non-responders. This may underestimate the percentage of responders in the intended population. However, taken together, the three approaches provide a useful range for understanding the efficacy of lorcaserin in the intended target population. All three approaches are reported in TABLE 11, and the longitudinal profile of the percentage of 5% responders over time is depicted side by side for each approach in FIGURE 12.

The substantial percentage of early withdrawals, and the relationship between early withdrawal and less weight loss was also apparent in Study 009 and 011. On average, subjects in these studies who withdrew early had lost less weight at the time of withdrawal, compared to the weight loss at the corresponding time period in subjects who completed the study. I made a similar recommendation concerning the 5% weight loss responder endpoint in my review of those studies.²

The discontinuation of enrollment into the lorcaserin qd arm affected the analysis plan for this arm: With three primary efficacy endpoints (weight as a change from baseline, the percentage of subjects who lost at least 5% of baseline body weight and the percentage of subjects who lost at least 10% of baseline body weight) and two dose arms to compare against the placebo arm (lorcaserin 10 mg bid and lorcaserin 10 mg qd), the applicant pre-specified an ordered gate-keeping sequence of comparisons. Part 3.2.3 of this review describes the gate-keeping sequence. However, I believe that the discontinuation of enrollment into the lorcaserin qd arm about halfway through the enrollment period affected the approach to analyzing the qd arm. This is because the implementation of Protocol Amendment 3 (discontinuing the lorcaserin qd arm) created two enrollment subgroups. In my opinion, the lorcaserin qd arm should be compared against the subgroup of the placebo arm that was also enrolled prior to Protocol Amendment 3. I also believe that the assessment of the lorcaserin qd arm should be separated from the gate-keeping sequence, and viewed as exploratory. While the statistical comparisons within the enrollment subgroup are valid, I believe that the interpretation of their clinical significance is a review issue. This separation of the lorcaserin qd arm from the gate-keeping sequence did not affect the evaluation of the lorcaserin bid arm, because none of the evaluations of the bid arm depended on outcomes from the qd arm.

2.2 Data Sources

Submissions and data that I reviewed for the complete response resubmission of NDA 022529/0 are summarized in TABLE 3.

TABLE 3 Data sources for this submission

Number	Date	Description
0034	12/23/2011	Complete response submission, including study report and data files for Study APD356-010 "Bloom-DM"
0050	2/13/12	Response to FDA information requests, including a pooled vital signs database
\\cdesub1\evsprod\NDA_022529		

² See the statistical review of NDA 022529/0 (submitted 12/22/2009). Figure 6 in this review depicts the time course of average weight loss in subjects who discontinued and subjects who completed, by study and dose arm.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

I do not have review concerns about data and analysis quality in the parts of the submission that I reviewed.

3.2 Evaluation of Efficacy

3.2.1. Study design and endpoints

Design: Study 010 was designed to evaluate the effects of lorcaserin on overweight or obese subjects with type 2 diabetes during 52 weeks of treatment. The study was designed as a randomized, double-blind, placebo-controlled clinical trial. All subjects received dietary and exercise counseling at each visit.

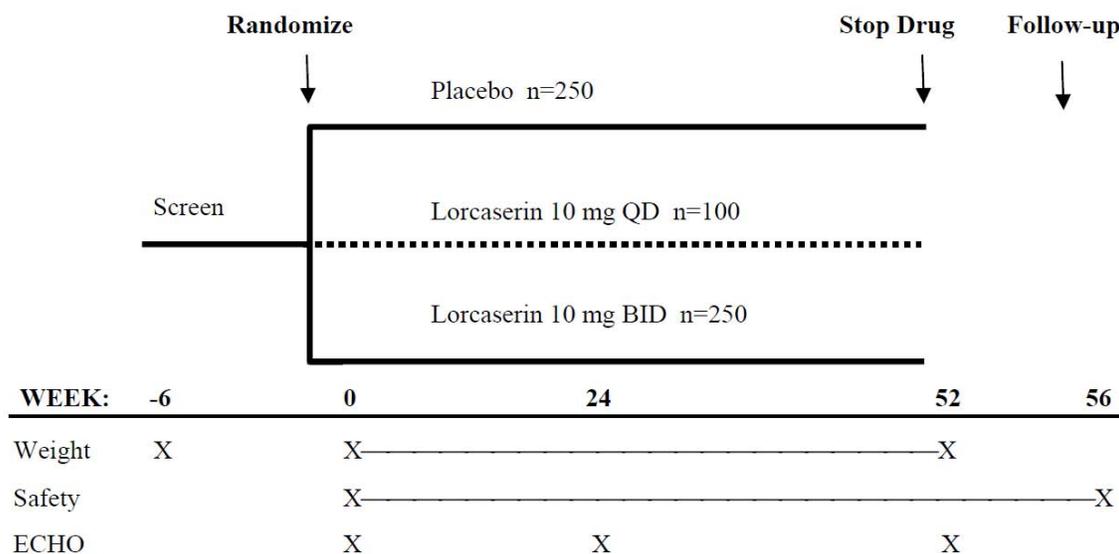
The study design was modified during the enrollment period by an amendment (Protocol amendment 3) which discontinued one of the active treatment arm. Prior to Amendment 3, subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups: placebo, lorcaserin 10 mg once a day (qd) or lorcaserin 10 mg twice a day (bid). Due to slow enrollment, the total enrollment target was reduced from 750 subjects (250/arm) by discontinuing randomization to the low dose group. Subjects screened after the implementation of Amendment 3 were randomized in a 1:1 ratio to placebo or lorcaserin 10 mg bid. Subjects randomized into the lorcaserin 10 mg qd group remained enrolled in the study to complete all planned study procedures. A schematic of the study design is included in FIGURE 2. Eligible subjects were randomized to receive study medication for 52 weeks, with periodic follow-up visits to assess efficacy and safety endpoints. Inclusion criteria included: male or female, aged between 18 and 65 years, body mass index between 27.0 and 45.0 kg/m², and with type 2 diabetes, HbA1c between 7 and 10%.

Acceptable therapies for diabetes included treatment with metformin, sulfonylurea (SFU) or either agent in combination with other oral medications (e.g., DPP-IV inhibitors, meglitinides or acarbose) at a stable dose for at least 3 months prior to screening. If treated with thiazolidinediones (TZDs) in combination with SFUs or metformin, the dose of TZD had to have been stable for at least 6 months prior to screening. Diabetes therapies that were excluded were the use of insulin in any form, the use of exenatide, or the use of pramlintide within 3 months prior to screening.

Subjects were required to participate in the Arena Healthy Lifestyle Program® diet program as prescribed by their study dietician/counselor. The prescribed diet consisted of approximately 600 calories less per day than the subject's calculated Estimated Energy Requirement (EER). The EER was calculated using WHO criteria with a fixed activity factor of 1.3 for most patients.

For patients who engaged in ≥ 1 hour/day of aerobic exercise, an activity factor of 1.4 was used. The Arena Healthy Lifestyle Program also included an exercise program.

FIGURE 2 Study 010; Schematic of the study design



Source: Study 010 report, Appendix 16.1.9, Figure 1

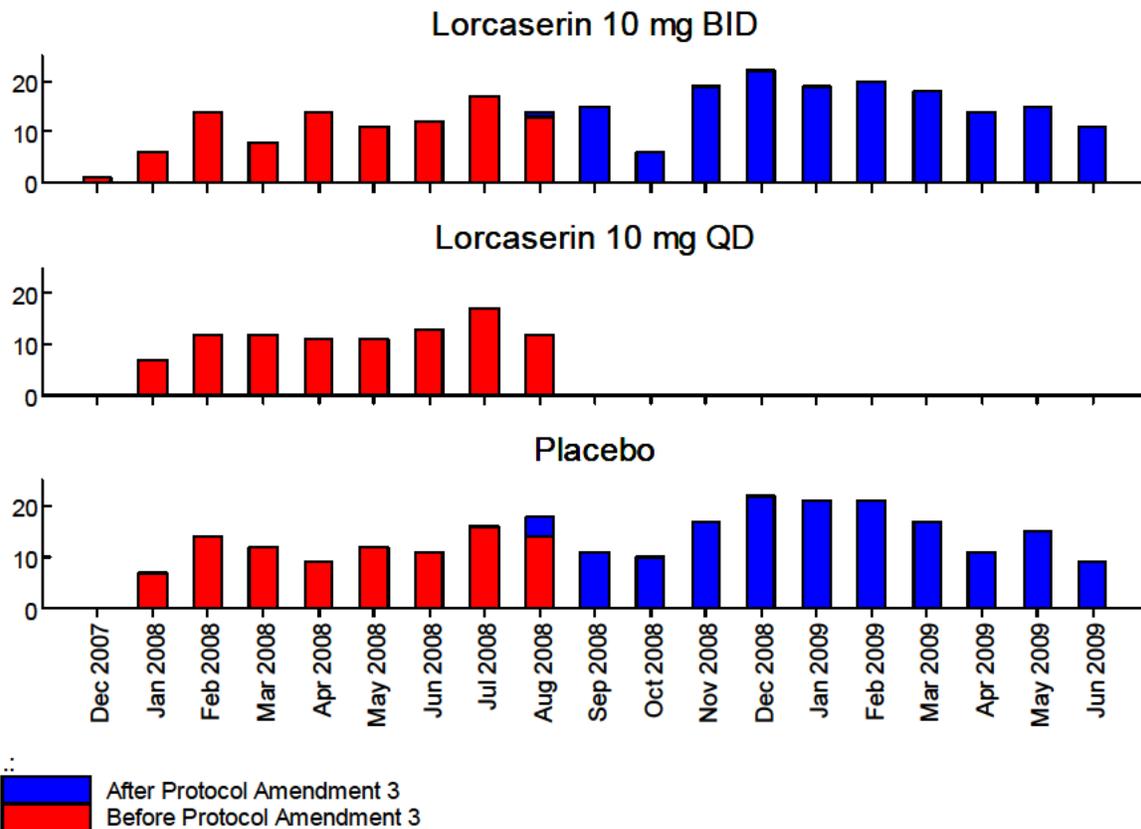
Randomization: The randomization was stratified by the following two factors: HbA1c ($< 9\%$ and $\geq 9\%$), and medication used to treat diabetes: (sulfonylurea alone or in combination, and metformin alone or in combination). Subjects who were taking both metformin and a sulfonylurea were included in the sulfonylurea group. The rationale for including subjects who used both metformin and a SFU in the SFU group was related to the greater theoretical risk of hypoglycemia with SFUs than with metformin.

Study sites, enrollment, and discontinuation of the lorcaserin qd arm: Study 010 was conducted in 64 investigative sites within the U.S. After about eight months of enrollment, Amendment 3 to the study protocol was implemented. This amendment suspended enrollment into the lorcaserin 10 mg qd arm. The reason that the applicant gave for suspending the lorcaserin qd arm was the low overall recruitment rate into the study. Enrollment into the lorcaserin 10 mg bid arm and the placebo arm continued for another 10 months. The rate of enrollment was fairly constant across the entire 18 month period, with 286 subjects enrolled prior to Amendment 3, and 318 subjects enrolled after Amendment 3 (FIGURE 3).

After Protocol 3 was implemented, an additional 8 sites were included in the study, and 5 sites stopped enrolling subjects (FIGURE 4). The majority of sites, 44 of the 64, enrolled from 1 to 10 subjects. The median enrollment at a site was 8 subjects, with a minimum of 1 and maximum of 47.

The applicant commented that the lorcaserin 10 mg qd group was enrolled over a different time frame and from a different spectrum of investigators. For this reason, the applicant stated that it was not strictly appropriate to compare the lorcaserin qd group to the overall placebo or the lorcaserin 10 mg group³. However, I believe that there was a reasonable enough overlap between the study sites of the two enrollment subgroups to consider them to be fairly similar (FIGURE 4). I agree with the applicant concerning the evaluation of the lorcaserin 10 mg qd group, but for a different reason, which is that I believe that the lorcaserin 10 mg qd arm should be compared against the subgroup of the placebo arm that was enrolled and randomized contemporaneously with the qd arm.

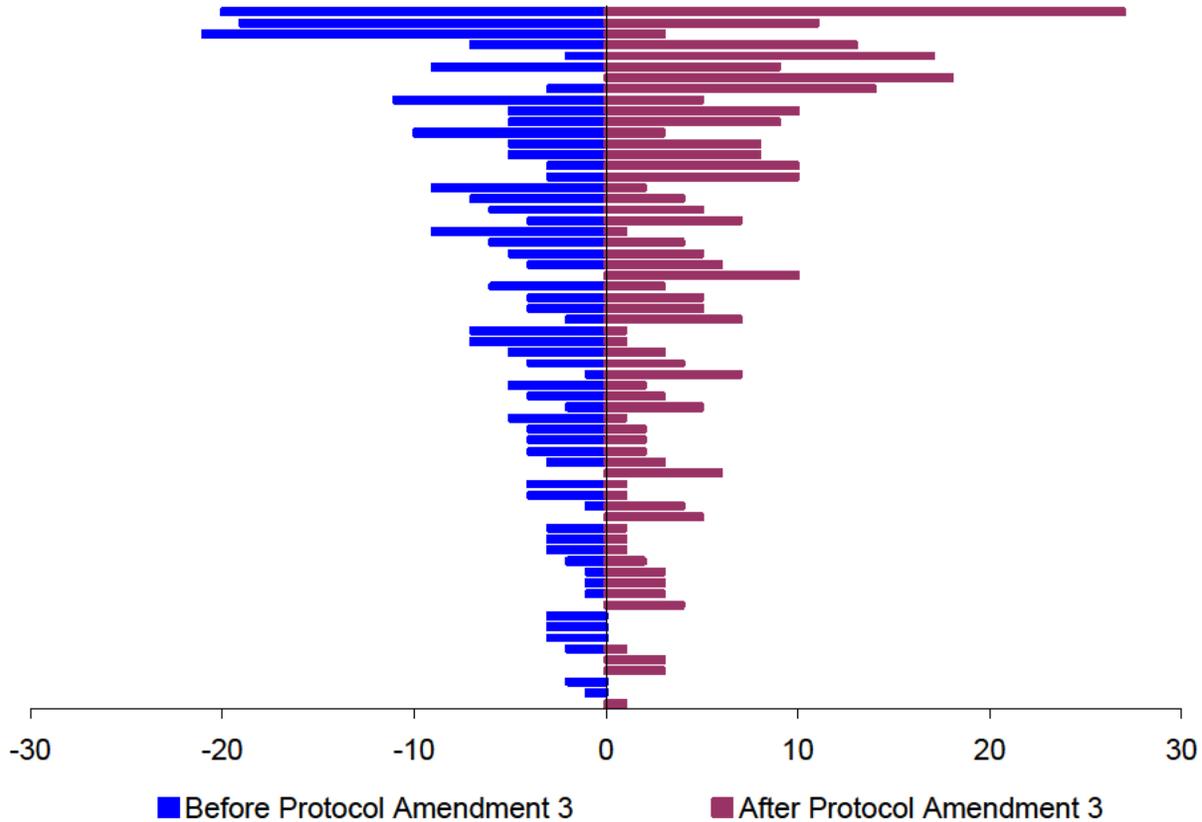
FIGURE 3 Study 010; Enrollment by month and treatment arm, before and after Protocol Amendment 3. Protocol Amendment 3 discontinued the Lorcaserin qd arm.



Source: Analysis by this reviewer

³ See Part 11.4.1 of the Study 010 report (p. 59/914)

FIGURE 4 Study 010; Number of subjects enrolled by study site, before and after Protocol Amendment 3. Each horizontal bar represents one site.



Source: Analysis by this reviewer

Statistical power and the size of the study: The applicant planned for the size of the three-arm study with the following assumptions:

- 15% of subjects in the placebo arm will achieve a 5% or greater weight loss between baseline and week 52 (“5% responders”).
- 30% of subjects in each lorcaserin arm would be 5% responders
- A two-sided α of 0.025 for each comparison, lorcaserin 10 mg bid vs. placebo and lorcaserin 10 mg qd vs placebo
- A 40% dropout rate at week 52

Based on a two-sample test of equality of binomial proportions, the applicant calculated that 147 subjects per arm provided 80% power. Allowing for the dropout rate resulted in an estimate of 250 subjects per arm.

As a result of Amendment 3 to the study protocol, which terminated enrollment into the lorcaserin qd arm, the total enrollment for Study 010 was estimated at 600; 250 each in the placebo and lorcaserin 10 mg bid arms, and 100 in the lorcaserin 10 mg qd arm.

The applicant designed and powered the study to address the guidance documents that concern weight management from both the FDA and the European Medicines Agency (EMA). Each agency's guidance document describes the criteria for clinical significance somewhat differently, as shown below:

FDA Guidance for Industry: Developing Products for Weight Management (2007 Draft)

In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant
- The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.

Part IV. B. 3c "Efficacy benchmarks"

EMA Guideline on Clinical Evaluation of Medicinal Products Used in Weight Control, 2007

Demonstration of a clinically significant degree of weight loss of at least 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs. Proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12-month period.

Part 4.2.1 "Primary endpoints"

Efficacy endpoints: The applicant specified the following three primary endpoints:

- Proportion of subjects who lose at least 5% of their baseline body weight at week 52 ("5% responders")
- Change from baseline in body weight at week 52
- Proportion of subjects who lose at least 10% of their baseline body weight at week 52 ("10% responders")

These endpoints are drawn from the guidance documents of both the FDA and the EMA, as shown below:

FDA Guidance for Industry: Developing Products for Weight Management (2007 Draft)

The efficacy of a weight-management product should be assessed by analyses of both mean and categorical changes in body weight.

- Mean: The difference in mean percent loss of baseline body weight in the active-product versus placebo-treated group.
- Categorical: The proportion of subjects who lose at least 5 percent of baseline body weight in the active-product versus placebo-treated group.

Part IV.B. 3a “Efficacy Endpoints”

EMA Guideline on Clinical Evaluation of Medicinal Products Used in Weight Control, 2007

Weight loss is the primary endpoint. ... Proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12-month period. ... Weight loss should be documented both as absolute weight loss and by other appropriate measures (such as percentage body weight loss).

Part 4.2.1 “Primary endpoints”

Secondary efficacy endpoints: The protocol for Study 010 included the following secondary efficacy endpoints:

- Change from baseline in:
 - HbA1c
 - Total body fat
 - Lean body mass
 - Systolic and diastolic blood pressure
- Percent change from baseline in:
 - LDL-cholesterol
 - Total cholesterol
 - HDL-cholesterol
 - Triglycerides

3.2.2. Subject disposition, demographic and baseline categories

Protocol specifications for discontinuation: The study protocol described the following circumstances that would lead to withdrawal of a patient from the study or from study medication:

(1) *Circumstances that were not specifically related to diabetes:* The protocol for Study 010 provided for the discontinuation from therapy or from the study for any of the following reasons:

- Confirmation of a pregnancy
- Development of an illness or adverse event that would interfere with continued participation
- Non-compliance with the trial procedures or study drug
- Request of the sponsor or regulatory agency
- Subject could withdraw consent
- Subject was lost to follow-up
- The investigator determined that it was not in the best interest of the subject to continue in the study.

(2) *Circumstances that were related to diabetes:* Investigators were encouraged not to increase or add medications for diabetes prior to the week 12 visit in the event that weight loss during that time might reduce the need for diabetes medication. The protocol included the following guidelines concerning diabetes therapies, which included criteria for discontinuing a subject from the study due to inadequate glucose control:

- If the majority of fasting plasma glucose (FPG) self-monitoring readings were ≥ 140 mg/dL at the 12-week or subsequent study visit, or if several self-monitored FPG readings between scheduled visits at 12 weeks or later were > 240 mg/dL, the investigator should consider increasing the anti-hyperglycemic drug dose. The recommended order in which to increase dose or add additional agents was: (1) if on a single agent, increase the dose of that agent; (2) if on more than one agent: (a) increase metformin to maximum tolerated or recommended dose; (b) increase or add another agent (TZD, DPP-IV inhibitor, etc.).
- If a patient has either (1) HbA1c increase of $\geq 1.5\%$ from baseline at any scheduled measurement or (2) HbA1c $\geq 11\%$ at any scheduled measurement, or (3) FPG measured in the clinical laboratory > 270 mg/dL on two consecutive study visits, should be withdrawn from the study and referred to his/her primary care physician for management of uncontrolled diabetes.

The protocol also described circumstances and guidelines for the reduction of diabetes medication if a subject experienced hypoglycemic events.

Subject disposition: A substantial percentage of randomized subjects, 33.6%, withdrew from the study prior to week 52 (TABLE 4A). A large percentage of early withdrawal is typical of weight loss studies, and so this finding is not unexpected. The percentage of early discontinuation was greater in the placebo arm than in the lorcaserin arms. The time dynamics of disposition for each arm is depicted in FIGURE 5A. The key reasons for early discontinuation are the following:

- *Withdrawal of consent:* The reason for withdrawal identified by the largest number of discontinuing subjects was “withdrawal of consent” (14.9% of randomized subjects; TABLE 4A). Within the “withdrawal of consent” category, only 11 (2% of randomized

subjects) described “lack of efficacy” as the reason for withdrawing, which I am interpreting as a subject’s dissatisfaction with his/her weight loss (TABLE 4B). The “lack of efficacy” description was obtained from the text field for capturing additional comments from the clinical report form, concerning the reason for withdrawal. Two other subjects withdrew consent for reasons that appeared to be related to weight (TABLE 4B). The text entries from other subjects who withdrew consent encompassed a variety of reasons that did not appear to be related to weight.

- *Adverse events:* Adverse events accounted for the early discontinuation of 13.3% of randomized subjects in the lorcaserin arms and 4.3% in the placebo arm (TABLE 4A).
- *Lost to follow-up:* Subjects who were lost to follow-up made up another 6.0% of randomized subjects (TABLE 4A). The attempts to locate these subjects, including documented telephone calls and certified letters, were documented in the database.
- *Discontinuation for diabetes-related reasons:* I identified only three subjects who discontinued from the study for reasons related to the control of diabetes, of which one was the most clearly related to the criteria for HbA1c that were described in the protocol (TABLE 4B). This identification came from evaluating the text entries for the reason for withdrawal of consent for 2 subjects and for investigator decision for 1 subject.

Subject disposition and the implementation of Protocol Amendment 3: Noteworthy in Study 010 is the fairly high percentage of completers in the lorcaserin 10 mg qd arm (TABLE 4), compared to the retention in the other two arms. The higher retention is a feature of all three arms in the enrollment period prior to Protocol Amendment 3 (FIGURE 5B). Because of this difference, the lorcaserin qd arm has a greater retention than the other two arms of the study, when viewed across the entire enrollment period (FIGURE 5A, TABLE 4).

In the lorcaserin bid arm, subjects had a fairly similar distribution across the set of reasons for discontinuing both before and after Protocol Amendment 3 (FIGURE 6). In contrast, in the placebo group, a greater percentage of randomized subjects either withdrew consent or were lost to follow-up after Protocol Amendment 3 compared to the percentages in these categories before the amendment (FIGURE 6).

The enrollment after Amendment 3 was characterized by a greater percentage of subjects with BMI ≤ 35 kg/m², a greater percentage of male subjects, and a greater percentage of subjects with HbA1c ≤ 8.0 , compared to the enrollment before the amendment (FIGURE 7 - FIGURE 9). A subject who enrolled after Protocol Amendment 3 with baseline BMI ≤ 35 kg/m² was somewhat more likely to discontinue relative to a subject with baseline BMI > 35 , compared to subjects in these two BMI subgroups who enrolled before Protocol Amendment 3 (FIGURE 7). This relationship was apparent in the lorcaserin bid arm but not in the placebo arm. Similarly, subjects who enrolled after protocol Amendment 3 with HbA1c ≤ 8.0 was somewhat more likely to discontinue relative to a subject with baseline HbA1c > 8.0 , compared to subjects in these two HbA1c subgroups who enrolled before Protocol Amendment 3 (FIGURE 8). This relationship was also apparent only in the lorcaserin bid arm and not in the placebo arm. Discontinuation relative to gender appeared to be fairly similar between the two enrollment subgroups (FIGURE 9).

In my opinion, these findings reinforce the importance of evaluating the lorcaserin 10 mg qd arm by comparing it to the subgroup of the placebo arm that was enrolled prior to Protocol Amendment 3. The lorcaserin 10 mg bid arm can be compared to the placebo arm using the entire enrollment period. This comparison can also be subdivided by the amendment date into two subgroup comparisons, as an exploratory analysis. Although the study was not powered for a statistical comparison between the two dose arms, I believe that the most useful exploratory comparison between the two dose arms comes from the subgroup that enrolled prior to Protocol Amendment 3.

Disposition and weight loss: Subjects in the lorcaserin arms who discontinued early were less likely to have achieved a target weight loss of at least 5% of their baseline body weight at the time of discontinuation, compared to subjects in the lorcaserin arms who completed the study (FIGURE 10). In contrast, the percentage of 5% responders in the placebo arm was fairly similar among those who did and those who did not complete the study.

Changes in medications to treat diabetes: The applicant noted that across treatment groups, the majority of subjects had no net change in total daily dose of diabetes medications (TABLE 5). The average metformin dose increased from baseline to week 52 in all treatment groups. In the SFUs, glitazones and gliptins, the direction of change was toward a reduction in average daily dose in the lorcaserin arms and towards an increase in average daily dose in the placebo arm (TABLE 5).

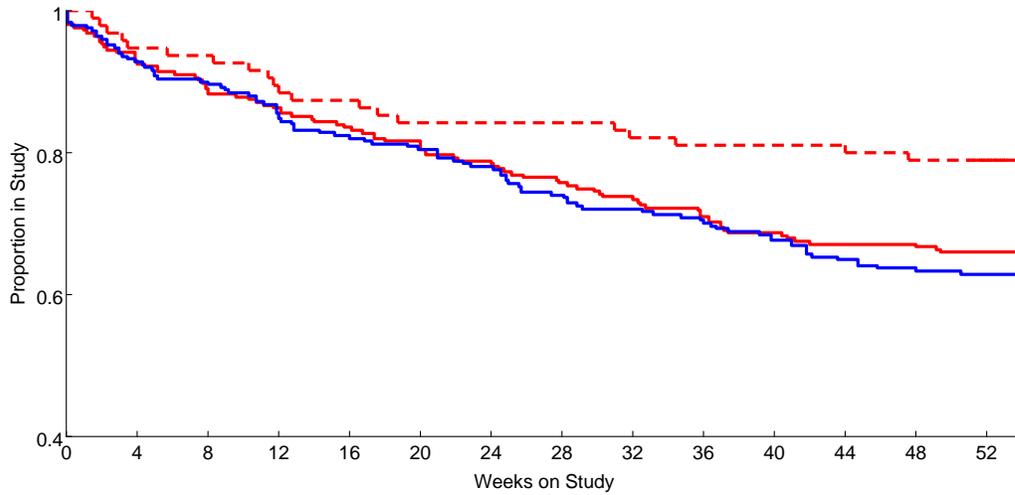
Subject demographic and baseline characteristics of subjects enrolled in Study 010 are summarized in TABLE 6. Approximately equal numbers of male and female subjects were enrolled. The distribution across the major racial groups was approximately 60% Caucasian, 20% African American and 15% Hispanic/Latino. The average baseline body weight was somewhat greater than 100 kg, with average BMI 36 kg/m². All enrolled subjects were taking either metformin, a sulfonylurea, or both at the start of the study. The average baseline HbA1c was 8.1.

TABLE 4 Disposition of subjects in Study 010 at week 52

	Lorcaserin 10 mg BID	Study 010 Lorcaserin 10 mg QD	Placebo
A. Disposition¹			
Number randomized	256	95	253
No. (%) who completed	169 (66.0%)	75 (78.9%)	157 (62.1%)
No. (%) who withdrew prior to week 52	87 (34.0%)	20 (21.1%)	96 (37.9%)
Reason for withdrawal:			
Withdrawal of consent	32 (12.5%)	8 (8.4%)	50 (19.8%)
Lost to follow-up	20 (7.8%)	3 (5.5%)	14 (5.5%)
Adverse event	22 (8.6%)	6 (4.3%)	11 (4.3%)
Combined other reasons	13 (5.1%)	3 (5.5%)	21 (8.3%)
B. Expansion of two categories of reasons for withdrawal:			
Withdrawal of consent	32	8	50
Lack of efficacy (weight-related)	2	4	5
Other weight-related reason ²	0	0	2
Diabetes related reason ³	0	0	2
Other reasons	30	4	38
Combined other reasons	13	3	21
Non-compliance	3	1	10
PI decision, diabetes related ⁴	0	0	1
Sponsor decision	3	1	5
Other	7	1	5
<i>Notes</i>			
¹ For percentages, the number of subjects randomized was used as the denominator.			
² Placebo arm, withdrawal of consent for weight-related reasons: Subject 1228-0447 “felt he had lost too much weight”; Subject 1187-0287 “satisfied with her current weight”			
³ Placebo arm, withdrawal of consent for diabetes-related reasons: Subject 1216-0548 “stated her blood sugars were going too high due to study meds”; Subject 1250-0227 “was put on insulin per DR in ER, insulin not allowed per protocol, subject withdrew consent”			
⁴ Lorcaserin 10 mg qd arm, PI decision; Subject 1236-0263 “A1c increase > 1.5% from baseline at week 36”			
<i>Sources:</i> Study 010 clinical report, Figure 2, Table 5, and additional analysis by this reviewer			

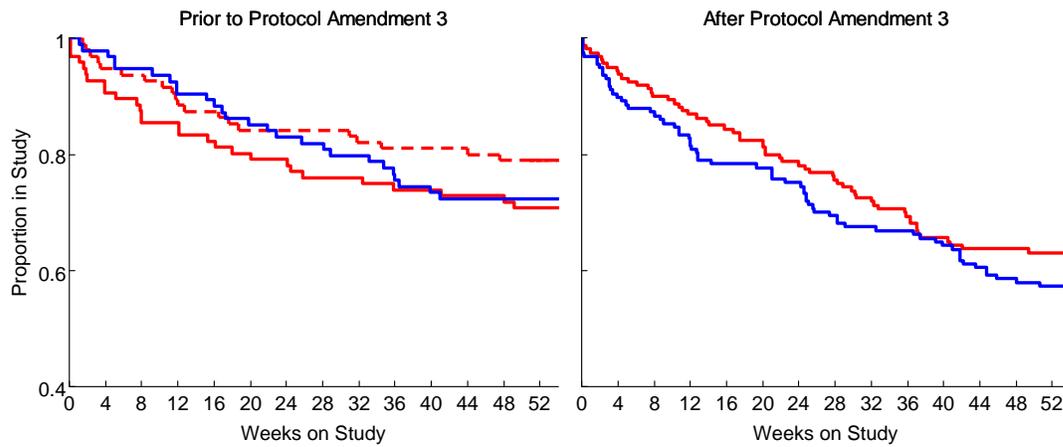
FIGURE 5 Disposition of subjects in Study 010 by week 52

A. Disposition for all randomized subjects



∴
 — Lorcaserin 10 mg BID
 - - Lorcaserin 10 mg QD
 — Placebo

B. Disposition subdivided by the implementation of Protocol Amendment 3

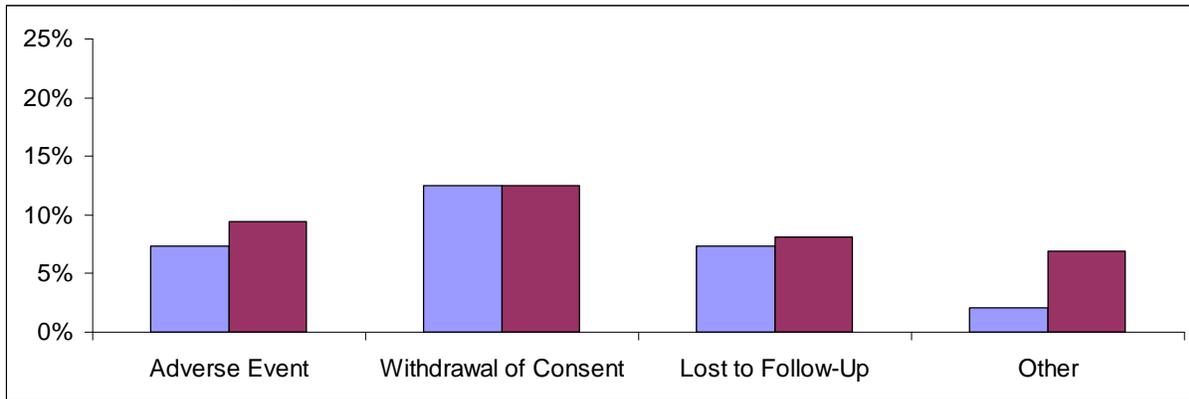


∴
 — Lorcaserin 10 mg BID
 - - Lorcaserin 10 mg QD
 — Placebo

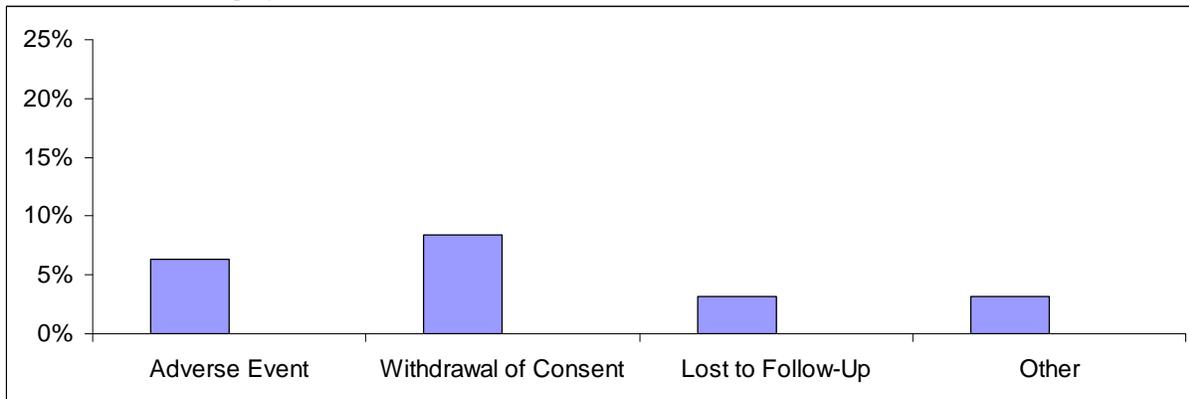
Source: Analysis by this reviewer

FIGURE 6 Study 010; Reason for early discontinuation by study arm and enrollment subgroup defined by the implementation of Protocol Amendment 3

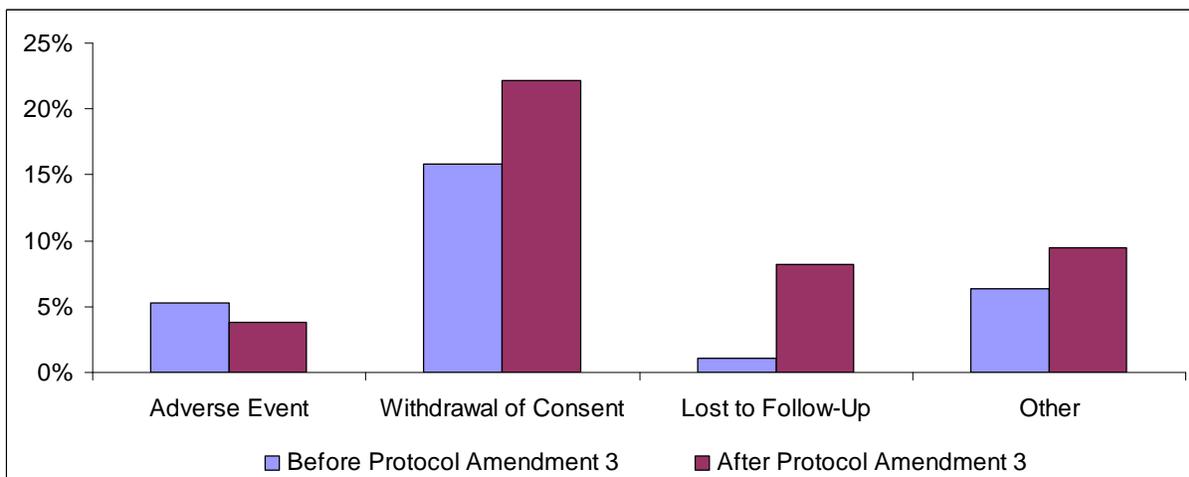
Lorcaserin 10 mg bid



Lorcaserin 10 mg qd



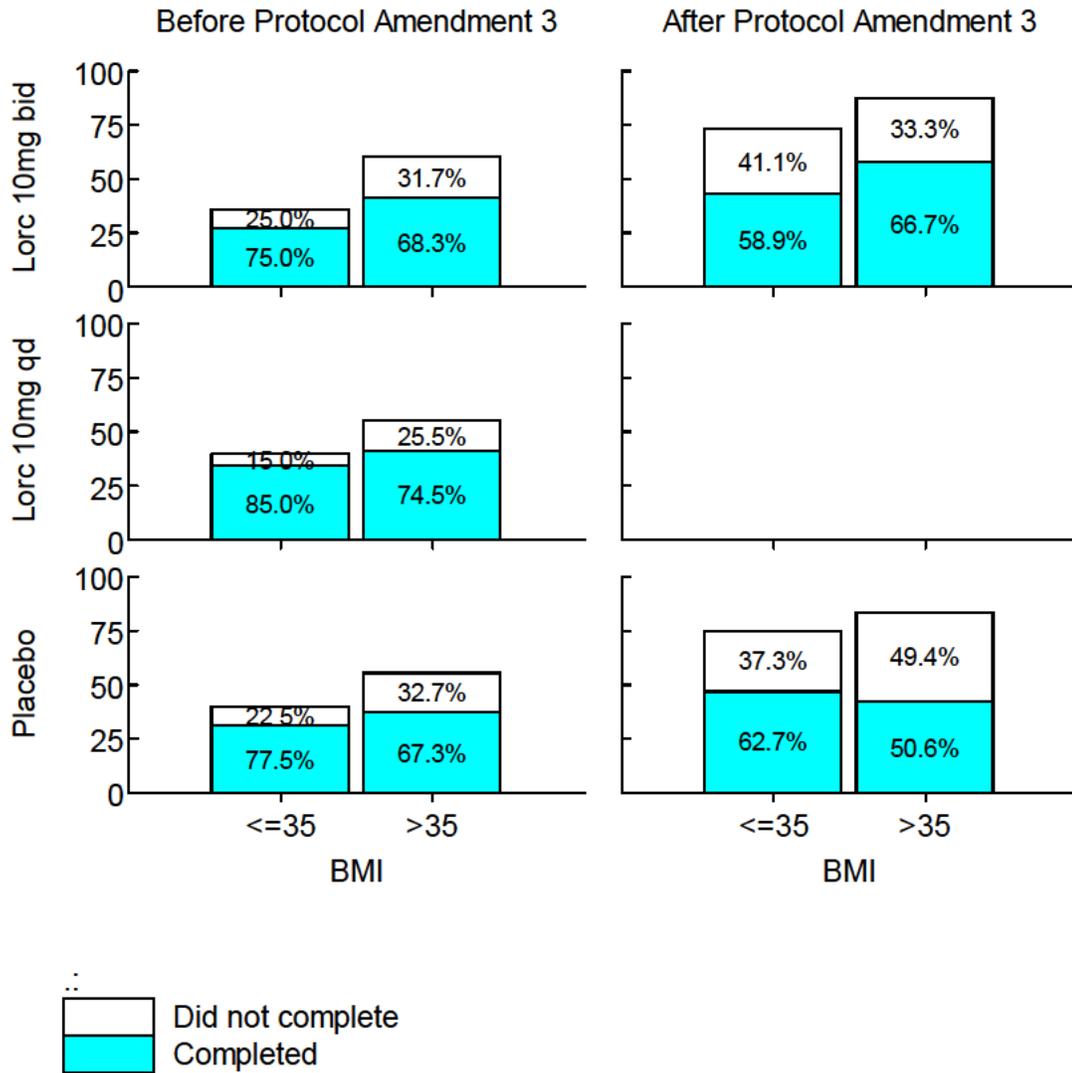
Placebo



Note: Percentages were calculated with respect to the number of subjects randomized by treatment arm and enrollment subgroup

Source: Analysis by this reviewer

FIGURE 7 Percentage of early withdrawals (before week 52) in Study 010, and the relationship to baseline BMI



Source: Analysis by this reviewer

FIGURE 8 Percentage of early withdrawals (before week 52) in Study 010, and the relationship to screening HbA1c

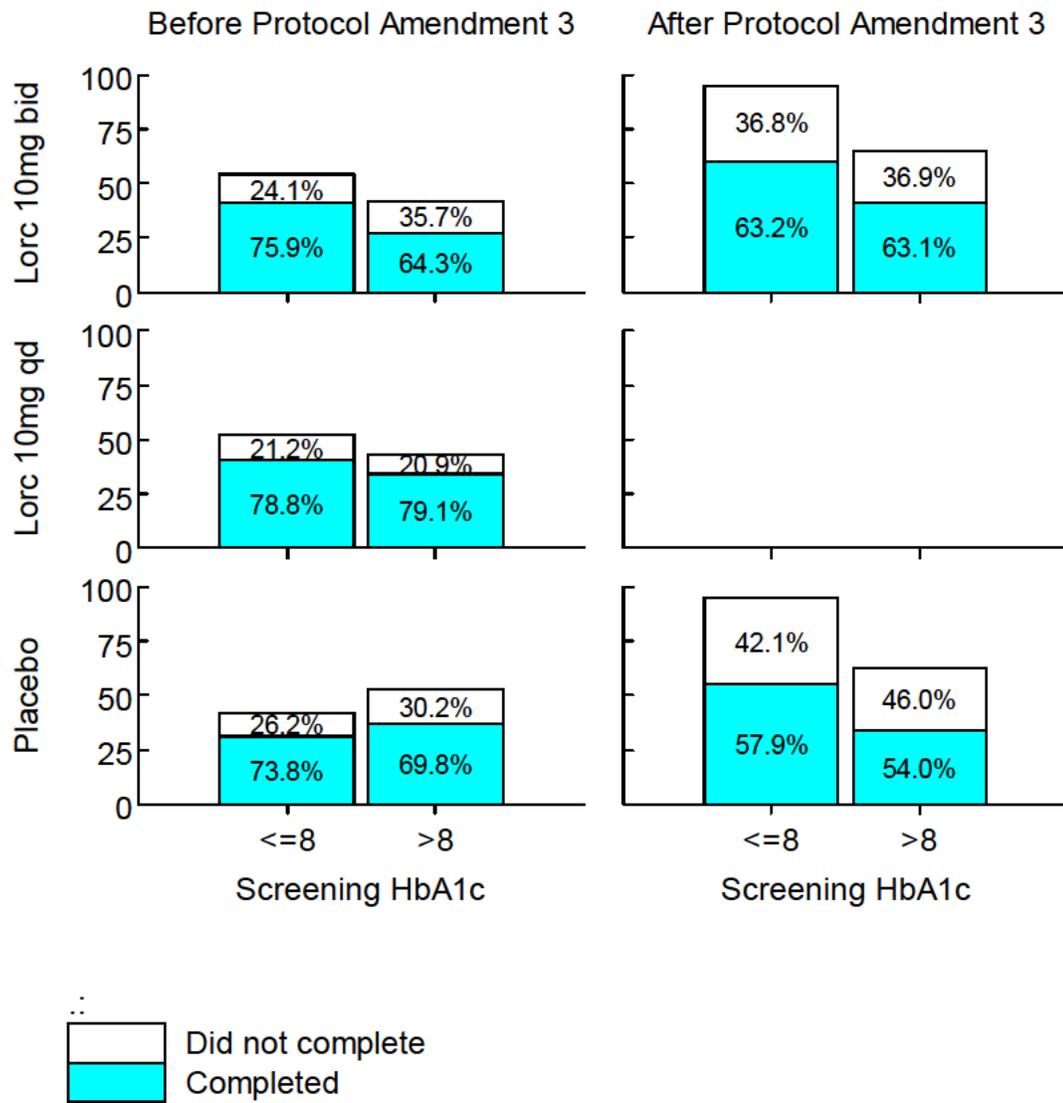
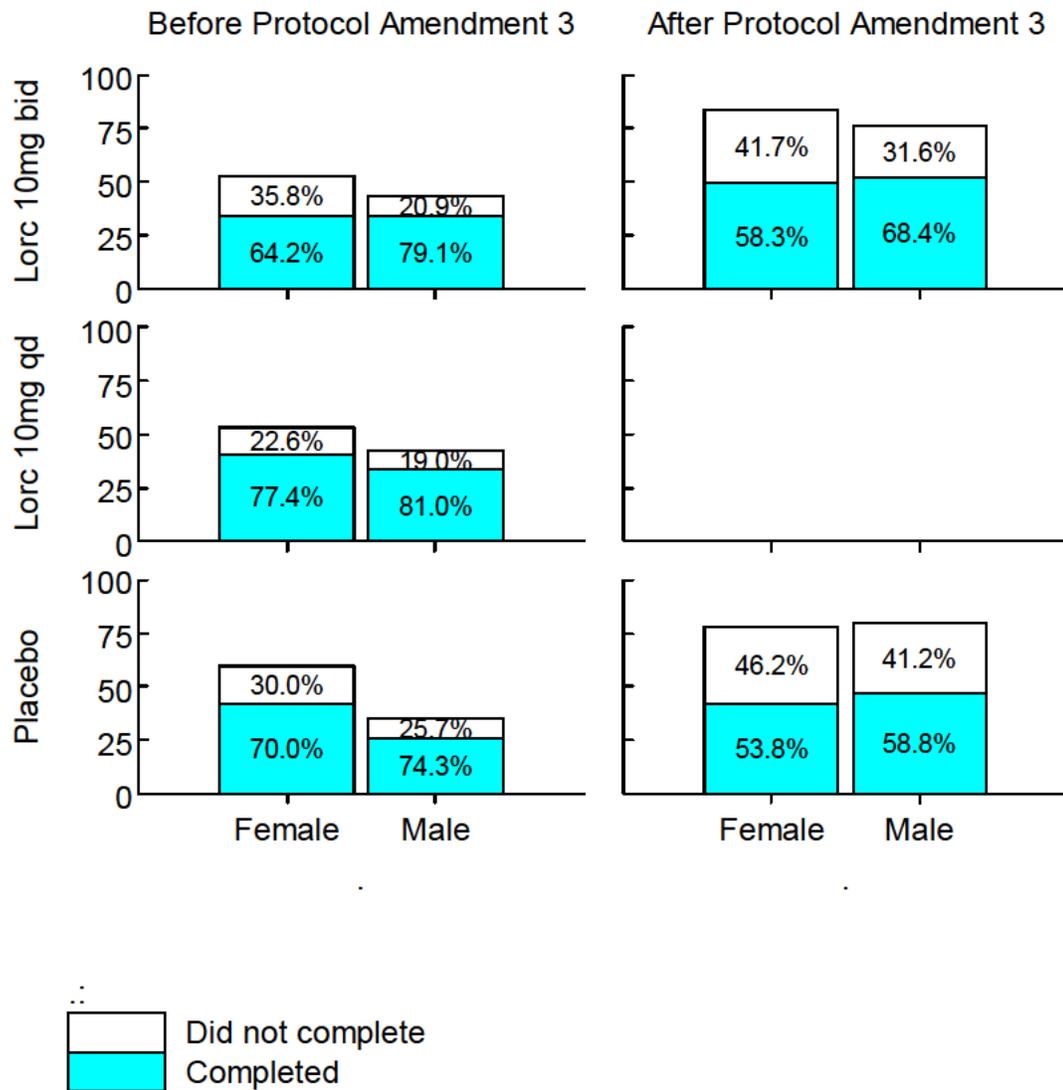
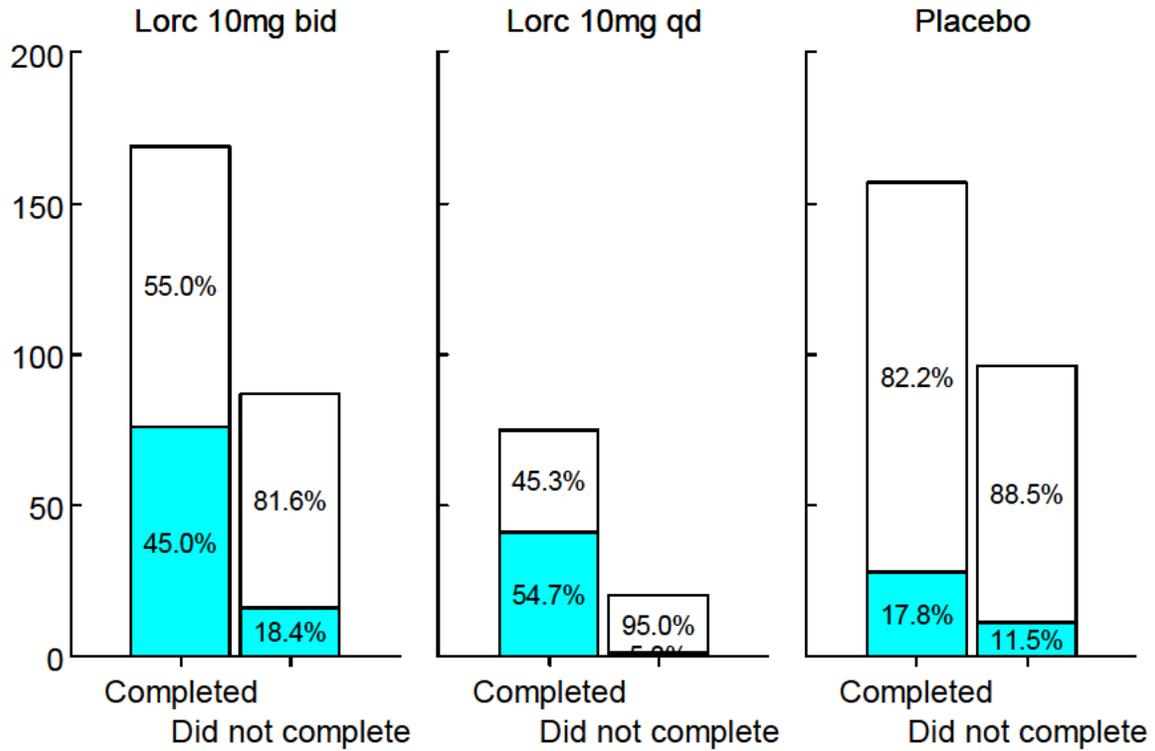


FIGURE 9 Percentage of early withdrawals (before week 52) in Study 010, and the relationship to sex

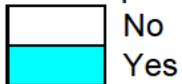


Source: Analysis by this reviewer

FIGURE 10 Percentage of subjects who were 5% responders at the time of either: (1) dropping out of Study 010 or (2) completing Week 52 of Study 010



5% Responder (Based on Last Observation):



Source: Analysis by this reviewer

TABLE 5 Study 010; Changes in use of drugs to treat Type 2 diabetes during the 52-week double-blind period

Parameter	Placebo N=252	Lorcaserin 10 mg BID N=256	Lorcaserin 10 mg QD N=95
Change in total daily dose (n[%])^a			
Decrease	29 (11.7)	43 (17.1)	22 (23.4)
No change	161 (64.9)	172 (68.5)	58 (61.7)
Increase	55 (22.2)	34 (13.5)	11 (11.7)
Patients discontinuing all diabetes meds (n[%])	1 (0.4)	3 (1.2%)	0
Mean (sd) % daily dose change^b			
Metformin	6.6(40.1)	-0.8 (35.9)	3.0 (36.6)
SFU	6.5 (98.9)	-16.0 (63.0)	-24.6 (58.0)
Glitazone	3.3 (89.0)	-16.4 (40.3)	-21.3 (57.9)
Gliptin	-6.9 (34.1)	-4.3 (20.9)	-16.7 (38.9)
Patients starting new drug by class (n[%])^c			
Metformin	3 (1.2)	3 (1.2)	1 (1.1)
SFU	10 (4.0)	9 (3.5)	3 (3.2)
Glitazone	9 (3.6)	3 (1.2)	1 (1.1)
Gliptin	13 (5.1)	10 (3.9)	3 (3.2)
Patients stopping drug by class (n[%])^c			
Metformin	0 (0.0)	10 (3.9)	2 (2.1)
SFU	8 (3.2)	21 (8.2)	13 (14.0)
Glitazone	4 (1.6)	8 (3.1)	8 (8.4)
Gliptin	3 (1.2)	1 (0.4)	2 (2.1)

Notes:
^a Total daily dose of all anti-hyperglycemic agents
^b For medications with missing dose, data are omitted
^c Refers to initiation of new drug between randomization and final study visit

Source: 2.7.3 Summary of clinical efficacy, Table 22

TABLE 6 Subject demographic and baseline characteristics in the randomized subjects in Study 010

	Lorcaserin 10mg bid n=256	Lorcaserin 10mg qd n=95	Placebo n=252
Number of randomized subjects			
Age (years)			
Mean \pm SD	53.2 \pm 8.3	53.1 \pm 8.0	52.0 \pm 9.3
Median	55.0	54.0	53.0
Range	30 to 65	26 to 65	21 to 65
Sex			
Female (n, %)	137 (53.5%)	53 (55.8%)	137 (54.4%)
Male (n, %)	119 (46.5%)	42 (44.2%)	115 (45.6%)
Race ¹			
Caucasian/White	150 (58.6%)	49 (51.6%)	166 (65.9%)
African American/ Black	55 (21.5%)	26 (27.4%)	45 (17.9%)
Hispanic/Latino	39 (15.2%)	17 (17.9%)	27 (10.7%)
Asian	11 (4.3%)	3 (3.2%)	8 (3.2%)
Native Hawaiian / Pacific Islander	0	0	0
American Indian / Alaska Native	0	0	0
Other	1 (0.4%)	0	6 (2.4%)
Diabetes Medication Used ¹			
Metformin but not SU (n, %)	127 (49.6%)	48 (50.5%)	126 (49.8%)
SU but not Metformin (n, %)	20 (7.8%)	7 (7.4%)	23 (9.1%)
SU and Metformin (n, %)	109 (42.6%)	40 (42.1%)	104 (41.1%)
Weight (kg)			
Mean \pm SD	103.7 \pm 17.0	106.0 \pm 19.4	102.6 \pm 18.1
Median	101.8	107.3	100.2
Range	63.3 to 150.6	69.1 to 156.9	53.0 to 158.6
BMI (kg/m ²)			
Mean \pm SD	36.2 \pm 4.5	36.1 \pm 4.8	35.9 \pm 4.5
Median	36.0	36.6	35.5
Range	27.0 to 44.9	28.2 to 45.0	27.2 to 45.0
HbA1c (%)			
Mean \pm SD	8.1 \pm 0.8	8.1 \pm 0.8	8.1 \pm 0.8
Median	7.8	7.9	7.9
Range	6.9 to 10.0	7.0 to 10.0	7.0 to 10.0
HbA1c \geq 9.0 (n, %)	47 (18.4%)	14 (14.7%)	45 (17.9%)
HbA1c < 9.0 (n, %)	209 (81.6%)	81 (85.3%)	207 (82.1%)
<i>Note:</i> ¹ The stratification variable combined the two categories of SU with and without metformin.			
<i>Source:</i> Study 010 clinical report, Table 7, and additional analysis by this reviewer			

3.2.3. Statistical methodologies

Analysis populations: The applicant used the following analysis populations in Study 010:

Modified Intent-to-Treat (MITT) Population: The MITT population consisted of all randomized subjects who had a baseline measurement, who received at least one dose of study medication, and who had a post-randomization measurement. Subject data was analyzed according to the treatment assigned at randomization, regardless of the treatment received during the course of the trial. Data collected after subjects discontinued from treatment was not included in the primary analysis. The last observation on or prior to discontinuation was carried forward (LOCF) and used in the analysis. At least 98% of randomized subjects were in the MITT populations (TABLE 8).

The LOCF imputation method has been used in previous Phase 3 studies of lorcaseerin, and is described in the Agency's 2007 draft weight management guidance (TABLE 7). However, the Office of Biostatistics is currently evaluating methods for dealing with endpoints from subjects who discontinue in the course of a study. In my opinion, extending the study results to the intended population is complicated by the large percentage of discontinuations and the relationship between weight loss and the tendency to drop out.

TABLE 7 Statistical considerations from the 2007 draft weight management guidance

The analysis of (percentage) weight change from baseline should use ANOVA or ANCOVA with baseline weight as a covariate in the model. The analysis should be applied to the last observation carried forward on treatment in the modified ITT population defined as subjects who received at least one dose of study drug and have at least one post-baseline assessment of body weight. Sensitivity analyses employing other imputation strategies should assess the effect of dropouts on the results. The imputation strategy should always be prespecified and should consider the expected dropout patterns and the time-course of weight changes in the treatment groups. No imputation strategy will work for all situations, particularly when the dropout rate is high, so a primary study objective should be to keep missing values to a minimum. Repeated measures analyses can be used to analyze longitudinal weight measurements but should estimate the treatment effect at the final time point. Statistical models should incorporate as factors any variables used to stratify the randomization. As important as assessing statistical significance is estimating the size of the treatment effect. If statistical significance is achieved on the co-primary endpoints, type 1 error should be controlled across all clinically relevant secondary efficacy endpoints intended for product labeling.

Part VI. C. Statistical Considerations, Analysis Methods

Intended W52 Population (IW52): The IW52 population included all randomized subjects who had a post-baseline body weight recorded within 2 weeks of the scheduled 52-week visit. This included subjects who withdrew from the study prior to week 52, and returned for a body weight measurement within 2 weeks of their scheduled week 52 visit.

Completers Population (CP): The completers population included all patients who completed the study.

TABLE 8 Analysis populations defined for Study 010

	Lorcaserin 10 mg BID	Lorcaserin 10 mg QD	Placebo
Number randomized	256	95	253
Safety population, n (%)	256 (100%)	95 (100%)	252 (99.8%)
Modified Intent-to-Treat population, n (%)	251 (98.0%)	94 (98.9%)	248 (98.0%)
Completers population, n (%)	169 (66.0%)	75 (78.9%)	157 (62.1%)
Intended Week 52 population, n (%)	175 (68.4%)	77 (81.1%)	165 (65.2%)

Source: Study 010 report, Table 5

Statistical analysis methods for the primary efficacy endpoint

Continuous endpoint: Change in weight was analyzed with analysis of covariance (ANCOVA) models with treatment, baseline body weight, baseline HbA1c measurement (≤ 9.0 , and > 9.0), and baseline medication stratum (Metformin only, or Sulfonylurea with or without metformin). Other continuous efficacy endpoints were analyzed using the above ANCOVA method described for body weight, substituting the relevant baseline measurement as the covariate. As a secondary analysis for the change from baseline in body weight and the percent change from baseline in body weight, a mixed model repeated measures analysis was conducted.

Categorical endpoints: The yes/no occurrence of 5% responders was analyzed with a logistic regression model with effects for treatment, gender and baseline body weight. The same approach was used to analyze the 10% responder endpoint.

Approach to multiplicity:

Control of Type I error among primary endpoints in the lorcaserin 10 mg bid vs placebo comparison: The applicant described an ordered gate-keeping sequence of comparisons for the three primary efficacy endpoints. The endpoints were evaluated in the following sequence for the lorcaserin 10 mg bid versus placebo comparison: 1) the proportion of 5% responders; 2) the change from baseline in body weight; and 3) the proportion of 10% responders. Each endpoint was evaluated at the two-tailed α of 0.05.

The lorcaserin 10 mg qd vs placebo comparisons: The comparisons of lorcaserin 10 mg qd were carried out conditionally, if: (1) the lorcaserin 10 mg bid versus placebo was statistically significant for a given endpoint, and if: (2) the lorcaserin 10 mg qd versus placebo comparisons of the endpoint(s) with higher testing priority were also statistically significant. The applicant commented that this procedure preserved the overall Type I error rate for testing the primary efficacy hypothesis.

However, I believe that the discontinuation of enrollment into the lorcaserin qd arm affects the approach to analyzing the qd arm. The implementation of Protocol Amendment 3 created two enrollment subgroups. In my opinion, the lorcaserin qd arm should be compared against the subgroup of the placebo arm that was also enrolled prior to Protocol Amendment 3. I also

believe that the assessment of the lorcaserin qd arm should be separated from the gate-keeping sequence, and viewed as exploratory. While the statistical comparisons within the enrollment subgroup are valid, I believe that the interpretation of their clinical significance is a review issue. This separation of the lorcaserin qd arm from the pre-specified gate-keeping sequence would not affect the evaluation of the lorcaserin bid arm, because none of the evaluations of the bid arm depend on results from the qd arm.

Control of Type I error in the analysis of secondary efficacy endpoints: The applicant grouped secondary endpoints into five families. Within each family, the endpoints were prioritized in the order shown in the lists below:

- Glycemic endpoints (HbA1c, fasting glucose, fasting insulin, HOMA-IR)
- Lipid endpoints (TG, HDL, LDL, Total Cholesterol)
- Blood pressure endpoints (systolic blood pressure, diastolic blood pressure)
- Body composition family (total body fat)
- Quality of life (total score)

The secondary hypotheses were tested at the 0.05 level, conditionally on the statistical significance of the 5% responder endpoint. Within each family grouping, the endpoints were tested at the 0.05 level in a gate-keeping sequence in the order shown.

3.2.4. Results and Conclusions

Continuous endpoint: After one year of treatment with lorcaserin 10 mg bid, subjects in Study 010 lost a statistically significant amount of weight. Expressed as a percent change from baseline, the placebo-adjusted average weight loss was 3.1%, with a 95% confidence interval of 2.2% to 3.9% (TABLE 9, result 2). I confirmed this result. Expressed as weight loss in kg, the placebo-adjusted average weight loss was -3.1 kg, with a 95% confidence interval of 2.2 to 3.9 kg (TABLE 9, result 1). These two expressions are very similar because the average baseline was close to 100 kg in each arm. Because of this similarity, I will use the “percent change from baseline” expression in further review comments about the continuous endpoint. This result was consistent across different versions of the analysis population and different methods of analysis (TABLE 9).

The results for the continuous endpoint supports the criterion for statistical significance as described in the Agency’s weight management guidance, but it does not provide statistical support for the criterion that the observed difference in mean weight loss between the active product and the placebo should be at least five percent. This is because the placebo-adjusted effect of lorcaserin 10 mg bid was statistically significantly less than 5% (TABLE 9, all results).

The placebo-adjusted effect of lorcaserin 10 mg bid was similar in the two enrollment subgroups subdivided by the implementation of Protocol Amendment 3 (TABLE 10). The adjusted effect of the two lorcaserin dose arms was also fairly similar (obtained in the pre-amendment subgroup; TABLE 10). The greater change from baseline in mean body weight and the greater retention in the study was a feature of all three arms in the pre-amendment subgroup compared to the two

arms in the post-amendment subgroup (TABLE 10). I did not find a source for this difference between subgroups in my analysis of demographic and baseline characteristics (see part 3.2.3 of this review).

Categorical endpoints: After one year of treatment with lorcaserin 10 mg bid, a statistically significantly greater percentage of subjects lost at least 5% of their baseline body weight, compared to placebo (TABLE 11, result 1). Expressed as a difference in percentages, the percentage of 5% weight loss responders was 27.3% greater (absolute) in the lorcaserin arm than in the placebo arm (TABLE 11). The results from the analysis of the MITT population are supported by the results of the analyses of the intended week 52 population and the completers population (TABLE 11, results 2 and 3). I conducted an additional sensitivity analysis that classified dropouts as non-responders. The results from this analysis were statistically significant, but the percentage of responders was lower than the estimate from the MITT/LOCF method (TABLE 11, result 4). The observed results from primary and other supportive analyses that used LOCF imputation supported the criteria for efficacy, as described in the Agency's weight management guidance:

- the proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group; and
- the difference between groups is statistically significant

The results for the 10% weight loss responders were also statistically significant (TABLE 11).

In my opinion, the 5% responder endpoint is a key endpoint in these studies because of the substantial percentage of early withdrawals. It may be reasonable to extend the study results to the intended target population in terms of the percentage of subjects who could be expected to lose at least 5% of their baseline body weight after 52 weeks of lorcaserin, with early withdrawals classified as non-responders. The placebo-adjusted effect of lorcaserin can be expressed as the odds of being classified as a 5% responder with lorcaserin compared to placebo, along with the 95% confidence interval.

Longitudinal profile of weight results: The applicant has provided a longitudinal profile of weight results, for both the continuous and the categorical responses (FIGURE 11). These results are from the MITT/LOCF analysis population. These profiles suggest that weight loss takes place up to about week 28, at which point the percentage of weight loss responders stays fairly constant and then declines somewhat in the final months leading up to week 52. However, because of the large percentage of dropouts and the relationship between dropping out and being unsuccessful in weight loss, the choice of analysis population to depict longitudinally is not straightforward. The completers population and the MITT/LOCF population may each present an overly optimistic profile relative to the intended target population (FIGURE 12). The 5% responders in the MITT population, with dropouts imputed as non-responders, may be more representative of the target population. This profile has the lowest percentage of responders by month compared to the completers and the MITT/LOCF populations (FIGURE 12). The longitudinal profile of 5% responders in the MITT population with non-responder imputation is also depicted separately in FIGURE 13. The apparent decline in the percentage of weight loss

responders in the final months leading up to week 52 is most apparent in the longitudinal profiles that do not use the LOCF imputation.

Key secondary efficacy endpoints: In general, the results from the secondary efficacy endpoints supported the efficacy of the lorcaserin 10 mg bid arm compared to the placebo arm. I did not review the lorcaserin 10 mg qd arm for the key secondary endpoints except to note that the results were also generally supportive. With respect to the pre-specified sequence of testing within each group of endpoints, the results are as follows:

- A. *Glycemic endpoints:* The first and second endpoints in the sequence for this group, HbA1c and fasting plasma glucose, both had statistically significant comparisons between lorcaserin and placebo (TABLE 13). The third endpoint, fasting insulin, was not significantly different. Based on the pre-specified analysis plan, the results for the fourth endpoint, HOMA-IR were not considered.
- B. *Lipids:* The first endpoint in the sequence for this group, triglycerides, did not have a statistically significant comparison between lorcaserin and placebo (TABLE 13). For this reason, the remaining endpoints, HDL-C, LDL-C and total cholesterol were not considered.
- C. *Blood pressure:* Neither endpoint in this group had a statistically significant comparison between lorcaserin and placebo (TABLE 13).
- D. *Body composition:* Total body fat, the only endpoint in this group, had a statistically significant difference between lorcaserin and placebo in the direction of a superior decrease of total body fat in the lorcaserin arm (TABLE 13).
- E. *Quality of life:* The overall score for quality of life, the only endpoint in this group, did not have a statistically significant difference between lorcaserin and placebo (TABLE 13).

TABLE 9 Study 010; Weight as a change from baseline at week 52 (kg and %); results from primary and supportive analyses

Study 010 Treatment groups	N	Baseline mean (kg) (SD)	Adjusted mean % change from baseline at Week 52 ± SE ¹	Difference in adjusted mean % change, Lorcaserin - placebo (95% CI)	P-value vs. placebo
1. Change from baseline (kg); MITT/LOCF, primary ANCOVA model					
Lorcaserin 10 mg bid	251	103.5 kg (17.2)	-4.7 kg ± 0.4	-3.1 kg (-4.0, -2.2)	<0.0001
Placebo	248	102.3 kg (18.0)	-1.6 kg ± 0.4		
2. Percent change from baseline (%); MITT/LOCF, primary ANCOVA model					
Lorcaserin 10 mg bid	251	103.5 kg (17.2)	-4.5% ± 0.4	-3.1% (-3.9, -2.2)	<0.0001
Placebo	248	102.3 kg (18.0)	-1.5% ± 0.4		
3. Percent change from baseline (%); IW52 population, primary ANCOVA model					
Lorcaserin 10 mg bid	175	104.4 (18.1)	-5.3 ± 0.5	-3.4 (-4.5, -2.3)	<0.0001
Placebo	165	101.4 (18.2)	-1.8 ± 0.5		
4. Percent change from baseline (%); Completers population, primary ANCOVA model					
Lorcaserin 10 mg bid	169	104.7 (17.9)	-5.5 ± 0.5	-3.7 (-4.9, -2.5)	<0.0001
Placebo	157	101.7 (18.3)	-1.7 ± 0.5		
5. Percent change from baseline (%); MITT with no imputation, Mixed Model Repeated Measures					
Lorcaserin 10 mg bid	251	103.5 kg (17.2)	-5.2 ± 0.4	-3.4 (-4.4, -2.3)	<0.0001
Placebo	248	102.3 kg (18.0)	-1.8 ± 0.4		
<i>Sources:</i> From the Study 010 clinical report:					
1. Table 9					
2. Table 10					
3. Table 14.2.3.2					
4. Table 14.2.3.1					
5. Analysis by this reviewer. The mixed model repeated measures analysis model was implemented in Proc Mixed (SAS Version 9.2), with an unstructured covariance structure.					

TABLE 10 Study 010; Weight as a percent change from baseline at week 52; results from before and after Protocol Amendment 3 (which discontinued the qd arm)

Study 010 Treatment groups	N	Baseline mean (kg) (SD)	Adjusted mean % change from baseline at Week 52 ± SE ¹	Difference in adjusted mean % change, Lorcaserin - placebo (95% CI)	P-value vs. placebo
Weight as percent change from baseline (%); MITT/LOCF, primary ANCOVA model¹					
1. Entire data base (across the entire recruitment period)					
Lorcaserin 10 mg bid	251	103.5 kg (17.2)	-4.50% ± 0.35	-3.05% (-3.90, -2.20)	<0.0001
Placebo	248	102.3 kg (18.0)	-1.45% ± 0.36		
2. Subgroup enrolled prior to Protocol Amendment 3					
Lorcaserin 10 mg bid	93	103.8 (15.8)	-5.44% ± 0.50	-3.20% (-4.59, -1.82)	<0.0001
Lorcaserin 10 mg qd ²	94	106.5 (19.5)	-5.31% ± 0.50	-3.07% (-4.46, -1.69)	<0.0001
Placebo	94	102.8 (17.8)	-2.24% ± 0.50		
3. Subgroup enrolled after Protocol Amendment 3					
Lorcaserin 10 mg bid	158	102.7 (17.7)	-4.47% ± 0.39	-2.98% (-4.08, -1.88)	<0.0001
Placebo	154	101.1 (18.0)	-1.49% ± 0.40		
<i>Notes:</i>					
¹ All analyses conducted with the MITT/LOCF analysis population, using the primary ANCOVA model, conducted by this reviewer.					
² The comparison of the lorcaserin 10 mg bid vs lorcaserin 10 mg qd arms has a p-value of 0.9275 (in the subgroup enrolled prior to Protocol Amendment 3)					

TABLE 11 Study 010; 5% and 10% weight loss responders; results from primary and supportive analyses for the lorcaserin 10 mg bid arm vs. placebo

Treatment groups	N	Number of responders (%)	Difference in proportions ¹ (95% CI)	Odds ratio ² (95% CI)	p-value ² vs. placebo
% of subjects achieving ≥ 5% weight loss at week 52					
1. Primary analysis: MITT; LOCF					
Lorcaserin 10 mg bid	251	94 (37.5%)	27.3 (13.8, 28.9)	3.1 (2.1, 4.8)	<0.0001
Placebo	248	40 (16.1%)			
2. Supportive analysis: I_W52 analysis population					
Lorcaserin 10 mg bid	175	75 (42.9%)	23.5 (14.0, 33.0)	3.3 (2.0, 5.4)	< 0.0001
Placebo	165	32 (19.4%)			
3. Supportive analysis: Completers					
Lorcaserin 10 mg bid	168	75 (44.6%)	26.7 (17.1, 36.3)	3.9 (2.3, 6.5)	< 0.0001
Placebo	156	28 (17.9%)			
4. Supportive analysis: MITT with non-responder imputation for subjects who did not complete 52 weeks of study medication					
Lorcaserin 10 mg bid	259	75 (29.0%)	18.2 (11.4, 24.9)	3.4 (2.1, 5.4)	<0.0001
Placebo	259	28 (10.8%)			
% of subjects achieving ≥ 10% weight loss at week 52					
5. Primary analysis: MITT1; LOCF					
Lorcaserin 10 mg bid	251	41 (16.3%)	11.9 (6.7, 17.1)	4.1 (2.1, 8.1)	< 0.0001
Placebo	248	11 (4.4%)			
6. Supportive analysis: I_W52 analysis population					
Lorcaserin 10 mg bid	175	35 (20.0%)	13.3 (6.3, 20.4)	3.6 (1.8, 7.3)	0.0004
Placebo	165	11 (6.7%)			
7. Supportive analysis: Completers					
Lorcaserin 10 mg bid	168	35 (20.8%)	15.1 (7.9, 22.2)	4.3 (2.0, 9.2)	0.0002
Placebo	156	9 (5.8%)			
<i>Notes:</i>					
¹ The difference in proportions and 95% CI were calculated using normal approximation.					
² The odds ratios and p-values were calculated by using the logistic regression model specified for the primary analysis, with effects for treatment, gender and baseline body weight.					
<i>Sources:</i>					
Study 010 clinical report, 1. Table 8	2. Table 14.2.2 3. Table 14.2.1	4. Analysis by this reviewer 5. Table 11	6. Table 14.2.6 7. Table 14.2.5		

TABLE 12 Study 010; 5% weight loss responders; subdivided by the implementation of Protocol Amendment 3

Treatment groups	N	Number of responders (%)	Difference in proportions ¹ (95% CI)	Odds ratio ² (95% CI)	p-value ² vs. placebo
% of subjects achieving ≥ 5% weight loss at week 52 (MITT/LOCF)					
1. Entire data base (across the entire recruitment period)					
Lorcaserin 10 mg bid	251	94 (37.5%)	27.3 (13.8, 28.9)	3.1 (2.1, 4.8)	<0.0001
Placebo	248	40 (16.1%)			
2. Subgroup enrolled prior to Protocol Amendment 3					
Lorcaserin 10 mg bid	93	41 (44.1%)	22.8 (9.5, 35.5)	3.0 (1.6, 5.7)	0.0009
Lorcaserin 10 mg qd ³	94	42 (44.7%)	23.4 (10.1, 36.0)	3.1 (1.6, 6.0)	0.0006
Placebo	94	20 (21.3%)			
3. Subgroup enrolled after Protocol Amendment 3					
Lorcaserin 10 mg bid	158	53 (33.5%)	20.6 (11.4, 29.6)	3.4 (1.9, 6.1)	<0.0001
Placebo	154	20 (13.0%)			
<i>Notes:</i>					
¹ The difference in proportions and 95% CI were calculated using normal approximation.					
² The odds ratios and p-values were calculated by using the logistic regression model specified for the primary analysis, with effects for treatment, gender and baseline body weight.					
³ The comparison of the lorcaserin 10 mg bid vs lorcaserin 10 mg qd arms has a p-value of 0.8758 (in the subgroup enrolled prior to Protocol Amendment 3)					
<i>Sources:</i> Study 10 clinical report, Table 8, and additional analysis by this reviewer					

Figure 11 Primary weight endpoints over time by treatment group: MITT/LOCF analysis population

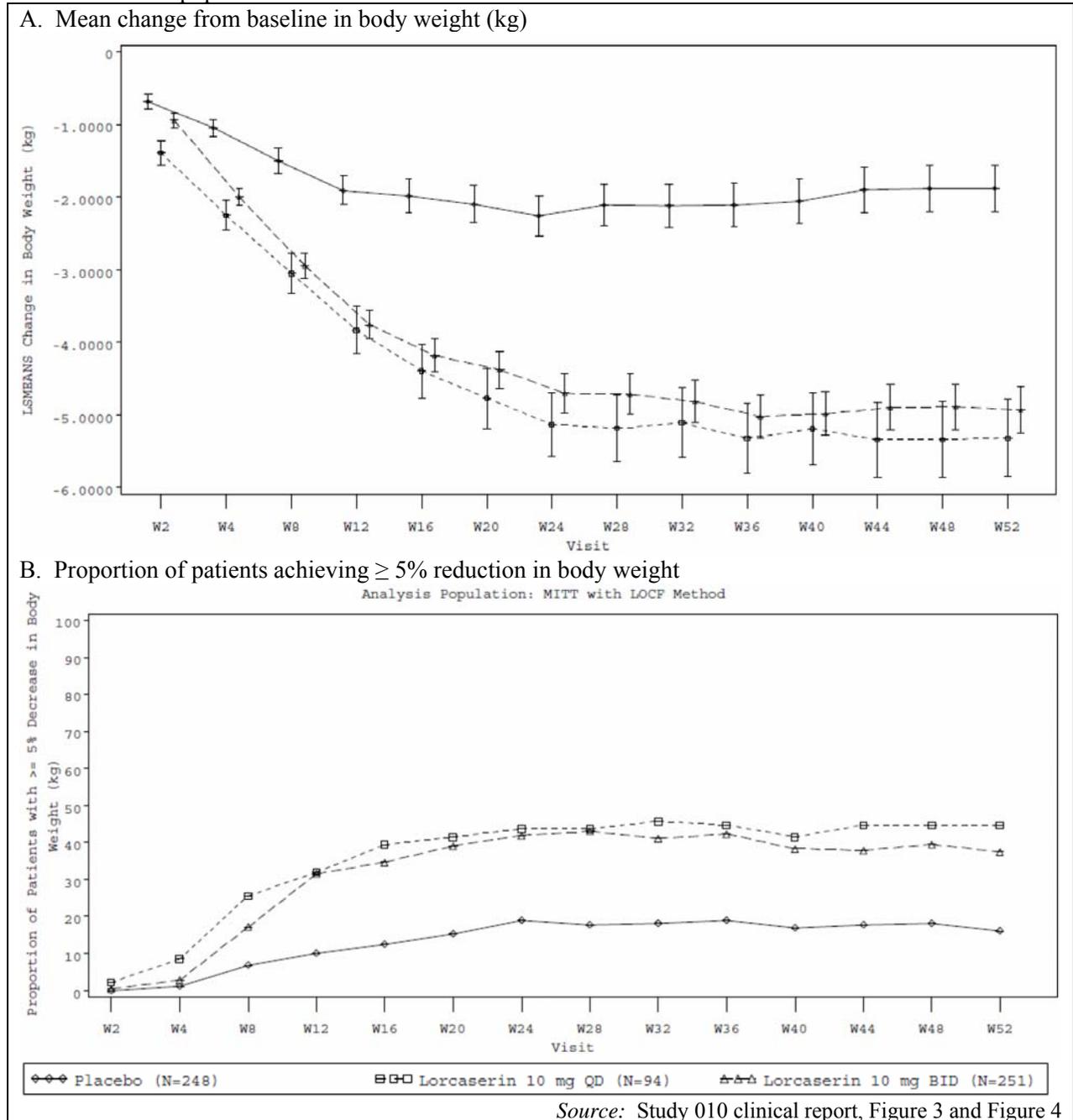


FIGURE 12 Study 010; Percentage of 5% responders by visit week; (1) Completers; (2) MITT with LOCF imputation; and (3) MITT with non-responder imputation

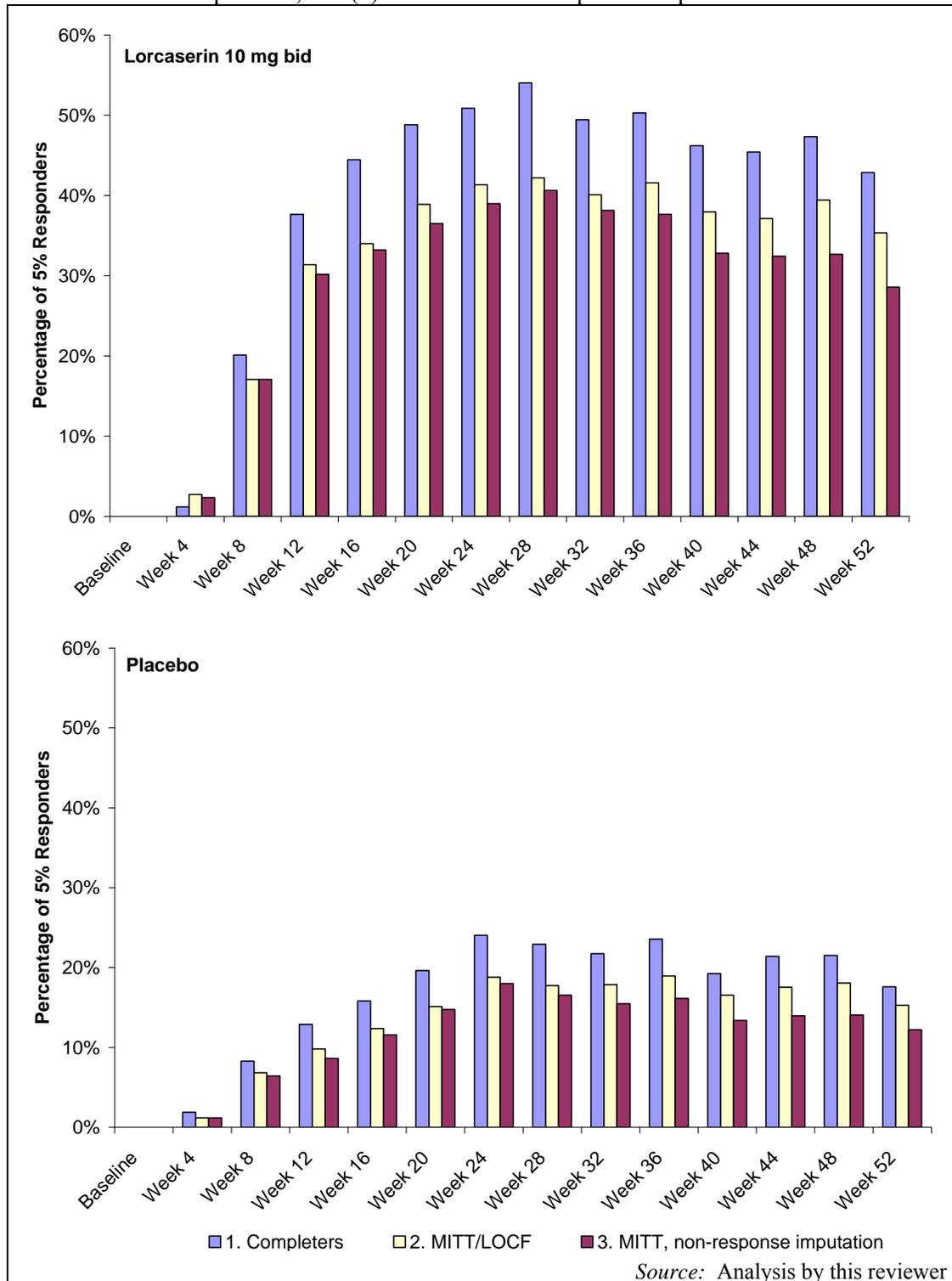
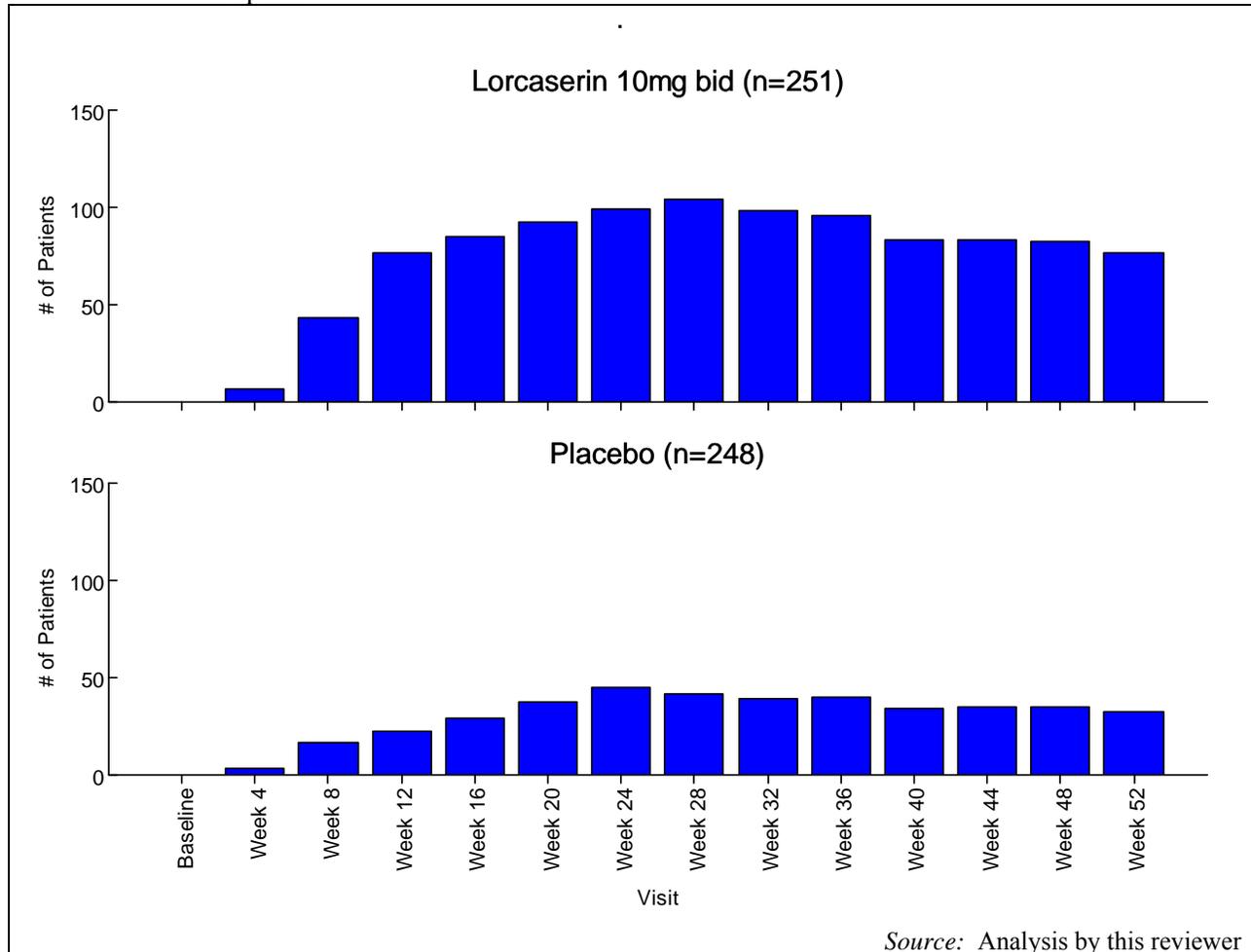


FIGURE 13 Study 010; 5% responders by study visit, MITT with non-responder imputation for dropouts



Source: Analysis by this reviewer

TABLE 13 Study 010; key secondary efficacy endpoints; results from the analysis of pre-specified groups of endpoints with a sequence of testing within each group

Study 010 Treatment groups	N	Baseline mean (SD)	Adjusted mean change from baseline at Week 52 ± SE ¹	Difference in adjusted mean change, Lorcaserin - placebo (95% CI)	P-value vs. placebo
A. Glycemic endpoints ^{1,2}					
1. HbA1c (%)					
Lorcaserin 10 mg bid	251	8.1 (0.9)	-0.9 ± 0.1	-0.5 (-0.7, -0.3)	<0.0001
Placebo	248	8.0 (0.9)	-0.4 ± 0.1		
2. Fasting Plasma Glucose (mg/dL)					
Lorcaserin 10 mg bid	251	163.3 (48.3)	-27.4 ± 2.5	-15.5 (-21.5, -9.5)	<0.0001
Placebo	248	160.0 (41.6)	-11.9 ± 2.5		
3. Fasting Insulin (uIU/mL)					
Lorcaserin 10 mg bid	251	15.0 (10.0)	-3.0 ± 0.7	-1.4 (-3.1, 0.4)	0.1203
Placebo	248	16.2 (14.7)	-1.6 ± 0.7		
4. HOMA-IR					
Lorcaserin 10 mg bid	251	2.3 (1.4)	-0.5 ± 0.1	-0.3 (-0.6, -0.1)	0.0216
Placebo	248	2.3 (1.4)	-0.2 ± 0.1		
<i>Notes:</i>					
¹ All endpoints in Group A were expressed as a change from baseline at week 52, and analyzed with the primary ANCOVA model, with the baseline level of the dependent variable included as a covariate.				<i>Sources:</i> From the Study 010 clinical report:	
² Endpoints are listed in the pre-specified order for testing within this group.				1. Table 17	
				2. Table 18	
				3. Table 19	
				4. Table 20	
B. Lipid endpoints ^{3,4}					
1. Triglycerides (mg/dL)					
Lorcaserin 10 mg bid	251	172.1 (103.6)	-10.7% ± 2.2	-5.9% (-11.9, 0.1)	0.0541
Placebo	248	163.5 (87.5)	-3.9% ± 2.2		
2. HDL-C (mg/dL)					
Lorcaserin 10 mg bid	251	45.3 (11.0)	5.2% ± 1.0	3.6% (1.1, 6.2)	0.0047
Placebo	248	45.7 (12.7)	1.6% ± 1.0		
3. LDL-C (mg/dL)					
Lorcaserin 10 mg bid	251	95.0 (30.4)	4.2% ± 2.5	-0.8% (-7.1, 5.5)	0.8015
Placebo	248	94.6 (30.2)	5.0% ± 2.6		
4. Total Cholesterol (mg/dL)					
Lorcaserin 10 mg bid	251	173.5 (35.3)	-0.7% ± 1.1	-0.5% (-3.3, 2.3)	0.7136
Placebo	248	172.0 (35.7)	-0.1% ± 1.2		
³ All endpoints in Group B were expressed as a percent change from baseline at week 52, and analyzed with the primary ANCOVA model, with the baseline level of the dependent variable included as a covariate.				<i>Sources:</i> From the Study 010 clinical report:	
⁴ Endpoints are listed in the pre-specified order for testing within this group.				1. Table 23	
				2. Table 24	
				3. Table 25	

Study 010 Treatment groups	N	Baseline mean (SD)	Adjusted mean change from baseline at Week 52 \pm SE ¹	Difference in adjusted mean change, Lorcaserin - placebo (95% CI)	P-value vs. placebo
4. Table 26					
C. Blood Pressure Endpoints ⁵					
1. Systolic Blood Pressure (mmHg)					
Lorcaserin 10 mg bid	251	126.6 (12.7)	-0.8 \pm 0.8	0.1 (-1.9, 2.2)	0.8905
Placebo	248	126.5 (13.5)	-0.9 \pm 0.9		
2. Diastolic Blood Pressure (mmHg)					
Lorcaserin 10 mg bid	251	77.9 (8.0)	-1.1 \pm 0.6	-0.4 (-1.8, 1.0)	0.5633
Placebo	248	78.7 (7.9)	-0.7 \pm 0.6		
⁵ Both endpoints in Group C were expressed as a change from baseline at week 52, and analyzed with the primary ANCOVA model, with the baseline level of the dependent variable included as a covariate.				<i>Sources:</i> From the Study 010 clinical report: 1. Table 30 2. Table 31	
D. Body Composition ⁶					
1. Total Body Fat (%)					
Lorcaserin 10 mg bid	251	43.1 (8.1)	-1.7 \pm 0.6	-1.8 (-3.1, -0.4)	0.0116
Placebo	248	43.2 (6.5)	0.0 \pm 0.5		
⁶ The endpoint in Group D was expressed as a change from baseline at week 52, and analyzed with the primary ANCOVA model, with the baseline level of total body fat included as a covariate.				<i>Source:</i> From the Study 010 clinical report, Table 32	
E. Quality of life ^{7,8}					
1. Overall converted score					
Lorcaserin 10 mg bid	251	74.7 (16.2)	11.3 \pm 0.7	1.1 (-0.7, 2.8)	0.2206
Placebo	248	74.0 (17.6)	10.2 \pm 0.7		
⁷ The endpoint in Group E was expressed as a change from baseline at week 52, and analyzed with the primary ANCOVA model, with the baseline level of the overall score included as a covariate.				<i>Source:</i> From the Study 010 clinical report, Table 36	
⁸ A change in the overall converted score in the positive direction represents an improvement in the overall quality of life.					

3.2.5. Comparisons across Study 009, Study 011, and Study 010

The original NDA 022529 submission for lorcaserin included the results from two large Phase 3 studies, APD356-009 (Bloom) and APD356-011 (Blossom)⁴. Both studies enrolled adults between ages 18 and 65 years who were either obese (BMI ≥ 30 kg/m²), or overweight with at least one weight related co-morbid condition (BMI 27-30 kg/m²). Diabetes was an exclusion from both of these studies. In Study 009, 3182 subjects were randomized in a 1:1 ratio to lorcaserin 10 mg bid: placebo. In Study 011, 4008 subjects were randomized in a ratio of 2:1:2 to lorcaserin 10 mg bid: lorcaserin 10 mg qd: placebo. In both studies, the primary efficacy endpoint was evaluated after 52 weeks. Study 009 was continued for a second year, with a re-randomization of lorcaserin subjects to either continue with lorcaserin or to switch to placebo in a 2:1 ratio. Subjects who had been randomized to placebo in the first year were continued on placebo.

Demographic and baseline characteristics: On average, the diabetic subjects in Study 010 were about 10 years older than the subjects in Study 009 and Study 011 (TABLE 14). Study 010 enrolled approximately equal numbers of men and women, while approximately 80% of the subjects in Study 009 and Study 011 were women. These differences in age and gender distribution are likely to reflect the clinical characteristics of subjects with type 2 diabetes. The distribution of subjects across racial and ethnic subgroups was similar in all three studies (TABLE 14). The average baseline body weight was somewhat greater in Study 010 compared to the other two studies, although the average BMI was fairly similar across the three studies (TABLE 14).

Disposition: The percentage of subjects who completed the 52 weeks of Study 010 was greater, 66.4% over all three arms, than in the 52 weeks of Study 009 (50.2%) or Study 011 (55.5%; TABLE 15). The difference in completion rate between the diabetic study and the two non-diabetic studies appears to be mainly in terms of the “withdrawal of consent” and “lost to follow-up” categories. In my opinion, this difference is consistent with a higher level of motivation among the diabetic subjects compared to the non-diabetic subjects. However, I note that there was no specific assessment of motivation to confirm this interpretation. The percentage of subjects who withdrew from the study because of adverse events was fairly similar across the three studies (TABLE 15).

Weight change from baseline at week 52: All three studies had fairly similar estimates of the placebo-adjusted effect of lorcaserin 10 mg bid at 52 weeks. For average weight change, the adjusted effect was -3.1% of baseline in Study 010, -3.0% in Study 011 and -3.7% in Study 009 (TABLE 16). For the percentage of 5% weight loss responders, the adjusted difference in percentage from the placebo arm was 27.3% in Study 010, 22.2% in Study 011 and 27.2 in Study 009 (TABLE 17). In the diabetic study 010, the effect of lorcaserin 10 mg bid was fairly similar to the effect

⁴ See the statistical review for NDA 022529/0 (NDA submitted on 12/22/2009)

of lorcaserin 10 mg qd (TABLE 16, TABLE 17). In contrast, the results from the two dose arms in Study 011 were consistent with a dose-response relationship. I note that none of the studies was powered for a statistical comparison between lorcaserin dose arms.

TABLE 14 Subject demographic and baseline characteristics in the randomized subjects in Study 009, Study 011 and Study 010

Number of randomized subjects (n)	Study 009 "Bloom"		Study 011 "Blossom"			Study 010 "Bloom-DM"		
	Lorcaserin 10mg bid n=1595	Placebo n=1587	Lorcaserin 10mg qd n=802	Lorcaserin 10mg bid n=1603	Placebo n=1603	Lorcaserin 10mg bid n=256	Lorcaserin 10mg qd n=95	Placebo n=252
Age (years)								
Mean ± SD	43.7 ± 11.3	44.4 ± 11.1	43.7 ± 11.7	43.8 ± 11.8	43.7 ± 11.8	53.2 ± 8.3	53.1 ± 8.0	52.0 ± 9.3
Median	44.0	45.0	44.0	44.0	44.0	55.0	54.0	53.0
Range	18 to 66	18 to 66	18 to 65	18 to 65	18 to 65	30 to 65	26 to 65	21 to 65
Sex								
Female (n, %)	1323 (82.9%)	1334 (84.1%)	657 (81.9%)	1290 (80.4%)	1251 (78.0%)	137 (53.5%)	53 (55.8%)	137 (54.4%)
Male (n, %)	272 (17.1%)	253 (15.9%)	145 (18.1%)	313 (19.5%)	352 (22.0%)	119 (46.5%)	42 (44.2%)	115 (45.6%)
Race ¹								
Caucasian/White	1081 (67.8%)	1048 (66.0%)	539 (67.2%)	1081 (67.4%)	1066 (66.5%)	150 (58.6%)	49 (51.6%)	166 (65.9%)
African American/ Black	300 (18.8%)	299 (18.8%)	160 (20.0%)	306 (19.1%)	319 (19.9%)	55 (21.5%)	26 (27.4%)	45 (17.9%)
Hispanic/Latino	181 (11.3%)	213 (13.5%)	86 (10.7%)	174 (10.9%)	181 (11.3%)	39 (15.2%)	17 (17.9%)	27 (10.7%)
Asian	12 (0.8%)	9 (0.6%)	3 (0.4%)	12 (0.7%)	10 (0.6%)	11 (4.3%)	3 (3.2%)	8 (3.2%)
Native Hawaiian / Pacific Islander	1 (0.0%)	1 (0.0%)	4 (0.5%)	10 (0.6%)	6 (0.4%)	0	0	0
American Indian / Alaska Native	11 (0.7%)	4 (0.3%)	7 (0.9%)	7 (0.4%)	10 (0.6%)	0	0	0
Other	9 (0.6%)	11 (0.7%)	3 (0.4%)	13 (0.8%)	11 (0.7%)	1 (0.4%)	0	6 (2.4%)
Weight (kg)								
Mean ± SD	100.4 ± 15.7	99.7 ± 15.6	100.1 ± 16.7	100.5 ± 15.6	100.8 ± 16.2	103.7 ± 17.0	106.0 ± 19.4	102.6 ± 18.1
Median	99.0	98.3	97.5	99.1	99.0	101.8	107.3	100.2
Range	62.6 to 156.9	62.7 to 156.0	64.9 to 185.4	64.1 to 159.3	63.9 to 165.9	63.3 to 150.6	69.1 to 156.9	53.0 to 158.6
BMI (kg/m ²)								
Mean ± SD	36.2 ± 4.3	36.1 ± 4.3	35.9 ± 4.3	36.1 ± 4.3	36.0 ± 4.2	36.2 ± 4.5	36.1 ± 4.8	35.9 ± 4.5
Median	35.8	35.7	35.2	35.6	35.5	36.0	36.6	35.5
Range	26.8 to 46.2	26.7 to 46.5	26.4 to 46.8	26.7 to 52.5	27.1 to 46.6	27.0 to 44.9	28.2 to 45.0	27.2 to 45.0

Sources: Studies 009 and 011: Analysis by this reviewer. Study 010: Clinical report, Table 7, and additional analysis by this reviewer

TABLE 15 Disposition of subjects in Study 009, Study 011 and Study 010 at week 52

	Study 009 "Bloom"		Study 011 "Blossom"			Study 010 "Bloom-DM"		
	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Lorcaserin 10 mg QD	Placebo	Lorcaserin 10 mg BID	Lorcaserin 10 mg QD	Placebo
Number randomized	1595	1587	1603	802	1603	256	95	253
No. (%) who completed	883 (55.4)	715 (45.1)	917 (57.2)	473 (59.0)	834 (52.0)	169 (66.0)	75 (78.9)	157 (62.1)
No. (%) who withdrew prior to week 52	712 (44.6)	872 (54.9)	686 (42.8)	329 (41.0)	769 (48.0)	87 (34.0)	20 (21.1)	96 (37.9)
Reason for withdrawal:								
Withdrawal of consent	307 (19.2)	439 (27.7)	293 (18.3)	162 (20.2)	376 (23.5)	32 (12.5)	8 (8.4)	50 (19.8)
Lost to follow-up	191 (12.0)	226 (14.2)	198 (12.4)	83 (10.3)	234 (14.6)	20 (7.8)	3 (5.5)	14 (5.5)
Adverse event	113 (7.1)	106 (6.7)	115 (7.2)	50 (6.2)	74 (4.6)	22 (8.6)	6 (4.3)	11 (4.3)
Combined other reasons ¹	101 (6.3)	100 (6.3)	80 (5.0)	34 (4.2)	85 (5.3)	13 (5.1)	3 (5.5)	21 (8.3)

Note:

¹ For "combined other reasons," the following discontinuation categories were combined: Protocol Deviation/ noncompliance, Sponsor decision, PI decision and Other discontinuation reason."

Sources: For Study 009 and 011: Integrated summary of efficacy, Table 4, and additional analysis by this reviewer. For Study 010: clinical study report, Table 5

TABLE 16 Weight as a percent change from baseline at week 52 in Study 009, Study 011 and Study 010

Study Treatment arms	N	Baseline mean (kg) ± SE	Adjusted mean % change from baseline at Week 52 ± SE ¹	Difference in adjusted mean % change, Lorcaserin - placebo (95% CI)	P-value vs. placebo
Weight as percent change from baseline (%); MITT/LOCF, primary ANCOVA model¹					
1. Study 009 “Bloom”					
Lorcaserin 10 mg bid	1538	100.4 ± 0.4	-5.9 ± 0.2	-3.7 (-4.1, -3.3)	<0.0001
Placebo	1499	99.7 ± 0.4	-2.2 ± 0.1		
2. Study 011 “Blossom”					
Lorcaserin 10 mg bid	1561	100.3 ± 0.4	-5.8 ± 0.2	-3.0 (-3.4, -2.6)	<0.0001
Lorcaserin 10 mg qd	771	100.1 ± 0.6	-4.7 ± 0.2	-1.9 (-2.5, -1.4)	<0.0001
Placebo	1541	100.8 ± 0.4	-2.8 ± 0.2		
3. Study 010 “Bloom-DM”					
Lorcaserin 10 mg bid	251	103.5 ± 1.1	-4.7 ± 0.4	-3.1 (-4.0, -2.2)	<0.0001
Lorcaserin 10 mg qd	94	106.5 ± 2.0	-5.3 ± 0.5	-3.1 (-4.5, -1.7)	<0.0001
Placebo for bid comparison ²	248	102.3 ± 1.1	-1.6 ± 0.4		
Placebo for qd comparison ²	94	102.8 ± 1.8	-2.2 ± 0.2		
<i>Notes:</i>					
¹ All analyses conducted with the MITT/LOCF analysis population, using the primary ANCOVA model, conducted by this reviewer.					
² In Study 010, the lorcaserin bid arm was compared against the entire placebo arm. The lorcaserin qd arm was compared against the contemporaneously enrolled subgroup of the placebo arm that was enrolled prior to Protocol Amendment 3.					
<i>Sources:</i>					
1. Study 090 report, Table 11					
2. Study 011 report, Table 11					
3. Study 010 report, Table 10 for the bid comparison, and analysis by this reviewer for the qd comparison					

TABLE 17 5% weight loss responders at Week 52 in Study 009, Study 011 and Study 010

Study Treatment arms	N	Number of responders (%)	Difference in proportions ¹ (95% CI)	Odds ratio ² (95% CI)	p-value ² vs. placebo
% of subjects achieving ≥ 5% weight loss at week 52 (MITT/LOCF)					
1. Study 009 “Bloom”					
Lorcaserin 10 mg bid	1538	731 (47.5%)	27.2 (24.0, 30.5)	3.6 (3.1, 4.2)	<0.0001
Placebo	1499	304 (20.3%)			
2. Study 011 “Blossom”					
Lorcaserin 10 mg bid	1561	737 (47.2%)	22.2 (18.9, 25.5)	2.7 (2.3, 3.1)	<0.0001
Lorcaserin 10 mg qd	771	310 (40.2%)	15.2 (11.1, 19.3)	2.0 (1.7, 2.4)	<0.0001
Placebo	1541	385 (25.0%)			
3. Study 010 “Bloom-DM”					
Lorcaserin 10 mg bid	251	94 (37.5%)	27.3 (13.8, 28.9)	3.1 (2.1, 4.8)	<0.0001
Lorcaserin 10 mg qd	94	42 (44.7%)	23.4 (10.1, 36.0)	3.1 (1.6, 6.0)	0.0006
Placebo for the bid comparison ³	248	40 (16.1%)			
Placebo for the qd comparison ³	94	20 (21.3%)			
<i>Notes:</i>					
¹ The difference in proportions and 95% CI were calculated using normal approximation.					
² The odds ratios and p-values were calculated by using the logistic regression model specified for the primary analysis, with effects for treatment, gender and baseline body weight.					
³ In Study 010, the lorcaserin bid arm was compared against the entire placebo arm. The lorcaserin qd arm was compared against the contemporaneously enrolled subgroup of the placebo arm that was enrolled prior to Protocol Amendment 3.					
<i>Sources:</i>					
1. Study 009 clinical report, Table 10					
2. Study 011 clinical report, Table 9					
3. Study 010 clinical report, Table 8 for the lorcaserin bid comparison, and additional analysis by this reviewer for the lorcaserin qd comparison					

3.3 Evaluation of Safety

An evaluation of the safety of lorcaserin is included in the clinical review by Dr. Julie Golden, M.D., and in the statistical review of specific safety issues by Dr. Xiao Ding, Ph.D.

4. Findings in Special/Subgroup Populations

4.1 Sex, Race, Age and Geographic Region

Sex: Males and females were fairly similar in the mean placebo-adjusted effect of lorcaserin, for both the 10 mg qd dose and the 10 mg bid dose (FIGURE 14).

Race: The placebo-adjusted effect of lorcaserin in the two minority subgroups African American / Black and Hispanic / Latino was fairly similar to the majority subgroup Caucasian / White, for both the 10 mg qd dose and the 10 mg bid dose (FIGURE 15).

Age: The enrollment criteria in both studies excluded subjects who were over 65 years old, and so the comparative effect of lorcaserin in this older age group could not be evaluated in these studies.

Geographic Region: Study 010 was conducted entirely within the U.S. For this reason, I did not evaluate the effect of geographic region further.

4.2 Other Special/Subgroup Populations

Additional subgroup analysis for the continuous weight endpoint:

Baseline BMI: Baseline BMI did not appear to affect the placebo-adjusted effect of the lorcaserin 10 mg bid dose on weight, expressed as a percent change from baseline at week 52 (FIGURE 16A). However, the lorcaserin qd dose did not appear to be as effective in subjects with baseline BMI over 40 kg/m² as it was in subjects with lower baseline BMI (FIGURE 16B; p=0.0271 for the BMI subgroup by treatment interaction in the lorcaserin 10 mg qd by placebo arm comparison).

Diabetes medication: Subjects with metformin but no sulfonylureas (SFU) as diabetes medication had more weight loss on average with the lorcaserin 10 mg bid dose than subjects with SFUs (FIGURE 17A; p=0.0430 for the diabetes medication subgroup by treatment interaction in the lorcaserin 10 mg bid by placebo arm comparison). However, diabetes medication did not appear to affect the effect of lorcaserin 10 mg qd arm (FIGURE 17B).

Baseline HbA1c: Baseline HbA1c, when expressed in terms of the stratification variable, with a cutpoint at 9.0, did not appear to affect the placebo-adjusted effect of lorcaserin in either dose arm (FIGURE 18). However, the percentage of subjects with a baseline HbA1c \geq 9.0 was fairly small (18%). As an additional exploratory analysis, I evaluated the effect of baseline HbA1c,

using 8.0 as the cutpoint, for the comparison between lorcaserin 10 mg bid and placebo. The cutpoint of 8.0 subdivides the subjects into fairly equally-sized subgroups. Subjects with baseline HbA1c < 8.0 had a greater placebo-adjusted mean weight loss with lorcaserin 10 mg bid than subjects with baseline HbA1c \geq 8.0 (treatment arm by baseline HbA1c subgroup interaction $p = 0.0209$; FIGURE 19).

Subgroup analysis for the HbA1c change from baseline at week 52:

Subjects with baseline HbA1c \geq 8.0 had a greater placebo-adjusted mean decrease in HbA1c at week 52, compared to subjects with baseline HbA1c < 8.0 (treatment arm by baseline HbA1c subgroup interaction $p=0.0603$, FIGURE 20). This relationship between baseline HbA1c and change from baseline in HbA1c at study endpoint has also been identified in several anti-diabetic drugs.

FIGURE 14 Study 010, Weight loss at week 52: Interaction with sex

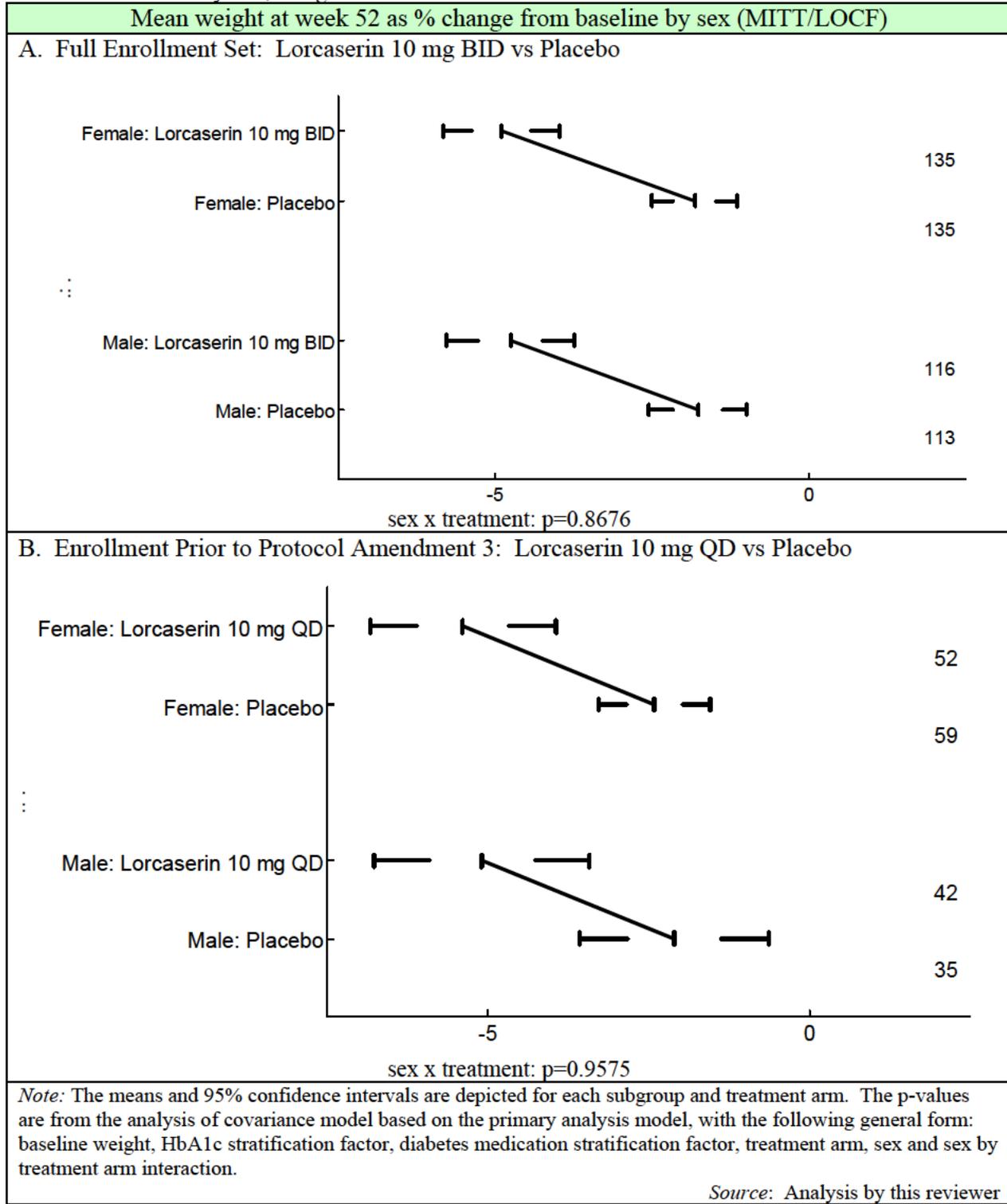


FIGURE 15 Study 010, Weight loss at week 52: Interaction with race

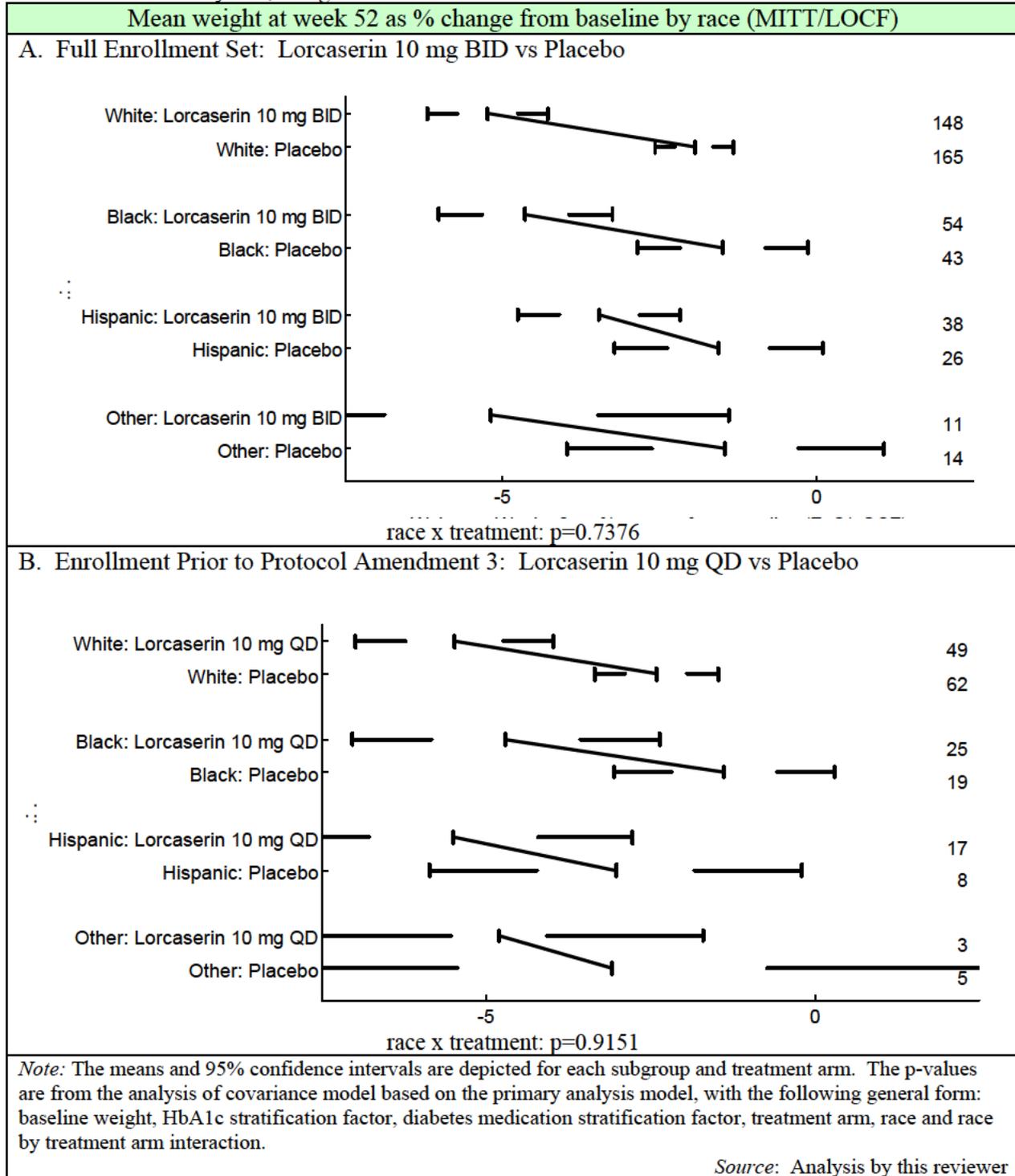


FIGURE 16 Study 010, Weight loss at week 52: Interaction with baseline BMI

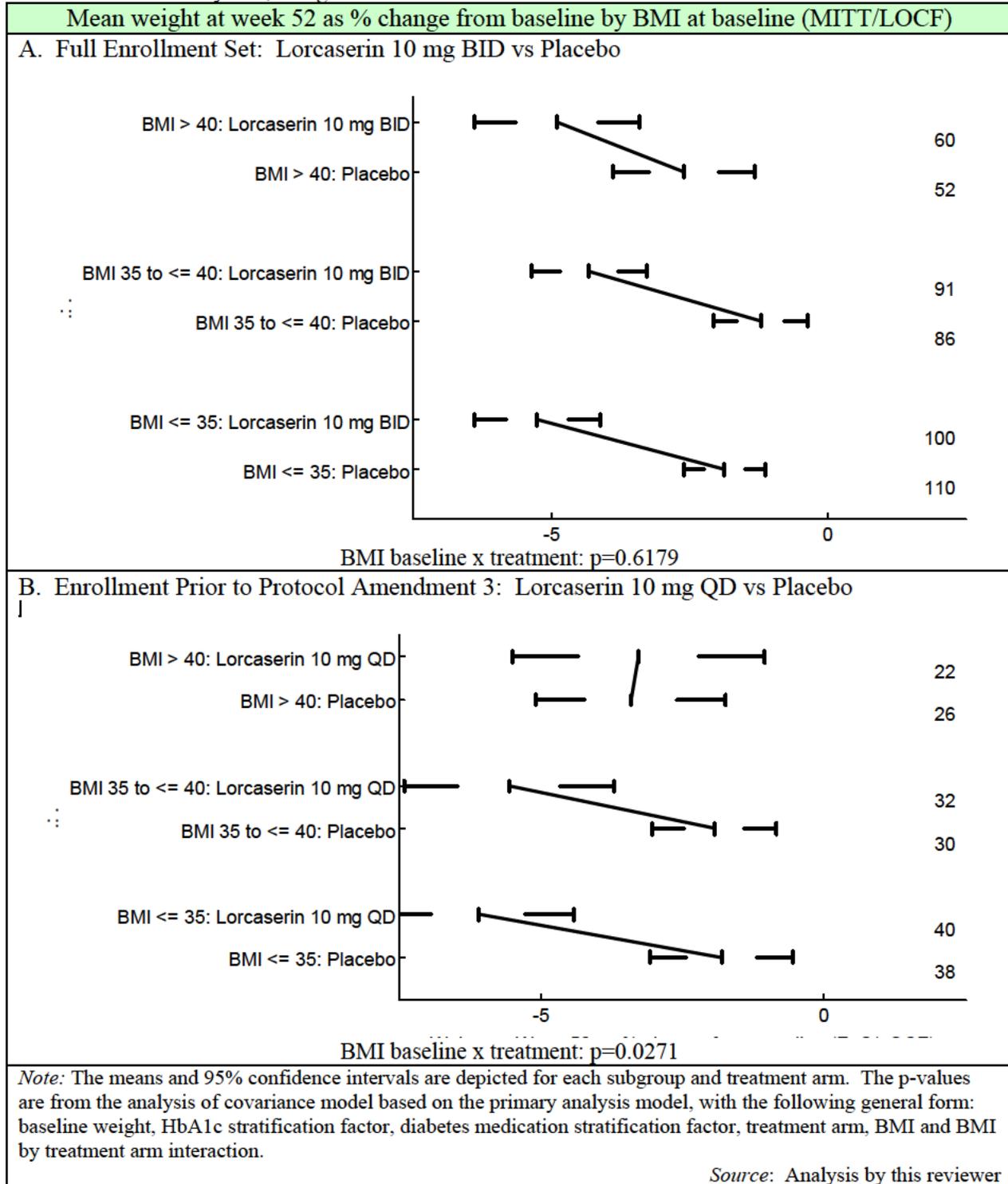


FIGURE 17 Study 010, Weight loss at week 52: Interaction with diabetes medication

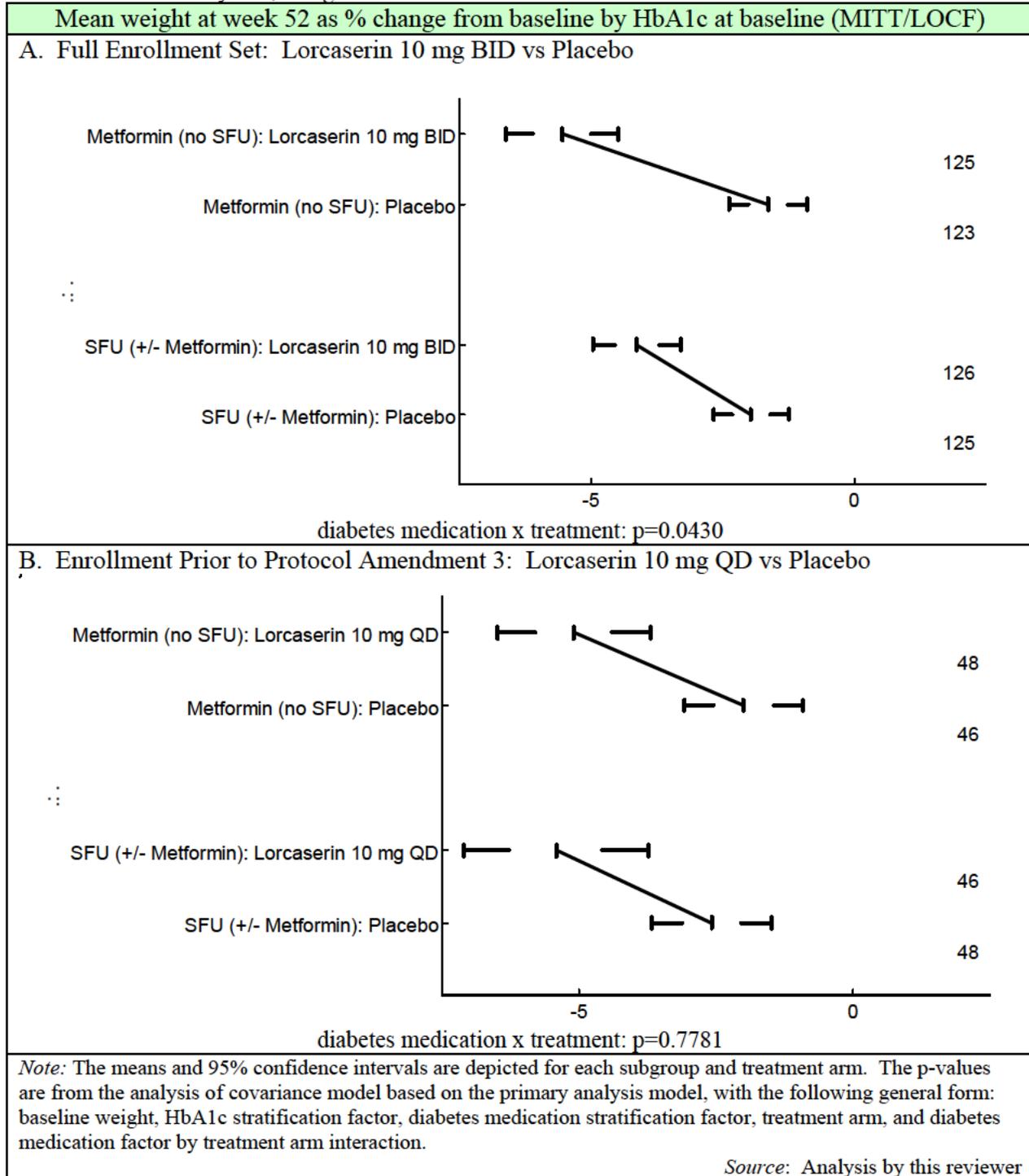


FIGURE 18 Study 010, Weight loss at week 52: Interaction with HbA1c at baseline (9.0 cutpoint)

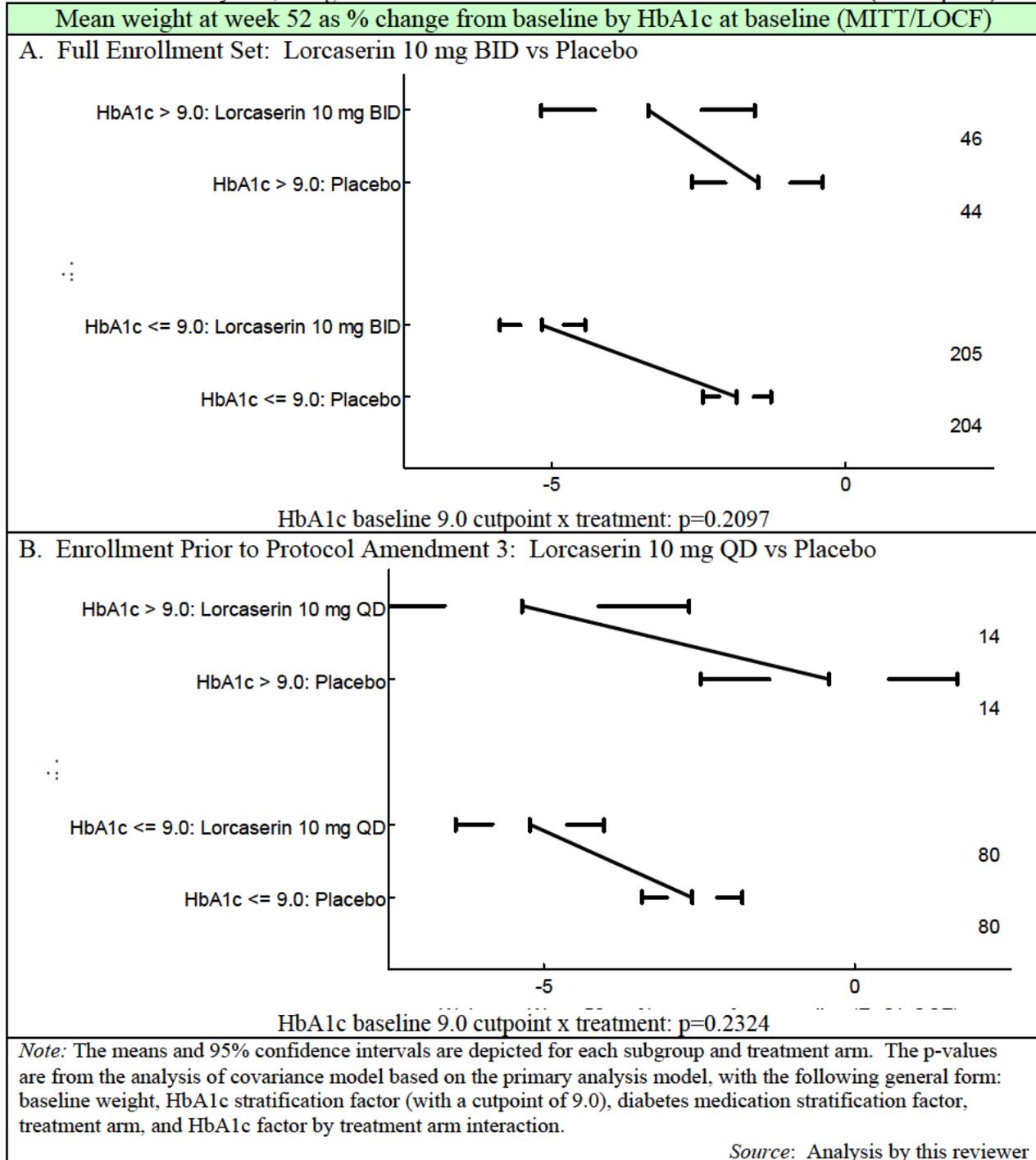


FIGURE 19 Study 010, Weight loss at week 52: Interaction with HbA1c at baseline (8.0 cutpoint)

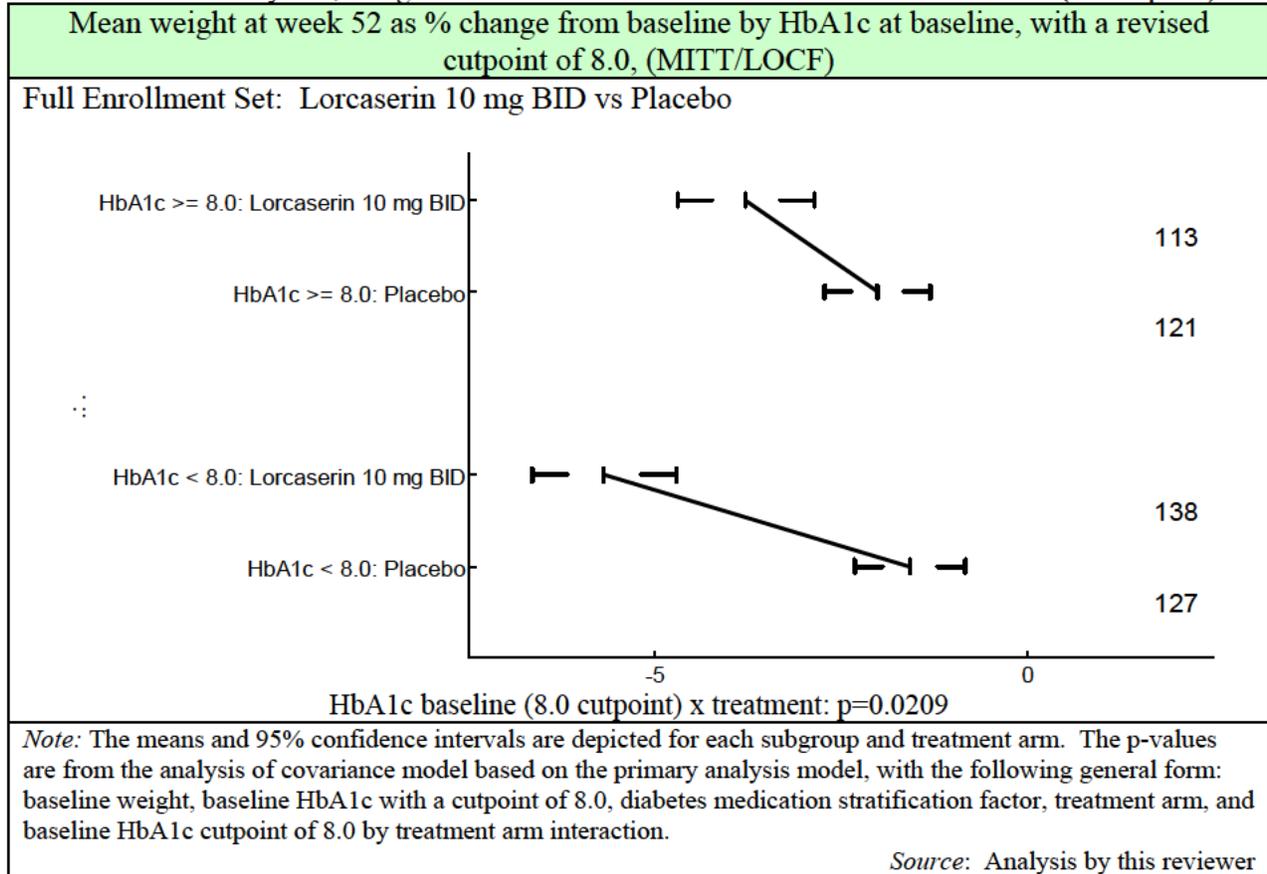
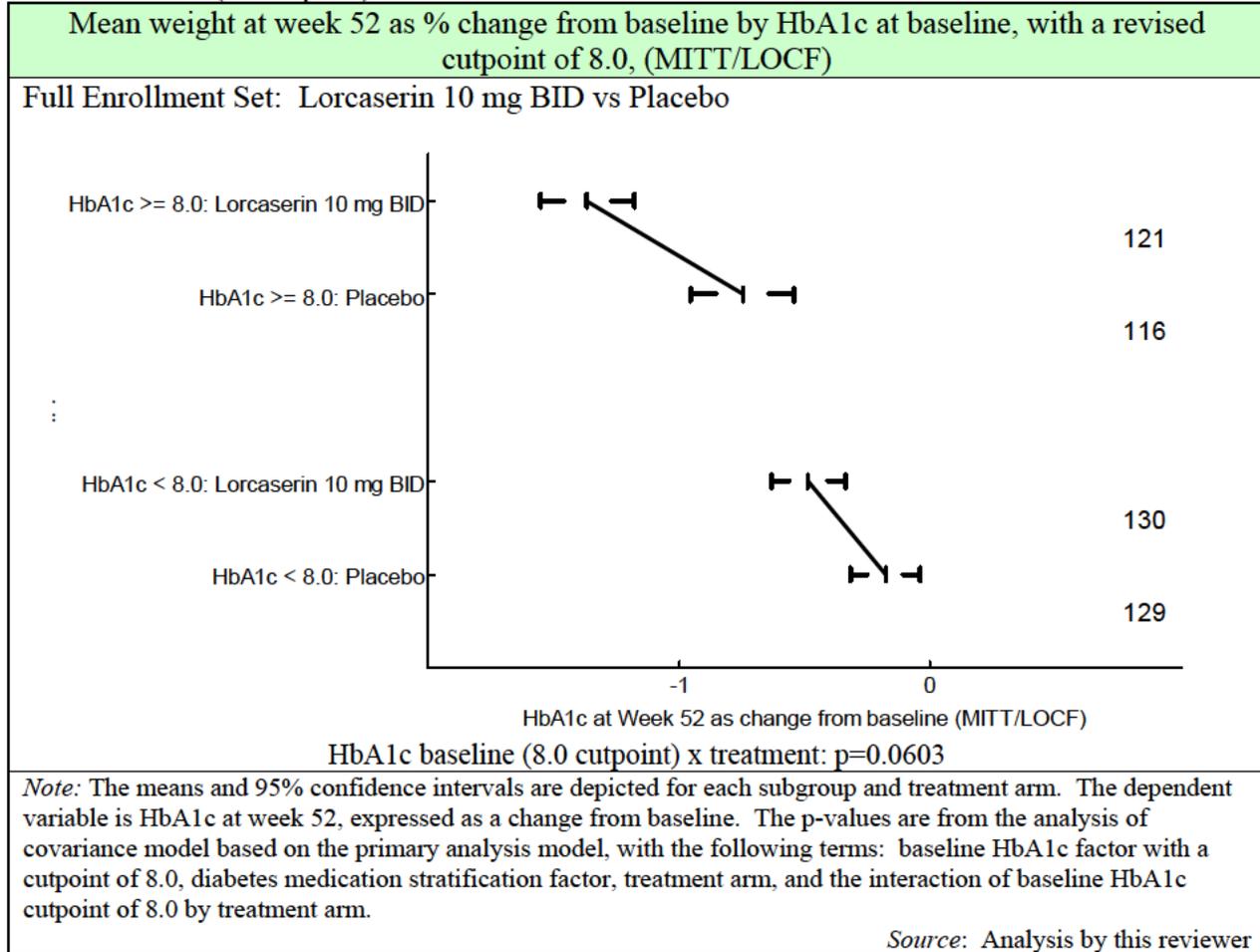


FIGURE 20 Study 010, HbA1c change from baseline at week 52: Interaction with HbA1c at baseline (8.0 cutpoint)



5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

A key issue in Study 010 was the substantial percentage of randomized subjects, 34%, who withdrew prior to week 52. The extent of dropout, and the relationship between ongoing weight loss and tendency to drop out, focuses the analysis on the categorical version of the weight endpoint. Patients who withdrew early were likely to be within 5% of their baseline weight at the time of withdrawal. This is consistent with classifying early withdrawals as 5% non-responders. A reasonable measure of efficacy to extend the study conclusions to the intended target population is the placebo-adjusted odds of being classified as a 5% responder. This measure can encompass the intention-to-treat population by classifying early dropouts as 5% non-responders.

Although the substantial percentage of dropouts in Study 010 was a key issue, this percentage was actually lower than it was in Study 009 (50%) or Study 011 (56%). This may reflect differences between the diabetic and non-diabetic study populations.

Study 010 had an estimated placebo-adjusted effect of lorcaserin 10 mg bid at 52 weeks that was fairly similar to the estimates from Study 009 and Study 011. For average weight change, the adjusted effect was -3.1% of baseline in Study 010, -3.0% in Study 011 and -3.7% in Study 009. For the percentage of 5% weight loss responders, the adjusted difference in percentage from the placebo arm was 27.3% in Study 010, 22.2% in Study 011 and 27.2 in Study 009. In the diabetic Study 010, the effect of lorcaserin 10 mg bid was fairly similar to the effect of lorcaserin 10 mg qd. In contrast, the results from the two dose arms in Study 011 were consistent with a dose-response relationship. I note that neither study was powered for a statistical comparison between lorcaserin dose arms.

5.2 Conclusions

All three studies had similar estimates of the placebo-adjusted effect of lorcaserin 10 mg bid at 52 weeks (TABLE 1). The consistency of the efficacy results across Studies 010, 009 and 011 supports the collective evidence for the efficacy of lorcaserin 10 mg bid. However, the efficacy endpoints, while statistically significant, do not fully meet the benchmarks for clinical significance that are described in the Agency's Weight Management Guidance (2007):

- For the continuous endpoint, the guidance states that the difference in mean weight loss between the active product and placebo-treated groups should be at least 5% and the difference should be statistically significant. For all three studies, the placebo-adjusted percentage change from baseline at week 52 was statistically significant. However, in each of the three studies, the placebo-adjusted effect of lorcaserin was statistically significantly less than 5%.

- For the categorical endpoint, at least 5% of weight loss at week 52, the guidance states that the observed percentage of responders should be at least 35% and at least double the percentage in the placebo-treated group. These criteria are met in all three studies, when the last observation carried forward (LOCF) method was used to impute the 52-week results from subjects who discontinued early. However, these results are somewhat sensitive to the imputation method. When early dropouts are classified as non-responders, Studies 009 and 011 meet the criteria for the categorical endpoint but Study 010 does not.

In my opinion, the 5% responder endpoint is a key endpoint because of the substantial percentage of early withdrawals in all three studies. Because of the relationship between dropping out and being less successful at weight loss in these studies, I believe it is reasonable to classify dropouts as non-responders. This approach may be a reasonable way to extend the study results to the intended target population.

This review has focused on the lorcaserin 10 mg bid dose, because it was evaluated in all three studies. The results for the lorcaserin 10 mg qd dose were consistent with a dose-response relationship in the non-diabetic subjects in Study 011, but were fairly similar to the lorcaserin 10 mg bid dose in the diabetic subjects of Study 010.

5.3 Recommendations for Labeling

The discussions for labeling of lorcaserin (b) (4) are at the early stages at the time of this review. This review does not include a summary of recommendations for the label.

Checklist

Number of Pivotal Studies: 1 in this complete response resubmission

Trial Specification

Protocol Number (s):	Study APD356-010, BLOOM-DM
Phase:	Phase 3
Control:	Placebo controlled
Blinding:	Double blind
Number of Centers:	64
Region(s) (Country):	US
Duration:	52-week primary treatment period
Treatment Arms:	placebo, lorcaserin 10 mg qd (enrollment of this arm was discontinued after Protocol Amendment 3 was instituted), and lorcaserin 10 mg bid.
Treatment Schedule:	Twice daily oral medication
Randomization:	
Ratio:	1:1:1, modified to 1:1 after protocol amendment 3 (see note above)
Method of Randomization:	IVRS
If stratified, then the Stratification Factors:	two stratification factors: baseline HbA1c (< 9% and ≥ 9%); and diabetes medication (sulfonylureas, either alone or in combination, and metformin, either alone or in combination). A subject taking both SFUs and metformin was included in the SFU stratum.
Primary Endpoint:	Weight as a change from baseline at week 52: (1) the continuous version; and (2) the percentage of 5% weight loss responders, and (3) the percentage of 10% weight loss responders
Primary Analysis Population:	MITT/LOCF
Statistical Design:	superiority evaluation
Adaptive Design?	No
Primary Statistical Methodology:	Analysis of covariance for the co-primary continuous weight loss endpoint and logistic regression for the co-primary categorical weight loss responder endpoint
Interim Analysis?	No
DSMB?	Yes
Sample Size:	
Sample size determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable?	Yes
Statistic =	two-sample test of equality of binomial proportions
Power =	80%
Δ =	30%(active) – 15%(placebo) = 15%
α =	0.05, two-tailed

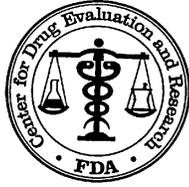
- Was there an alternative analysis in case of violation of assumption; e.g., Lack of normality, proportional hazards assumption violation? No
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? Protocol Amendment 3 discontinued enrollment into the lorcaserin 10 mg qd arm about half way through the enrollment period.
- Were the covariates pre-specified in the protocol? Yes
- Did the applicant perform sensitivity analyses? Yes
- How were the missing data handled? Primary method was LOCF; a sensitivity analysis was conducted using MMRM and no imputation
- Was there a multiplicity involved?
If yes, multiple arms? Yes
Multiple endpoints? Yes
Which method was used to control for type I error? Pre-specified gate-keeping sequence
- Multiple secondary endpoints: Are they being included in the label? If yes, method to control for type 1 error. Yes: pre-specified families of secondary endpoints, each with a pre-specified priority list, evaluated conditionally on the statistical significance of the primary endpoints.
- Were subgroup analyses performed? Yes
- Were there any discrepancies between the protocol / statistical analysis plan vs. the study report? No
- Overall, was the study positive? Yes (statistically superior weight loss in the active group compared to the placebo)

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/s/

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05/22/2012

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-529 / SN 0034

Drug Name: Lorqess (Lorcaserin hydrochloride, Lorcaserin, APD356)

Indication(s): Weight management, including weight loss and maintenance of weight loss

Applicant: Arena Pharmaceuticals

Date(s): Submitted December 27, 2011

Review Priority: Standard

Biometrics Division: Division of Biometrics VII

Statistical Reviewer: Xiao Ding, Ph.D.

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Project Manager: Pat Madara (DMEP)

Keywords: NDA review, clinical studies, noninferiority, safety, valvulopathy

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1 Executive Summary

This statistical review and evaluation was performed in response to a consultation from the Division of Biometrics 2 (DB2) for New Drug Application (NDA) 22-529/034 (received December 27, 2011) for lorcaserin tablets. One new phase 3 clinical trial, Study APD356-010 was submitted in this NDA resubmission which is in addition to two previously reviewed Phase 3 trials, Studies APD356-009 and APD356-011 which were submitted in the original application. This statistical review assesses echocardiogram related safety endpoints in all the randomized phase 3 clinical trials of lorcaserin (Studies APD356-009, APD356-010, and APD356-011).

Based on a previously agreed non-inferiority margin of 1.5¹ for the relative risk ratio, the pooled analysis of all three phase 3 randomized placebo-controlled clinical trials failed to rule out that the lorcaserin 10 mg twice-a-day (BID) regimen was inferior to the placebo in the risk of developing FDA-defined valvulopathy (aortic regurgitation mild or greater, or mitral regurgitation moderate or greater) at 52 weeks. Based on the pre-specified primary analysis, the relative risk ratio of the pooled lorcaserin 10 mg BID group compared to the pooled placebo group was 1.16 with a 95% CI of (0.81, 1.67).

Further evaluation of each component of FDA-defined valvulopathy found that the lorcaserin 10 mg BID regimen was statistically significantly associated with an increased risk of developing moderate or greater mitral regurgitation at 52 weeks. Compared to the pooled placebo group, the relative risk ratio of the pool lorcaserin 10 mg BID group was 1.95 with a 95% CI of (1.05, 3.59). In contrast, the risk of developing mild or greater aortic regurgitation appeared to be lower in the pooled lorcaserin 10 mg BID group than in the pooled placebo group. The pooled relative risk ratio between lorcaserin 10 mg BID regimen and placebo was 0.89 with a 95% CI of (0.56, 1.42).

Compared to placebo, the lorcaserin 10 mg BID regimen was found to be associated with an increase in at least one of the four valvular regurgitations (aortic valve, mitral valve, pulmonary valve, and tricuspid valve). The incidence of developing increased valvular regurgitation was statistically significantly higher at the nominal $\alpha=0.05$ level in the pooled lorcaserin 10 mg BID group than in the pooled placebo group. The pooled relative risk ratio between lorcaserin 10 mg BID regimen and placebo was 1.11 with a 95% CI of (1.05, 1.18).

¹ During the development process of this NDA application, the Agency continuously emphasized that ruling out a 50% increased in the incidence of FDA-defined valvulopathy was both an important and a clinically meaningful requirement for the applicant. As such, the Agency stated that data in the NDA must be able to rule out a relative risk for FDA-defined valvulopathy of at least 1.5 (powered at 80%). The

(b) (4)
(b) (4) In the FDA Pre-Meeting Response for the pre-NDA meeting on August 12, 2009 for IND 69888, the Agency informed the applicant that at a minimum, the echocardiographic data must be robust enough to rule out a relative risk of 1.5 for FDA-defined valvulopathy.

2 Introduction

2.1 Overview

Lorcaserin hydrochloride (lorcaserin), a selective serotonin 2C (5-HT_{2C}) receptor agonist, was submitted by the applicant as a new agent to reduce body weight. The proposed indication is for weight management, including weight loss and maintenance of weight loss in obese subjects (BMI \geq 30 kg/m²), or overweight subjects (BMI \geq 27- 30 kg/m²) who have one or more weight-related co-morbid medical conditions.

The original New Drug Application (NDA), 22-529, dated December 22, 2009, consisted of two Phase 3 studies, Study APD356-009 and Study APD356-011 in support of the safety and efficacy of lorcaserin for the indication of weight management. On October 22, 2010, the agency issued a Complete Response Letter on the application because of several non-clinical, clinical and labeling approval deficiencies. The listed clinical approval deficiency was “The weight-loss efficacy of lorcaserin 10 mg twice a day relative to placebo in overweight and obese individuals without type 2 diabetes is marginal”. The agency also requested the application “submit the final study report for the trial of lorcaserin in overweight and obese individuals with type 2 diabetes (BLOOM-DM)”.

The applicant submitted one new Phase 3, double-blinded, randomized, placebo-controlled, clinical trial, Study APD356-010 (i.e. BLOOM-DM) in this application. The review is an updated analysis of the echocardiogram data that incorporates information from all three phase 3 studies. Please see the statistical review by Dr. Xiao Ding dated 9/27/2010 for a review of the echocardiogram data based on the two studies (Studies APD356-009 and APD356-011) as they were submitted in the original application.

2.2 Data Sources

In this submission, the applicant submitted electronic documents and datasets for Study APD356-010 and integrated datasets for all three phase 3 studies. The following files available within the CDER Electronic Document Room (EDR) were utilized in this review.

<\\Cdsub1\evsprod\NDA022529\0034\m5\datasets\iss-ise\analysis>

<\\Cdsub1\evsprod\NDA022529\0034\m5\datasets\apd356-010\analysis>

<\\Cdsub1\evsprod\NDA022529\0034\m5\datasets\apd356-010\listings>

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3 Statistical Evaluation

This review is focused on evaluation of echocardiogram data. For a complete statistical evaluation of the efficacy results, please refer to the review authored by Dr. Janice Derr.

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. Because the applicant only submitted 4 updated datasets for Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), additional data were requested by the review team on February 7, 2012. The applicant submitted other updated datasets for ISE and ISS on February 13, 2012. The reviewer was able to perform all analyses using the submitted data.

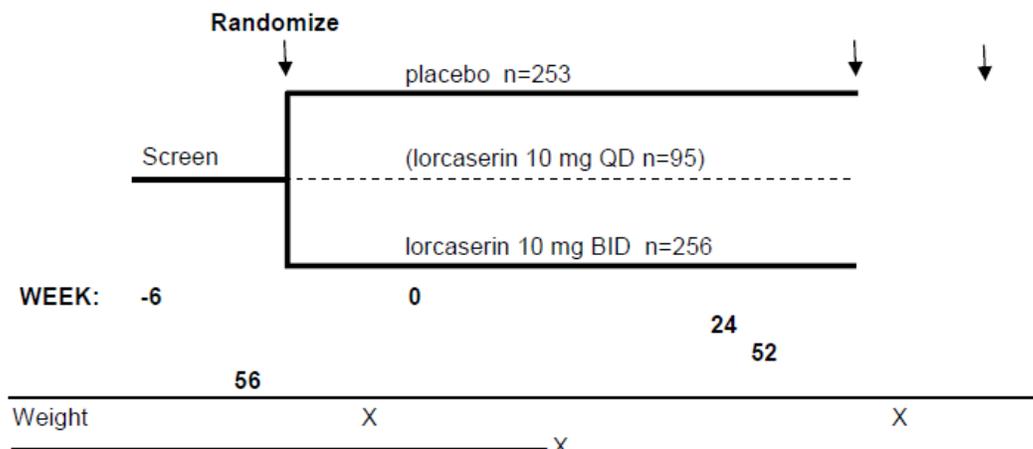
3.2 Evaluation of Safety

This safety review is focused on the evaluation of echocardiograms of Studies APD356-010, as well as the pooled analysis of all three phase 3 trials (Studies APD356-009, APD356-010 and APD356-011). All analyses are between the randomized treatment groups, Lorcaserin and Placebo. Please see the statistical review by Dr. Xiao Ding dated 9/27/2010 for more details of the evaluation of echocardiograms for Study APD356-009 and Study APD356-011.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Study APD356-010 was a 52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of lorcaserin in overweight and obese subjects with type 2 diabetes mellitus (schematic of the trial design is shown in Figure 1). Patients enrolled into the study prior to the implementation of protocol Amendment 03 were randomized in a 1:1:1 fashion to one of the three treatment groups: placebo, lorcaserin 10 mg once-a-day (QD), or lorcaserin 10 mg twice-a-day (BID). Due to slow enrollment, the total enrollment target was reduced by discontinuing randomization to the low dose (QD) group. Patients enrolled after the implementation of protocol Amendment 03 were randomized in a 1:1 ratio to 1 of 2 treatment groups: placebo or lorcaserin 10 mg twice-a-day (BID). Patients randomized into the lorcaserin 10 mg QD group prior to the implementation of Amendment 03 remained enrolled in the trial to complete all planned study procedures. A total of 604 subjects were randomized in Study APD356-010, with 253 subjects randomized to placebo, 95 to lorcaserin QD, and 256 to lorcaserin BID respectively. Study APD356-010 was also known as the BLOOM-DM study. Study APD356-010 was powered to provide 84% or more power to detect efficacy difference between the lorcaserin groups and the placebo group, provided that 30% of lorcaserin-treated subjects and 15% of placebo-treated subjects achieved a 5% or greater weight loss between baseline and week 52.

Figure 1: Study Design of APD356-010

Source: Applicant's APD356-010 Clinical Study Report, Figure 1.

3.2.1.2 Endpoints

A comprehensive echocardiographic monitoring process was implemented in the phase 3 studies of lorcaserin to evaluate the changes in echocardiographic valvular regurgitation scores. The primary endpoint to evaluate echocardiogram was the proportion of subjects who developed echocardiographic criteria known as "FDA-defined valvulopathy" (also called FDA valvulopathy) during clinical studies. FDA-defined valvulopathy, which was originally based on the FDA's evaluation of reported cases of cardiac valvular disease in subjects exposed to fenfluramine² is defined as follows:

Echocardiograms were assessed at screening and at Weeks 24 and 52 (or early termination) in all three studies (Studies APD356-009, APD356-010, and APD356-011). At each time point, both the mitral regurgitation (MR) and aortic regurgitation (AR) were scored as: absent, trace, mild, moderate, or severe based on the reading of the echocardiogram. These readings were then used to define FDA valvulopathy. All the echocardiograms were read by 2 different readers blinded to the treatment assignment. Any discrepant readings between the readers were adjudicated by a third reader.

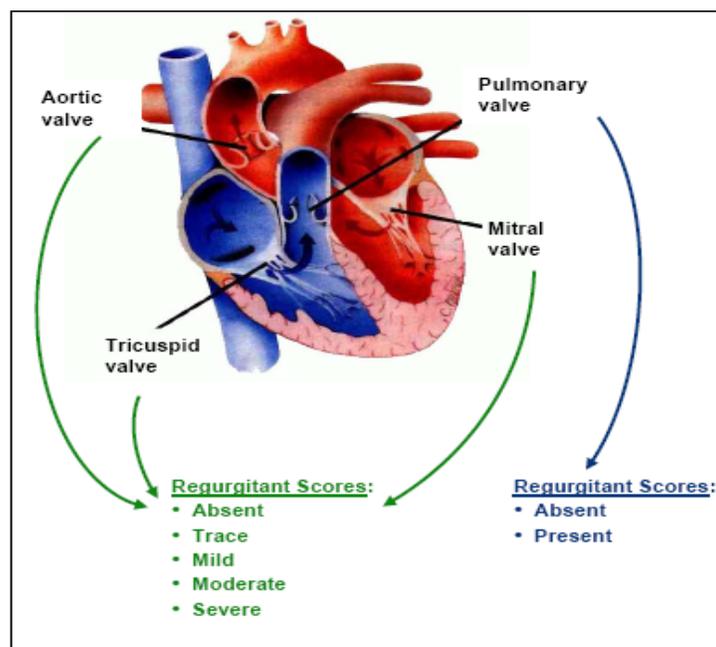
FDA valvulopathy: Echocardiographic findings of MILD or greater aortic regurgitation (AR) *or* MODERATE or greater mitral regurgitation (MR).

The protocol-defined primary echocardiographic endpoint for the pooled phase 3 trials was the proportion of subjects who developed FDA-defined valvulopathy from Baseline to Week 52. Therefore, subjects with FDA-defined valvulopathy at baseline were excluded from the analyses of primary endpoint.

² Fenfluramine was approved by FDA in 1973 for use as an appetite suppressant in the management of obesity. In 1997 the manufacturer voluntarily withdraw fenfluramine from the US market.

In addition to the assessment of FDA-defined valvulopathy, the changes in individual valvular regurgitant scores were also evaluated to compare the safety between the lorcaserin regimens and the placebo. A diagram of the individual valvular regurgitant scores is provided in Figure 2.

Figure 2: Diagram of Cardiac Valves and Individual Valvular Regurgitant Score



Source: Applicant's Summary of Clinical Safety, Figure 3.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

As shown in Table 1, in the intent-to-treat population (ITT population) of Study APD356-010, defined as all randomized subjects, baseline demographics and characteristics were similar among the treatment groups. All subjects in Studies APD356-010 were between the ages of 21 and 65 years. Approximately 54% of subjects were female and more than 60% were Caucasian. In Study APD356-010, more than 4% of the subjects had FDA-defined Valvulopathy at baseline.

Table 1: Study APD356-010 Baseline Demographics by Treatment Group (ITT Population)

	Study APD356-010		
	Placebo (N=253)	Lorcaserin 10 mg QD (N=95)	Lorcaserin 10 mg BID (N=256)
Age (years)			
Mean (SD)	52.1 (9.3)	53.1 (8.0)	53.2 (8.3)
Range	21-65	26-65	30-65
Weight (kg)			
Mean (SD)	102.3 (18.2)	106.0 (19.5)	103.5 (17.1)
Range	53.2-158.6	68.3-157.4	63.8-151.6
BMI (kg/m²)			
Mean (SD)	35.8 (4.6)	36.2 (4.8)	36.1 (4.5)
Range	27.3-46.4	28.3-45.9	26.9-45.0
Gender, n (%)			
Female	138 (54.6)	53 (55.8)	137 (53.5)
Male	115 (45.4)	42 (44.2)	119 (46.5)
Race, n (%)			
White	167 (66.0)	49 (51.6)	150 (58.6)
Black	45 (17.8)	26 (27.4)	55 (21.5)
Hispanic	27 (10.7)	17 (17.9)	39 (15.2)
Others	14 (5.5)	3 (3.1)	12 (4.7)
Valvulopathy, n (%)			
Valvulopathy	10 (4.0)	9 (9.5)	9 (3.5)
Non-valvulopathy	242 (95.6)	86 (90.5)	247 (96.5)
Unknown	1 (0.4)	0 (0)	0 (0)

Source: Created by reviewer.

Among the 604 randomized subjects in the ITT population from Study APD356-010, approximately 34% of them discontinued study prior to week 52. As presented in Table 2, the incidence of study discontinuation was similar between the placebo group and the lorcaserin 10 mg BID group, but was lower in the lorcaserin 10 mg QD group. The most common reason reported for study discontinuation was withdrawal of consent, which accounted for 14.9% in Study APD356-010. The safety population included all randomized subjects who received at least one dose of the randomized study treatment. As shown in Table 2, among the 604 randomized subjects in Study APD356-010, a total of 603 (99.8%) subjects were included in the safety population.

Table 2: Study APD356-010 Discontinuation by Treatment Group (ITT Population)

	Study APD356-010		
	Placebo (N=253)	Lorcaserin 10 mg QD (N=95)	Lorcaserin 10 mg BID (N=256)
Safety Population	252 (99.6%)	95 (100%)	256 (100%)
Discontinued before week 52	96 (37.9%)	20 (21.1%)	87 (34.0%)
Withdraw Consent	50 (19.8%)	8 (8.4%)	32 (12.5%)
Lost to follow-up	15 (5.5%)	3 (3.2%)	20 (7.8%)
Adverse event	11 (4.4%)	6 (6.3%)	22 (8.6%)
Protocol deviation	10 (4.0%)	1 (1.1%)	3 (1.2%)
Sponsor Decision	5 (2.0%)	1 (1.1%)	3 (1.2%)
PI decision	1 (0.4%)	0 (0%)	0 (0%)
Other	5 (2.0%)	1 (1.1%)	7 (2.7%)

Source: Created by reviewer.

3.2.3 Statistical Methodologies

3.2.3.1 Methods of Imputing Missing

For subjects with only a baseline echocardiogram, baseline data are not carried forward. For subjects with at least one post baseline echocardiogram measurement, the last observation carried forward (LOCF) method was used to impute missing data for the overall analysis of echocardiographic parameters at week 52. Subjects who discontinued from the trials prior to week 52 but returned for a week 52 echo were also included in the pooled safety analyses.

***Reviewer's comment:** Although the LOCF method to impute the missing values was pre-specified in the protocol, this method can lead to biased point estimates and variances. This is especially problematic when the study discontinuation rate is high and disproportional between different treatment arms. Several sensitivity analyses were conducted to assess the robustness of the results. See Section 3.2.4.2 for more details.*

3.2.3.2 Analysis of Relative Risk

Consistent with the review dated 9/27/2010 that incorporated data from the previous two studies (Studies APD356-009 and APD356-011), a non-inferiority margin of 1.5 for relative risk ratio is used in this review for evaluation of FDA-defined valvulopathy. The comparison of proportions between the lorcaserin 10 mg BID group and the placebo group is performed using the protocol-defined Cochran-Mantel-Haenszel (CMH) test with study as stratification factor. The two-sided 95% confidence intervals for between-group relative risk ratios were constructed based upon the stratified Mantel-Haenszel approach utilizing the pooled phase 3 data from Studies APD356-009, APD356-010, and APD356-011. For each individual study, the two-sided 95% confidence intervals were conducted using the normal approximation to the binomial distribution.

Reviewer's comment: Stratification by trial ensures that a population of subjects is compared within a given trial and thus the inference is based on the randomization of patients within each trial.

3.2.3.3 Analyses of Incidence Rate

In this review, as exploratory analyses, Mantel-Haenszel incidence rate difference and Mantel-Haenszel incidence rate ratio were applied to compare the incidence rate of FDA-defined valvulopathy event between lorcaserin and placebo. The unit of analysis was a subject-year of follow-up and the stratification factor was the trial.

Reviewer's comment: Because the assessment of FDA-defined valvulopathy was conducted only at Week 24 and Week 52, caution is needed when interpreting the exploratory results of incidence rate.

3.2.4 Results and Conclusions

3.2.4.1 FDA-defined Valvulopathy at Week 52

At week 52, the status of FDA-defined valvulopathy for subjects in the safety population is shown in Table 3. In the pooled phase 3 safety population from Study APD356-009, Study APD356-010, and Study APD356-011, approximately 2% of the subjects had FDA-defined valvulopathy at week 52, while 73% of the subjects did not have FDA-defined valvulopathy. Note that about 35% of the subjects had echocardiogram data missing at week 52. Note that subjects with FDA-defined valvulopathy at baseline were excluded from the analyses.

Table 3: Status of FDA-Defined Valvulopathy at Week 52 by Treatment Group (Safety Population)

Number (%) of subjects		FDA-defined valvulopathy	Non FDA-defined Valvulopathy	Unknown
Study APD356-009	Placebo (N=1584)	26 (1.6%)	940 (59.3%)	618 (39.0%)
	Lorcaserin 10 mg BID (N=1593)	33 (2.1%)	1058 (66.4%)	502 (31.5%)
Study APD356-010	Placebo (N=252)	4 (1.6%)	182 (72.2%)	66 (26.2%)
	Lorcaserin 10 mg QD (N=95)	7 (7.4%)	73 (76.8%)	15 (15.8%)
	Lorcaserin 10 mg BID (N=256)	12 (4.7%)	172 (67.2%)	72 (28.1%)
Study APD356-011	Placebo (N=1601)	46 (2.9%)	960 (60.0%)	595 (37.2%)
	Lorcaserin 10 mg QD (N=801)	20 (2.5%)	530 (66.2%)	251 (31.3%)
	Lorcaserin 10 mg BID (N=1602)	50 (3.1%)	1030 (64.3%)	522 (32.6%)
Total (N=7784)		198 (2.5%)	4945 (63.5%)	2641 (33.9%)

Source: Created by reviewer.

Only considering subjects randomized to receive lorcaserin 10 mg BID or placebo, 5,249 subjects (76.2%) in the safety population did not have FDA-defined valvulopathy at baseline and had at least one echocardiogram data available post randomization. The incidence of FDA-defined valvulopathy at week 52 among these subjects is presented in Table 4, using the protocol defined LOCF method to impute the missing data. In Study APD356-010 the incidence of FDA-defined valvulopathy at week 52 was 2.86% in the lorcaserin 10 mg BID group and was 0.48% in the placebo group. The relative risk ratio between lorcaserin and placebo was 5.97 with a 95% CI of (0.73, 49.17). Pooling the three phase 3 studies APD356-009, APD356-010, and APD356-011 together, the Mantel-Haenszel relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.16 with a 95% CI of (0.81, 1.67). Based on the pooled analysis, the upper limit of the 95% confidence interval exceeded the non-inferiority margin of 1.5.

Table 4: Incidence of FDA-Defined Valvulopathy at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

		Total Subject *	Number of Event **	Incidence	Relative Risk (95% CI)	Pooled Relative Risk *** (95% CI)
Study APD356-009	Placebo	1191	28	2.35%	1.13 (0.69, 1.85)	1.16 (0.81, 1.67)
	Lorcaserin 10 mg BID	1278	34	2.66%		
Study APD356-010	Placebo	209	1	0.48%	5.97 (0.73, 49.17)	
	Lorcaserin 10 mg BID	210	6	2.86%		
Study APD356-011	Placebo	1153	23	1.99%	1.00 (0.57, 1.75)	
	Lorcaserin 10 mg BID	1208	24	1.99%		
Total		5249	116	2.21%		

* Number without missing, excluding baseline valvulopathy.

** Number of FDA-defined Valvulopathy at Week 52 using LOCF.

*** Stratified Mantel-Haenszel approach.

Source: Created by reviewer.

3.2.4.1.1 Each Component of FDA-defined Valvulopathy at Week 52

As discussed in Section 3.2.1.2, the FDA-defined valvulopathy is defined as echocardiographic findings of mild or greater aortic regurgitation (AR) or moderate or greater mitral regurgitation (MR). Therefore the primary endpoint (FDA-defined valvulopathy at Week 52) can be viewed as a composite endpoint of two components: mild or greater AR at Week 52, and moderate or greater MR at Week 52. Based upon a request from the clinical team each component of FDA-defined valvulopathy was evaluated at Week 52 as a sensitivity analysis to the primary analysis results presented in Table 4. Same as the primary analysis, 5,249 subjects (76.2%) in the safety population did not have FDA-defined valvulopathy at baseline and had at least one echocardiogram data available post randomization; therefore the pooled analyses of AR and MR included 5,249 subjects.

The incidence of mild or greater AR at week 52 is presented in Table 5. In Study APD356-010 the incidence of mild or greater AR at week 52 was 1.90% in the lorcaserin 10 mg BID group and was 0.48% in the placebo group. The relative risk ratio between lorcaserin and placebo was 2.51 with a 95% CI of (0.43, 14.54). Pooling the three phase 3 studies APD356-009, APD356-010, and APD356-011 together, the Mantel-Haenszel relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 0.89 with a 95% CI of (0.56, 1.42).

**Table 5: Incidence of Mild or Greater AR at Week 52 (LOCF) by Treatment Group
(Safety Population, Subjects with Baseline Valvulopathy Excluded)**

		Total Subject *	Number of Event **	Incidence	Relative Risk (95% CI)	Pooled Relative Risk *** (95% CI)
Study APD356-009	Placebo	1191	18	1.51%	0.96 (0.69, 1.34)	0.89 (0.56, 1.42)
	Lorcaserin 10 mg BID	1278	18	1.41%		
Study APD356-010	Placebo	209	1	0.48%	2.51 (0.43, 14.54)	
	Lorcaserin 10 mg BID	210	4	1.90%		
Study APD356-011	Placebo	1153	18	1.56%	0.84 (0.62, 1.13)	
	Lorcaserin 10 mg BID	1208	13	1.08%		
Total		5249	72	1.37%		

* Number without missing, excluding baseline valvulopathy.

** Number of Mild or Greater Aortic Regurgitation at Week 52 using LOCF.

*** Stratified Mantel-Haenszel approach.

Source: Created by reviewer.

The incidence of moderate or greater MR at week 52 is presented in Table 6. In Study APD356-010 the incidence of moderate or greater MR at week 52 was 0.95% in the lorcaserin 10 mg BID group and was 0% in the placebo group. The relative risk ratio between lorcaserin and placebo was un-definable. Pooling the three phase 3 studies APD356-009, APD356-010, and APD356-011 together, the Mantel-Haenszel relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.95 with a 95% CI of (1.05, 3.59). Compared to placebo, the lorcaserin 10 mg BID regimen was statistically significantly associated with a higher risk of developing moderate or greater mitral regurgitation within 52 weeks.

Table 6: Incidence of Moderate or Greater MR at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

		Total Subject *	Number of Event **	Incidence	Relative Risk (95% CI)	Pooled Relative Risk *** (95% CI)
Study APD356-009	Placebo	1191	10	0.84%	1.31 (0.80, 2.14)	1.95 (1.05, 3.59)
	Lorcaserin 10 mg BID	1278	17	1.33%		
Study APD356-010	Placebo	209	0	0%	--	
	Lorcaserin 10 mg BID	210	2	0.95%		
Study APD356-011	Placebo	1153	5	0.43%	1.67 (0.80, 3.48)	
	Lorcaserin 10 mg BID	1208	12	0.99%		
Total		5249	46	0.88%		

* Number without missing, excluding baseline valvulopathy.

** Number of Moderate or Greater Mitral Regurgitation at Week 52 using LOCF.

*** Stratified Mantel-Haenszel approach.

Source: Created by reviewer.

3.2.4.2 Sensitivity Analysis for FDA-defined Valvulopathy

3.2.4.2.1 FDA-defined Valvulopathy at Week 24

In the safety population, 4,984 subjects (72.4%) from the lorcaserin 10 mg BID group and the placebo group did not have FDA-defined valvulopathy at baseline, and had week 24 echocardiogram data. Note that data for week 24 is not imputed as there are no echocardiograms taken prior to week 24; thus subjects with an unknown status at week 24 are not included in the denominator. The incidence of FDA-defined valvulopathy at week 24 among these subjects is presented in Table 7. In Study APD356-010, the incidence of FDA-defined valvulopathy at week 24 was 2.46% in the lorcaserin 10 mg BID group and was 1.94% in the placebo group. The relative risk ratio between lorcaserin and placebo was 1.27 with a 95% CI of (0.35, 4.66). These results were similar to those for Study APD356-009 and Study APD356-011. Pooling all three phase 3 Studies APD356-009, APD356-010, and APD356-011 together, the Mantel-Haenszel relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.18 with a 95% CI of (0.80, 1.73). Similar to the week 52 results, the 95% confidence interval exceeded the 1.5 non-inferiority margin for the pooled analysis.

**Table 7: Incidence of FDA-Defined Valvulopathy at Week 24 by Treatment Group
(Safety Population, Subjects with Baseline Valvulopathy Excluded)**

		Total Subject *	Number of Event **	Incidence	Relative Risk (95% CI)	Pooled Relative Risk *** (95% CI)
Study APD356-009	Placebo	1089	21	1.93%	1.07 (0.60, 1.90)	1.18 (0.80, 1.73)
	Lorcaserin 10 mg BID	1213	25	2.06%		
Study APD356-010	Placebo	206	4	1.94%	1.27 (0.35, 4.66)	
	Lorcaserin 10 mg BID	203	5	2.46%		
Study APD356-011	Placebo	1103	20	1.81%	1.27 (0.72, 2.26)	
	Lorcaserin 10 mg BID	1170	27	2.31%		
Total		4984	102	2.05%		

* Number without missing, excluding baseline valvulopathy.

** Number of FDA-defined Valvulopathy at Week 24.

*** Stratified Mantel-Haenszel approach.

Source: Created by reviewer.

3.2.4.2.2 FDA-defined Valvulopathy at Week 52 for Completers

In addition to using LOCF for imputing missing FDA-defined valvulopathy, a completers analysis was performed as a sensitivity analysis. Subjects are considered completers if they completed all 52 weeks of treatment. Among the 7,784 subjects in the safety population from Studies APD356-009, APD356-010, and APD356-011, 4,224 (54.3%) subjects completed the full 52 weeks of study drug treatment. In this completers population, the risk of developing FDA-defined valvulopathy was also compared between the lorcaserin 10 mg BID treatment group and the placebo group. The incidence of FDA-defined valvulopathy at week 52 is presented in Table 8 for subjects in the completers population without FDA-defined valvulopathy at baseline. In Study APD356-010, the incidence was 3.82% in the lorcaserin 10 mg BID group and was 0% in the placebo group. Based on all three studies, the pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.03 with a 95% CI of (0.68, 1.57) for the week 52 completers analysis.

Table 8: Incidence of FDA-Defined Valvulopathy at Week 52 by Treatment Group (Completers Population, Subjects with Baseline Valvulopathy Excluded)

		Total Subject *	Number of Event **	Incidence	Relative Risk (95% CI)	Pooled Relative Risk *** (95% CI)
Study APD356-009	Placebo	698	21	3.01%	1.12 (0.65, 1.95)	1.03 (0.68, 1.57)
	Lorcaserin 10 mg BID	857	29	3.38%		
Study APD356-010	Placebo	147	0	0%	--	
	Lorcaserin 10 mg BID	157	6	3.82%		
Study APD356-011	Placebo	790	19	2.41%	0.63 (0.32, 1.27)	
	Lorcaserin 10 mg BID	853	13	1.52%		
Total		3502	88	2.51%		

* Number without missing, excluding baseline valvulopathy.

** Number of FDA-defined Valvulopathy at Week 52.

*** Stratified Mantel-Haenszel approach.

Source: Created by reviewer.

3.2.4.2.3 FDA-defined Valvulopathy at Week 24 or Week 52

Among subjects in the safety population from Studies APD356-009, APD356-010 and APD356-011, a total of 229 subjects had FDA-defined valvulopathy at week 24, while a total of 198 subjects had FDA-defined valvulopathy at week 52. As shown in Table 9, among the 229 subjects who had FDA-defined valvulopathy at week 24, 82 subjects had no FDA-defined valvulopathy at week 52. One possible explanation for these subjects' valvulopathy to disappear was the improvement of valvular regurgitation over time; another possible reason might be caused by the discrepancy between echocardiogram readers and the fact that echocardiograms for the same subject were not consistently evaluated by the same readers over time.

Table 9: Comparison of FDA-Defined Valvulopathy Status at Week 24 versus Week 52 (Safety Population)

		Week 24 Status			Total
		Valvulopathy	Non-Valvulopathy	Unknown	
Week 52 Status	Valvulopathy	114	78	6	198
	Non-Valvulopathy	82	4575	288	4945
	Unknown	33	949	1659	2641
	Total	229	5602	1953	7784

Source: Created by reviewer.

Another way to evaluate the risk of developing FDA-defined valvulopathy from baseline to week 52 is to compare the incidence of FDA-defined valvulopathy at either week 24 or

week 52. In this sensitivity analysis, subjects who had valvulopathy at either week 24 or week 52 were considered as valvulopathy cases. As shown in Table 10, the pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.16 with a 95% CI of (0.86, 1.56). Similar to results depicted in Table 4 (week 52 safety population) or Table 5 (week 24 safety population), the non-inferiority of the lorcaserin 10 mg BID regimen compared to placebo exceeded the 1.5 non-inferiority margin.

Table 10: Incidence of FDA-Defined Valvulopathy at either Week 24 or Week 52 by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

		Total Subject *	Number of Event **	Incidence	Relative Risk (95% CI)	Pooled Relative Risk *** (95% CI)
Study APD356-009	Placebo	1191	38	3.19%	1.10 (0.72, 1.69)	1.16 (0.86, 1.56)
	Lorcaserin 10 mg BID	1278	45	3.52%		
Study APD356-010	Placebo	209	4	1.91%	1.99 (0.61, 6.51)	
	Lorcaserin 10 mg BID	210	8	3.81%		
Study APD356-011	Placebo	1153	34	2.95%	1.12 (0.72, 1.76)	
	Lorcaserin 10 mg BID	1208	40	3.31%		
Total		5249	169	3.22%		

* Number without missing, excluding baseline valvulopathy.

** Number of FDA-defined Valvulopathy at Week 24 or Week 52 (Worst Status at Week 24 or 52).

*** Stratified Mantel-Haenszel approach.

Source: Created by reviewer.

3.2.4.2.4 FDA-defined Valvulopathy based on Single Reader

In lorcaserin Phase 3 studies, all the echocardiograms were read by 2 different readers. Any discrepant readings between the readers were adjudicated by a third reader.

The results in Table 4 were based on adjudicated echocardiogram readings from both Reader A and Reader B. In order to assess the impact of the poor agreement between the two readers and the potential adjudication noise, the analysis results for FDA-defined valvulopathy based on the readings from Reader A or Reader B are shown in Table 9 and Table 10, respectively.

When only using the echocardiogram readings from Reader A (the primary reader), the pooled relative risk ratio between lorcaserin 10 mg BID regimen and placebo was 1.26 with a 95% CI of (0.90, 1.76), with respect to the risk of developing FDA-defined valvulopathy from baseline to week 52. Results are shown in Table 11.

Table 11: Incidence of FDA-Defined Valvulopathy Based on Reader A at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

		Total Subject *	Number of Event **	Incidence	Relative Risk (95% CI)	Pooled Relative Risk *** (95% CI)
Study APD356-009	Placebo	1188	24	2.02%	1.36 (0.81, 2.27)	1.26 (0.90, 1.76)
	Lorcaserin 10 mg BID	1277	35	2.74%		
Study APD356-010	Placebo	210	5	2.38%	0.80 (0.22, 2.94)	
	Lorcaserin 10 mg BID	210	4	1.90%		
Study APD356-011	Placebo	1152	29	2.52%	1.25 (0.78, 2.02)	
	Lorcaserin 10 mg BID	1204	38	3.16%		
Total		5241	135	2.58%		

* Number without missing, excluding baseline valvulopathy.

** Number of FDA-defined Valvulopathy at Week 52 using LOCF.

*** Stratified Mantel-Haenszel approach.

Source: Created by reviewer.

Similar results were found when only using the readings from Reader B (the secondary reader); results are shown in Table 12. The pooled relative risk ratio between lorcaserin and placebo was 1.19 with a 95% CI of (0.83, 1.71).

Table 12: Incidence of FDA-Defined Valvulopathy Based on Reader B at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

		Total Subject *	Number of Event **	Incidence	Relative Risk (95% CI)	Pooled Relative Risk *** (95% CI)
Study APD356-009	Placebo	1178	28	2.38%	0.93 (0.55, 1.56)	1.19 (0.83, 1.71)
	Lorcaserin 10 mg BID	1267	28	2.21%		
Study APD356-010	Placebo	207	4	1.93%	2.26 (0.71, 7.23)	
	Lorcaserin 10 mg BID	206	9	4.37%		
Study APD356-011	Placebo	1147	19	1.66%	1.35 (0.76, 2.42)	
	Lorcaserin 10 mg BID	1207	27	2.24%		
Total		5212	115	2.21%		

* Number without missing, excluding baseline valvulopathy.

** Number of FDA-defined Valvulopathy at Week 52 using LOCF.

*** Stratified Mantel-Haenszel approach.

Source: Created by reviewer.

When looking at the relative risk of FDA-defined valvulopathy for each individual reader (Table 11 and 12), the results are consistent with that reported when valvulopathy scores are adjudicated (Table 4). Each of these analysis demonstrated that the relative risk exceeded the non-inferiority margin of 1.5.

3.2.4.3 Exploratory Analysis of Valvulopathy Incidence Rate

In this section, several exploratory analyses were done to explore the incidence rate of newly developed FDA-defined valvulopathy event within 52 weeks. Only considering subjects randomized to receive lorcaserin 10 mg BID or placebo, 5,249 subjects in the safety population did not have FDA-defined valvulopathy at baseline, and had at least one echocardiogram data available post randomization. The incidence rate of developing new FDA-defined valvulopathy within 52 weeks among these subjects is presented in Table 13. In Study APD356-009, the incidence rate of FDA-defined valvulopathy within 52 weeks was 39.4 events per 1,000 person-years in the lorcaserin 10 mg BID group and was 36.5 events per 1,000 person-years in the placebo group. In Study APD356-010, the incidence rate was 42.6 events per 1,000 person-years in the lorcaserin 10 mg BID group and was 21.5 events per 1,000 person-years in the placebo group. In Study APD356-011, the incidence rate was 37.1 events per 1,000 person-years in the lorcaserin 10 mg BID group and was 33.2 events per 1,000 person-years in the placebo group.

Table 13: Summary of Valvulopathy Incidence Rate by Study and Treatment Group (Safety Population)

		Total Subject *	Total Follow-up	Number of Event **	Incidence Rate (per 1,000 person-years)
Study APD356-009	Placebo	1191	1039.9	38	36.5
	Lorcaserin 10 mg BID	1278	1142.1	45	39.4
Study APD356-010	Placebo	209	186.2	4	21.5
	Lorcaserin 10 mg BID	210	188.0	8	42.6
Study APD356-011	Placebo	1153	1024.3	34	33.2
	Lorcaserin 10 mg BID	1208	1078.1	40	37.1
Over	Placebo	2553	2250.4	76	33.8
All	Lorcaserin 10 mg BID	2696	2408.2	93	38.6
Total		5249	4658.6	169	36.3

* Number without missing, excluding baseline valvulopathy.

** Number of newly developed FDA-defined Valvulopathy events within 52 Weeks.

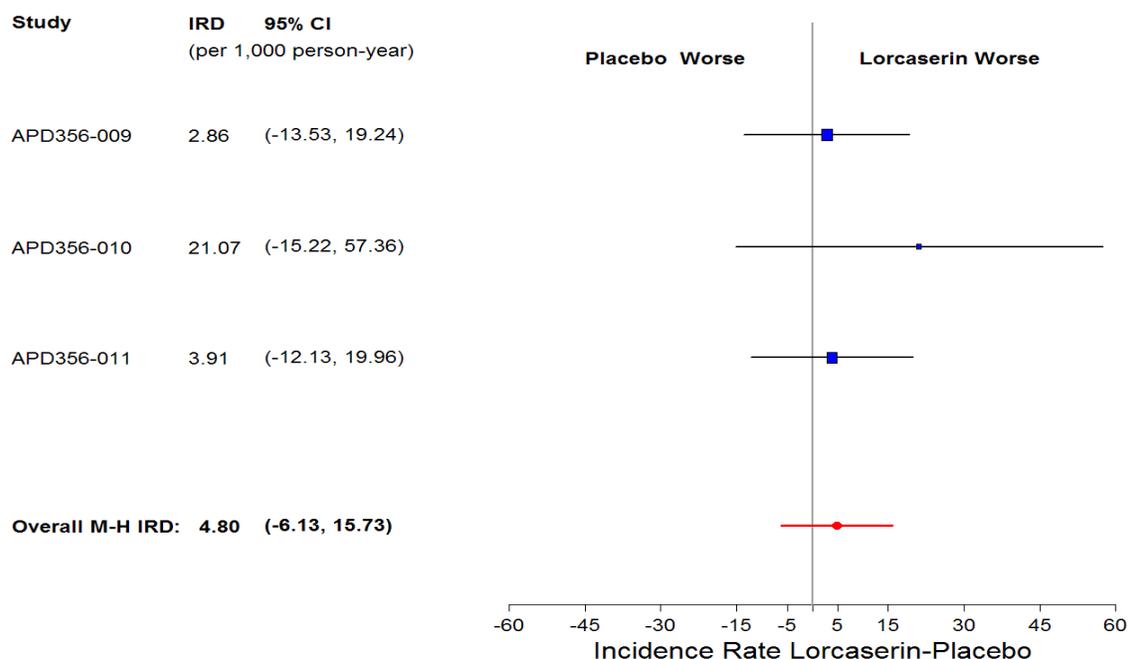
Source: Created by reviewer.

Reviewer’s comment: Because new FDA-defined valvulopathy events were only assessed twice within 52 weeks (at Week 24 and Week 52, respectively), plus that the measurement of follow-up duration and the calculation of incidence rate were not pre-specified, the analysis results based on incidence rate should be interpreted with caution.

Pooling the three phase 3 studies APD356-009, APD356-010, and APD356-011 together, a total of 93 newly developed FDA-defined valvulopathy events were reported within 52³ weeks in the lorcaserin 10 mg BID group (incidence rate of 38.6 per 1,000 person-years), and a total of 76 newly developed FDA-defined valvulopathy events in the placebo group (incidence rate of 33.8 per 1,000 person-years).

The forest plot of the analysis results of incidence rate difference of developing new FDA-defined valvulopathy events within 52 weeks is presented in Figure 3. The individual incidence rate difference between the lorcaserin 10 mg BID group and the placebo group was 2.86 per 1,000 person-years, 21.07 per 1,000 person-years, and 3.91 per 1,000 person-years for Studies APD356-009, APD356-010 and APD356-011, respectively. Based on the Mantel-Haenszel approach stratified by study, the overall incidence rate difference between lorcaserin 10 mg BID and placebo was 4.80 newly developed FDA-defined valvulopathy events per 1,000 person-years of follow-up, with a 95% CI of (-6.13, 15.73).

Figure 3: Forest Plot of Incidence Rate Difference of Newly Developed Valvulopathy (Safety Population)

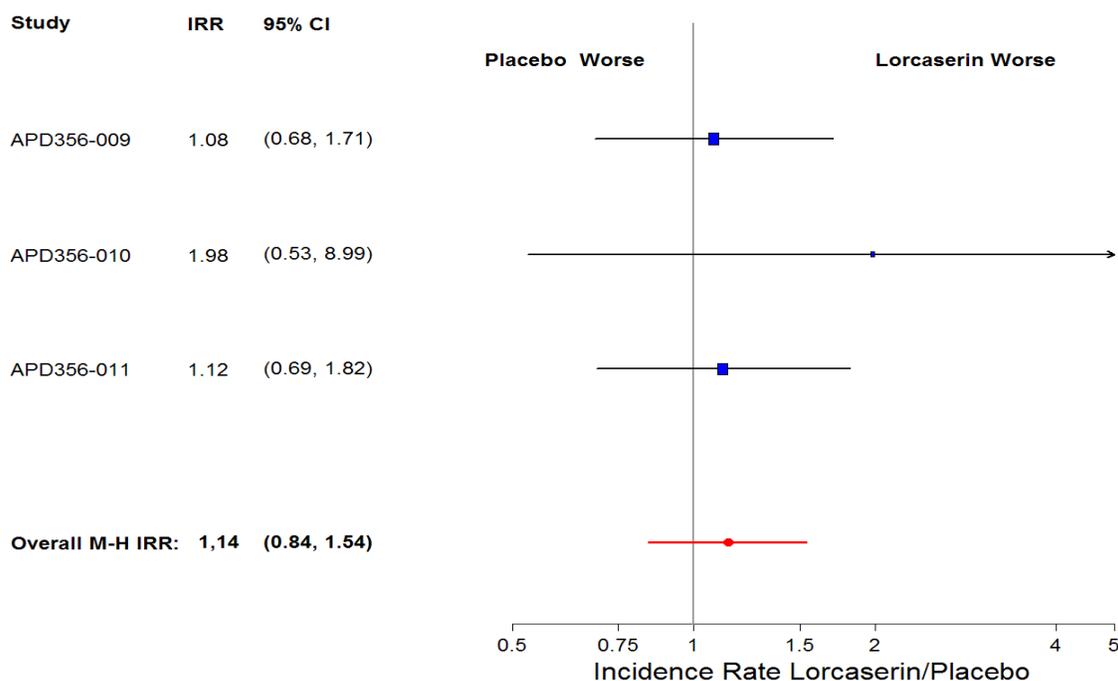


Source: Created by reviewer.

³ This includes cases of valvulopathy reported at 24 weeks or 52 weeks. For subjects with valvulopathy reported both at 24 weeks and 52 weeks, only the Week 24 cases of valvulopathy are included.

The forest plot of the analysis results of incidence rate ratio of developing new FDA-defined valvulopathy events within 52 weeks is presented in Figure 4. The individual incidence rate ratio between the lorcaserin 10 mg BID group and the placebo group was 1.08, 1.98 and 1.12 for Studies APD356-009, APD356-010 and APD356-011, respectively. Based on the Mantel-Haenszel approach stratified by study, the overall incidence rate ratio between lorcaserin 10 mg BID and placebo was 1.14 with a 95% CI of (0.84, 1.54).

Figure 4: Forest Plot of Incidence Rate Ratio of Newly Developed Valvulopathy (Safety Population)



Source: Created by reviewer.

3.2.4.4 Individual Valvular Regurgitation

In order to evaluate the risk of increased individual valvular regurgitation between the lorcaserin groups and the placebo group, the proportions of subjects who experienced any increase in aortic (AR), mitral (MR), pulmonary (PR), or tricuspid regurgitation (TR) from baseline to week 52 are summarized in Table 14. The LOCF method was used for subjects who had data available at week 24 but not at week 52. The comparison of proportions between the lorcaserin 10 mg BID group and the placebo group is presented in Table 15. Compared with the placebo group, the proportion of increasing individual valvular regurgitations including AR, MR, PR, and TR was consistently higher in the lorcaserin 10 mg BID group than in the placebo group. Furthermore, 46.88% of the subjects in the pooled lorcaserin 10 mg BID group experienced increase in at least one of the four individual valvular regurgitations, compared to 42.02% of the subjects in the

placebo group. The pooled relative risk ratio between lorcaserin 10 mg BID regimen and placebo was 1.11 with a 95% CI of (1.05, 1.18).

Table 14: Summary of Any Increase in Valvular Regurgitation from Baseline to Week 52 (LOCF) by Treatment Group (Safety Population)

Number (%)* of subjects	Study 009		Study 010		Study 011		Total
	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	
Aortic Valve	101 (8.5%)	128 (10.0%)	15 (6.9%)	34 (15.5%)	68 (5.7%)	68 (5.3%)	414 (7.7%)
Mitral Valve	265 (22.2%)	302 (23.6%)	33 (15.2%)	40 (18.3%)	204 (17.0%)	243 (19.1%)	1087 (20.2%)
Pulmonary Valve	209 (18.4%)	231 (19.3%)	38 (17.6%)	25 (11.5%)	148 (12.4%)	201 (15.8%)	852 (16.3%)
Tricuspid Valve	204 (17.4%)	246 (19.6%)	31 (14.3%)	37 (16.9%)	183 (15.3%)	209 (16.4%)	910 (17.0%)
Any Valve[^]	561 (47.0%)	655 (51.3%)	83 (38.3%)	101 (46.1%)	454 (37.8%)	543 (42.6%)	2397 (44.5%)

* The denominator of the percentage was the number of subjects without missing values, for each individual valvular regurgitation.

[^] Subject with increase for more than one valve was only counted once.

Source: Created by reviewer.

Table 15: Proportion of Subjects with Any Increase in Valvular Regurgitation from Baseline to Week 52 (LOCF) (Safety Population)

	Pooled Placebo	Pooled Lorcaserin 10 mg BID	Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	CMH test p-value
AR	7.04%	8.30%	1.18 (0.98, 1.42)	0.08
MR	19.21%	21.11%	1.10 (0.99, 1.22)	0.09
PR	15.51%	17.00%	1.10 (0.97, 1.24)	0.14
TR	16.13%	17.89%	1.11 (0.98, 1.25)	0.09
Any Valve	42.02%	46.88%	1.11 (1.05, 1.18)	<0.001

Source: Created by reviewer.

Similar as Table 14 and Table 15 for week 52, summaries of the valvular regurgitation increase from baseline to week 24 are shown in Table 16 and Table 17. The proportion of subjects with increase in at least one of the four individual valvular regurgitations was 45.38% in the pooled lorcaserin 10 mg BID group, and was 41.06% in the pooled placebo group. The pooled relative risk ratio was 1.11 with a 95% CI of (1.04, 1.18), suggesting that the lorcaserin 10 mg BID group had statistically significantly higher risk of developing increase in at least one of the four valvular regurgitations. In addition, the proportion was always higher in the pooled lorcaserin 10 mg BID group than in the pooled placebo group, with respect to each of the individual valvular regurgitation. The differences between lorcaserin and placebo were statistically significant at the nominal $\alpha=0.05$ significance level for mitral valve and tricuspid valve.

Table 16: Summary of Any Increase in Valvular Regurgitation from Baseline to Week 24 by Treatment Group (Safety Population)

Number (%)* of subjects	Study 009		Study 010		Study 011		Total
	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	
Aortic Valve	97 (8.9%)	125 (10.3%)	22 (10.3%)	32 (15.1%)	68 (5.9%)	75 (6.1%)	419 (8.2%)
Mitral Valve	208 (19.1%)	262 (21.6%)	37 (17.3%)	52 (24.5%)	188 (16.4%)	234 (19.0%)	981 (19.2%)
Pulmonary Valve	174 (17.8%)	192 (17.7%)	41 (19.3%)	27 (12.9%)	149 (13.1%)	203 (16.5%)	786 (16.2%)
Tricuspid Valve	176 (16.4%)	225 (19.0%)	28 (13.1%)	39 (18.4%)	171 (14.9%)	216 (17.5%)	855 (16.9%)
Any Valve[^]	476 (43.6%)	573 (47.2%)	95 (44.4%)	110 (51.9%)	437 (38.0%)	524 (42.4%)	2215 (43.3%)

* The denominator of the percentage was the number of subjects without missing values, for each individual valvular regurgitation.

[^] Subject with increase for more than one valve was only counted once.

Source: Created by reviewer.

Table 17: Proportion of Subjects with Any Increase in Valvular Regurgitation from Baseline to Week 24 (Safety Population)

	Pooled Placebo	Pooled Lorcaserin 10 mg BID	Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	CMH test p-value
AR	7.62%	8.72%	1.15 (0.95, 1.38)	0.15
MR	17.64%	20.60%	1.17 (1.02, 1.31)	0.007
PR	15.60%	16.72%	1.07 (0.94, 1.22)	0.30
TR	15.41%	18.24%	1.18 (1.05, 1.34)	0.008
Any Valve	41.06%	45.38%	1.11 (1.04, 1.18)	0.002

Source: Created by reviewer.

3.2.4.4.1 Increase in Valvular Regurgitation Except 'Absent' to 'Trace'

The change of valvular regurgitation from 'Absent' to 'Trace' may not be clinically meaningful. Therefore, this analysis evaluates the risk of developing increases in individual valvular regurgitation except for increases of 'Absent' to 'Trace'. For subjects with any increase (except 'Absent' to 'Trace') in aortic (AR), mitral (MR), pulmonary (PR), or tricuspid regurgitation (TR) from baseline to week 52 (LOCF), the proportions in each treatment group and the comparison between lorcaserin 10 mg BID and placebo are shown in Table 18 and Table 19. For each of the individual regurgitation in mitral or tricuspid valve, the proportion of subjects with an increase except 'Absent' to 'Trace' was statistically significantly higher at the nominal $\alpha=0.05$ level in the lorcaserin 10 mg BID group than in the placebo group. However, a slightly higher proportion of subjects in the placebo group had increased aortic valvular regurgitation compared to the lorcaserin 10 mg BID group. In the pooled lorcaserin 10 mg BID group, 32.37% of the subjects had an increase except 'Absent' to 'Trace' in at least one of the four individual regurgitations, compared to 28.24% in the pooled placebo group. The relative risk ratio between

lorcaserin 10 mg BID regimen and placebo for an increase of any valve that excludes cases of ‘Absent’ to ‘Trace’ was 1.15 with a 95% CI of (1.06, 1.24).

Table 18: Summary of Any Increase *Except* ‘Absent’ to ‘Trace’ in Valvular Regurgitation from Baseline to Week 52 (LOCF) by Treatment Group (Safety Population)

Number (%)* of subjects	Study 009		Study 010		Study 011		Total
	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	
Aortic Valve	18 (1.5%)	18 (1.4%)	1 (0.5%)	5 (2.3%)	19 (1.6%)	14 (1.1%)	75 (1.4%)
Mitral Valve	113 (9.5%)	134 (10.5%)	11 (5.1%)	20 (9.1%)	90 (7.5%)	121 (9.5%)	489 (9.1%)
Pulmonary Valve	209 (18.4%)	231 (19.3%)	38 (17.6%)	25 (11.5%)	148 (12.4%)	201 (15.8%)	852 (16.3%)
Tricuspid Valve	121 (10.3%)	159 (12.6%)	18 (8.3%)	25 (11.4%)	117 (9.8%)	151 (11.9%)	591 (11.1%)
Any Valve[^]	369 (30.9%)	440 (34.4%)	57 (26.3%)	61 (27.9%)	312 (36.0%)	396 (31.1%)	1635 (30.4%)

* The denominator of the percentage was the number of subjects without missing values, for each individual valvular regurgitation.

[^] Subject with increase for more than one valve was only counted once.

Source: Created by reviewer.

Table 19: Proportion of Subjects with Any Increase *Except* ‘Absent’ to ‘Trace’ in Valvular Regurgitation from Baseline to Week 52 (LOCF) (Safety Population)

	Pooled Placebo	Pooled Lorcaserin 10 mg BID	Mantel-Haenszel ‘Pooled’ Relative Risk (95% CI)	CMH test p-value
AR	1.45%	1.34%	0.92 (0.59, 1.44)	0.71
MR	8.19%	9.92%	1.21 (1.02, 1.43)	0.03
PR	15.51%	17.00%	1.10 (0.97, 1.24)	0.14
TR	9.88%	12.18%	1.23 (1.06, 1.44)	0.008
Any Valve	28.24%	32.37%	1.15 (1.06, 1.24)	0.001

Source: Created by reviewer.

With respect to subjects who experienced any increase except ‘Absent’ to ‘Trace’ from baseline to week 24, the proportions and the comparisons are shown in Table 20 and Table 21. For AR, MR, PR, and TR, the proportion was consistently higher in the lorcaserin 10 mg BID group than in the placebo group. Furthermore, the proportion of increase in MR and TR was statistically significantly higher at the nominal $\alpha=0.05$ level for lorcaserin than placebo. Similar as the results for week 52 in Table 19, the proportions of subjects with any increase in valvular regurgitation from baseline to week 24 were 31.28% and 27.82% in the lorcaserin and placebo groups respectively. The proportion was statistically significantly higher in the lorcaserin 10 mg BID group, with a relative risk ratio of 1.12 and a 95% CI of (1.03, 1.22) for increases of any valve at week 24.

Table 20: Summary of Any Increase except ‘Absent’ to ‘Trace’ in Valvular Regurgitation from Baseline to Week 24 by Treatment Group (Safety Population)

Number (%)* of subjects	Study 009		Study 010		Study 011		Total
	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	
Aortic Valve	12 (1.1%)	19 (1.6%)	4 (1.9%)	4 (1.9%)	19 (1.7%)	15 (1.2%)	73 (1.4%)
Mitral Valve	94 (8.6%)	132 (10.9%)	13 (6.1%)	27 (12.7%)	86 (7.5%)	113 (9.2%)	465 (9.1%)
Pulmonary Valve	174 (17.8%)	192 (17.7%)	41 (19.3%)	27 (12.9%)	149 (13.1%)	203 (16.5%)	786 (16.2%)
Tricuspid Valve	104 (9.7%)	149 (12.6%)	16 (7.5%)	25 (11.8%)	110 (9.6%)	162 (13.1%)	566 (11.2%)
Any Valve[^]	320 (29.3%)	391 (32.2%)	63 (29.4%)	64 (30.2%)	300 (26.1%)	377 (30.5%)	1515 (29.6%)

* The denominator of the percentage was the number of subjects without missing values, for each individual valvular regurgitation.

[^] Subject with increase for more than one valve was only counted once.

Source: Created by reviewer.

Table 21: Proportion of Subjects with Any Increase except ‘Absent’ to ‘Trace’ in Valvular Regurgitation from Baseline to Week 24 (Safety Population)

	Pooled Placebo	Pooled Lorcaserin 10 mg BID	Mantel-Haenszel ‘Pooled’ Relative Risk (95% CI)	CMH test p-value
AR	1.43%	1.43%	1.01 (0.64, 1.59)	0.98
MR	7.86%	10.23%	1.30 (1.09, 1.55)	0.003
PR	15.60%	16.72%	1.07 (0.94, 1.22)	0.30
TR	9.45%	12.77%	1.35 (1.15, 1.58)	<0.001
Any Valve	27.82%	31.28%	1.12 (1.03, 1.22)	0.007

Source: Created by reviewer.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

In the following sections, safety results for FDA-defined valvulopathy are presented for specific subgroups. It should be noted that these analyses are exploratory in nature to assess general trends. No protocol-defined multiplicity adjustments were provided and as such the statistical analysis does not include a multiplicity adjustment in the results that follow.

Gender

Only considering subjects randomized to receive lorcaserin 10 mg BID or placebo, a total of 5,249 subjects (76.2%) in the safety population did not have FDA-defined valvulopathy at baseline, and had at least one echocardiogram data available post

randomization. Among these subjects, 4,109 subjects (78%) were female, while 1,140 subjects (22%) were male. The incidence of FDA-defined valvulopathy at week 52 (LOCF) for female or male subjects is presented in Table 22. The pooled Mantel-Haenszel relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.17 with a 95% CI of (0.78, 1.77) for females. Similarly, among male subjects, the pooled relative risk ratio between lorcaserin and placebo was 1.11 with a 95% CI of (0.51, 2.42).

Table 22: Incidence of FDA-Defined Valvulopathy at Week 52 (LOCF) by Gender and Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

			Total Subject *	Number of Event **	Incidence	Relative Risk (95% CI)	Pooled Relative Risk *** (95% CI)
Females	Study APD356-009	Placebo	990	23	2.32%	1.11 (0.64, 1.93)	1.17 (0.78, 1.77)
		Lorcaserin 10 mg BID	1043	27	2.59%		
	Study APD356-010	Placebo	117	1	0.85%	1.04 (0.07, 16.50)	
		Lorcaserin 10 mg BID	112	1	0.89%		
	Study APD356-011	Placebo	884	16	1.81%	1.26 (0.67, 2.39)	
		Lorcaserin 10 mg BID	963	22	2.28%		
Total			4109	90	2.19%		
Males	Study APD356-009	Placebo	201	5	2.49%	1.20 (0.39, 3.71)	1.11 (0.51, 2.42)
		Lorcaserin 10 mg BID	235	7	2.98%		
	Study APD356-010	Placebo	209	0	0%	-	
		Lorcaserin 10 mg BID	210	5	5.10%		
	Study APD356-011	Placebo	269	7	2.60%	0.31 (0.07, 1.50)	
		Lorcaserin 10 mg BID	245	2	0.82%		
Total			1140	26	2.28%		

* Number without missing, excluding baseline valvulopathy.

** Number of FDA-defined Valvulopathy at Week 52 using LOCF.

*** Stratified Mantel-Haenszel approach.

Source: Created by reviewer.

Race

Subgroup analyses for FDA-defined valvulopathy by race category are presented in Table 23. Similar as the subgroup analyses of gender, among the 5,249 subjects in the safety population for analysis, 3,662 subjects (69.7%) were White or Caucasian, 932 subjects

(17.8%) were Black or African American, 537 subjects (10.2%) were Hispanic or Latino, with 118 subjects (2.3%) were of other races.

Among White or Caucasian subjects, the pooled Mantel-Haenszel relative risk ratio between the lorcasein 10 mg BID group and the placebo group was 1.09 with a 95% CI of (0.72, 1.64). Similarly, the pooled relative risk ratio between lorcasein and placebo was 1.65 with a 95% CI of (0.65, 4.17) for Black or African American subjects. Among Hispanic or Latino subjects, the pooled Mantel-Haenszel relative risk ratio between the lorcasein 10 mg BID group and the placebo group was 0.35 with a 95% CI of (0.04, 3.06).

Table 23: Incidence of FDA-Defined Valvulopathy at Week 52 (LOCF) by Race Category and Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

			Total Subject *	Number of Event **	Incidence	Relative Risk (95% CI)	Pooled Relative Risk *** (95% CI)
White or Caucasian	Study APD356-009	Placebo	835	23	2.75%	1.03 (0.59, 1.79)	1.09 (0.72, 1.64)
		Lorcaserin 10 mg BID	918	26	2.83%		
	Study APD356-010	Placebo	138	1	0.72%	4.31 (0.49, 38.08)	
		Lorcaserin 10 mg BID	128	4	3.13%		
	Study APD356-011	Placebo	794	17	2.14%	0.99 (0.51, 1.91)	
		Lorcaserin 10 mg BID	849	18	2.12%		
Total			3662	89	2.43%		
Black or African American	Study APD356-009	Placebo	202	4	1.98%	1.39 (0.40, 4.85)	1.65 (0.65, 4.17)
		Lorcaserin 10 mg BID	218	6	2.75%		
	Study APD356-010	Placebo	38	0	0%	-	
		Lorcaserin 10 mg BID	44	2	4.55%		
	Study APD356-011	Placebo	219	3	1.37%	1.38 (0.31, 6.11)	
		Lorcaserin 10 mg BID	211	4	1.90%		
Total			932	19	2.04%		
Hispanic or Latino	Study APD356-009	Placebo	136	0	0%	-	0.35 (0.04, 3.06)
		Lorcaserin 10 mg BID	118	1	0.85%		
	Study APD356-010	Placebo	22	0	0%	-	
		Lorcaserin 10 mg BID	31	0	0%		
	Study APD356-011	Placebo	113	3	2.65%	-	
		Lorcaserin 10 mg BID	117	0	0%		
Total			537	4	0.74%		

* Number without missing, excluding baseline valvulopathy.

** Number of FDA-defined Valvulopathy at Week 52 using LOCF.

*** Stratified Mantel-Haenszel approach.

Source: Created by reviewer.

Age

Subgroup analyses for FDA-defined valvulopathy by age category (≤ 50 years old or >50 years old) are presented in Table 24. Among subjects with age less than 50 the pooled relative risk ratio for FDA-defined valvulopathy was 1.47 with a 95% CI of (0.81, 2.69).

In general, the incidence of FDA-defined valvulopathy was higher among older subjects than among younger subjects given that the overall incidence was 3.86% for subjects older than 50 years and 1.36% for subjects with an age ≤ 50 years. Similarly, among subjects older than 50 years the pooled relative risk ratio between lorcaserin and placebo was 1.02 with a 95% CI of (0.65, 1.61).

Table 24: Incidence of FDA-Defined Valvulopathy at Week 52 (LOCF) by Age Group and Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

			Total Subject *	Number of Event **	Incidence	Relative Risk (95% CI)	Pooled Relative Risk *** (95% CI)
Age ≤ 50	Study APD356-009	Placebo	744	11	1.48%	1.40 (0.66, 2.97)	1.47 (0.81, 2.69)
		Lorcaserin 10 mg BID	821	17	2.07%		
	Study APD356-010	Placebo	79	0	0%	-	
		Lorcaserin 10 mg BID	73	2	2.74%		
	Study APD356-011	Placebo	745	6	1.81%	1.27 (0.44, 3.64)	
		Lorcaserin 10 mg BID	782	8	2.28%		
Total			3244	44	1.36%		
Age > 50	Study APD356-009	Placebo	447	17	3.80%	0.98 (0.51, 1.89)	1.02 (0.65, 1.61)
		Lorcaserin 10 mg BID	457	17	3.72%		
	Study APD356-010	Placebo	137	1	0.77%	3.80 (0.43, 33.51)	
		Lorcaserin 10 mg BID	130	4	2.92%		
	Study APD356-011	Placebo	408	17	4.17%	0.90 (0.46, 1.76)	
		Lorcaserin 10 mg BID	426	16	3.76%		
Total			2005	72	3.59%		

* Number without missing, excluding baseline valvulopathy.

** Number of FDA-defined Valvulopathy at Week 52 using LOCF.

*** Stratified Mantel-Haenszel approach.

Source: Created by reviewer.

4.2 Other Special/Subgroup Populations

No other subgroups or populations were assessed.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The pre-specified primary endpoint of the echocardiogram evaluation was the proportion of subjects who developed FDA-defined valvulopathy at week 52.

The stratified Mantel-Haenszel relative risk ratio between lorcaserin and placebo was 1.16 with a 95% confidence interval of (0.81, 1.67). The lorcaserin 10 mg BID group failed to demonstrate the non-inferiority to the placebo group at week 52, given the upper limit of the confidence interval exceeded the pre-specified non-inferiority margin of 1.5. Similar results were shown in several sensitivity analyses for the incidence of FDA-defined valvulopathy. Therefore, the pooled data from Studies APD356-009, APD356-010, and APD356-011 could not robustly rule out a relative risk of 1.5 for lorcaserin 10 mg BID regimen in the risk of developing FDA-defined valvulopathy from baseline to week 52. Detailed analysis results are provided in Section 3.2.4.1 and Section 3.2.4.2.

It is of clinical interest to further evaluate each component of FDA-defined valvulopathy (mild or greater aortic regurgitation, or moderate or greater mitral regurgitation) in a pooled analysis of the three Phase 3 trials. The lorcaserin 10 mg BID regimen was found to be associated with statistically significantly higher risk of developing moderate or greater *mitral regurgitation* at 52 weeks. The stratified Mantel-Haenszel relative risk ratio between lorcaserin and placebo was 1.95 with a 95% confidence interval of (1.05, 3.59). In contrast, the risk of developing mild or greater *aortic regurgitation* had a lower point estimate of the relative risk ratio in the pooled lorcaserin 10 mg BID group than in the pooled placebo group. The stratified Mantel-Haenszel relative risk ratio between lorcaserin and placebo was 0.89 with a 95% confidence interval of (0.56, 1.42). More details of the evaluation of each component can be found in Section 3.2.4.1.1.

In order to explore the incidence rate of newly developed FDA-defined valvulopathy event within 52 weeks, several exploratory analyses were conducted to compare the incidence rate between the lorcaserin 10 mg BID group and the placebo group. Based on the Mantel-Haenszel approach stratified by study, the overall incidence rate ratio between lorcaserin 10 mg BID and placebo was 1.14 with a 95% CI of (0.84, 1.54). Alternatively, the overall incidence rate difference between lorcaserin 10 mg BID and placebo was 4.80 newly developed FDA-defined valvulopathy events per 1,000 person-years of follow-up, with a 95% CI of (-6.13, 15.73). More details of this assessment can be found in Section 3.2.4.3.

With respect to the risk of developing increased valvular regurgitation at week 52 for at least one valve among aortic, mitral, pulmonary, and tricuspid valves, the incidence was

statistically significantly higher at the nominal $\alpha=0.05$ level in the lorcaserin 10 mg BID group than in the placebo group in each study separately. Pooling Studies APD356-009, APD356-010, and APD356-011 together, the stratified Mantel-Haenszel relative risk ratio was 1.11 with a 95% confidence interval of (1.05, 1.18), indicating that the difference between lorcaserin and placebo was statistically significant (46.88% versus 42.02%, $p<0.001$). More details of this assessment can be found in Section 3.2.4.4.

5.2 Conclusions and Recommendations

Based on a non-inferiority margin of 1.5 for the relative risk ratio, the pooled analysis of all three phase 3 randomized placebo-controlled clinical trials failed to rule out that the lorcaserin 10 mg twice-a-day (BID) regimen was inferior to the placebo in the risk of developing FDA-defined valvulopathy (aortic regurgitation mild or greater, or mitral regurgitation moderate or greater) at 52 weeks. Compared to the pooled placebo group, the relative risk ratio of the pooled lorcaserin 10 mg BID group was 1.16 with a 95% CI of (0.81, 1.67).

Compared to placebo, the lorcaserin 10 mg BID regimen was found to be associated with an increase in at least one of the four valvular regurgitations (aortic valve, mitral valve, pulmonary valve, and tricuspid valve). The incidence of developing increased valvular regurgitation was statistically significantly higher at the nominal $\alpha=0.05$ level in the pooled lorcaserin BID group than in the pooled placebo group. The pooled relative risk ratio between lorcaserin 10 mg BID regimen and placebo was 1.11 with a 95% CI of (1.05, 1.18).

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Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number: NDA 22-529
Drug name: Lorcaserin hydrochloride hemihydrate
Indication(s): 104 Week Carcinogenicity in Rats and Mice
Applicant: Arena Pharmaceuticals Corporation
Documents Reviewed: Electronic submission
Dated 2009-12-18
Electronically submitted dataset
Dated 2009-12-18
Electronically submitted dataset (corrected)
Dated 2010-07-30

Review Priority: Standard

Biometrics Division: Division of Biometrics 7
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Keywords: Animal Rat Mouse Carcinogenicity

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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 APD356 in rats and mice when administered orally by gavage once daily at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Alavi.

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 one control group. Two hundred and seventy (b)(4)[CrI (b)(4)(SD)] rats of each sex were initially randomly allocated to three treatment groups and one control group, with sixty five animals of each sex being assigned to the control, low dose, and medium dose dose groups, and seventy five animals of each sex being assigned to the high dose group. The dose levels for the treatment groups were 10, 30, and 100 mg/kg/day.

The vehicle for the test was deionized water, administered as a dosage volume of 5 ml/kg, once per day. The control animals received this vehicle.

During the administration period animals were checked twice daily for morbidity, mortality, injury, and availability of food and water (with a third check per day for mortality after week 53). A clinical exam was performed weekly (and daily in the first two weeks of the study) where any palpable masses were noted, and an evaluation was performed of various external organs (skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs, feet).

A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

2.1 Sponsor’s analyses

2.1.1 Survival analysis

Mortality data were analyzed according to the Kaplan-Meier [6] product limit method to test for trend in survival times across the four groups. If significant evidence of a trend is found ($\alpha = 0.05$) then the analysis proceeds to pairwise tests between each of the three treatment groups and the control group.

Among males, a significant ($p < 0.0001$) trend was found, and the difference in survival between the animals in the high dose group and the control group was subsequently found to be strongly significant ($p < 0.0001$).

Among females, there was also evidence of a trend ($p < 0.0001$), and all three treatment groups were found to have significantly inferior survival when compared with the control group. The p -value for the log-rank test was 0.0240 for the comparison of the low dose group with the control group, and less than 0.0001 for the comparisons of both the mid and high dose group with the control group.

2.1.2 Tumor data analysis

For each tumor type, both survival-adjusted and survival-unadjusted methods were used to detect possible carcinogenicity effects. A trend test (using the Armitage-Cochran [1] method and ordinal coefficients) and a set of pairwise tests of incidence versus control, using Fisher's exact test were conducted, based on survival-unadjusted data. The survival-adjusted tests followed Peto's method [8], using time intervals of 0–50 weeks, 51–80 weeks, 81 weeks to the end of the study, and terminal sacrifice. In addition to analyzing individual tumor types, the sponsor also considered three composite endpoints for both male and female animals:

1. Hepatocellular adenomas and carcinomas were considered together.
2. Adenocarcinomas and fibroadenomas of the mammary gland were considered together.
3. Malignant schwannomas were considered together, regardless of their location in the body.

Table 1 indicates the results found by the sponsor to be significant, using survival-adjusted tests, and the corresponding p -values (taken from table 4.2.1 of final report addendum). p -values less than 0.05 are indicated in bold.

Table 1: Tumor types found by the sponsor to be significant

Organ	Tumor type	p -value of test			
		Trend	Pairwise test vs control		
			Low Dose	Mid Dose	High Dose
Female rats					
Mammary gland	Fibroadenoma	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Adenocarcinoma/fibroadenoma	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Adenocarcinoma	< 0.0001	0.0726	0.0201	< 0.0001
Uterus with cervix	Glandular polyp	0.0032	1.0000	0.0454	0.1882
Male rats					
All organs	Malignant schwannoma	< 0.0001	1.0000	0.2387	0.0037
Brain	Astrocytoma	< 0.0001	1.0000	0.1767	0.0019
Mammary gland	Fibroadenoma	0.0001	0.4627	0.0561	0.0020
	Adenocarcinoma/Fibroadenoma	< 0.0001	0.4627	0.0132	0.0006
Skin/Skin, subcutis	schwannoma	0.0030	1.0000	0.4821	0.0478
	Squamous cell carcinoma	0.0008	1.0000	0.0612	0.0245
	Fibroma	< 0.0001	0.1707	0.0091	< 0.0001
Thyroid gland	Follicular cell adenoma	0.0357	0.0423	0.0669	0.0139

2.2 Reviewer's analysis

2.2.1 Survival Analysis

To verify the sponsor's analyses and to perform additional analysis 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.

Kaplan-Meier plots of the survival rates for the two sexes are shown in figures 1 and 2. The results of the significance tests for trend and homogeneity are presented in table 3 (on page 7). Intercurrent mortality data are presented in table 2 (on page 6).

The p -values for both the test of trend and the test of homogeneity are less than 0.0001 for both female and male rats. These tests, together with visual inspection of the Kaplan-Meier curves provides strong evidence that APD356 is indeed linked with increased mortality.

To further understand this relationship, a sequence of log-rank tests were conducted to compare survival of each treatment group with the control group. The results of these tests are shown in table 4. It is clear from these results that the female rats have experienced significantly increased mortality at every dose level. The male rats have only experienced significantly increased mortality at the high dose level.

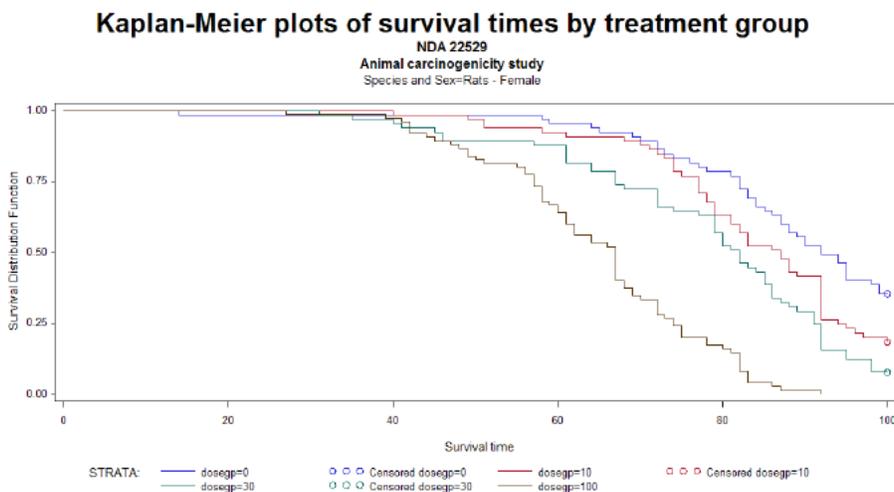
Table 2: Intercurrent mortality data across treatment groups

Species & Sex	Dose group	Dosage (mg/kg)	Number and percentage alive								
			Start	52 weeks	(%)	78 weeks	(%)	90 weeks	(%)	Termination	(%)
Rats - Female	Control	0	65	64	98.5	52	80.0	36	55.4	0	0.0
	Low dose	10	65	61	93.8	46	70.8	27	41.5	0	0.0
	Mid dose	30	65	58	89.2	41	63.1	19	29.2	0	0.0
	High dose	100	75	61	81.3	15	20.0	1	1.3	0	0.0
Rats - Male	Control	0	65	59	90.8	50	76.9	41	63.1	24	36.9
	Low dose	10	65	63	96.9	51	78.5	38	58.5	18	27.7
	Mid dose	30	65	60	92.3	51	78.5	37	56.9	22	33.8
	High dose	100	75	71	94.7	36	48.0	15	20.0	0	0.0

Table 3: Results of tests of survival homogeneity across treatment groups

Species and Sex	Number of dose groups	p -value (trend)	p -value (homogeneity)
Rats - Female	4	< 0.0001	< 0.0001
Rats - Male	4	< 0.0001	< 0.0001

Figure 1: Survival plots for female rats



2.2.2 Tumor data analysis

Theoretical underpinnings The tumor data were analyzed for dose response relationships and pairwise comparisons of tumor incidence in each of the treated groups versus the control group. Both the dose response relationship tests and pairwise comparisons were performed using the poly- k method described in the paper of Bailer and Portier[2] and developed in the paper of Bieler and Williams[3]. In this method, given a tumor type T , an animal h that lives the full study period (w_m) or dies before the terminal sacrifice with at least one tumor of type T gets a score of $s_h = 1$. An animal that dies at week w_h before the end of the study without such a tumor gets a score of

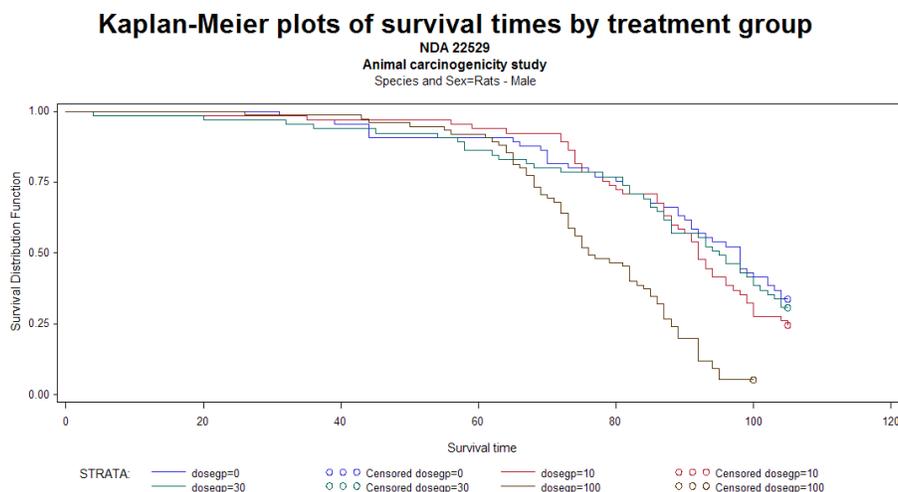
$$s_h = \left(\frac{w_h}{w_m} \right)^k < 1.$$

The adjusted group size is defined as $\sum_h s_h$. 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

Table 4: Log-rank tests of difference of survival between dose groups and controls (rats only)

Sex	Low dose		Mid dose		High dose	
	χ^2	p -value	χ^2	p -value	χ^2	p -value
Female	4.8542	0.0276	17.6363	< 0.0001	74.3302	< 0.0001
Male	1.1539	0.2827	0.2011	0.6538	32.3988	< 0.0001

Figure 2: Survival plots for male rats



up to the end of the study or if each animal develops at least one tumor of type T , 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. The test is repeated for each tumor type of T .

One critical point for poly- k test is the choice of the appropriate value of k , which depends on the relationship between tumor onset time and increased dose. For long term 104 week standard rat and mouse studies, a value of $k = 3$ is suggested in the literature. Hence, this reviewer used $k = 3$ for the analysis of this data. For the calculation of p -values the exact permutation method was used. The tumor rates and the p -values of the tested tumor types are listed in Table 6 on page 17.

For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of significance levels $\alpha = 0.005$ 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 study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control the FDA guidance suggested the use of test levels $\alpha = 0.01$ 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 [7]. In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin [9] showed that this rule for multiple testing for dose response relationship is also suitable for poly- k tests.

Reviewer's findings All individual tumor types reported in the data were tested. The following combination endpoints were also tested at the request of pharmacology reviewers request:

- All mammary tumors
- All malignant mammary tumors
- All mammary adenocarcinomas and fibroadenomas
- All brain tumors

- All malignant brain tumors
- All Gliomas
- All schwannomas.
- Hepatocellular adenomas and carcinomas
- Fibromas and fibrosarcomas of the the skin (subcutis)
- Squamous papillomas and squamous carcinomas of the skin
- Squamous papillomas and squamous carcinomas of the skin, together with keratoacanthomas
- Thyroidal follicular cell adenomas and carcinomas
- Cervical adenocarcinomas and glandular polyps

The results of the analyses of individual tumor types are presented in table 6 (page 17). The results of the analyses of composite endpoints are presented in table 7 (on page 47). The tumor types that showed p -values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of control and treated groups for at least one sex are shown in table 8 (on page 51).

Some of the composite endpoint analyses are redundant. Every female rat with a brain tumor had a malignant brain tumor, so the tables for female rats with brain tumors and female rats with malignant brain tumors are identical. This is not true of the male rats, where two rats (one in the mid dose group and one in the high dose group) did develop benign brain tumors but did not develop malignant brain tumors. Additionally, in female rats, all the animals who developed mammary tumors developed either adenocarcinomas or fibroadenomas, so the table of adenocarcinomas and fibroadenomas is identical to the table of all mammary tumors.

There are a great number of tumor types for which at least one significant result has been reported. However, many of these tumor types are instances of leukemia, and in fact are attributable to just a handful of animals who were found to have signs of leukemia in many sites. The appearance of these results in the table of significant outcomes is due to the fact that with the high mortality rate in the high dose group, a pattern where just two high dose animals develop a tumor, and none do in the other groups, yields a significant trend. In many of these cases, it was the same two animals who developed the tumors. These results should therefore be seen as duplicates of one another. Grouping all leukemias together does not yield any significant results. The results for all leukemias in rats have been included in table 7

Aside from the instances of leukemia, the following tumor types were found to have significant results ($\alpha < 0.05$) in at least one pairwise test, or the test of trend:

Brain	Astrocytoma
Liver	Hepatocellular adenoma
Lung	Carcinoma
Mammary gland	Adenocarcinoma
	Fibroadenoma
Skin	Carcinoma
Skin – subcutis	Fibroma
	Fibroma sarcoma
	Schwannoma
Thymus gland	Fibrosarcoma
	Schwannoma
Thyroid gland	C-cell adenoma
	Follicular adenoma
Cervix	Glandular polyps

Among these, only the tumors of the thymus gland and the C-cell adenomas of the thyroid gland failed to remain significant in either the test of trend or the pairwise comparison of the high

dose with the control after making the appropriate multiplicity adjustments. These tumors will not be discussed further here. Additionally, the test of trend of incidence of fibrosarcomas of the skin was found to be slightly significant for the female rats (assuming that this is considered to be a rare cancer). However, only three rats in all developed such tumors; two high dose females and one control male, so it is not possible to make a strong conclusion about whether APD356 has a carcinogenicity effect for this type of tumor.

All instances of carcinoma of the lung were classified as “secondary”, and so will not be discussed further here.

The remaining nine tumor types are therefore the tumor types for which the results of *both* the test of trend and the pairwise test between the control and high dose groups are significant, even after adjusting for multiplicity. Therefore, even if we take a conservative approach of requiring both tests to be significant, we must consider the study to have found strongly suggestive evidence of all of these effects.

Of these nine tumor types, three groups stand out as being worthy of particular attention.

Mammary tumors The first group are the mammary tumors. In the case of the adenocarcinomas, the results of both the trend test and the pairwise comparison between the high dose group and the low dose group were strongly significant ($p < 0.0001$) for the female rats. However, the poly-3 adjusted incidence rate was very high, even in the control group (50.6% — it was 91% in the high dose group), suggesting that these rats were especially prone to mammary adenocarcinomas. Nonetheless, it must be recognised that there was a strong dose response, so that the most likely explanation is that APD356 was at least contributing to the incidence of these tumors.

Among the male rats, the trend was significant at the 5% level, but none of the pairwise comparisons were significant. However, the raw numbers are still striking — no male rats in the control or low dose groups developed mammary adenocarcinomas, but 2 animals in each of the mid and high dose groups did (for adjusted incidence rates of 4.5% and 5.7% respectively). After adjusting for the multiplicity of endpoints being tested, such results would not normally be considered noteworthy, but in conjunction with the clear carcinogenicity effect displayed in the female study, these results can be seen as strongly corroboratory.

The results for mammary fibroadenomas were even more striking. Among the females, the p -value of the test of trend and the p -value for all three comparisons with control were all less than 0.0001. The incidence rates were 39% for the control animals, but 86%, 94% and 88% for the low, mid, and high dose animals respectively. Among the male rats, the test of trend ($p = 0.0017$) and the pairwise test between the control group and the high dose group ($p = 0.0054$) were both significant, even after adjusting for multiplicity. No male control animals developed mammary fibroadenomas, but the rate was 8.8% in the mid dose group and 17% in the high dose group.

Given these results, it is not surprising that the analysis of all mammary adenocarcinomas and fibroadenomas (and so, by extension, the identical analysis all mammary tumors in female rats) yield strongly significant results in the test for trend, and at all dose levels (in the case of female rats), and in the test of trend, and the high-control comparison (male rats). The p -values were less than 0.0001 for the test of trend in the female rats, and for the comparisons between both the mid and high dose groups with control. The p -value of the comparison between the low dose group and the control group was 0.0004. Strikingly, the incidence rates for the female rats were exceptionally high: 69% for the controls, and above 90% for each of the treatment groups. For the male rats, the p -value for the test of trend was 0.0008, and the p -value for the comparison test between the control and high dose animals was 0.0009. Both of these results remain significant after adjusting for multiplicity. These strong results for the male rats are driven by the fact that eight male animals developed mammary adenocarcinomas or fibromas in the high dose group (22%) compared with none in the control group.

The analysis of malignant mammary tumors in female rats is the same as the analysis of mammary adenocarcinomas (as all the animals who developed a malignant mammary tumor developed a mammary adenocarcinoma), and so produces the same results. Among the male rats however, the results for malignant mammary tumors are weaker than the results for adenocarcinomas; this is due to the presence of three male rats who developed blood cancers with secondary tumors reported in the mammary glands (two control animals with lymphoma, and one high dose animal

with leukemia).

Skin tumors The second group worthy of detailed elaboration are skin tumors, especially in male rats. In the case of subcutaneous fibromas, the test of trend has a p -value less than 0.0001, and the test of comparison with control is significant for both the mid and high dose groups ($p = 0.0175$ and $p < 0.0001$ respectively). The incidence rates show a clear trend: 6.5% for the controls, 15% for the low dose group, 24% for the mid dose group, and 43% for the high dose group.

Also compelling are the results for subcutaneous schwannomas: the test for trend has a p -value of 0.0006, and the test of comparison between the high dose group and the control has a p -value of 0.0147. In fact, only six male rats developed subcutaneous schwannomas; five were in the high dose group, and the other was in the mid dose group. No female rats developed such tumors.

Additionally, the male rats also displayed a significant dose response ($p = 0.0030$) and pairwise comparison between the high dose group and control ($p = 0.0147$) for squamous carcinomas of the skin. Nine male rats developed such tumors; four in the mid dose group and five in the high dose group. No control animals developed these tumors.

In the case of all of these tumor types, the results from the females were less remarkable; only four female rats (one in the high dose group, the remainder in the low dose group) developed subcutaneous fibromas, and none at all developed schwannomas, or squamous carcinomas of the skin.

When subcutaneous fibromas and fibrosarcomas are combined, the results remain significant for male rats, although this is largely due to the fact that fibromas, which were already known to be significant, dominate the fibrosarcomas numerically. The p values for the test of trend and pairwise comparison of the high dose group with the control group are $p = 0.0001$ and $p = 0.0002$ respectively. Among female rats, slightly significant results are also found for this combined endpoint; the low survival rate for the high dose group mean that although only three high dose animals developed such tumors (compared with no control animals), this was enough to reach significance at the 5% level; the p -value of the comparison between the high dose group and the control group was 0.0354. The test of trend was also significant, with a p -value of 0.0388.

When squamous papillomas and carcinomas are combined for male rats, the results are similar to the analysis of squamous carcinomas, the results being just slightly diluted by the addition of four animals who developed squamous papillomas (one each in the control and mid dose groups, and two in the high dose group). When squamous papillomas and carcinomas are further combined with keratoacanthomas, the test of trend is significant $p = 0.0009$, but the comparison test between the high dose group and control group is not significant at the 1% level — the p -value is 0.0114. This is weaker than the result for squamous tumors alone because of the case of a keretoacanthoma in one of the control rats. No female rats developed any of these three types of tumor.

Astrocytomas and other brain tumors The most frequently reported brain tumors in the study were astrocytomas. Among male rats, the poly-3 adjusted incidence rate was 2.2% in the control group, but 8.8% in the mid dose group, and 22% in the high dose group. Unsurprisingly the test of trend was strongly significant ($p = 0.0002$), as was the pairwise test between the controls and the high dose group ($p = 0.0056$). These results easily meet the criteria for multiplicity adjustment, and so provide strong evidence of a carcinogenic effect. However, as with the skin tumors, the results among the female rats were not so notable, with only three rats (two in the low dose group and one in the high dose group) developing these tumors. (By comparison, 13 male rats developed astrocytomas; 12 of them in the mid or high dose groups.)

When all brain tumors were combined, the results remained significant (test for trend: $p = 0.0001$, pairwise test between controls and high dose group: $p = 0.0059$). However, these results were largely driven by the astrocytomas; only eleven male mice developed brains tumors without developing astrocytomas (three controls, one each in the low and mid dose groups, and four high dose animals), five of which had leukemia or lymphoma. Consideration of only malignant brain tumors yields similar results, as only two animals (one in the mid dose group and one in the high dose group) developed benign brain tumors (the corresponding p -values are 0.0002 and 0.0099). When all gliomas are combined (including astrocytomas, carcinomas, mixed gliomas, oligodendrogliomas

and reticulosis) the results were similar, with a strongly significant trend ($p < 0.0001$) and difference between the control and high dose groups ($p = 0.0026$).

Other single tumor types Of the remaining noteworthy tumor types, in the case of follicular adenomas of the thyroid gland, the test of trend ($p = 0.0035$) and pairwise comparisons of both the low and the high dose group with control ($p = 0.0278$ and $p = 0.0011$ respectively) appear strongly significant in male rats, and the comparison between the mid dose group with the control group just missed significance ($p = 0.0583$). While no control animals developed such tumors, five low dose, four mid dose, and eight high dose animals did. The results from the female rats, while not significant, provide at least partial corroboration: the test of trend has a p -value of 0.0969.

The other two types of tumor (hepatocellular adenoma of the liver, and glandular polyps of the cervix), while both providing strong, although not overwhelming, evidence of a carcinogenic effect in one sex (females in the case of glandular polyps of the cervix, males in the case of the hepatocellular adenomas), there are no instances at all of these types of tumors being detected in the other sex (although this is to be expected in the case of the polyps of the cervix). For details, see table 8.

Other composite endpoints When all schwannomas are combined, the most striking feature is the high poly-3 adjusted incidence rate in the high dose male group: 23%. Given that no control or low dose male rats, and eleven mid and high dose rats (two in the mid dose group and nine in the high dose group) developed schwannomas, it is not surprising that the p -values for both the test of trend and for the test of comparison between the control group and the high dose group are strongly significant ($p < 0.0001$ and $p = 0.0006$ respectively). Six of these animals (five in the high dose group and one in the mid dose group) had subcutaneous schwannomas. It is not possible to make any firm statements about the effect of APD356 on the development of schwannomas in female rats, as only one female rat (in the mid dose group) developed a schwannoma.

When all hepatocellular adenomas and carcinomas are combined, we find, in the male study, a pattern of two control animals, four low dose animals, four mid dose animals, and ten high dose animals with these tumors. The corresponding test of trend is strongly significant ($p = 0.0012$), as is the pairwise comparison between the controls and the high dose animals ($p = 0.0048$). These are stronger p -values than were reported for hepatocellular adenomas on their own. (Only two female rats, one control and one high dose animal, developed such tumors — the results are not significant.)

In the case of thyroidal follicular adenomas and carcinomas, the test for trend and the comparison between the control and high dose groups both yield significant results in the male rats ($p = 0.0053$ and $p = 0.0028$ respectively). However, these results are unsurprising given the strong results already observed in the analysis of follicular adenomas; including the follicular carcinomas added just one case to each dose level.

Finally, the analysis of adenocarcinomas and benign glandular polyps of the uterus and cervix yields a significant result for the test of trend $p = 0.0189$, but not for any of the pairwise comparisons of the groups. Note that only one animal (a control animal) developed a uterine/cervical adenocarcinoma, but that six animals developed benign glandular polyps; three each in the mid and high dose groups. The comparison of the incidences of the just the polyps in the control and high dose groups yields a result that is just significant ($p = 0.0354$), but fails to retain its significance after adjusting for multiplicity.

Survival analysis of time to death with mammary tumor Finally, two survival analyses have been performed. The endpoint are (non-sacrificed) death with a malignant mammary tumor, and (non-sacrificed) death with a malignant brain tumor. All other forms of death, including sacrifice, are considered censoring. A log-rank test of homogeneity has been performed, and Kaplan-Meier curves have been plotted. The results are summarized in table 5. Note that no attempt has been made to incorporate cause of death into this analysis — the event of interest is simply all-cause death *after* developing a malignant mammary or malignant brain tumor. The results tell us little except in the cases of mammary tumors in female rats and brain tumors in male rats, as the event

rates is quite low in the other cases. In these two cases, however, the impact of the high tumor incidence rates is clearly visible in the survival plots.

Table 5: Results of survival analysis using death with tumor as an endpoint

Sex and species	<i>p</i> -value of log rank test
Death with malignant mammary tumor	
Rats - female	< 0.0001
Mice - female	0.6786
Death with malignant brain tumor	
Rats - female	0.1534
Rats - male	< 0.0001
Mice - female	0.4438
Mice - male	0.5868

The survival plots are shown as figures 3 and 4 (for the mammary tumors) and figures 5–8 (for the brain tumors).

Figure 3

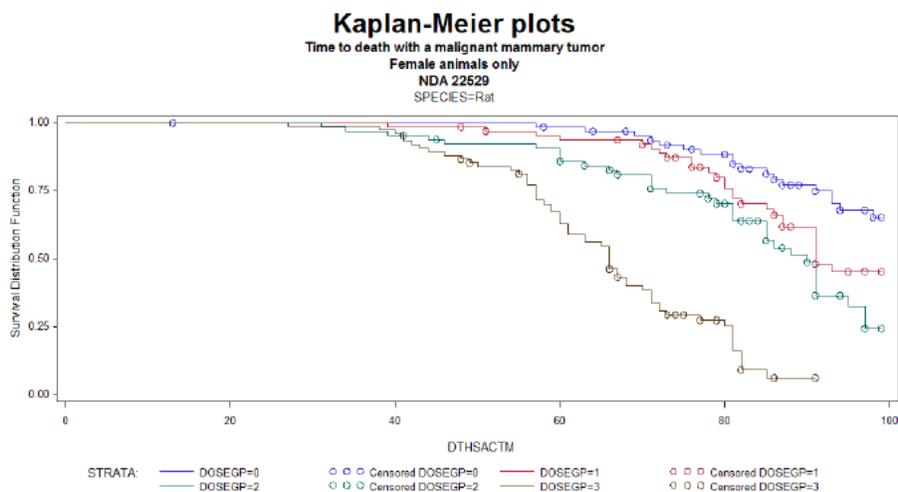


Figure 4

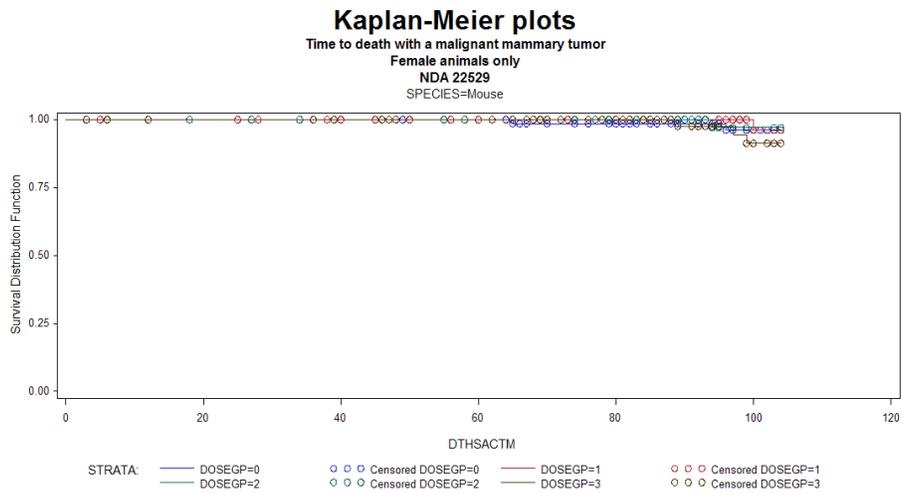


Figure 5

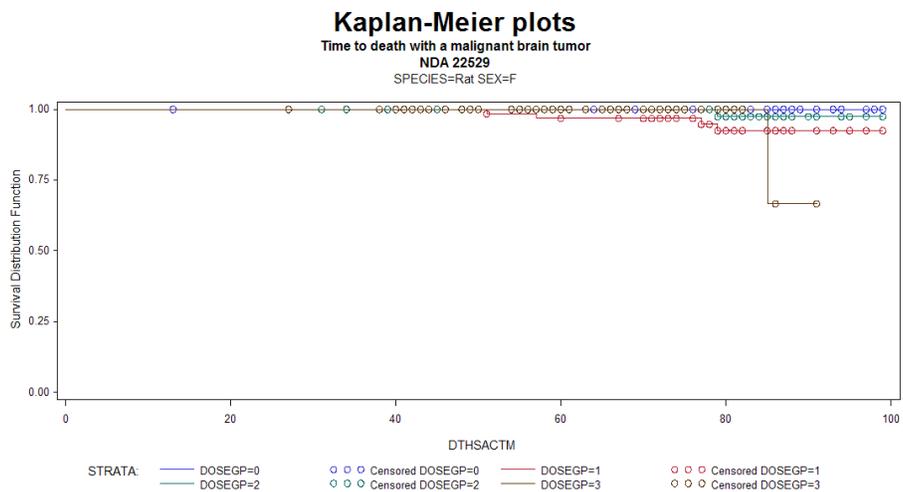


Figure 6

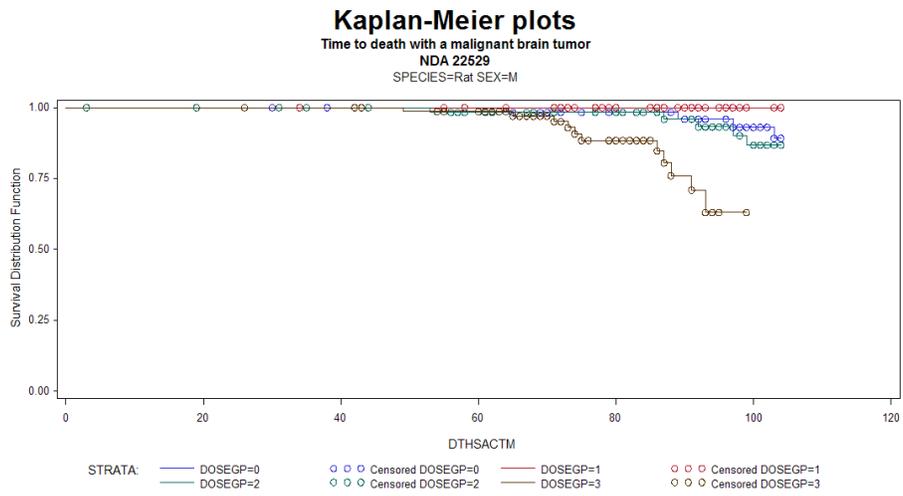


Figure 7

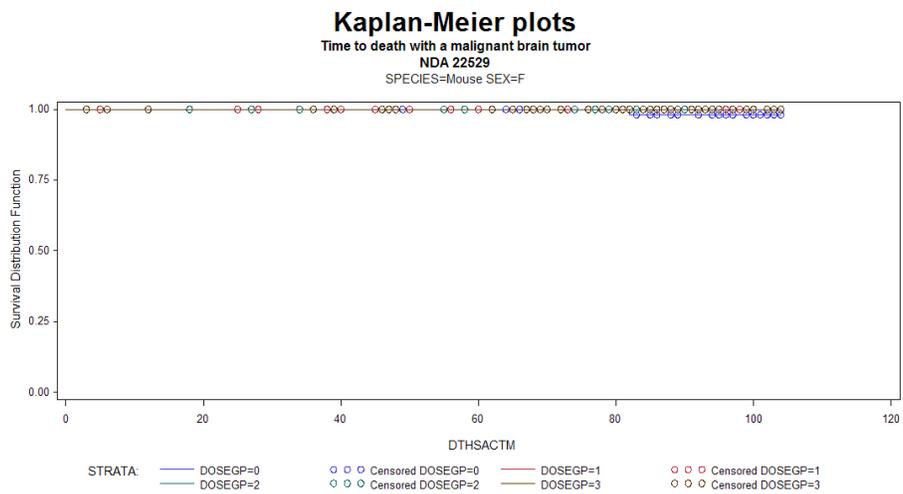


Figure 8

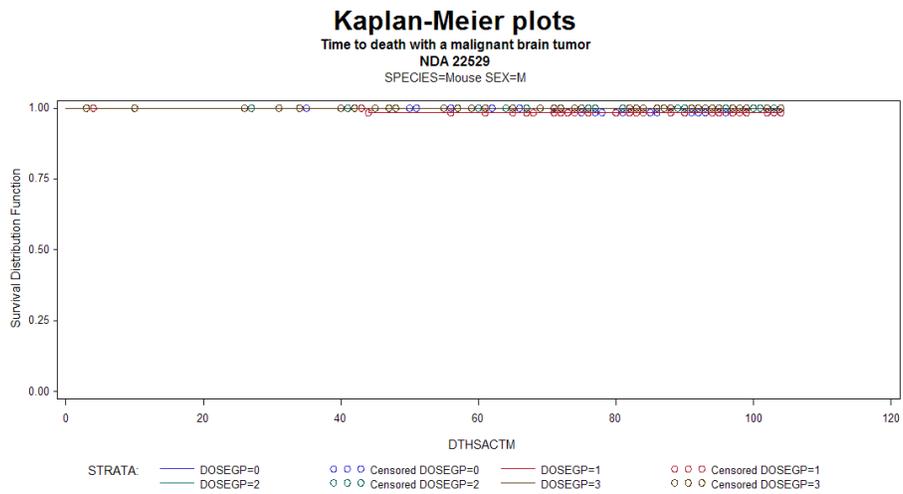


Table 6: Table of all reported neoplastic tumors in rat study

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose	
adipose tissue	CARCINOMA, RETE TEST	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%	
			Observed number of cases	0	0	0	1	
	HIBERNOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%	
			Observed number of cases	0	0	0	1	
	LIPOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%	
			Observed number of cases	0	0	0	1	
adipose tissue, brown	HIBERNOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%	
			Observed number of cases	0	0	0	1	
adipose tissue, brown, intersca	HIBERNOMA	Female	<i>p</i> -value of pairwise and trend tests	.1586			.3286	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	4.2%	
			Observed number of cases	0	0	0	1	
adrenal glands	ADENOMA, CORTICAL	Female	<i>p</i> -value of pairwise and trend tests	.1000		.4268	.3286	
			Poly-3 adjusted incidence rate	.00%	.00%	2.8%	4.3%	
			Observed number of cases	0	0	1	1	
			Male	<i>p</i> -value of pairwise and trend tests	.1477		.4886	.4304
				Poly-3 adjusted incidence rate	.00%	.00%	2.3%	2.9%
				Observed number of cases	0	0	1	1
		CARCINOMA, CORTICAL	Female	<i>p</i> -value of pairwise and trend tests	.7078	.2142		
				Poly-3 adjusted incidence rate	.00%	4.8%	.00%	.00%
				Observed number of cases	0	2	0	0
	CARCINOMA, RETE TEST	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%	
			Observed number of cases	0	0	0	1	
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.7141	1.000	.7472	1.000	
			Poly-3 adjusted incidence rate	2.2%	.00%	2.3%	.00%	
			Observed number of cases	1	0	1	0	
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%	
			Observed number of cases	0	0	0	2	
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659			

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
	OSTEOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.2%	.00%
			Observed number of cases	0	0	1	0
	PHEOCHROMOCYTOMA	Female	<i>p</i> -value of pairwise and trend tests	.7945	.6384	.5735	1.000
			Poly-3 adjusted incidence rate	4.2%	4.8%	5.6%	.00%
			Observed number of cases	2	2	2	0
		Male	<i>p</i> -value of pairwise and trend tests	.9860	.9584	.9584	.9975
			Poly-3 adjusted incidence rate	19%	9.0%	9.0%	2.9%
			Observed number of cases	9	4	4	1
	RENAL MESENCHYMAL TU	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.5695	.4944	.4944	
			Poly-3 adjusted incidence rate	.00%	2.3%	2.3%	.00%
			Observed number of cases	0	1	1	0
aorta	HIBERNOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
bone marrow, femur	LEUKEMIA, GRANULOCYT	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.1%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.8633	1.000	.8708	1.000
			Poly-3 adjusted incidence rate	4.3%	.00%	2.2%	.00%
			Observed number of cases	2	0	1	0
	SARCOMA, HISTIOCYTIC	Female	<i>p</i> -value of pairwise and trend tests	.3889		.4198	
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	.00%
			Observed number of cases	0	0	1	0
		Male	<i>p</i> -value of pairwise and trend tests	.5613	.4944	.2416	
			Poly-3 adjusted incidence rate	.00%	2.3%	4.5%	.00%
			Observed number of cases	0	1	2	0
	SCHWANNOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
bone marrow, sternum	LEUKEMIA, GRANULOCYT	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.1%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.7111	1.000	.7416	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.2%	.00%
			Observed number of cases	1	0	1	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.5695	.4944	.4944	
			Poly-3 adjusted incidence rate	.00%	2.3%	2.3%	.00%

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	0	1	1	0
bone, femur	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	.7111	1.000	.7416	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.2%	.00%
			Observed number of cases	1	0	1	0
bone, sternum	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	.7111	1.000	.7416	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.2%	.00%
			Observed number of cases	1	0	1	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
brain	ASTROCYTOMA	Female	<i>p</i> -value of pairwise and trend tests	.2661	.2199		.3286
			Poly-3 adjusted incidence rate	.00%	4.7%	.00%	4.3%
			Observed number of cases	0	2	0	1
		Male	<i>p</i> -value of pairwise and trend tests	.0002	1.000	.1804	.0056
			Poly-3 adjusted incidence rate	2.2%	.00%	8.8%	22%
			Observed number of cases	1	0	4	8
	CARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.7069	.2255		
			Poly-3 adjusted incidence rate	.00%	4.6%	.00%	.00%
			Observed number of cases	0	2	0	0
	GRANULAR CELL TUMOR	Male	<i>p</i> -value of pairwise and trend tests	.1477		.4886	.4304
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	2.9%
			Observed number of cases	0	0	1	1
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.7141	1.000	.7472	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.3%	.00%
			Observed number of cases	1	0	1	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	MIXED GLIOMA	Female	<i>p</i> -value of pairwise and trend tests	.3931		.4268	

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	.00%	.00%	2.8%	.00%
			Observed number of cases	0	0	1	0
		Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	OLIGODENDROGLIOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	RETICULOSIS	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
cavity, abdominal	CARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
	HIBERNOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.1484		.4944	.4304
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	2.9%
			Observed number of cases	0	0	1	1
	SARCOMA, UNDIFFERENT	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	SCHWANNOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
cavity, thoracic	HIBERNOMA	Male	<i>p</i> -value of pairwise and trend tests	.2000			.4231
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	SCHWANNOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
coagulating glands	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
endocardium	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
epididymides	CARCINOMA, RETE TEST	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.3647	.2416		.4304
			Poly-3 adjusted incidence rate	.00%	4.5%	.00%	2.9%

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	0	2	0	1
	SARCOMA, UNDIFFERENT	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
esophagus	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	4.3%	.00%	.00%	.00%
			Observed number of cases	2	0	0	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7805	.2416		
			Poly-3 adjusted incidence rate	.00%	4.5%	.00%	.00%
			Observed number of cases	0	2	0	0
eyes	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	SCHWANNOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
eyes, optic nerves	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
harderian glands	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
heart	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.7141	1.000	.7472	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.3%	.00%
			Observed number of cases	1	0	1	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.3667	1.000	1.000	.6725
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	2.9%
			Observed number of cases	1	0	0	1
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.9268	.7472	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	2.3%	.00%	.00%
			Observed number of cases	1	1	0	0
	OSTEOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.2%	.00%
			Observed number of cases	0	0	1	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7805	.2416		
			Poly-3 adjusted incidence rate	.00%	4.5%	.00%	.00%
			Observed number of cases	0	2	0	0
joint, tibiofemoral	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	.7111	1.000	.7416	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.2%	.00%
			Observed number of cases	1	0	1	0
kidneys	ADENOMA, TUBULAR CEL	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.9244	.7416	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	2.3%	.00%	.00%
			Observed number of cases	1	1	0	0

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
	CARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.1586			.3286
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	4.2%
			Observed number of cases	0	0	0	1
	CARCINOMA, TRANSITIO	Female	<i>p</i> -value of pairwise and trend tests	.3889		.4198	
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	.00%
			Observed number of cases	0	0	1	0
	CARCINOMA, TUBULAR C	Female	<i>p</i> -value of pairwise and trend tests	.1586			.3286
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	4.3%
			Observed number of cases	0	0	0	1
		Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.7141	1.000	.7472	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.3%	.00%
			Observed number of cases	1	0	1	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LIPOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LIPOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.2%	.00%	.00%
			Observed number of cases	0	1	0	0
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.8633	1.000	.8708	1.000
			Poly-3 adjusted incidence rate	4.3%	.00%	2.2%	.00%
			Observed number of cases	2	0	1	0
	RENAL MESENCHYMAL TU	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.6738	.2416	.4944	
			Poly-3 adjusted incidence rate	.00%	4.5%	2.3%	.00%

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	0	2	1	0
	SCHWANNOMA	Male	<i>p</i> -value of pairwise and trend tests	.4606		.4886	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
lacrimal glands, exorbital	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	.7111	1.000	.7416	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.2%	.00%
			Observed number of cases	1	0	1	0
large intestine, cecum	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7805	.2416		
			Poly-3 adjusted incidence rate	.00%	4.5%	.00%	.00%
			Observed number of cases	0	2	0	0
large intestine, colon	LEIOMYOMA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.2%	.00%
			Observed number of cases	0	0	1	0
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7805	.2416		
			Poly-3 adjusted incidence rate	.00%	4.5%	.00%	.00%
			Observed number of cases	0	2	0	0
large intestine, rectum	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7805	.2416		

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	.00%	4.5%	.00%	.00%
			Observed number of cases	0	2	0	0
	SARCOMA, UNDIFFERENT	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
liver	ADENOMA, HEPATOCELLU	Male	<i>p</i> -value of pairwise and trend tests	.0033	.7472	.4915	.0302
			Poly-3 adjusted incidence rate	2.2%	2.3%	4.5%	16%
			Observed number of cases	1	1	2	6
	CARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.1895	.4659		.3286
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	4.2%
			Observed number of cases	0	1	0	1
	CARCINOMA, HEPATOCEL	Female	<i>p</i> -value of pairwise and trend tests	.2930	1.000	1.000	.5524
			Poly-3 adjusted incidence rate	2.1%	.00%	.00%	4.2%
			Observed number of cases	1	0	0	1
		Male	<i>p</i> -value of pairwise and trend tests	.0770	.3000	.3000	.1067
			Poly-3 adjusted incidence rate	2.2%	6.6%	6.7%	11%
			Observed number of cases	1	3	3	4
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.7141	1.000	.7472	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.3%	.00%
			Observed number of cases	1	0	1	0
	LEUKEMIA, GRANULOCYT	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.1%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.8633	1.000	.8708	1.000
			Poly-3 adjusted incidence rate	4.3%	.00%	2.2%	.00%
			Observed number of cases	2	0	1	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
	SARCOMA, HISTIOCYTIC	Female	<i>p</i> -value of pairwise and trend tests	.3889		.4198	
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	.00%
			Observed number of cases	0	0	1	0
		Male	<i>p</i> -value of pairwise and trend tests	.7533	.1166	.2416	
			Poly-3 adjusted incidence rate	.00%	6.7%	4.5%	.00%
			Observed number of cases	0	3	2	0
	SARCOMA, UNDIFFERENT	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
lung	CARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.0065	.0483	.0005	.0016
			Poly-3 adjusted incidence rate	.00%	9.3%	22%	22%
			Observed number of cases	0	4	9	6
	CARCINOMA, BRONCHIOL	Female	<i>p</i> -value of pairwise and trend tests	.3931		.4268	
			Poly-3 adjusted incidence rate	.00%	.00%	2.8%	.00%
			Observed number of cases	0	0	1	0
	CARCINOMA, HEPATOCEL	Male	<i>p</i> -value of pairwise and trend tests	.5676	.4944	.4886	
			Poly-3 adjusted incidence rate	.00%	2.3%	2.3%	.00%
			Observed number of cases	0	1	1	0
	CARCINOSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	.1586			.3286
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	4.3%
			Observed number of cases	0	0	0	1
	FIBROSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	HEMANGIOSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	.3931		.4268	
			Poly-3 adjusted incidence rate	.00%	.00%	2.8%	.00%
			Observed number of cases	0	0	1	0
	HIBERNOMA	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.2%	.00%	.00%
			Observed number of cases	0	1	0	0
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.7141	1.000	.7472	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.3%	.00%
			Observed number of cases	1	0	1	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	0	0	0	2
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	.8633	1.000	.8708	1.000
			Poly-3 adjusted incidence rate	4.3%	.00%	2.2%	.00%
			Observed number of cases	2	0	1	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.9268	.7472	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	2.3%	.00%	.00%
			Observed number of cases	1	1	0	0
	OSTEOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.2%	.00%
			Observed number of cases	0	0	1	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.6641	.2416	.2416	
			Poly-3 adjusted incidence rate	.00%	4.5%	4.5%	.00%
			Observed number of cases	0	2	2	0
	SCHWANNOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
lymph node, axillary	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
lymph node, cervical	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.2%	.00%
			Observed number of cases	0	0	1	0
lymph node, hepatic	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
lymph node, iliac	HEMANGIOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
lymph node, inguinal	CARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.3931		.4268	
			Poly-3 adjusted incidence rate	.00%	.00%	2.8%	.00%
			Observed number of cases	0	0	1	0
	CARCINOMA, SQUAMOUS	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	HEMANGIOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
lymph node, mandibular	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.8633	1.000	.8708	1.000
			Poly-3 adjusted incidence rate	4.3%	.00%	2.2%	.00%
			Observed number of cases	2	0	1	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.4281		.2416	
			Poly-3 adjusted incidence rate	.00%	.00%	4.5%	.00%
			Observed number of cases	0	0	2	0
lymph node, mediastinal	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.9214	.4915	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	4.5%	.00%	.00%
			Observed number of cases	1	2	0	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.5695	.4944	.4944	
			Poly-3 adjusted incidence rate	.00%	2.3%	2.3%	.00%
			Observed number of cases	0	1	1	0

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
lymph node, mesenteric	CARCINOMA, RETE TEST	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	HEMANGIOMA	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.8633	1.000	.8708	1.000
			Poly-3 adjusted incidence rate	4.3%	.00%	2.2%	.00%
			Observed number of cases	2	0	1	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
	SARCOMA, HISTIOCYTIC	Female	<i>p</i> -value of pairwise and trend tests	.3889		.4198	
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	.00%
			Observed number of cases	0	0	1	0
		Male	<i>p</i> -value of pairwise and trend tests	.5613	.4944	.2416	
			Poly-3 adjusted incidence rate	.00%	2.3%	4.5%	.00%
			Observed number of cases	0	1	2	0
lymph node, renal	RENAL MESENCHYMAL TU	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
mammary gland	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	< 0.0001	.1407	.0632	< 0.0001
			Poly-3 adjusted incidence rate	51%	62%	66%	91%
			Observed number of cases	28	34	35	60
		Male	<i>p</i> -value of pairwise and trend tests	.0464		.2416	.1883
			Poly-3 adjusted incidence rate	.00%	.00%	4.5%	5.7%

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	0	0	2	2
	CARCINOSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	.1586			.3286
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	4.3%
			Observed number of cases	0	0	0	1
	FIBROADENOMA	Female	<i>p</i> -value of pairwise and trend tests	< 0.0001	< 0.0001	< 0.0001	< 0.0001
			Poly-3 adjusted incidence rate	39%	86%	94%	88%
			Observed number of cases	20	47	53	45
		Male	<i>p</i> -value of pairwise and trend tests	.0017	.4944	.0583	.0054
			Poly-3 adjusted incidence rate	.00%	2.3%	8.8%	17%
			Observed number of cases	0	1	4	6
	HEMANGIOSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	.3931		.4268	
			Poly-3 adjusted incidence rate	.00%	.00%	2.8%	.00%
			Observed number of cases	0	0	1	0
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	4.3%	.00%	.00%	.00%
			Observed number of cases	2	0	0	0
mediastinum	CARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.1895	.4659		.3286
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	4.2%
			Observed number of cases	0	1	0	1
mesentery/peritoneum	CARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
	SARCOMA, UNDIFFERENT	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
multicentric neoplasm	HEMANGIOMA	Female	<i>p</i> -value of pairwise and trend tests	.3931		.4268	
			Poly-3 adjusted incidence rate	.00%	.00%	2.8%	.00%
			Observed number of cases	0	0	1	0
		Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
	HEMANGIOSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	.4037		.0777	
			Poly-3 adjusted incidence rate	.00%	.00%	8.2%	.00%
			Observed number of cases	0	0	3	0
		Male	<i>p</i> -value of pairwise and trend tests	.4883	1.000	.8708	.8152
			Poly-3 adjusted incidence rate	4.3%	.00%	2.3%	2.9%
			Observed number of cases	2	0	1	1
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.3226	1.000	.7472	.6787
			Poly-3 adjusted incidence rate	2.2%	.00%	2.3%	2.9%
			Observed number of cases	1	0	1	1
	LEUKEMIA, GRANULOCYT	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.1%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.7444	.2668	.3897	1.000
			Poly-3 adjusted incidence rate	2.1%	7.1%	5.7%	.00%
			Observed number of cases	1	3	2	0
		Male	<i>p</i> -value of pairwise and trend tests	.4883	1.000	.8708	.8152
			Poly-3 adjusted incidence rate	4.3%	.00%	2.2%	2.9%
			Observed number of cases	2	0	1	1
	SARCOMA, HISTIOCYTIC	Female	<i>p</i> -value of pairwise and trend tests	.3889		.4198	
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	.00%
			Observed number of cases	0	0	1	0
		Male	<i>p</i> -value of pairwise and trend tests	.5428	.0583	.2416	.4304
			Poly-3 adjusted incidence rate	.00%	8.8%	4.5%	2.9%
			Observed number of cases	0	4	2	1
nerve, sciatic	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose	
ovaries	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659			
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%	
			Observed number of cases	0	1	0	0	
	SARCOMA, UNDIFFERENT	Female	<i>p</i> -value of pairwise and trend tests	.1586			.3286	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	4.3%	
			Observed number of cases	0	0	0	1	
	SEX-CORD/STROMAL TUM	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659			
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%	
			Observed number of cases	0	1	0	0	
pancreas	ADENOMA, ISLET CELL	Female	<i>p</i> -value of pairwise and trend tests	.5084	.2583	1.000	.5524	
			Poly-3 adjusted incidence rate	2.1%	7.2%	.00%	4.3%	
			Observed number of cases	1	3	0	1	
			Male	<i>p</i> -value of pairwise and trend tests	.0778	.9377	.9377	.3286
				Poly-3 adjusted incidence rate	11%	4.5%	4.5%	16%
				Observed number of cases	5	2	2	6
	CARCINOMA, ISLET CEL	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000	
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%	
			Observed number of cases	1	0	0	0	
	CARCINOMA, RETE TEST	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%	
			Observed number of cases	0	0	0	1	
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000	
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%	
			Observed number of cases	1	0	0	0	
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%	
			Observed number of cases	0	0	0	1	
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659			
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%	
			Observed number of cases	0	1	0	0	
		Male	<i>p</i> -value of pairwise and trend tests	.8633	1.000	.8708	1.000	
			Poly-3 adjusted incidence rate	4.3%	.00%	2.2%	.00%	
			Observed number of cases	2	0	1	0	
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304	
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%	

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	0	1	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.3358	.2416	.4944	.4304
			Poly-3 adjusted incidence rate	.00%	4.5%	2.3%	2.9%
			Observed number of cases	0	2	1	1
parathyroid glands	ADENOMA	Female	<i>p</i> -value of pairwise and trend tests	.1586			.3286
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	4.3%
			Observed number of cases	0	0	0	1
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
peyers patch	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.4758	.4659	.4268	
			Poly-3 adjusted incidence rate	.00%	2.4%	2.9%	.00%
			Observed number of cases	0	1	1	0
		Male	<i>p</i> -value of pairwise and trend tests	.7111	1.000	.7416	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.2%	.00%
			Observed number of cases	1	0	1	0
pituitary gland	ADENOMA, PARS DISTAL	Female	<i>p</i> -value of pairwise and trend tests	.9992	.4959	.9758	.9987
			Poly-3 adjusted incidence rate	83%	84%	68%	57%
			Observed number of cases	50	46	31	20
		Male	<i>p</i> -value of pairwise and trend tests	.9723	.9623	.9699	.9939
			Poly-3 adjusted incidence rate	61%	45%	45%	37%
			Observed number of cases	32	22	22	15
	ADENOMA, PARS INTERM	Male	<i>p</i> -value of pairwise and trend tests	.2512	.4944		.4231
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
	CARCINOMA, PARS DIST	Female	<i>p</i> -value of pairwise and trend tests	.7069	.2255		
			Poly-3 adjusted incidence rate	.00%	4.6%	.00%	.00%
			Observed number of cases	0	2	0	0
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
prostate gland	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	.8633	1.000	.8708	1.000
			Poly-3 adjusted incidence rate	4.3%	.00%	2.2%	.00%
			Observed number of cases	2	0	1	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
salivary gland, mandibular	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
salivary gland, parotid	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.3889		.4198	
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	.00%
			Observed number of cases	0	0	1	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	OSTEOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
salivary gland, sublingual	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
seminal vesicles	CARCINOMA, RETE TEST	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
skeletal muscle	OSTEOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.2%	.00%
			Observed number of cases	0	0	1	0
skeletal muscle, biceps femoris	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
skin	ADENOMA, SEBACEOUS C	Female	<i>p</i> -value of pairwise and trend tests	.6759	.4719		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	0	1	0	0
	CARCINOMA, SQUAMOUS	Male	<i>p</i> -value of pairwise and trend tests	.0030		.0583	.0147
			Poly-3 adjusted incidence rate	.00%	.00%	8.8%	14%
			Observed number of cases	0	0	4	5
	CARCINOMA, ZYMBALS G	Female	<i>p</i> -value of pairwise and trend tests	.3889		.4198	
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	.00%
			Observed number of cases	0	0	1	0
	HEMANGIOSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	.3931		.4268	
			Poly-3 adjusted incidence rate	.00%	.00%	2.8%	.00%
			Observed number of cases	0	0	1	0
	KERATOACANTHOMA	Male	<i>p</i> -value of pairwise and trend tests	.1682	.7472	1.000	.3949
			Poly-3 adjusted incidence rate	2.2%	2.3%	.00%	5.7%
			Observed number of cases	1	1	0	2
	LYMPHANGIOMA	Female	<i>p</i> -value of pairwise and trend tests	.1586			.3286
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	4.3%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.7035	.7176	.6745	1.000
			Poly-3 adjusted incidence rate	2.1%	2.4%	2.8%	.00%
			Observed number of cases	1	1	1	0
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	PAPILLOMA, SQUAMOUS	Male	<i>p</i> -value of pairwise and trend tests	.1142	1.000	.7472	.3949
			Poly-3 adjusted incidence rate	2.2%	.00%	2.3%	5.8%
			Observed number of cases	1	0	1	2
skin, subcutis	FIBROMA	Female	<i>p</i> -value of pairwise and trend tests	.3709	.1011		.3286
			Poly-3 adjusted incidence rate	.00%	7.1%	.00%	4.3%
			Observed number of cases	0	3	0	1
		Male	<i>p</i> -value of pairwise and trend tests	< 0.0001	.1577	.0175	< 0.0001
			Poly-3 adjusted incidence rate	6.5%	15%	24%	43%
			Observed number of cases	3	7	11	17
	FIBROSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	.0242			.1048

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	8.4%
			Observed number of cases	0	0	0	2
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	FIBROUS HISTIOCYTOMA	Male	<i>p</i> -value of pairwise and trend tests	.0732	.4944		.1821
			Poly-3 adjusted incidence rate	.00%	2.2%	.00%	5.8%
			Observed number of cases	0	1	0	2
	HEMANGIOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.7111	1.000	.7416	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.3%	.00%
			Observed number of cases	1	0	1	0
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	LIPOMA	Male	<i>p</i> -value of pairwise and trend tests	.5676	.4944	.4886	
			Poly-3 adjusted incidence rate	.00%	2.3%	2.3%	.00%
			Observed number of cases	0	1	1	0
	LIPOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.2%	.00%	.00%
			Observed number of cases	0	1	0	0
	LYMPHANGIOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.1%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	OSTEOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7805	.2416		
			Poly-3 adjusted incidence rate	.00%	4.5%	.00%	.00%
			Observed number of cases	0	2	0	0
	SARCOMA, UNDIFFERENT	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304
			Poly-3 adjusted incidence rate	.00%	2.2%	.00%	2.9%
			Observed number of cases	0	1	0	1
	SCHWANNOMA	Male	<i>p</i> -value of pairwise and trend tests	.0006		.4944	.0147
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	14%
			Observed number of cases	0	0	1	5

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
small intestine, duodenum	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
	SARCOMA, UNDIFFERENT	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
small intestine, ileum	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7805	.2416		
			Poly-3 adjusted incidence rate	.00%	4.5%	.00%	.00%
			Observed number of cases	0	2	0	0
small intestine, jejunum	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7805	.2416		
			Poly-3 adjusted incidence rate	.00%	4.5%	.00%	.00%
			Observed number of cases	0	2	0	0
spinal cord, lumbar	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.2%	.00%
			Observed number of cases	0	0	1	0
spinal cord, thoracic	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
spleen	CARCINOMA, RETE TEST	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	FIBROSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	HEMANGIOMA	Male	<i>p</i> -value of pairwise and trend tests	.1484		.4944	.4304
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	2.9%
			Observed number of cases	0	0	1	1
	HEMANGIOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	0	0	0	1
	LEIOMYOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.7141	1.000	.7472	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.3%	.00%
			Observed number of cases	1	0	1	0
	LEUKEMIA, GRANULOCYT	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.1%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.8633	1.000	.8708	1.000
			Poly-3 adjusted incidence rate	4.3%	.00%	2.2%	.00%
			Observed number of cases	2	0	1	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
	SARCOMA, HISTIOCYTIC	Female	<i>p</i> -value of pairwise and trend tests	.3889		.4198	
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	.00%
			Observed number of cases	0	0	1	0
		Male	<i>p</i> -value of pairwise and trend tests	.6641	.2416	.2416	
			Poly-3 adjusted incidence rate	.00%	4.5%	4.5%	.00%
			Observed number of cases	0	2	2	0
	SARCOMA, UNDIFFERENT	Female	<i>p</i> -value of pairwise and trend tests	.1586			.3286
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	4.3%
			Observed number of cases	0	0	0	1
stomach, glandular	CARCINOMA, RETE TEST	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.3647	.2416		.4304
			Poly-3 adjusted incidence rate	.00%	4.5%	.00%	2.9%
			Observed number of cases	0	2	0	1
	SARCOMA, UNDIFFERENT	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
stomach, nonglandular	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	PAPILLOMA, SQUAMOUS	Male	<i>p</i> -value of pairwise and trend tests	.9268	.7472	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	2.3%	.00%	.00%
			Observed number of cases	1	1	0	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7273	.4944		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
testes	ADENOMA, INTERSTITIA	Male	<i>p</i> -value of pairwise and trend tests	.3335	.2997	.4915	.3949
			Poly-3 adjusted incidence rate	2.2%	6.8%	4.5%	5.8%
			Observed number of cases	1	3	2	2
	CARCINOMA, RETE TEST	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
	Lymphoma	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	Mesothelioma	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
thymus gland	Carcinoma, Rete Test	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	Fibrosarcoma	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
	Leukemia	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	Leukemia, Large Gran	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	Lymphoma	Female	<i>p</i> -value of pairwise and trend tests	.7074	.2199		
			Poly-3 adjusted incidence rate	.00%	4.7%	.00%	.00%
			Observed number of cases	0	2	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.4883	1.000	.8708	.8152
			Poly-3 adjusted incidence rate	4.3%	.00%	2.2%	2.9%
			Observed number of cases	2	0	1	1
	Osteosarcoma	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.2%	.00%
			Observed number of cases	0	0	1	0
	Sarcoma, Histiocytic	Male	<i>p</i> -value of pairwise and trend tests	.5695	.4944	.4944	
			Poly-3 adjusted incidence rate	.00%	2.3%	2.2%	.00%
			Observed number of cases	0	1	1	0
	Sarcoma, Undifferent	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	Schwannoma	Male	<i>p</i> -value of pairwise and trend tests	.0410			.1821
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	0	0	0	2
	THYMOMA	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.1%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
thyroid gland	ADENOMA, C-CELL	Female	<i>p</i> -value of pairwise and trend tests	.0296	.6064	.8980	.0900
			Poly-3 adjusted incidence rate	6.3%	7.1%	2.8%	19%
			Observed number of cases	3	3	1	5
		Male	<i>p</i> -value of pairwise and trend tests	.4104	.9663	.2549	.7081
			Poly-3 adjusted incidence rate	13%	4.5%	20%	11%
			Observed number of cases	6	2	9	4
	ADENOMA, FOLLICULAR	Female	<i>p</i> -value of pairwise and trend tests	.0969	.6299	.2021	.2027
			Poly-3 adjusted incidence rate	4.2%	4.8%	11%	12%
			Observed number of cases	2	2	4	3
		Male	<i>p</i> -value of pairwise and trend tests	.0035	.0278	.0583	.0011
			Poly-3 adjusted incidence rate	.00%	11%	8.8%	21%
			Observed number of cases	0	5	4	8
	CARCINOMA, C-CELL	Female	<i>p</i> -value of pairwise and trend tests	.3889		.4198	
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	.00%
			Observed number of cases	0	0	1	0
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	CARCINOMA, FOLLICULA	Male	<i>p</i> -value of pairwise and trend tests	.1828	.7472	.4915	.3949
			Poly-3 adjusted incidence rate	2.2%	2.3%	4.5%	5.9%
			Observed number of cases	1	1	2	2
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	.7141	1.000	.7472	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	2.3%	.00%
			Observed number of cases	1	0	1	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	4.3%	.00%	.00%	.00%
			Observed number of cases	2	0	0	0
tongue	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
trachea	FIBROSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	LYMPHOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
ureters	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	4.3%	.00%	.00%	.00%
			Observed number of cases	2	0	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2570	.4944		.4304
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	2.9%
			Observed number of cases	0	1	0	1
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.7805	.2416		
			Poly-3 adjusted incidence rate	.00%	4.5%	.00%	.00%
			Observed number of cases	0	2	0	0
urinary bladder	LEIOMYOSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	LEUKEMIA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1
	PAPILLOMA, TRANSITIO	Female	<i>p</i> -value of pairwise and trend tests	.5679	.2142	.4268	
			Poly-3 adjusted incidence rate	.00%	4.8%	2.9%	.00%
			Observed number of cases	0	2	1	0
	SARCOMA, HISTIOCYTIC	Male	<i>p</i> -value of pairwise and trend tests	.8635	.1166		
			Poly-3 adjusted incidence rate	.00%	6.7%	.00%	.00%
			Observed number of cases	0	3	0	0
	SARCOMA, UNDIFFERENT	Male	<i>p</i> -value of pairwise and trend tests	.4639		.4944	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
uterus with cervix	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.1%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	GRANULAR CELL TUMOR	Female	<i>p</i> -value of pairwise and trend tests	.8950	.7176	1.000	1.000
			Poly-3 adjusted incidence rate	2.1%	2.4%	.00%	.00%
			Observed number of cases	1	1	0	0
	HEMANGIOMA	Female	<i>p</i> -value of pairwise and trend tests	.1000		.4268	.3286
			Poly-3 adjusted incidence rate	.00%	.00%	2.8%	4.3%
			Observed number of cases	0	0	1	1
	HEMANGIOSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	.3931		.4268	
			Poly-3 adjusted incidence rate	.00%	.00%	2.8%	.00%
			Observed number of cases	0	0	1	0
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
	POLYP, GLANDULAR	Female	<i>p</i> -value of pairwise and trend tests	.0078		.0739	.0354
			Poly-3 adjusted incidence rate	.00%	.00%	8.5%	12%

Table 6: All reported neoplastic tumors in rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	0	0	3	3
	POLYP, STROMAL	Female	<i>p</i> -value of pairwise and trend tests	.0637	1.000	.6745	.2496
			Poly-3 adjusted incidence rate	2.1%	.00%	2.8%	8.5%
			Observed number of cases	1	0	1	2
	SARCOMA, HISTIOCYTIC	Female	<i>p</i> -value of pairwise and trend tests	.3889		.4198	
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	.00%
			Observed number of cases	0	0	1	0
vagina	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.1%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	GRANULAR CELL TUMOR	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.1%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.6736	.4659		
			Poly-3 adjusted incidence rate	.00%	2.4%	.00%	.00%
			Observed number of cases	0	1	0	0
	POLYP	Female	<i>p</i> -value of pairwise and trend tests	.1000		.4268	.3286
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	4.2%
			Observed number of cases	0	0	1	1
	SCHWANNOMA	Female	<i>p</i> -value of pairwise and trend tests	.3889		.4198	
			Poly-3 adjusted incidence rate	.00%	.00%	2.9%	.00%
			Observed number of cases	0	0	1	0
zymbal's gland	CARCINOMA, ZYMBALS G	Male	<i>p</i> -value of pairwise and trend tests	.2048			.4304
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.9%
			Observed number of cases	0	0	0	1

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Table 7: Table of composite endpoints in rat study

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
All mammary tumors	Female	<i>p</i> -value of pairwise and trend tests	< 0.0001	0.0004	< 0.0001	< 0.0001
		Adjusted incidence rate (%)	69.19	93.43	98.94	98.23
		Number of animals with tumor	40	56	61	70
		Adjusted number of animals at risk	57.81	59.94	61.66	71.26
	Male	<i>p</i> -value of pairwise and trend tests	0.0008	0.8708	0.1263	0.009

Table 7: Composite endpoints in rat study (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
		Adjusted incidence rate (%)	4.32	2.26	13.05	23.98
		Number of animals with tumor	2	1	6	9
		Adjusted number of animals at risk	46.29	44.20	45.97	37.53
Mammary adenocarcinomas and fibroadenomas	Female	<i>p</i> -value of pairwise and trend tests	< 0.0001	0.0004	< 0.0001	< 0.0001
		Adjusted incidence rate (%)	69.19	93.43	98.94	98.23
		Number of animals with tumor	40	56	61	70
		Adjusted number of animals at risk	57.81	59.94	61.66	71.26
	Male	<i>p</i> -value of pairwise and trend tests	0.0003	0.4944	0.0131	0.0009
		Adjusted incidence rate (%)	0	2.26	13.05	21.71
		Number of animals with tumor	0	1	6	8
		Adjusted number of animals at risk	45.73	44.20	45.97	36.86
Malignant mammary tumors	Female	<i>p</i> -value of pairwise and trend tests	< 0.0001	0.1407	0.0632	< 0.0001
		Adjusted incidence rate (%)	50.64	62.44	66.40	90.91
		Number of animals with tumor	28	34	35	60
		Adjusted number of animals at risk	55.29	54.45	52.71	66.00
	Male	<i>p</i> -value of pairwise and trend tests	0.0885	1	0.6747	0.3711
		Adjusted incidence rate (%)	4.32	0	4.48	8.41
		Number of animals with tumor	2	0	2	3
		Adjusted number of animals at risk	46.29	44.01	44.65	35.69
All brain tumors	Female	<i>p</i> -value of pairwise and trend tests	0.3984	0.0508	0.4268	0.3286
		Adjusted incidence rate (%)	0	8.89	2.83	4.32
		Number of animals with tumor	0	4	1	1
		Adjusted number of animals at risk	47.66	44.99	35.29	23.15
	Male	<i>p</i> -value of pairwise and trend tests	0.0001	0.6927	0.3555	0.0059
		Adjusted incidence rate (%)	8.51	2.28	13.10	32.03
		Number of animals with tumor	4	1	6	13
		Adjusted number of animals at risk	47.00	44.01	45.80	47.59
Brain gliomas	Female	<i>p</i> -value of pairwise and trend tests	0.2260	0.2199	0.4268	0.3286
		Adjusted incidence rate (%)	0	4.71	2.83	4.32
		Number of animals with tumor	0	2	1	1

Table 7: Composite endpoints in rat study (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
		Adjusted number of animals at risk	47.66	42.43	35.29	23.15
	Male	<i>p</i> -value of pairwise and trend tests	0.0001	0.8708	0.2801	0.0026
		Adjusted incidence rate (%)	4.30	2.27	10.96	28.19
		Number of animals with tumor	2	1	5	11
		Adjusted number of animals at risk	46.48	44.01	45.63	39.03
Malignant brain tumors	Male	<i>p</i> -value of pairwise and trend tests	0.0002	0.9688	0.4858	0.0099
		Adjusted incidence rate (%)	8.51	2.27	10.92	30.20
		Number of animals with tumor	4	1	5	12
		Adjusted number of animals at risk	47.00	44.01	45.80	39.73
All schwannomas	Female	<i>p</i> -value of pairwise and trend tests	0.3889	.	0.4198	.
		Adjusted incidence rate (%)	0	0	2.87	0
		Number of animals with tumor	0	0	1	0
		Adjusted number of animals at risk	47.66	41.39	34.81	22.78
	Male	<i>p</i> -value of pairwise and trend tests	< 0.0001	.	0.214	0.0006
		Adjusted incidence rate (%)	0	0	4.50	23.03
		Number of animals with tumor	0	0	2	9
		Adjusted number of animals at risk	45.73	44.01	44.44	39.07
Hepatocellular adenomas and carcinomas	Female	<i>p</i> -value of pairwise and trend tests	0.293	1	1	0.5524
		Adjusted incidence rate (%)	2.0982	0	0	4.243
		Number of animals with tumor	1	0	0	1
		Adjusted number of animals at risk	47.66	41.394	34.805	23.568
	Male	<i>p</i> -value of pairwise and trend tests	0.0012	0.3279	0.3279	0.0048
		Adjusted incidence rate (%)	4.3272	8.8648	8.8759	25.672
		Number of animals with tumor	2	4	4	10
		Adjusted number of animals at risk	46.22	45.122	45.066	38.953
Subcutaneous fibromas and fibrosarcomas	Female	<i>p</i> -value of pairwise and trend tests	0.0388	0.1011	.	0.0354
		Adjusted incidence rate (%)	0	7.1006	0	12.368
		Number of animals with tumor	0	3	0	3
		Adjusted number of animals at risk	47.66	42.25	34.805	24.256

Table 7: Composite endpoints in rat study (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
	Male	<i>p</i> -value of pairwise and trend tests Adjusted incidence rate (%) Number of animals with tumor Adjusted number of animals at risk	0.0001 8.5334 4 46.875	0.2611 15.056 7 46.492	0.0397 24.21 11 45.436	0.0002 42.999 17 39.536
Squamous papillomas and carcinomas of the skin	Male	<i>p</i> -value of pairwise and trend tests Adjusted incidence rate (%) Number of animals with tumor Adjusted number of animals at risk	0.001 2.19 1 45.726	1 0 0 44.008	0.1066 10.85 5 46.073	0.0126 18.97 7 36.897
Squamous tumors or keratoacanthomas (skin)	Male	<i>p</i> -value of pairwise and trend tests Adjusted incidence rate (%) Number of animals with tumor Adjusted number of animals at risk	0.0007 4.36 2 45.84	0.8750 2.27 1 44.01	0.2264 10.852 5 46.07	0.0114 23.61 9 38.12
Thyroidal F-cell adenomas and carcinomas	Female	<i>p</i> -value of pairwise and trend tests Adjusted incidence rate (%) Number of animals with tumor Adjusted number of animals at risk	0.0969 4.159 2 48.088	0.6299 4.7805 2 41.837	0.2021 11.263 4 35.514	0.2027 12.421 3 24.152
	Male	<i>p</i> -value of pairwise and trend tests Adjusted incidence rate (%) Number of animals with tumor Adjusted number of animals at risk	0.0053 2.1869 1 45.726	0.0551 13.188 6 45.495	0.1014 10.971 5 45.574	0.0028 23.892 9 37.67
Cervical adenocarcinoma or glandular polyps	Female	<i>p</i> -value of pairwise and trend tests Adjusted incidence rate (%) Number of animals with tumor Adjusted number of animals at risk	0.0189 2.0919 1 47.802	1 0 0 41.394	0.2058 8.4519 3 35.495	0.1088 12.072 3 24.85
All leukemias	Female	<i>p</i> -value of pairwise and trend tests Adjusted incidence rate (%) Number of animals with tumor Adjusted number of animals at risk	1 2.09 1 47.88	1 0 0 41.39	1 0 0 34.81	1 0 0 22.78
	Male	<i>p</i> -value of pairwise comparison with control	0.1192	1	0.7472	0.4056

Table 7: Composite endpoints in rat study (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
		Adjusted incidence rate (%)	2.18	0	2.27	5.67
		Number of animals with tumor	1	0	1	2
		Adjusted number of animals at risk	45.89	44.01	44.15	35.25

Table 8: Table of neoplastic tumors in rat study with at least one significant result

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose	
adrenal glands	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%	
			Observed number of cases	0	0	0	2	
			Adjusted number at risk	45.73	44.01	43.98	35.25	
aorta	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%	
			Observed number of cases	0	0	0	2	
			Adjusted number at risk	45.73	44.01	43.98	35.25	
brain	ASTROCYTOMA	Female	<i>p</i> -value of pairwise and trend tests	.2661	.2199		.3286	
			Poly-3 adjusted incidence rate	.00%	4.7%	.00%	4.3%	
			Observed number of cases	0	2	0	1	
			Adjusted number at risk	47.66	42.43	34.81	23.15	
			Male	<i>p</i> -value of pairwise and trend tests	.0002	1.000	.1804	.0056
				Poly-3 adjusted incidence rate	2.2%	.00%	8.8%	22%
				Observed number of cases	1	0	4	8
				Adjusted number at risk	45.73	44.01	45.63	36.94
		LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
				Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
				Observed number of cases	0	0	0	2
				Adjusted number at risk	45.73	44.01	43.98	35.25
epididymides	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883	
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%	
			Observed number of cases	0	0	0	2	

Table 8: Significant results from rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Adjusted number at risk	45.73	44.01	43.98	35.25
harderian glands	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0429 .00% 0 45.73	.00% .00% 0 44.01	.00% .00% 0 43.98	.1883 5.7% 2 35.25
heart	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0429 .00% 0 45.73	.00% .00% 0 44.01	.00% .00% 0 43.98	.1883 5.7% 2 35.25
kidneys	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0429 .00% 0 45.73	.00% .00% 0 44.01	.00% .00% 0 43.98	.1883 5.7% 2 35.25
lacrimal glands, exorbital	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0429 .00% 0 45.73	.00% .00% 0 44.01	.00% .00% 0 43.98	.1883 5.7% 2 35.25
liver	ADENOMA, HEPATOCELLU	Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0033 2.2% 1 45.89	.7472 2.3% 1 44.01	.4915 4.5% 2 44.15	.0302 16% 6 37.04
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0429 .00% 0 45.73	.00% .00% 0 44.01	.00% .00% 0 43.98	.1883 5.7% 2 35.25
lung	CARCINOMA	Female	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0065 .00% 0 47.66	.0483 9.3% 4 43.10	.0005 22% 9 40.49	.0016 22% 6 27.23

Table 8: Significant results from rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0429 .00% 0 45.73	.00% 0 44.01	.00% 0 43.98	.1883 5.7% 2 35.25
lymph node, mandibular	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0429 .00% 0 45.73	.00% 0 44.01	.00% 0 43.98	.1883 5.7% 2 35.25
lymph node, mesenteric	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0429 .00% 0 45.73	.00% 0 44.01	.00% 0 43.98	.1883 5.7% 2 35.25
mammary gland	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	< 0.0001 51% 28 55.29	.1407 62% 34 54.45	.0632 66% 35 52.71	< 0.0001 91% 60 66.00
		Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0464 .00% 0 45.73	.00% 0 44.01	.2416 4.5% 2 44.65	.1883 5.7% 2 35.02
		Female	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	< 0.0001 39% 20 51.69	< 0.0001 86% 47 54.73	< 0.0001 94% 53 56.13	< 0.0001 88% 45 51.33
		Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0017 .00% 0 45.73	.4944 2.3% 1 44.20	.0583 8.8% 4 45.30	.0054 17% 6 35.53
	FIBROADENOMA	Female	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	< 0.0001 39% 20 51.69	< 0.0001 86% 47 54.73	< 0.0001 94% 53 56.13	< 0.0001 88% 45 51.33
		Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0017 .00% 0 45.73	.4944 2.3% 1 44.20	.0583 8.8% 4 45.30	.0054 17% 6 35.53
		Female	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	< 0.0001 39% 20 51.69	< 0.0001 86% 47 54.73	< 0.0001 94% 53 56.13	< 0.0001 88% 45 51.33
		Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate Observed number of cases Adjusted number at risk	.0017 .00% 0 45.73	.4944 2.3% 1 44.20	.0583 8.8% 4 45.30	.0054 17% 6 35.53
multicentric neoplasm	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests Poly-3 adjusted incidence rate	.0429 .00%	.00% 0	.00% 0	.1883 5.7%

Table 8: Significant results from rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	0	0	0	2
			Adjusted number at risk	45.73	44.01	43.98	35.25
skin	CARCINOMA, SQUAMOUS	Male	<i>p</i> -value of pairwise and trend tests	.0030		.0583	.0147
			Poly-3 adjusted incidence rate	.00%	.00%	8.8%	14%
			Observed number of cases	0	0	4	5
			Adjusted number at risk	45.73	44.01	45.66	36.40
skin, subcutis	FIBROMA	Female	<i>p</i> -value of pairwise and trend tests	.3709	.1011		.3286
			Poly-3 adjusted incidence rate	.00%	7.1%	.00%	4.3%
			Observed number of cases	0	3	0	1
			Adjusted number at risk	47.66	42.25	34.81	23.23
		Male	<i>p</i> -value of pairwise and trend tests	< 0.0001	.1577	.0175	< 0.0001
			Poly-3 adjusted incidence rate	6.5%	15%	24%	43%
			Observed number of cases	3	7	11	17
			Adjusted number at risk	46.18	46.49	45.44	39.54
	FIBROSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	.0242			.1048
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	8.4%
			Observed number of cases	0	0	0	2
			Adjusted number at risk	47.66	41.39	34.81	23.81
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	2.2%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
			Adjusted number at risk	46.42	44.01	43.98	33.69
	SCHWANNOMA	Male	<i>p</i> -value of pairwise and trend tests	.0006		.4944	.0147
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	14%
			Observed number of cases	0	0	1	5
			Adjusted number at risk	45.73	44.01	44.44	36.74
spleen	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
			Adjusted number at risk	45.73	44.01	43.98	35.25

Table 8: Significant results from rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
stomach, glandular	LEUKEMIA, LARGE GRAN	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
			Adjusted number at risk	45.73	44.01	43.98	35.25
thymus gland	FIBROSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.0429			.1883
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
			Adjusted number at risk	45.73	44.01	43.98	35.14
	SCHWANNOMA	Male	<i>p</i> -value of pairwise and trend tests	.0410			.1821
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	5.7%
			Observed number of cases	0	0	0	2
			Adjusted number at risk	45.73	44.01	43.98	34.89
thyroid gland	ADENOMA, C-CELL	Female	<i>p</i> -value of pairwise and trend tests	.0296	.6064	.8980	.0900
			Poly-3 adjusted incidence rate	6.3%	7.1%	2.8%	19%
			Observed number of cases	3	3	1	5
			Adjusted number at risk	47.98	42.18	35.27	25.98
		Male	<i>p</i> -value of pairwise and trend tests	.4104	.9663	.2549	.7081
			Poly-3 adjusted incidence rate	13%	4.5%	20%	11%
			Observed number of cases	6	2	9	4
			Adjusted number at risk	46.54	44.20	44.21	35.26
	ADENOMA, FOLLICULAR	Female	<i>p</i> -value of pairwise and trend tests	.0969	.6299	.2021	.2027
			Poly-3 adjusted incidence rate	4.2%	4.8%	11%	12%
		Male	Observed number of cases	2	2	4	3
			Adjusted number at risk	48.09	41.84	35.51	24.15
			<i>p</i> -value of pairwise and trend tests	.0035	.0278	.0583	.0011
			Poly-3 adjusted incidence rate	.00%	11%	8.8%	21%
			Observed number of cases	0	5	4	8
			Adjusted number at risk	45.73	45.49	45.57	37.56
uterus with cervix	POLYP, GLANDULAR	Female	<i>p</i> -value of pairwise and trend tests	.0078		.0739	.0354

Table 8: Significant results from rat study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	.00%	.00%	8.5%	12%
			Observed number of cases	0	0	3	3
			Adjusted number at risk	47.66	41.39	35.49	24.85

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 one control group. Two hundred and seventy (CrI:CD-1TM(ICR)) mice of each sex were initially randomly allocated to three treatment groups and one control group, with sixty five animals of each sex being assigned to the low, medium, and high dose groups, and seventy five animals of each sex being assigned to the control groups. The dose levels for the treatment groups were 25, 50, and 100 mg/kg/day. After sixteen days of treatment, it was decided that 100 mg/kg/day was an excessive dose. After a two day “dosing holiday”, the daily dosage level for each of the three treatment groups was reduced: the high dose animals received 50 mg/kg/day, the mid dose animals received 25 mg/kg/day, and the low dose animals received a dose of 5 mg/kg/day, just 5% of the originally conceived maximum dose. In this review these dose groups are referred to as the low, medium, and high dose groups respectively.

Furthermore, ten additional animals per sex were added to the study, receiving 50 mg/kg/day, for the whole course of the study. The rationale for adding these animals was that after the early mortality for the 100 mg/kg/day group, it was anticipated that additional animals would be needed in the 50 mg/kg dose group. These animals were to be added to the high dose group, despite their different early experiences.

The vehicle for the test was deionized water, administered as a dosage volume of 5 ml/kg, once per day. The control animals received this vehicle.

During the administration period animals were checked twice daily for morbidity, mortality, injury, and availability of food and water (with a third check per day for mortality after week 53). A clinical exam was performed weekly (and daily in the first two weeks of the study) where any palpable masses were noted, and an evaluation was performed of various external organs (skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs, feet).

A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

3.1 Sponsor’s analyses

3.1.1 Survival analysis

Mortality data were analyzed according to the Kaplan-Meier [6] product limit method to test for trend in survival times across the four groups. If significant evidence of a trend is found ($\alpha = 0.05$) then the analysis proceeds to pairwise tests between each of the three treatment groups and the control group.

The results of these formal statistical tests have not been reported, but the sponsor does provide a Kaplan-Meier survival plot (see figures 12 and 13) for each of the two sexes, and writes that

[T]he overall incidence of main study mortality was comparable to controls, with no definitive dose-response pattern, most especially when comparing the control group to the high-dose level of 50 mg/kg/day, as the survival was very similar for both sexes in these groups.

3.1.2 Tumor data analysis

For each tumor type, both survival-adjusted and survival-unadjusted methods were used to detect possible carcinogenicity effects. A trend test (using the Armitage-Cochran [1] method and ordinal coefficients) and a set of pairwise tests of incidence versus control, using Fisher’s exact test were conducted, based on survival-unadjusted data. The survival-adjusted tests followed Peto’s method [8], using time intervals of 0–50 weeks, 51–80 weeks, 81 weeks to the end of the study, and terminal sacrifice.

The sponsor found no significant results to report.

3.2 Reviewer's analysis

This reviewer independently performed survival and tumor data analyses from the mouse study. For the mouse data analyses this reviewer used similar methodologies as were used to analyze the data from the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1 Additional animals

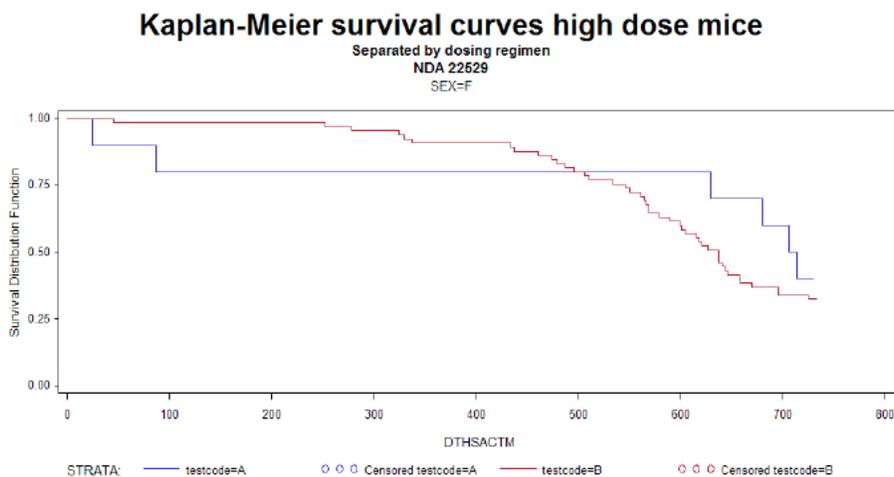
As mentioned above, at the time that the animals were transferred from one dose level to another (100 mg/kg to 50 mg/kg, 50 mg/kg to 25 mg/kg, and 25 mg/kg to 5 mg/kg), ten additional animals were added to the high dose group. These animals were to receive a consistent dose of 50 mg/kg for the entire course of the study. However, since their exposure history is different from that of the animals originally assigned to the high dose group, it is necessary to justify that these animals are indeed drawn from a comparable population before combining the two groups.

Given the small numbers of animals involved, there are few options to statistically test the proposition that the two groups of mice are comparable. It was decided to conduct a survival analysis, using a log-rank test. The Kaplan-Meier plots are presented in figures 9 and 10. The results of the log-rank test are presented in table 9.

Table 9: Test of equality of survival between 100/50 mg/kg mice and 50 mg/kg mice

Sex	χ_1^2 statistic	<i>p</i> -value
Female	0.5808	0.4461
Male	5.4816	0.0192

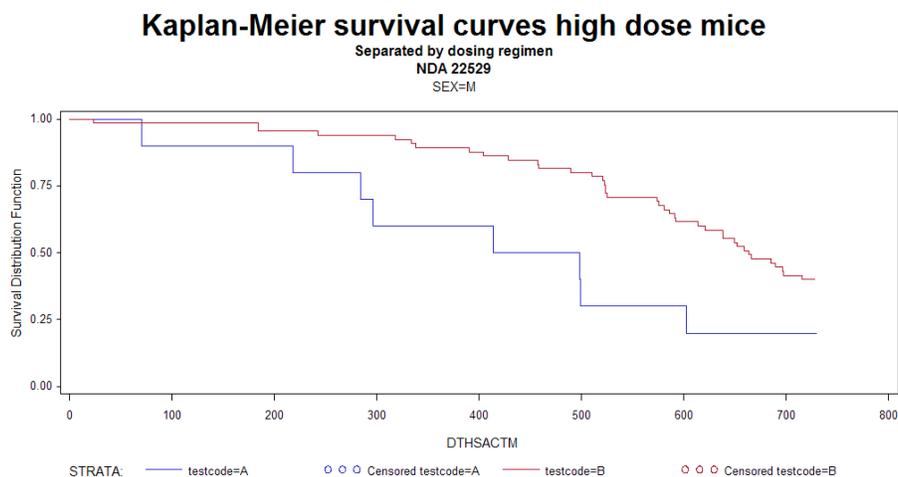
Figure 9



Based on this analysis, especially the strongly significant evidence for a difference in survival between the two groups of male mice ($p = 0.0192$), it is not possible to safely retain the hypothesis that the ten new recruits to the male study are truly comparable to the original 65 high dose males. Therefore, the new male recruits are not included in the analysis of the study.

In and of themselves, the results for the female mice do not provide evidence to justify excluding the new recruits from the analysis. Nonetheless, with such a small number of animals under

Figure 10



consideration, such the log-rank test has low power, so the absence of a significant difference in survival should not be construed as strong evidence of homogeneity of survival times.

The usual procedure in such cases would be to consider the time-weighted average dose of the two groups of animals. In this case, since the transition occurred so early (after 16 days), the original animals did indeed receive an average dose close to 50 mg/day. The actual average daily dose depends on when the animal dies. See figure 11.

Some of this information is also presented in table 10.

Table 10: Average daily dose of 100/50 mg/kg mice at various possible death times

Time of death (weeks):	5	13	26	52	78	104
Average daily dose (mg/kg):	70.0	57.7	53.8	51.9	51.5	50.9

This it appears that the animals who switched from 100 mg/kg to 50 mg/kg will have received average daily doses fairly close to 50 mg/kg, as long as they lived a reasonably long time. In light of these calculations, and after discussion with other statistical reviewers, it has been decided that it is reasonable to include the new recruits to the high dose group, in the female study only.

3.2.2 Survival analysis

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.

Kaplan-Meier plots of the survival rates for the two sexes are shown in figures 12 and 13. The results of the significance tests for trend and homogeneity are presented in table 12. Intercurrent mortality data are presented in table 11.

The p -values for the test of trend are 0.3565 and 0.3305 for female and male mice respectively, and the p -values for survival heterogeneity are also non significant (0.8800 and 0.5579 respectively) (see table 3). Furthermore, the survival plots show no visually discernible indications of differences in survival outcomes across groups. From these data, therefore, there is no evidence to suggest that the dose level had an impact on survival times, either among male of female mice.

Figure 11: Average daily dose of high dose mice at time of death

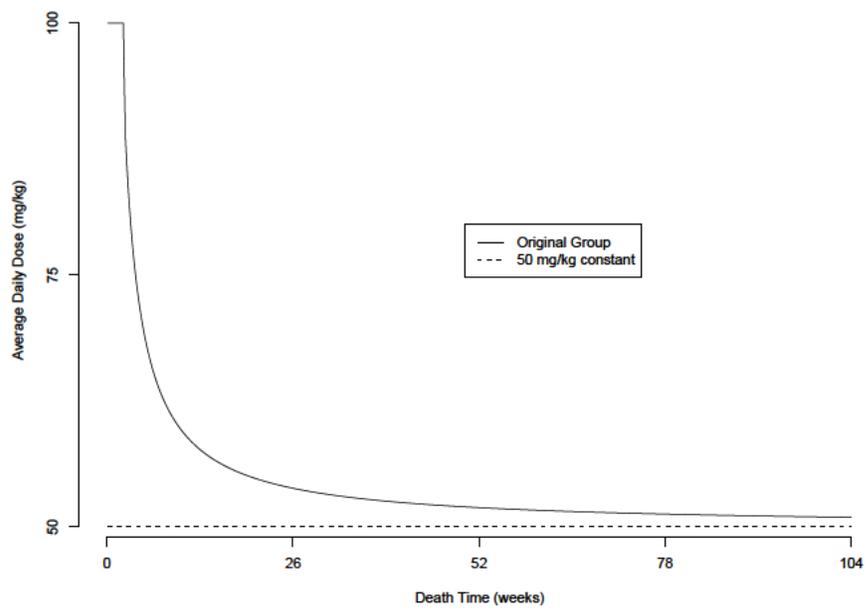


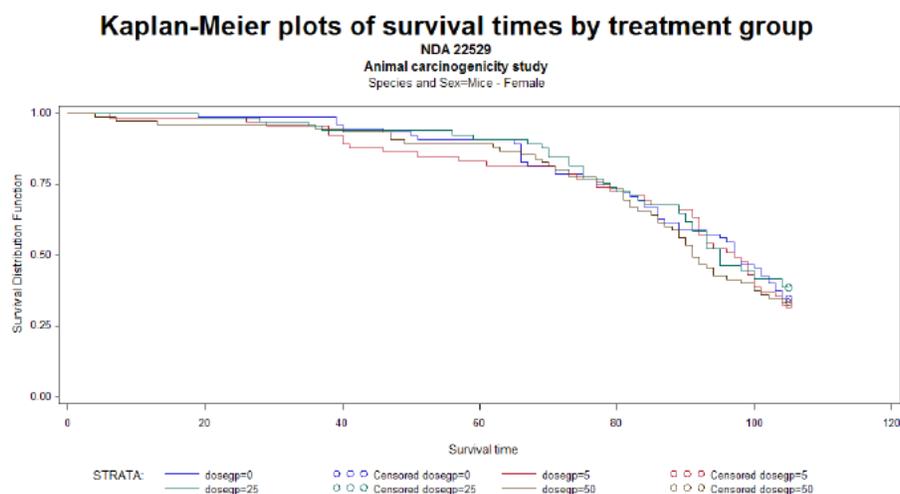
Table 11: Intercurrent mortality data across treatment groups (mice)

Species & Sex	Dose group	Dosage (mg/kg)	Number and percentage alive								
			Start	52 weeks	(%)	78 weeks	(%)	90 weeks	(%)	Termination	(%)
Mice - Female	Control	0	75	68	90.7	56	74.7	44	58.7	28	37.3
	Low dose	5	65	55	84.6	48	73.8	43	66.2	23	35.4
	Mid dose	25	65	61	93.8	50	76.9	42	64.6	27	41.5
	High dose	50	75	67	89.3	57	76.0	42	56.0	26	34.7
Mice - Male	Control	0	75	68	90.7	57	76.0	47	62.7	34	45.3
	Low dose	5	65	58	89.2	43	66.2	36	55.4	24	36.9
	Mid dose	25	65	59	90.8	50	76.9	37	56.9	20	30.8
	High dose	50	65	58	89.2	46	70.8	38	58.5	26	40.0

Table 12: Results of tests of survival homogeneity across treatment groups (mice)

Species and Sex	Number of dose groups	<i>p</i> -value (trend)	<i>p</i> -value (homogeneity)
Mice - Female	4	0.3565	0.8800
Mice - Male	4	0.3305	0.5579

Figure 12: Survival plots for female mice



3.2.3 Tumor data analysis

The same analyses were conducted in the mouse study as in the rat study (see section 3.1.2). The full table of detected tumors is presented in table 14. The same thirteen composite endpoints were also examined (except for an analysis of all leukemias); the results from these analyses are in table 15. An abridged table, consisting of just those tumors for which at least one *p*-value under 0.05 was detected (in either sex, in any of the pairwise comparisons with the control, or in the test of trend) is displayed in table 16.

Several of the composite endpoint analyses are redundant, however. Table 13 describes these endpoints and the redundancies.

Table 13: Composite endpoints in mice, and redundancies

Endpoint	Redundancy
All hepatocellular adenomas and carcinomas	This information is presented for both male and female mice in table 15.
All schwannomas	Only three mice developed schwannomas, and they all developed schwannomas in the uterus/cervix (all three were female). These results are presented in table 15, but duplicate the entry for schwannomas of the uterus/cervix in table 14.

Table 13: Composite endpoints and redundancies (continued)

Endpoint	Redundancy
All brain tumors	The table for female and male mice is presented in table 15, although the only brain tumor recorded among the female mice was a single oligodendroglioma, so the results for all brain tumors in female mice duplicates the entry for OLIGOD in table 14.
Malignant brain tumors	The results for male mice is presented in table 15. There were no malignant brain tumors reported among the female mice.
Gliomas	The results for both male and female mice are presented in table 15.
Mammary adenocarcinomas and fibroadenomas	No mammary tumors of any kind were detected among the male mice. Among the female mice, the only mammary tumors detected were adenocarcinomas. Accordingly, this row in table 15 duplicates the row for mammary adenocarcinomas in table 14
All mammary tumors	See above
Malignant mammary tumors	See above and note that all adenocarcinomas are by definition malignant
Subcutaneous fibromas and fibrosarcomas	This endpoint is reported for both male and female mice in table 15. However, no subcutaneous fibromas were reported in the mouse study, so this endpoint is identical to the entry for subcutaneous fibrosarcomas in table 14
Squamous papillomas and carcinomas of the skin	No such tumors were reported in the mouse study.
Squamous papillomas and carcinomas or keratoacanthomas of the skin	The only such tumor reported in the study was a single keratoacanthoma in the female mice study. Consequently the corresponding row in table 15 simply duplicates the row in table 14.
Thyroidal follicular adenomas and carcinomas	This endpoint is reported for both male and female mice in table 15. However, among the female mice, no follicular carcinomas were reported, so the endpoint reduces to the information contained in table 14 for thyroidal follicular adenomas.
Uterine/Cervical glandular polyps and adenocarcinomas	This endpoint is presented in table 15. However, since no glandular polyps were found in the mouse study, this entry reproduces the data on adenocarcinomas of the uterus with cervix, presented in table 14

Figure 13: Survival plots for male mice

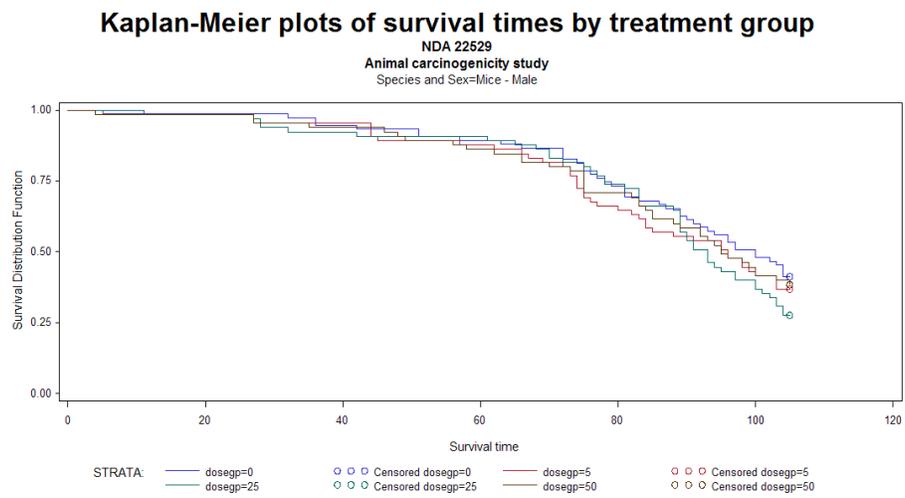


Table 14: Table of all reported neoplastic tumors in mouse study

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
adrenal glands	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.9261	.7092	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	2.3%	.00%	.00%
			Observed number of cases	1	1	0	0
	ADENOMA, SUBCAPSU	Female	<i>p</i> -value of pairwise and trend tests	.5261	.7092	.7152	.7374
			Poly-3 adjusted incidence rate	1.9%	2.3%	2.2%	2.0%
			Observed number of cases	1	1	1	1
		Male	<i>p</i> -value of pairwise and trend tests	.6630	.2474	.9119	.5687
			Poly-3 adjusted incidence rate	5.6%	11%	2.3%	6.8%
			Observed number of cases	3	5	1	3
	CARCINOMA, SUBCA	Female	<i>p</i> -value of pairwise and trend tests	.4947		.4639	
			Poly-3 adjusted incidence rate	.00%	.00%	2.2%	.00%
			Observed number of cases	0	0	1	0
	FIBROSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.4780		.4536	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	PHEOCHROMOCYTOMA	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
aorta	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.7263	.4583		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
bone, femur	OSTEOMA	Female	<i>p</i> -value of pairwise and trend tests	.2579			.4851
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.0%
			Observed number of cases	0	0	0	1
bone, sternum	CARCINOMA, BRONCHIOL	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	

Table 14: All reported neoplastic tumors in mouse study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
brain	ASTROCYTOMA	Male	<i>p</i> -value of pairwise and trend tests	.9141	.6927	1.000	1.000
			Poly-3 adjusted incidence rate	1.8%	2.3%	.00%	.00%
			Observed number of cases	1	1	0	0
	ME	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	OLIGOD	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
cavity, thoracic	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
coagulating glands	ADENOMA	Male	<i>p</i> -value of pairwise and trend tests	.2376			.4479
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.3%
			Observed number of cases	0	0	0	1
epididymides	SARCOMA, UNDIFF	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	3.7%	.00%	.00%	.00%
			Observed number of cases	2	0	0	0
harderian glands	ADENOCARCINOMA	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	ADENOMA	Female	<i>p</i> -value of pairwise and trend tests	.1885	.6258	.6436	.3204
			Poly-3 adjusted incidence rate	3.8%	4.5%	4.3%	7.9%
			Observed number of cases	2	2	2	4
		Male	<i>p</i> -value of pairwise and trend tests	.3155	.5473	.9087	.3860
			Poly-3 adjusted incidence rate	5.5%	6.9%	2.3%	8.9%
			Observed number of cases	3	3	1	4
heart	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.7263	.4583		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
	CARCINOMA, BRONCHIOL	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0

Table 14: All reported neoplastic tumors in mouse study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
	FIBROUS HISTIOCYTOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.8%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
kidneys	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	ADENOMA, TUBU	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	FIBROSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.4780		.4536	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
lacrimal glands, exorbital	FIBROUS HISTIOCYTOMA	Male	<i>p</i> -value of pairwise and trend tests	.2418			.4536
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.2%
			Observed number of cases	0	0	0	1
large intestine, colon	CARCINOMA, BRONCHIOL	Female	<i>p</i> -value of pairwise and trend tests	.7263	.4583		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
large intestine, rectum	LEIOMYOMA	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
liver	ADENOMA, HEPATO	Female	<i>p</i> -value of pairwise and trend tests	.1322	.7092	.7152	.2865
			Poly-3 adjusted incidence rate	1.9%	2.3%	2.2%	6.0%
			Observed number of cases	1	1	1	3
		Male	<i>p</i> -value of pairwise and trend tests	.9033	.0133	.4977	.6796
			Poly-3 adjusted incidence rate	7.3%	25%	9.1%	6.8%
			Observed number of cases	4	11	4	3
	CARCINOMA, HEPATOCEL	Female	<i>p</i> -value of pairwise and trend tests	.4974		.4694	
			Poly-3 adjusted incidence rate	.00%	.00%	2.2%	.00%
			Observed number of cases	0	0	1	0
		Male	<i>p</i> -value of pairwise and trend tests	.1116	.2263	.2418	.1285
			Poly-3 adjusted incidence rate	1.9%	7.0%	6.8%	9.1%

Table 14: All reported neoplastic tumors in mouse study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	1	3	3	4
	SCHWANNOMA	Female	<i>p</i> -value of pairwise and trend tests	.2618			.4902
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.0%
			Observed number of cases	0	0	0	1
lung	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.4927	.8453	1.000	.6685
			Poly-3 adjusted incidence rate	3.8%	2.3%	.00%	4.0%
			Observed number of cases	2	1	0	2
	ADENOMA, BRONCHIOLAR	Female	<i>p</i> -value of pairwise and trend tests	.3384	.1765	.0717	.3357
			Poly-3 adjusted incidence rate	5.7%	13%	17%	10%
			Observed number of cases	3	6	8	5
		Male	<i>p</i> -value of pairwise and trend tests	.7026	.2414	.8786	.5654
			Poly-3 adjusted incidence rate	15%	22%	9.1%	16%
			Observed number of cases	8	10	4	7
	CARCINOMA, BRONCHIOL	Female	<i>p</i> -value of pairwise and trend tests	.6503	.2725	.4415	.6763
			Poly-3 adjusted incidence rate	3.8%	8.8%	6.5%	4.0%
			Observed number of cases	2	4	3	2
		Male	<i>p</i> -value of pairwise and trend tests	.9922	.8640	.9802	.9963
			Poly-3 adjusted incidence rate	14%	9.2%	4.5%	2.3%
			Observed number of cases	8	4	2	1
	CARCINOMA, HEPATOCEL	Male	<i>p</i> -value of pairwise and trend tests	.7072	.4421		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
	FIBROSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.4780		.4536	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	FIBROUS HISTIOCYTOMA	Male	<i>p</i> -value of pairwise and trend tests	.4783	1.000	1.000	.6989
			Poly-3 adjusted incidence rate	1.8%	.00%	.00%	2.2%
			Observed number of cases	1	0	0	1
	GRANULOSA	Female	<i>p</i> -value of pairwise and trend tests	.7263	.4583		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
	LUTEOMA	Female	<i>p</i> -value of pairwise and trend tests	.2618			.4902
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.0%
			Observed number of cases	0	0	0	1
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	

Table 14: All reported neoplastic tumors in mouse study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	SARCOMA, HISTIOCYTIC	Female	<i>p</i> -value of pairwise and trend tests	.7263	.4583		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
lymph node, mandibular	FIBROSARCOMA	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	FIBROUS HISTIOCYTOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.8%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
lymph node, mediastinal	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.0655			.2329
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	4.0%
			Observed number of cases	0	0	0	2
	CARCINOMA, BRONCHIOL	Male	<i>p</i> -value of pairwise and trend tests	.7231	1.000	.6927	1.000
			Poly-3 adjusted incidence rate	1.8%	.00%	2.3%	.00%
			Observed number of cases	1	0	1	0
lymph node, mesenteric	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.7263	.4583		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
mammary gland	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.1305	.8411	.8460	.3116
			Poly-3 adjusted incidence rate	3.8%	2.3%	2.2%	8.0%
			Observed number of cases	2	1	1	4
multicentric neoplasm	HEMANGIOMA	Male	<i>p</i> -value of pairwise and trend tests	.8490	.8360	.6086	1.000
			Poly-3 adjusted incidence rate	3.7%	2.3%	4.6%	.00%
			Observed number of cases	2	1	2	0
	HEMANGIOSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
		Male	<i>p</i> -value of pairwise and trend tests	.7987	.7471	.7555	.9155
			Poly-3 adjusted incidence rate	5.6%	4.6%	4.5%	2.3%
			Observed number of cases	3	2	2	1
	LEUKEMIA	Female	<i>p</i> -value of pairwise and trend tests	.4974		.4694	
			Poly-3 adjusted incidence rate	.00%	.00%	2.1%	.00%
			Observed number of cases	0	0	1	0

Table 14: All reported neoplastic tumors in mouse study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
		Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.8%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LYMPHOMA	Female	<i>p</i> -value of pairwise and trend tests	.1661	.3540	.2424	.2000
			Poly-3 adjusted incidence rate	15%	20%	22%	23%
			Observed number of cases	8	9	11	12
		Male	<i>p</i> -value of pairwise and trend tests	.5294	.6775	.5225	.6997
			Poly-3 adjusted incidence rate	7.4%	7.0%	9.0%	6.7%
			Observed number of cases	4	3	4	3
	SARCOMA,	Female	<i>p</i> -value of pairwise and trend tests	.8428	.7438	.8824	.9002
			Poly-3 adjusted incidence rate	11%	8.9%	6.4%	6.0%
			Observed number of cases	6	4	3	3
ovaries	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.9261	.7092	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	2.3%	.00%	.00%
			Observed number of cases	1	1	0	0
	CYSTADENOMA	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	3.8%	.00%	.00%	.00%
			Observed number of cases	2	0	0	0
	GRANULOSA	Female	<i>p</i> -value of pairwise and trend tests	.9261	.7092	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	2.3%	.00%	.00%
			Observed number of cases	1	1	0	0
	GRANULOSA CE	Female	<i>p</i> -value of pairwise and trend tests	.7041	.8453	.8547	.8674
			Poly-3 adjusted incidence rate	3.8%	2.3%	2.2%	2.0%
			Observed number of cases	2	1	1	1
	LUTEOMA	Female	<i>p</i> -value of pairwise and trend tests	.2618			.4902
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.0%
			Observed number of cases	0	0	0	1
pancreas	ADENOMA, IS	Female	<i>p</i> -value of pairwise and trend tests	.5054	1.000	1.000	.7374
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	2.0%
			Observed number of cases	1	0	0	1
parathyroid glands	ADENOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
pituitary gland	ADENOMA, PARS	Female	<i>p</i> -value of pairwise and trend tests	.6200	.4370	.7152	.7374
			Poly-3 adjusted incidence rate	1.9%	4.5%	2.2%	2.0%

Table 14: All reported neoplastic tumors in mouse study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Observed number of cases	1	2	1	1
		Male	<i>p</i> -value of pairwise and trend tests	.7072	.4421		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
	ADENOMA, PARS IN	Female	<i>p</i> -value of pairwise and trend tests	.2579			.4851
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.0%
			Observed number of cases	0	0	0	1
skeletal muscle, biceps femoris	FIBROUS HISTIOCYTOMA	Male	<i>p</i> -value of pairwise and trend tests	.2418			.4536
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.2%
			Observed number of cases	0	0	0	1
skin	KERATOA	Female	<i>p</i> -value of pairwise and trend tests	.4947		.4639	
			Poly-3 adjusted incidence rate	.00%	.00%	2.2%	.00%
			Observed number of cases	0	0	1	0
skin, subcutis	FIBROSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	.2618			.4902
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.0%
			Observed number of cases	0	0	0	1
		Male	<i>p</i> -value of pairwise and trend tests	.4751		.2032	
			Poly-3 adjusted incidence rate	.00%	.00%	4.5%	.00%
			Observed number of cases	0	0	2	0
	FIBROUS HISTIOCYTOMA	Female	<i>p</i> -value of pairwise and trend tests	.2579			.4851
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.0%
			Observed number of cases	0	0	0	1
		Male	<i>p</i> -value of pairwise and trend tests	.6825	.6009	.6103	.8369
			Poly-3 adjusted incidence rate	3.7%	4.6%	4.5%	2.2%
			Observed number of cases	2	2	2	1
small intestine, duodenum	SARCOMA, UNDIFF	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
small intestine, jejunum	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.2579			.4851
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.0%
			Observed number of cases	0	0	0	1
spinal cord, lumbar	AST	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
spleen	FIBROUS HISTIOCYTOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000

Table 14: All reported neoplastic tumors in mouse study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted incidence rate	1.8%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
stomach, glandular	ADENOMA	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
	GRANULOSA	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
stomach, nonglandular	PAPILLOMA, SQUAM	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
testes	ADENOMA, INTERSTIT	Male	<i>p</i> -value of pairwise and trend tests	.3743	1.000	.6978	.6978
			Poly-3 adjusted incidence rate	1.9%	.00%	2.3%	2.3%
			Observed number of cases	1	0	1	1
	CARCINOMA, INTERS	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
thymus gland	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.7263	.4583		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
	CARCINOMA, BRONCHIOL	Male	<i>p</i> -value of pairwise and trend tests	.7259	1.000	.6978	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	2.3%	.00%
			Observed number of cases	1	0	1	0
	FIBROUS HISTIOCYTOMA	Male	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.8%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	MESOTHELIOMA	Male	<i>p</i> -value of pairwise and trend tests	.4751		.4479	
			Poly-3 adjusted incidence rate	.00%	.00%	2.3%	.00%
			Observed number of cases	0	0	1	0
thyroid gland	ADENOMA	Female	<i>p</i> -value of pairwise and trend tests	.2579			.4851
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.0%
			Observed number of cases	0	0	0	1
	ADENOMA, FOLLICU	Female	<i>p</i> -value of pairwise and trend tests	.2579			.4851
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.0%
			Observed number of cases	0	0	0	1

Table 14: All reported neoplastic tumors in mouse study (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
		Male	<i>p</i> -value of pairwise and trend tests	.2418			.4536
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.2%
			Observed number of cases	0	0	0	1
	CARCINOMA, FOLL	Male	<i>p</i> -value of pairwise and trend tests	.7072	.4421		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0
urinary bladder	MESENCHYM	Male	<i>p</i> -value of pairwise and trend tests	.9154	.6914	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	2.3%	.00%	.00%
			Observed number of cases	1	1	0	0
uterus with cervix	ADENOCARCINOMA	Female	<i>p</i> -value of pairwise and trend tests	.9261	.7092	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	2.3%	.00%	.00%
			Observed number of cases	1	1	0	0
	ADENOMA	Female	<i>p</i> -value of pairwise and trend tests	1.000	1.000	1.000	1.000
			Poly-3 adjusted incidence rate	1.9%	.00%	.00%	.00%
			Observed number of cases	1	0	0	0
	LEIOMYOMA	Female	<i>p</i> -value of pairwise and trend tests	.0842	.7485	.5705	.2069
			Poly-3 adjusted incidence rate	5.5%	4.5%	6.5%	12%
			Observed number of cases	3	2	3	6
	LEIOMYOSARCOMA	Female	<i>p</i> -value of pairwise and trend tests	.2579			.4851
			Poly-3 adjusted incidence rate	.00%	.00%	.00%	2.0%
			Observed number of cases	0	0	0	1
	POLYP, STROMAL	Female	<i>p</i> -value of pairwise and trend tests	.2142	.2815	.0907	.2520
			Poly-3 adjusted incidence rate	9.5%	15%	21%	16%
			Observed number of cases	5	7	10	8
	SARCOMA, HISTIOCYTIC	Female	<i>p</i> -value of pairwise and trend tests	.8602	.0725	.0766	1.000
			Poly-3 adjusted incidence rate	1.9%	11%	11%	.00%
			Observed number of cases	1	5	5	0
	SCHWANNOMA	Female	<i>p</i> -value of pairwise and trend tests	.2115		.2126	.4902
			Poly-3 adjusted incidence rate	.00%	.00%	4.4%	2.0%
			Observed number of cases	0	0	2	1
vagina	SARCOMA, HISTIOCYTIC	Female	<i>p</i> -value of pairwise and trend tests	.7263	.4583		
			Poly-3 adjusted incidence rate	.00%	2.3%	.00%	.00%
			Observed number of cases	0	1	0	0

Table 15: Table of composite endpoints in mouse study

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
All brain tumors	Female	<i>p</i> -value of pairwise and trend tests	1	1	1	1
		Adjusted incidence rate (%)	1.89	0	0	0
		Number of animals with tumor	1	0	0	0
		Adjusted number of animals at risk	52.82	44.15	45.69	49.40
	Male	<i>p</i> -value of pairwise and trend tests	0.8051	0.6927	0.6927	1
		Adjusted incidence rate (%)	1.85	2.28	2.28	0
		Number of animals with brain tumor	1	1	1	0
Adjusted number of animals at risk	54.17	43.88	43.80	47.48		
Gliomas	Female	<i>p</i> -value of pairwise and trend tests	1	1	1	1
		Adjusted incidence rate (%)	1.89	0	0	0
		Number of animals with tumor	1	0	0	0
		Adjusted number of animals at risk	52.82	44.15	45.69	49.40
	Male	<i>p</i> -value of pairwise and trend tests	0.9177	0.6927	1	1
		Adjusted incidence rate (%)	1.85	2.28	0	0
		Number of animals with glioma	1	1	0	0
Adjusted number of animals at risk	54.17	43.88	43.57	49.40		
Malignant brain tumors	Male	<i>p</i> -value of pairwise and trend tests	0.9177	0.6927	1	1
		Adjusted incidence rate (%)	1.85	2.28	0	0
		Number of animals with tumor	1	1	0	0
		Adjusted number of animals at risk	54.17	43.88	43.57	47.48
All mammary tumors	Female	<i>p</i> -value of pairwise and trend tests	0.1305	0.8411	0.8460	0.3116
		Adjusted incidence rate (%)	3.76	2.26	2.18	8.00
		Number of animals with tumor	2	1	1	4
		Adjusted number of animals at risk	53.26	44.26	45.93	50.03
Malignant mammary tumors	Female	<i>p</i> -value of pairwise and trend tests	0.1305	0.8411	0.8460	0.3116
		Adjusted incidence rate (%)	3.76	2.26	2.18	8.00
		Number of animals with malignant tumor	2	1	1	4
		Adjusted number of animals at risk	53.26	44.26	45.93	50.03
Mammary adenocarcinomas and fibroadenomas	Female	<i>p</i> -value of pairwise and trend tests	0.1305	0.8411	0.8460	0.3116

Table 15: Composite endpoints in mouse study (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
		Adjusted incidence rate (%)	3.76	2.26	2.18	8.00
		Number of animals with tumor	2	1	1	4
		Adjusted number of animals at risk	53.26	44.26	45.93	50.03
Subcutaneous fibromas and fibrosarcomas	Female	<i>p</i> -value of pairwise and trend tests	0.2618	.	.	0.4902
		Adjusted incidence rate (%)	0	0	0	2.00
		Number of animals with tumor	0	0	0	1
		Adjusted number of animals at risk	52.33	44.15	45.69	50.08
	Male	<i>p</i> -value of pairwise and trend tests	0.4975	.	0.2032	.
		Adjusted incidence rate (%)	0	0	4.52	0
		Number of animals with tumor	0	0	2	0
		Adjusted number of animals at risk	53.50	42.95	42.25	47.48
Squamous tumor or keratoacanthoma (skin)	Female	<i>p</i> -value of pairwise and trend tests	0.4947	.	0.4639	.
		Adjusted incidence rate (%)	0	0	2.19	0
		Number of animals with tumor	0	0	1	0
		Adjusted number of animals at risk	52.32	44.15	45.69	49.40
Thyroidal follicular adenomas and carcinomas	Female	<i>p</i> -value of pairwise and trend tests	0.2579	.	.	0.4851
		Adjusted incidence rate (%)	0	0	0	2.02
		Number of animals with tumor	0	0	0	1
		Adjusted number of animals at risk	52.33	44.15	45.69	49.40
	Male	<i>p</i> -value of pairwise and trend tests	0.3027	0.4421	.	0.4752
		Adjusted incidence rate (%)	0	2.33	0	2.07
		Number of animals with tumor	0	1	0	1
		Adjusted number of animals at risk	53.50	42.95	43.57	48.31
Uterine/cervical glandular polyps or adenocarcinomas	Female	<i>p</i> -value of pairwise and trend tests	0.9261	0.7092	1	1
		Adjusted incidence rate (%)	1.91	2.26	0	0
		Number of animals with tumor	1	1	0	0
		Adjusted number of animals at risk	52.39	44.34	45.69	49.40
Hepatocellular adenomas and carcinomas	Female	<i>p</i> -value of pairwise and trend tests	0.1318	0.7092	0.4537	0.2865
		Adjusted incidence rate (%)	1.90	2.26	4.34	6.02
		Number of animals with tumor	1	1	2	3

Table 15: Composite endpoints in mouse study (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
	Male	Adjusted number of animals at risk	52.52	44.31	46.02	49.82
		<i>p</i> -value of pairwise and trend tests	0.7386	0.0009	0.2342	0.4040
		Adjusted incidence rate (%)	9.08	29.55	15.73	12.45
		Number of animals with tumor	5	13	7	6
		Adjusted number of animals at risk	55.05	44.00	44.50	48.20
All schwannomas	Female	<i>p</i> -value of pairwise and trend tests	0.2115	.	0.2126	0.4902
		Adjusted incidence rate (%)	0	0	4.38	2.00
		Number of animals with schwannoma	0	0	2	1
		Adjusted number of animals at risk	52.33	44.15	45.69	50.11

Table 16: Table of neoplastic tumors in mouse study with at least one significant result

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
liver	ADENOMA, HEPATOCELLULAR	Female	<i>p</i> -value of pairwise and trend tests	0.1322	0.7092	0.7152	0.2865
			Poly-3 adjusted incidence rate	1.9%	2.3%	2.2%	6.0%
			Observed number of cases	1	1	1	3
			Adjusted number at risk	52.52	44.36	45.69	49.82
		Male	<i>p</i> -value of pairwise and trend tests	0.9033	0.0133	0.4977	0.6796
			Poly-3 adjusted incidence rate	7.3%	25%	9.1%	6.8%
			Observed number of cases	4	11	4	3
			Adjusted number at risk	55.05	43.97	43.94	44.37

Reviewer’s findings Table 16 details the individual tumor types for which a p -value less than or equal to 0.05 was found for either the dose response or the test of proportion for at least one treatment group vs control, in at least one sex. In the mouse study, only one tumor type passed this threshold; benign hepatocellular adenomas. However, the significant result was only noted in the comparison between the low dose and control animals in the male group; there is no evidence of an increased incidence of such tumors among the higher dose groups, or among the female mice.

Furthermore, based on the same multiple testing adjustment procedure discussed in the Section 2.2.2, this p -value of 0.0133 does not rise to the level ($\alpha = 0.01$ for common tumors) needed to justify further attention.

Analysis of the composite endpoints yielded no significant or noteworthy results, except the pairwise comparison of hepatocellular adenomas and carcinomas between the low dose group and the control group. However, this result, which is largely driven by the high number of hepatocellular liver adenomas in the low dose group is not accompanied by statistically significant increased incidence rates in the higher dose groups or in the female study, although the female group does display a slightly increasing (but non significant) trend. While it is possible that this represents a genuine carcinogenicity effect, the evidence is weak at best.

On the other hand, given that hepatocellular adenomas were one of the tumor types for which increased incidence was associated with increased dosage in the rat study, the possible indication in mice should not be disregarded entirely.

4 Evaluation of the validity of the study

4.1 Suitability of dose levels

4.1.1 Issues of concern when selecting dose levels

The selection of an appropriate dose level for the high dose group is made difficult by the need to satisfy two competing imperatives: on the one hand, if the dose level is insufficiently high, then genuine carcinogenicity effects may not be apparent, but on the other hand, if the dose level is too high, then there is a risk of non-carcinogenic toxic effects killing the animals before they have a chance to demonstrate a carcinogenicity effect.

Haseman [5] suggested that a satisfactory balance between these two imperatives has been found when the following two conditions are both satisfied:

1. Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
2. 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 fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman [5] has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 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 considered as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward [4], suggested that “to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one year.”

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 [4], the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met:

1. 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.
2. The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical.
3. In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls.

4.1.2 Appropriateness of high dose in rat study

The study is a positive study, in that tumorigenic effects have been found in both male and female rats. In a positive study there is, in general, no need to verify that the study had the sensitivity needed to detect a tumorigenic effect; the very fact of the positive result means that an effect could be detected.

Table 17: Positive results in rat study

Organ	Male rats only	Male and Female rats	Female rats only
Single tumor types			
Brain	Astrocytoma		
Liver	Hepatocellular adenoma		
Lung			Carcinoma
Mammary gland		Fibroadenoma	Adenocarcinoma
Skin	Squamous cell carcinoma		
Skin, subcutis	Fibroma Schwannoma		Fibrosarcoma
Thyroid gland	Follicular adenoma		C-cell adenoma
Uterus with cervix			Glandular polyp
Composite tumor types			
All sites	Schwannomas		
Brain	All brain tumors Gliomas		
Liver	Hepatocellular adenomas and carcinomas		
Mammary gland		All mammary tumors Adenocarcinomas and fibroadenomas	Malignant mammary tumors
Skin	Squamous papillomas and carcinomas Squamous tumors and keratoacanthomas		
Skin, subcutis	Fibromas and fibrosarcomas		
Thyroid	F-cell adenomas and carcinomas		
Uterus with cervix			Adenocarcinomas or glandular polyp

However, in this case, the tumorigenic effects seem quite divergent across the sexes. Table 17 lists the positive results of the study by sex; very few tumor types were found to generate positive results in both male and female rats¹. Nonetheless, our criteria for the assessment of whether the dose posed a sufficient tumor challenge to the animals, and whether the dose was excessive (as described in section 4.1.1) are based on study-wide considerations, and are not applicable to individual tumor types (so that, for example, it is not appropriate to consider the female study to have been “negative for astrocytomas” — the study as a whole was a positive study). The presence

¹Note that in the case of mammary adenocarcinomas in male rats, the test of trend yielded a result that was significant at the 5% level, but was not significant after making an adjustment for multiplicity. Similarly, in the case of the composite endpoint of subcutaneous fibromas and fibrosarcomas in female rats, both the test of trend and the test of comparison between the high dose group and the control group were significant at the 5% level, but were not significant after adjusting for multiplicity.

of significant results in both the male and female rats is therefore sufficient justification for us to conclude that the dose selection was appropriate.

Table 18: Weight change by group

Species and Sex	Δ_C	Δ_L	$\frac{\Delta_L}{\Delta_C} - 1$	Δ_M	$\frac{\Delta_M}{\Delta_C} - 1$	Δ_H	$\frac{\Delta_H}{\Delta_C} - 1$
Rats - Female	276.5	295.1	+6.7%	288.3	+4.3%	.	.
Rats - Male	479.1	393.1	-18.0%	386.7	-19.3%	262.3	-45.3%
Mice - Female	13.50	13.85	+2.59%	13.52	+0.15%	13.52	+5.19%
Mice - Male	14.06	12.97	-7.75%	12.50	-11.10%	13.12	-6.68%

4.1.3 Appropriateness of high dose in mouse study

As noted above, the two main instruments that we use to assess the suitability of a dose level are the animals' weight change and their survival rates at certain key times. Intercurrent mortality data are presented in table 11 (on page 61).

We see that in the both studies, each treatment group had at least 20 survivors at termination, with a survival rate of at least 30%. At ninety weeks, each treatment group had at least 36 animals alive, and a survival rate above 55%. Accordingly, we can conclude that the number of animals alive was sufficient to meet Haseman's criterion; sufficient animals were exposed to the drug for a sustained period of time to allow for the detection of late developing tumors.

On the question of whether the dose levels were adequate, the first thing to note is that there is no evidence of a reduced survival rate among the high dose animals.

Summary data of the animals' weight gain are presented in table 18. In the case of the male mice, diminished weight gain can be observed in all three treated groups, although the magnitude of the diminished weight gain does not appear to be related to the dosage.

In the case of the female mice, the mean weight gain in all three treated groups exceeded the mean weight gain of the control group, so in this case we can certainly not conclude that the toxic effects of APD356 are diminishing weight gain.

Thus, while it is reasonable to assume that 50 mg/kg has not been an excessive dose, the evidence that it has been adequate is weak. Of the three criteria presented by Chu, Cueto and Ward, increased mortality is not in evidence in either the study of male or female mice. The diminished weight gain in the male mice is about or under 10% relative to the controls, and therefore meets our criterion, although there is no clear dose response relationship, and it is possible that the weight loss is in part attributable to therapeutic rather than toxic effects. Evidence of diminished weight gain is completely absent in the study of female mice. Accordingly, the determination of whether a daily dose of 50mg/kg was adequate is dependent on assessment of the third condition, "clinical signs or severe histopathologic toxic effects" attributable to the chemical. Such an assessment is outside the scope of this review, but if such evidence is not found, then it must be concluded that 50 mg/kg has not been shown to be an adequate maximum dose, especially in the female mice.

Standing against these concerns is the fact that preliminary results indicated that the dosage of 100 mg/kg was an excessive dose. While it is not the purpose of this review to speculate about the reasons for such a discrepancy, one possibility is that the toxicity of APD356 is subject to a very strong dose response between 50 mg/kg and 100 mg/kg.

4.2 Reporting of autolysis and missing organs

4.2.1 Rat Study

No organs were reported as either autolytic or unexamined in the updated dataset for the rat study (2010-07-30). However, there are organs of interest, including mammary glands (4 animals) and thymus glands (39 animals), which were reported as being unexamined in the original data submission. This change of classification has not been explained.

4.2.2 Mouse Study

No organs were reported as autolytic in the mouse study. The only organs that were widely reported as unexamined were the parathyroid gland (119 female mice and 115 male mice, from populations of 280 and 270 respectively, did not have their parathyroid glands examined), and the thymus gland (36 male mice are reported as having had their thymus glands unexamined). Given the numbers of animals for which the parathyroid gland was not examined, it must be concluded that this study cannot be viewed as informative regarding that organ.

5 Summary

5.1 Rat Study

The rat study has been largely successful in identifying several probable carcinogenic effects of APD356. Most noteworthy are the highly increased rates of mammary tumors in both male and female rats (both adenocarcinomas and fibroadenomas), skin tumors in male rats, astrocytomas in male rats, hepatocellular adenomas in male rats, follicular adenomas of the thymus gland in male rats, carcinomas of the lung in female rats and glandular polyps in female rats.

The high dose level for the male rats appears to have been well chosen. However, the high dose level for the female rats led to exceptionally high levels of mortality. This mortality was mainly driven by malignant mammary tumors, and so was likely a carcinogenic effect rather than a toxic effect. However, there is a concern that the exceptionally high level of malignant mammary tumors in the female rat population may have masked additional signals. The 30 mg/kg dose level may be a suitable surrogate maximum dose for the female rats. Using this dose level as the basis for pairwise comparisons with the control group yields no additional significant results.

It is also worth noting that even the female control group experienced high levels of mammary tumors (although the levels reported are within the range suggested by the historical control data), raising questions about the particular population of rats used in this study.

5.2 Mouse Study

No strong carcinogenic effects were noted in the mouse study, but the evidence that animals were subject to a sufficiently challenging dose is weak.

5.3 Comments on dosing

Selecting suitable dose levels for this drug has been difficult. In the case of the male rats, 100 mg/kg has been a good choice for a maximum dose. The dose level of 100 mg/kg has arguably been excessive for the female rats, although there has been no problem with animals dying before they have had a chance to develop tumors. However, by the usual benchmarks, a daily dose of 30 mg/kg would appear to be acceptable as a substitute maximum dose for the female rats, but not for the males.

In the case of the mice, 100 mg/kg was originally selected as the high dose, but this was abandoned as too high. However, the replacement “high dose”, 50 mg/kg does not appear to have been high enough to have served in this capacity. Taken together, these results suggest a highly idiosyncratic dose response, varying considerably between male and female rats, and with sharply different effects in mice as the dose changes between 50 mg/kg and 100 mg/kg.

References

- [1] P. Armitage. Tests for linear trends in proportions and frequencies. *Biometrics*, 11(3):375–386, 1955.
- [2] A J Bailer and C J Portier. Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. *Biometrics*, 44(2):417–31, 1988.

- [3] G S Bieler and R L Williams. Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics*, 49(3):793–801, 1993.
- [4] KC Chu, C Cueto, and JM Ward. Factors in the evaluation of 200 National Cancer Institute carcinogen bioassays. *Journal of toxicology and environmental health*, 8(1-2):251–280, 1981.
- [5] J K Haseman. A reexamination of false-positive rates carcinogenesis studies. *Fundamental and applied toxicology*, 3(4):334–339, 1983.
- [6] E.L. Kaplan and P. Meier. Non-parametric estimation from incomplete observations. *Journal of the American Statistical Association*, 53:457–481, 1958.
- [7] K K Lin and M A Rahman. Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs. *J Biopharm Stat*, 8(1):1–15; discussion 17–22, 1998.
- [8] R Peto, M C Pike, N E Day, R G Gray, P N Lee, S Parish, J Peto, S Richards, and J Wahrendorf. Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, NIL(2 Suppl):311–426, 1980.
- [9] M A Rahman and K K Lin. A comparison of false positive rates of peto and poly-3 methods for long-term carcinogenicity data analysis using multiple comparison adjustment method suggested by Lin and Rahman. *J Biopharm Stat*, 18(5):949–58, 2008.

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/s/

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11/02/2010

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Concur with review



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-529 / SN 000

Drug Name: Lorqess (Lorcaserin hydrochloride, Lorcaserin, APD356)

Indication(s): Weight management, including weight loss and maintenance of weight loss

Applicant: Arena Pharmaceuticals

Date(s): Submitted December 22, 2009

Review Priority: Standard

Biometrics Division: Division of Biometrics VII

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Keywords: NDA review, clinical studies, noninferiority, safety, valvulopathy

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1 Executive Summary

This statistical review and evaluation was performed in response to a consultation from the Division of Metabolism and Endocrinology Products (DMEP) for New Drug Application (NDA) 22-529/000 (received December 22, 2009) for lorcaserin tablets. The proposed indication for lorcaserin is weight management, including weight loss and maintenance of weight loss. This statistical review will assess the following safety parameters measured in Study APD356-009 and Study APD356-011: FDA-defined valvulopathy and the Beck Depression Inventory Second Edition (BDI-II) score.

1.1 Conclusions and Recommendations

Based on a non-inferiority margin of 1.5 for the relative risk ratio (see Section 1.3 for a discussion on the selection of the non-inferiority margin), the pooled analysis of two phase 3 randomized placebo-controlled clinical trials APD356-009 and APD356-011 failed to rule out that the lorcaserin 10 mg twice-a-day (BID) regimen was inferior to the placebo in the risk of developing FDA-defined valvulopathy (aortic regurgitation mild or greater, or mitral regurgitation moderate or greater) at 52 weeks.

Compared to placebo, the lorcaserin 10 mg BID regimen was found to be associated with an increase in at least one of the four valvular regurgitations (aortic valve, mitral valve, pulmonary valve, and tricuspid valve). The incidence of developing increased valvular regurgitation was statistically significantly higher at the nominal $\alpha=0.05$ level in the lorcaserin group than in the placebo group, in both Studies APD356-009 and APD356-011 separately, as well as in the pooled analysis of both studies.

Since the main focus of the pooled phase 3 studies was to evaluate FDA-defined valvulopathy, the sample sizes were not adequately powered for the assessment of the Beck Depression Inventory. For the assessment of the Beck Depression Inventory, no statistically significant difference between lorcaserin and placebo in the BDI-II total score was found. However, the incidence of severe depression at 52 weeks, defined as the proportion of subjects with a BDI-II total score greater than 28, was noticeably higher in the lorcaserin group than in the placebo group, in both Studies APD356-009 and APD356-011 separately, as well as in the pooled analysis of both studies. The corresponding 95% confidence interval for the pooled analysis included the null value of one but had a wide range, indicating that even the pooled phase 3 studies might not be powered to draw a definite conclusion.

Based on individual BDI-II items addressing specific questions related to depression, there does not appear to be a significant association between the lorcaserin regimen and an increase in suicidal thoughts. In contrast, the lorcaserin 10 mg BID regimen was found to be associated with statistically significantly higher risk of losing appetite, developing concentration difficulty and having tiredness or fatigue.

1.2 Brief Overview of Clinical Studies

In this NDA application, the applicant submitted two Phase 3 studies, Study APD356-009 and Study APD356-011, in support of the safety and efficacy of lorcaserin for the indication of weight management. Study APD356-009 was a 104-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of lorcaserin in obese subjects. Study APD356-011 was a 52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of lorcaserin in overweight and obese subjects. In the pooled data from Studies APD356-009 and APD356-011, a total of 4,000 subjects were randomized to receive lorcaserin regimens, while a total of 3,190 subjects were randomized to receive placebo.

Both Study APD356-009 and Study APD356-011 were individually powered to provide at least 95% power to detect the efficacy difference between the lorcaserin groups and the placebo group. In contrast, these studies might not be individually powered to draw sufficient statistical inference on safety parameters like FDA-defined valvulopathy and BDI-II score. Furthermore, the pooled analysis based on Studies APD356-009 and APD356-011 was powered to provide at least 80% power to declare non-inferiority of the lorcaserin BID group to the placebo group for a margin corresponding to a relative risk of 1.5% at Week 52 if the placebo rate was as least 2.7% annually.

1.3 Statistical Issues and Findings

The primary endpoint of the echocardiogram evaluation was the proportion of subjects who developed FDA-defined valvulopathy at week 52.

Once approved, a weight loss drug would be used by hundred of thousands of patients, many of whom would be at low short-term absolute risk for serious disease due to their body weight. It is clinically important to determine the excess risk acceptable for such a drug. During the development process of this NDA application, The Agency continuously emphasized that ruling out a 50% increased in the incidence of FDA-defined valvulopathy was both an important and a reasonable request for the applicant. As such, the Agency stated that data in the NDA must be able to rule out a relative risk for FDA-defined valvulopathy of at least 1.5 (powered at 80%). (b) (4)

In the FDA Pre-Meeting Response for the pre-NDA meeting on August 12, 2009 for IND 69888, the Agency informed the applicant that at a minimum, the echocardiographic data must be robust enough to rule out a relative risk of 1.5 for FDA-defined valvulopathy. Therefore, a non-inferiority margin of 1.5 for the relative risk ratio is used in this review.

As pre-specified in the applicant's Statistical Analysis Plan (SAP), phase 3 data from Studies APD356-009 and APD356-011 were pooled to evaluate the risk of FDA-defined valvulopathy. The comparison between the lorcaserin 10 mg BID group and the placebo

group is performed using the protocol-defined Cochran-Mantel-Haenszel (CMH) test with study as stratification factor. The two-sided 95% or 90% confidence intervals for between-group relative risk ratio were conducted using a stratified Mantel-Haenszel approach.

The pooled relative risk ratio between lorcaserin and placebo was 1.07 with a 95% confidence interval of (0.75, 1.55). The lorcaserin 10 mg BID group failed to demonstrate the non-inferiority to the placebo group at week 52, given the upper limit of the confidence interval exceeded the pre-specified non-inferiority margin of 1.5. Similar results were shown in several sensitivity analyses for the incidence of FDA-defined valvulopathy. Therefore, the pooled data from Studies APD356-009 and APD356-011 could not robustly rule out a relative risk of 1.5 for lorcaserin 10 mg BID regimen in the risk of developing FDA-defined valvulopathy from baseline to week 52. Detailed analysis results are provided in Section 3.1.6.1.1 and Section 3.1.6.1.2.

Although the last observation carried forward (LOCF) method to impute the missing values was pre-specified in the protocol, this method can lead to biased point estimates and variances. This is especially problematic when the study discontinuation rate is high and disproportional between different treatment arms. Several sensitivity analyses were conducted to assess the robustness of the results. Detailed analysis results are provided in Section 3.1.6.1.2.

With respect to the risk of developing increased valvular regurgitation at week 52 for at least one valve among aortic, mitral, pulmonary, and tricuspid valves, the incidence was statistically significantly higher at the nominal $\alpha=0.05$ level in the lorcaserin 10 mg BID group than in the placebo group in each study separately. Pooling Study APD356-009 and Study APD356-011 together, the pooled relative risk ratio was 1.11 with a 95% confidence interval of (1.04, 1.18), indicating that the difference between lorcaserin and placebo was statistically significant (46.94% versus 42.36%, $p=0.001$). More details of this assessment can be found in Section 3.2.3.1.2.

BDI-II total score was designed to assess the presence and severity of symptoms of depression. For the risk of developing severe depression defined as a BDI-total score greater than 28 at week 52, no statistically significant difference was found between lorcaserin and placebo. The pooled relative risk ratio between lorcaserin and placebo was 2.44 with a 95% confidence interval of (0.77, 7.77). The estimated relative risk of 2.44 and a wide confidence interval suggested that there might be a relationship between lorcaserin 10 mg BID regimen and increased risk of severe depression but the currently available data might not be powered to draw definite conclusion on it. More details of this assessment can be found in Section 3.2.3.2.1.

The BDI-II score for each individual item of the inventory corresponded to a specific category of depressive symptom or attitude. The following is a summary finding of four key items from the inventory.

- Based on BDI-II score for Item #9, there does not appear to be a significant relationship between lorcaserin and increased risk of suicidal thoughts. The

pooled relative risk ratio at week 52 was 1.17 with a 95% confidence interval of (0.59, 2.32).

- Based on BDI-II score for Item #18, the lorcaserin regimen was shown to be associated with an increase in risk of losing appetite. The pooled relative risk ratio between lorcaserin and placebo was 1.98 with a 95% confidence interval of (1.73, 2.27).
- Based on BDI-II score for Item #19, the lorcaserin regimen was shown to be associated with an increase in risk of developing concentration difficulty. The pooled relative risk ratio between lorcaserin and placebo was 1.14 with a 95% confidence interval of (1.03, 1.26).
- Based on BDI-II score for Item #20, the lorcaserin regimen was shown to be associated with an increase in risk of having tiredness or fatigue. The pooled relative risk ratio between lorcaserin and placebo was 1.11 with a 95% confidence interval of (1.04, 1.19).

More details of these analysis results can be found in Section 3.2.3.2.2 and in Section 3.2.3.2.3.

2 Introduction

2.1 Product Description

Lorcaserin hydrochloride (lorcaserin), a selective serotonin 2C (5-HT_{2C}) receptor agonist, was submitted by the applicant as a new agent to reduce body weight. The proposed indication is for weight management, including weight loss and maintenance of weight loss in obese subjects (BMI \geq 30 kg/m²), or overweight subjects (BMI \geq 27- 30 kg/m²) who have one or more weight-related co-morbid medical conditions.

2.2 Regulatory History

In FDA end-of-phase 2 meeting on May 1, 2006 for IND 69888, the Agency informed the applicant that it was important to determine the excess risk acceptable for a weight loss drug. Compared to an endpoint considering any increase in regurgitation at any valve, the Agency preferred a safety endpoint considering FDA-defined valvulopathy. The Agency also informed the applicant that a program designed to exclude a requirement for echocardiographic monitoring post approval would take into account the need to rule out a small increase in the risk for development of FDA-defined drug-induced valvulopathy (e.g., RR < 1.5).

Later in FDA comments to Arena submission dated 12 May 2006 on May 25, 2006, the Agency emphasized that ruling out a 50% increase in the incidence of FDA-defined valvulopathy is a reasonable request for a drug that if approved would be used by hundreds of thousands of patients, many of whom will be at low short-term absolute risk for serious disease due to their body weight.

In a letter from FDA to the applicant dated October 25, 2007, the Agency agreed with the applicant's proposal for the size and number of active arms in the additional pivotal trials. The Agency also reminded the applicant that data in the NDA must be able to rule out a relative risk for FDA-defined valvulopathy of at least 1.5 (80% power).

In the FDA Pre-Meeting Response for the pre-NDA meeting on August 12, 2009 for IND 69888, the Agency informed the applicant that at a minimum, the echocardiographic data must be robust enough to rule out a relative risk of 1.5 for FDA-defined valvulopathy.

2.3 Clinical Trial Overview

The applicant submitted the results of two phase 3, randomized, controlled clinical trials (APD356-009 and APD356-011) in support of the safety and efficacy of lorcaserin for weight management indication. Study APD356-009 was entitled “**Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) A 104-week, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Assess the Safety and Efficacy of Lorcaserin Hydrochloride in Obese Subjects**”. Study APD356-011 was entitled “**Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) A 52-Week, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Assess the Safety and Efficacy of Lorcaserin Hydrochloride in Overweight and Obese Subjects**”.

The study design and primary analyses between Study APD356-009 (especially the first phase of 52 weeks) and Study APD356-011 were similar. Therefore, an integrated evaluation of the safety based on pooled studies is presented in this statistical review, as well as separate interpretations of each study.

2.4 Data Sources

The applicant submitted electronic documents and datasets for both Study APD356-009 and Study APD356-011. The following files available within the CDER Electronic Document Room (EDR) were utilized in this review.

<\\Cdsub1\evsprod\NDA022529\0000\m5\datasets\iss-ise>
<\\Cdsub1\evsprod\NDA022529\0000\m5\datasets\apd356-009>
<\\Cdsub1\evsprod\NDA022529\0000\m5\datasets\apd356-011>

3 Statistical Evaluation

This review is focused on specific safety parameters, specifically evaluation of echocardiogram data and the Beck Depression Inventory score. For a complete statistical evaluation of the efficacy results, please refer to the review authored by Dr. Janice Derr.

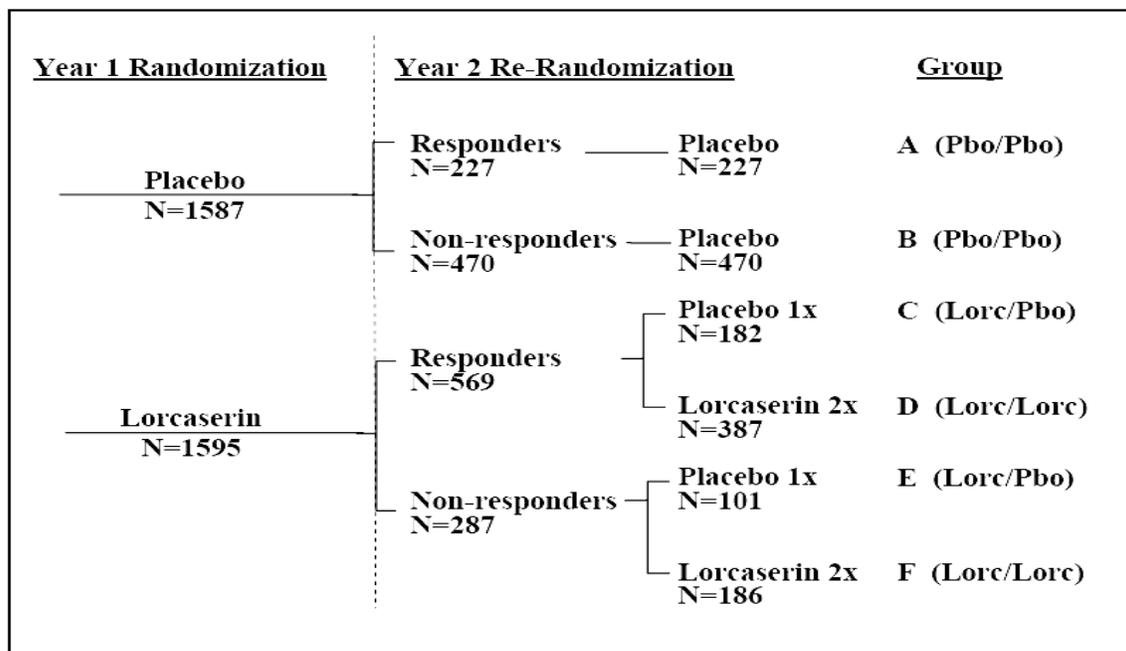
3.1 Evaluation of Safety

This safety review of Study APD356-009 and APD356-011 consists of a focused evaluation of Echocardiograms and BDI-II scores. All analyses are between the randomized treatment groups, Lorcaserin and Placebo.

3.1.1 Study Designs

Study APD356-009 was a 104-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of lorcaserin in obese subjects (schematic of the trial design is shown in Figure 1). In Year 1, a total of 3,182 subjects were randomized in a 1:1 fashion to one of the two treatment groups: placebo and lorcaserin 10 mg twice-a-day (BID). Subjects who completed the initial 52 weeks of treatment were eligible to continue in the study. Upon enrollment to Year 2 of the study, a total of 1,553 subjects were stratified as “responders” (5% body weight loss from Baseline to Week 52) or “non-responders” (< 5% body weight loss during the same time period). Subjects who received placebo during Year 1 remained on placebo for Year 2. Subjects who received lorcaserin during Year 1 were re-randomized within each of these two strata in a 2:1 ratio to either remain on lorcaserin 10 mg BID or switch to placebo, respectively. Study APD356-009 was also known as the BLOOM study. Study APD356-009 was powered to provide 95% or greater power to detect a difference of 5.5% between the lorcaserin 10 mg BID regimen and placebo, with respect to the proportion of subjects with 5% or greater weight loss in year 1.

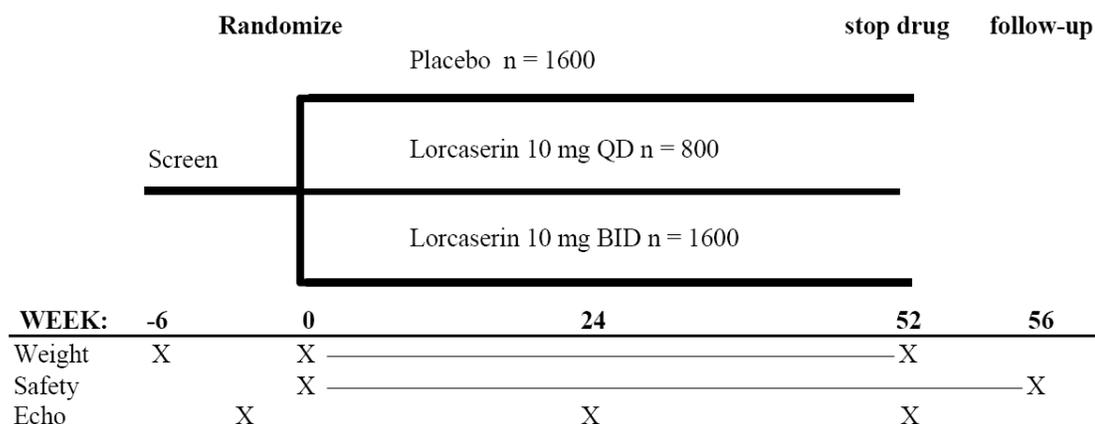
Figure 1: study Design of APD356-009



Note: Figure obtained from applicant’s clinical study report, page 24

As shown in Figure 2, Study APD356-011 was a 52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of lorcaserin in overweight and obese subjects. A total of 4,008 subjects were randomized in a 2:1:2 fashion to one of the three treatment groups: placebo, lorcaserin 10 mg once-a-day (QD), or lorcaserin 10 mg BID. Study APD356-011 was also known as the BLOSSOM study. Study APD356-011 was powered to provide 99% or more power to detect efficacy difference between the lorcaserin groups and the placebo group, provided that 30% of lorcaserin-treated subjects and 15% of placebo-treated subjects achieved a 5% or greater weight loss between baseline and week 52.

Figure 2: Study Design of APD356-011



Note: Figure obtained from applicant’s clinical study report, page 23

For both Study APD356-009 and Study APD356-011, the inclusion criteria consisted of male and female subjects, 18-66 years of age, who were considered obese based on a BMI of 30 to 45 kg/m² with or without a co-morbid condition, or who were considered overweight based on a BMI of 27 to 29.9 kg/m² with at least one co-morbid condition (hypertension, dyslipidemia, CV disease, glucose intolerance, sleep apnea).

In Study APD356-009, subjects were excluded from the study if the screening echocardiogram resulted in an aortic regurgitation rating of mild or greater, or mitral regurgitation rating of moderate or greater. In contrast, subjects with such conditions were included in Study APD356-011 as this exclusion criterion was removed by the applicant in a protocol amendment.

3.1.2 Subject Disposition, Demographic and Baseline Characteristics

As shown in Table 1, in the intent-to-treat population (ITT population), defined as all randomized subjects, baseline demographics and characteristics were similar among the treatment groups. All subjects in Studies APD356-009 and APD356-011 were between the ages of 18 and 66 years. More than 81% of subjects were female and more than 66% were Caucasian. In Study APD356-009, less than 0.2% of the subjects had FDA-defined

Valvulopathy at baseline, while more than 4% of the subjects in Study APD356-011 had FDA-defined Valvulopathy at baseline. This was due to the difference in exclusion criteria between Study APD356-009 and Study APD356-011. Subjects with aortic regurgitation mild or greater, or mitral regurgitation moderate or greater at screening were excluded in Study APD356-009 but not in Study APD356-011.

Table 1: Baseline Demographics by Treatment Group (ITT Population)

	Study APD356-009		Study APD356-011		
	Placebo (N=1587)	Lorcaserin 10 mg BID (N=1595)	Placebo (N=1603)	Lorcaserin 10 mg QD (N=802)	Lorcaserin 10 mg BID (N=1603)
Age (years)					
Mean (SD)	44.4 (11.1)	43.7 (11.3)	43.7 (11.8)	43.7 (11.7)	43.8 (11.8)
Range	18-66	18-66	18-65	18-65	18-65
Weight (kg)					
Mean (SD)	99.7 (15.6)	100.4 (15.7)	100.8 (16.2)	100.1 (16.7)	100.5 (15.6)
Range	62.7-156.0	62.6-156.9	63.9-165.9	64.9-185.4	64.1-159.3
BMI (kg/m²)					
Mean (SD)	36.1 (4.3)	36.2 (4.3)	36.0 (4.2)	35.9 (4.3)	36.1 (4.3)
Range	26.7-46.5	26.8-46.2	27.1-46.6	26.4-46.8	26.7-52.5
Gender, n (%)					
Female	1334 (84.1)	1323 (82.9)	1251 (78.0)	657 (81.9)	1290 (80.5)
Male	253 (15.9)	272 (17.1)	352 (22.0)	145 (18.1)	313 (19.5)
Race, n (%)					
White	1048 (66.0)	1081 (67.8)	1066 (66.5)	539 (67.2)	1081 (67.4)
Black	299 (18.9)	300 (18.8)	319 (19.9)	160 (20.0)	306 (19.1)
Hispanic	213 (13.4)	181 (11.3)	181 (11.3)	86 (10.7)	174 (10.8)
Others	27 (1.7)	33 (2.1)	37 (2.3)	17 (2.1)	42 (2.6)
Valvulopathy, n (%)					
Valvulopathy	5 (0.3)	1 (0.1)	66 (4.1)	31 (3.9)	83 (5.2)
Non-valvulopathy	1582 (99.7)	1593 (99.8)	1535 (95.8)	771 (96.1)	1518 (94.7)
Unknown	0 (0)	1 (0.1)	2 (0.1)	0 (0)	2 (0.1)

Source: Created by reviewer.

Among the 7,190 randomized subjects in the ITT population from Study APD356-009 and Study APD356-011, approximately 47% of them discontinued study prior to week 52. As presented in Table 2, there was an imbalance across treatment groups in the incidence of study discontinuation. In Study APD356-009, the incidence of study discontinuation was statistically significantly lower in the lorcaserin 10mg BID group than in the placebo group (44.6% versus 54.9%, $p < 0.0001$ Fisher's exact test). Compared to the placebo group, the incidence in Study APD356-011 was statistically significantly lower in the lorcaserin 10mg BID group (42.8% versus 48.0%, $p = 0.004$ Fisher's exact test) and in the lorcaserin 10mg QD group (41.0% versus 48.0%, $p = 0.001$ Fisher's exact test).

The most common reason reported for study discontinuation was withdrawal of consent, which accounted for 23.4% and 20.7% in Study APD356-009 and Study APD356-011 respectively. In Study APD356-009, 19.3% of the subjects in the Lorcaserin 10 mg BID

group discontinued study due to withdrawal of consent, which was statistically significantly lower than the incidence in the placebo group (27.7%) with p -value <0.0001 (Fisher's exact test). In Study APD356-011, the incidence of study discontinuation due to withdrawal of consent was also statistically significantly lower in the Lorcaserin 10 mg BID group than in the placebo group (18.3% versus 23.5%, $p=0.0003$ Fisher's exact test).

Table 2: Study Discontinuation by Treatment Group (ITT Population)

	Study APD356-009		Study APD356-011		
	Placebo (N=1587)	Lorcaserin 10 mg BID (N=1595)	Placebo (N=1603)	Lorcaserin 10 mg QD (N=802)	Lorcaserin 10 mg BID (N=1603)
Safety Population	1584 (99.8%)	1593 (99.9%)	1601 (99.9%)	801 (99.9%)	1602 (99.9%)
Discontinued before week 52	871 (54.9%)*	712 (44.6%)	769 (48.0%)^	329 (41.0%)	686 (42.8%)
Withdraw Consent	439 (27.7%)	307 (19.3%)	376 (23.5%)	162 (20.2%)	293 (18.3%)
Lost to follow-up	226 (14.2%)	191 (12.0%)	234 (14.6%)	83 (10.4%)	198 (12.4%)
Adverse event	106 (6.7%)	113 (7.1%)	74 (4.6%)	50 (6.2%)	115 (7.2%)
Protocol deviation	44 (2.8%)	47 (3.0%)	49 (3.1%)	20 (2.5%)	59 (3.7%)
Sponsor Decision	26 (1.6%)	25 (1.6%)	30 (1.9%)	10 (1.3%)	9 (0.6%)
PI decision	6 (0.4%)	9 (0.6%)	6 (0.4%)	4 (0.5%)	11 (0.7%)
Unknown	24 (1.5%)	20 (1.3%)	0 (0%)	0 (0%)	1 (0.1%)

* Placebo versus Lorcaserin 10 mg BID, $p<0.0001$

^ Placebo versus Lorcaserin 10 mg BID, $p=0.004$;

Placebo versus Lorcaserin 10 mg QD, $p=0.001$

Source: ISS Report, Table 4. Recreated by reviewer.

3.1.3 Populations

The analyses for all safety outcomes will be primarily based on the safety population. The safety population includes all randomized subjects who received at least 1 dose of double-blind study therapy; in addition, if a subject was found to have taken a study therapy for the entire duration of the study, different from that to which he/she was randomized, then the subject was to be counted in the treatment group of the drug he/she actually received. For inclusion in the safety population for a particular safety parameter, at least one post-baseline safety measurement was required for that parameter. Subjects who completed a full 52 weeks of study drug treatment (completers population) were also evaluated.

3.1.4 Endpoints

3.1.4.1 Valvulopathy

A comprehensive echocardiographic monitoring process was implemented in the phase 3 studies of lorcaserin to evaluate the changes in echocardiographic valvular regurgitation scores. The primary endpoint to evaluate echocardiogram was the proportion of subjects

who developed echocardiographic criteria known as “FDA-defined valvulopathy” (also called FDA valvulopathy) during clinical studies. FDA-defined valvulopathy, which was originally based on the FDA’s evaluation of reported cases of cardiac valvular disease in subjects exposed to fenfluramine (approved by FDA in 1973 for use as an appetite suppressant in the management of obesity; FDA asked the manufacturer to voluntarily withdraw from US market in 1997), is defined as follows:

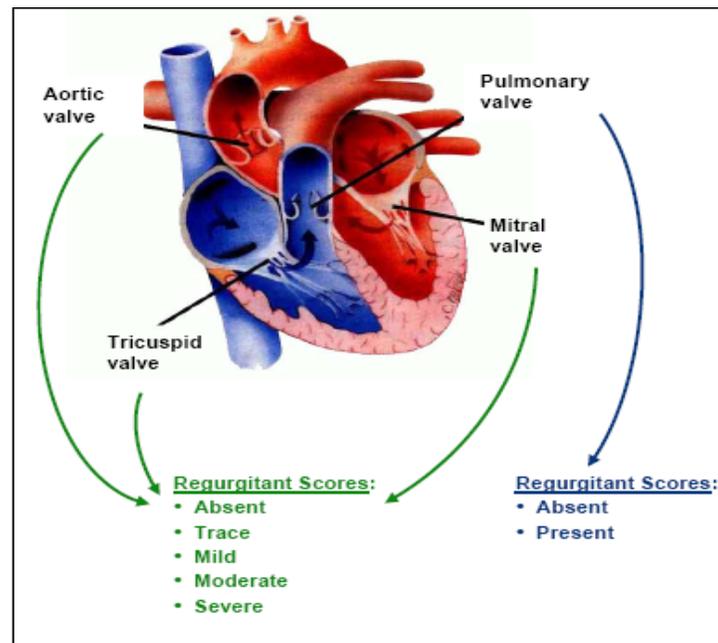
Echocardiograms were assessed at screening and at Weeks 24 and 52 (or early termination) in both Study APD356-009 (1st year) and Study APD356-011. At each time point, both the mitral regurgitation (MR) and aortic regurgitation (AR) were scored as: absent, trace, mild, moderate, or severe based on the reading of the echocardiogram. These readings were then used to define FDA valvulopathy.

FDA valvulopathy: Echocardiographic findings of MILD or greater aortic regurgitation (AR) *or* MODERATE or greater mitral regurgitation (MR)

The protocol-defined primary echocardiographic endpoint for the pooled phase 3 trials was the proportion of subjects who developed FDA-defined valvulopathy from Baseline to Week 52.

In addition to the assessment of FDA-define valvulopathy, the changes in individual valvular regurgitant scores were also evaluated to compare the safety between the lorcaserin regimens and the placebo. A diagram of the individual valvular regurgitant scores is provided in Figure 3.

Figure 3: Diagram of Cardiac Valves and Individual Valvular Regurgitant Score



Note: Figure obtained from applicant’s summary of clinical safety, page 103

3.1.4.2 Beck Depression Inventory

The Beck Depression Inventory Second Edition (BDI-II) is a 21-item self-report instrument in a multiple choice format to assess the presence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV). The BDI-II was revised in 1996 for consistency with the DSM-IV criteria.

In order to address prevailing concerns regarding depression and suicidal ideation in subjects taking weight management agents, BDI-II scores were assessed at screening and at Weeks 4, 12, 24, 36, and 52 (or early termination) in both Study APD356-009 (1st year) and Study APD356-011.

Each of the inventory items corresponds to a specific category of depressive symptom and/or attitude. Each category describes a specific behavioral manifestation of depression and consists of a graded series of four self-evaluative statements. The statements are rank ordered and weighted to reflect the range of severity of the symptom from neutral to maximum severity. Numerical values of 0, 1, 2, or 3 are assigned to each statement to indicate degree of severity.

3.1.5 Statistical Methodologies

In the following sections, statistical methods and tabulations are presented for the evaluation of safety only.

3.1.5.1 Valvulopathy Assessment

The main objective of the pooled phase 3 safety analysis was to demonstrate that similar change in heart valve regurgitation (as measured by the incidence of FDA-defined valvulopathy) was achieved in the lorcaserin 10 mg BID treatment arm compared to the placebo treatment arm. Subjects with FDA-defined valvulopathy at baseline would be excluded from the analyses.

Study APD356-009 was powered to provide 80% power to establish the non-inferiority of lorcaserin to placebo in the risk of developing FDA-defined valvulopathy, with the assumption of a 5% background valvulopathy rate in the placebo group. A non-inferiority margin of 2.5% in *risk difference* and a one-sided $\alpha=0.05$ significance level were used for Study APD356-009. Study APD356-011 was not individually powered for assessment of valvulopathy. Instead, the pooled analysis combining Studies APD356-009 and APD356-011 was powered to provide 80% power to declare non-inferiority of the lorcaserin group to the placebo group if the annual placebo rate was higher than 2.7%.

(b) (4)

Based on a one-sided test at $\alpha=0.05$ level of

significance to declare non-inferiority of lorcaserin, it was analogous to inspect a two-sided 90% confidence interval for the difference in proportion between lorcaserin and placebo. If the upper limit of this confidence interval (lorcaserin-placebo) was less than 1.25%, it would be concluded that lorcaserin is non-inferior to the placebo group by more than 1.25% according to the pooled phase 3 echocardiographic safety data. Based on the SAP provided by the applicant, the 2-sided 90% confidence interval will be constructed using the normal approximation to the binomial distribution for the two combined phase 3 trials.

Reviewer's comment:

(b) (4)

. In the FDA Pre-Meeting Response for the pre-NDA meeting on August 12, 2009 for IND 69888, the Agency informed the applicant that at a minimum, the echocardiographic data must be robust enough to rule out a relative risk of 1.5 for FDA-defined valvulopathy. Therefore, a non-inferiority margin of 1.5 for relative risk ratio is used in this review. In order to maintain the overall type I error rate at $\alpha=0.05$ level, two-sided 95% confidence interval was used. Therefore, when the upper limit of the 95% CI for the relative risk ratio between lorcaserin 10 mg BID and placebo was less than 1.5, the lorcaserin 10 mg BID regimen is considered non-inferior to the placebo in the risk of developing FDA-defined valvulopathy.

The null and alternative hypotheses for the main safety objective are as follows:

Null hypothesis: the incidence of FDA-defined valvulopathy in the lorcaserin 10 mg BID arm is higher (worse) than that in the placebo arm by a relative risk ratio of 1.5 or more.

Alternative hypothesis: the incidence of FDA-defined valvulopathy in the lorcaserin 10 mg BID arm is not higher (not worse) than that in the placebo arm by a relative risk ratio of 1.5 or more.

For FDA-defined valvulopathy, the comparison of proportions between the lorcaserin 10 mg BID group and the placebo group is performed using the protocol-defined Cochran-Mantel-Haenszel (CMH) test with study as stratification factor. The two-sided 95% or 90% confidence intervals for between-group relative risk ratio were conducted by a stratified Mantel-Haenszel approach based on pooled phase 3 data from Studies APD356-009 and APD356-011. For each individual study, the two-sided 95% or 90% confidence intervals were conducted using the normal approximation to the binomial distribution.

3.1.5.2 Assessment of Beck Depression Inventory

Based on the clinical input, the BDI-II total scores were summarized according to >28 (severe depression), ≤ 28 and >19 (moderate depression), ≤ 19 and >12 (mild depression), and ≤ 13 (none to minimal depression), using descriptive statistics by treatment group. In addition to the overall assessment of the BDI-II total scores, four individual components of the BDI-II scale were assessed further.

- For BDI-II Question #9, which refers to suicidal thoughts, the item score was dichotomized to a score of 0 or a score of 1 to 3.
- For BDI-II Question #18, which refers to changes in appetite, the item score was dichotomized to a score of 2A, or 3A or a score of 1A, 0, 1B, 2B, or 3B.
- For BDI-II Question #19, which refers to concentration difficulties, the item score was dichotomized to a score of 0 or a score of 1 to 3.
- For BDI-II Question #20, which refers to tiredness or fatigue, the item score was dichotomized to a score of 0 or a score of 1 to 3.

Each of the individual components is summarized categorically.

For the BDI-II score, the comparison of proportions between the lorcaserin 10 mg BID group and the placebo group was performed using the Cochran-Mantel-Haenszel (CMH) test with study as stratification factor. The two-sided 95% confidence intervals for between-group relative risk ratio was conducted by stratified Mantel-Haenszel approach based on pooled phase 3 data from Studies APD356-009 and APD356-011. For each individual study, the two-sided 95% confidence intervals were conducted using the normal approximation to the binomial distribution.

3.1.5.3 Methods of Imputing Missing

For subjects with only a baseline echocardiogram, baseline data are not carried forward. For subjects with at least one post baseline echocardiogram measurement, the last observation carried forward (LOCF) method was used to impute missing data for the overall analysis of echocardiographic parameters at week 24 and week 52. Subjects who discontinued from the trials prior to week 52 but returned for a week 52 echo were also included in the pooled safety analyses.

When computing the BDI-II total score or the score for a specific question, if the value of an individual item was missing at a given follow-up visit, the subject's most recent non-missing post baseline value for the item from a previous visit is used. If after this procedure a subject still has a missing item required for the evaluation of either the total score or the score for a specific question, the corresponding score will be considered to be missing and will not be included in the analyses.

Reviewer's comment: Although the LOCF method to impute the missing values was pre-specified in the protocol, this method can lead to biased point estimates and variances. This is especially problematic when the study discontinuation rate is high and disproportional between different treatment arms. Several sensitivity analyses were conducted to assess the robustness of the results. See Section 3.1.6.1.2 for more details.

3.1.6 Results and Conclusions

3.1.6.1 Echocardiograms

3.1.6.1.1 FDA-defined Valvulopathy at Week 52 and Week 24

At week 52, the status of FDA-defined valvulopathy for subjects in the safety population is shown in Table 3. In the pooled phase 3 safety population from Study APD356-009 and Study APD356-011, approximately 2% of the subjects had FDA-defined valvulopathy at week 52, while 73% of the subjects did not have FDA-defined valvulopathy. Note that about 35% of the subjects had echocardiogram data missing at week 52. Note that subjects with FDA-defined valvulopathy at baseline would be excluded from the analyses.

**Table 3: Status of FDA-Defined Valvulopathy at Week 52 by Treatment Group
(Safety Population, Subjects with Baseline Valvulopathy Excluded)**

Number (%) of subjects	Study APD356-009		Study APD356-011			Total (N=7181)
	Placebo (N=1584)	Lorcaserin 10 mg BID (N=1593)	Placebo (N=1601)	Lorcaserin 10 mg QD (N=801)	Lorcaserin 10 mg BID (N=1602)	
FDA-defined valvulopathy	26 (1.6%)	33 (2.1%)	46 (2.9%)	20 (2.5%)	50 (3.1%)	175 (2.4%)
Non FDA-defined Valvulopathy	940 (59.3%)	1058 (66.4%)	960 (60.0%)	530 (66.2%)	1030 (64.3%)	4518 (62.9%)
Unknown	618 (39.0%)	502 (31.5%)	595 (37.2%)	251 (31.3%)	522 (32.6%)	2488 (34.7%)

Source: Created by reviewer.

Only considering subjects randomized to receive lorcaserin 10 mg BID or placebo, 4,830 subjects in the safety population did not have FDA-defined valvulopathy at baseline, and had at least one echocardiogram data available post randomization. The incidence of FDA-defined valvulopathy at week 52 among these subjects is presented in Table 4, using the protocol defined LOCF method to impute the missing data. In Study APD356-009, the incidence of FDA-defined valvulopathy at week 52 was 2.66% in the lorcaserin 10 mg BID group and was 2.35% in the placebo group. The relative risk ratio between lorcaserin and placebo was 1.13 with a 95% CI of (0.69, 1.85). Similarly, in Study APD356-011, the incidence of FDA-defined valvulopathy at week 52 was 1.99% in the lorcaserin 10 mg BID group and was 1.99% in the placebo group. The relative risk ratio between lorcaserin and placebo was 1.00 with a 95% CI of (0.57, 1.75). Pooling the two phase 3 studies APD356-009 and APD356-011 together, the Mantel-Haenszel relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.07 with a 95% CI of (0.74, 1.55). Based on the pooled analysis, the upper limit of the 95% confidence interval exceeded the 1.5 non-inferiority margin.

Table 4: Incidence of FDA-Defined Valvulopathy at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

	Study APD356-009		Study APD356-011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing, excluding baseline valvulopathy	1191	1278	1153	1208	4830
FDA-defined Valvulopathy	28	34	23	24	109
Incidence of Valvulopathy	2.35%	2.66%	1.99%	1.99%	2.26%
Relative Risk (90% CI) [95% CI]	1.13 (0.75, 1.71) [0.69, 1.85]		1.00 (0.62, 1.60) [0.57, 1.75]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	1.07 (0.78, 1.46) [0.74, 1.55]				

Source: Created by reviewer.

At week 24, the status of FDA-defined valvulopathy is shown in Table 5. Among the 7,181 subjects in the safety population from both Study APD356-009 and Study APD356-011, approximately 3% developed FDA-defined valvulopathy at week 24, while 71% did not develop FDA-defined valvulopathy. In addition, about 26% of the subjects had echocardiogram data missing for week 24.

Table 5: Status of FDA-Defined Valvulopathy at Week 24 by Treatment Group (Safety Population)

Number (%) of subjects	Study APD356-009		Study APD356-011			Total (N=7181)
	Placebo (N=1584)	Lorcaserin 10 mg BID (N=1593)	Placebo (N=1601)	Lorcaserin 10 mg QD (N=801)	Lorcaserin 10 mg BID (N=1602)	
FDA-defined valvulopathy	22 (1.4%)	25 (1.6%)	50 (3.1%)	30 (3.8%)	71 (4.4%)	198 (2.8%)
Non FDA-defined Valvulopathy	1069 (67.5%)	1188 (74.6%)	1102 (68.8%)	597 (74.5%)	1166 (22.8%)	5122 (71.3%)
Unknown	493 (31.1%)	380 (23.9%)	449 (28.0%)	174 (21.7%)	1365 (22.8%)	1861 (25.9%)

Source: Created by reviewer.

In the safety population, 4,575 subjects from the lorcaserin 10 mg BID group and the placebo group did not have FDA-defined valvulopathy at baseline, and had week 24 echocardiogram data. Note that data for week 24 is not imputed as there are no echocardiograms taken prior to week 24; thus subjects with an unknown status as presented in Table 5 are not included in the denominator. The incidence of FDA-defined valvulopathy at week 24 among these subjects is presented in Table 6. In Study APD356-009, the incidence of FDA-defined valvulopathy at week 24 was 2.06% in the lorcaserin 10 mg BID group and was 1.93% in the placebo group. The relative risk ratio between lorcaserin and placebo was 1.07 with a 95% CI of (0.60, 1.90). In Study APD356-011, the incidence of FDA-defined valvulopathy at week 24 was 2.31% in the lorcaserin 10 mg BID group and was 1.81% in the placebo group. The relative risk ratio between

lorcaserin and placebo was 1.27 with a 95% CI of (0.72, 2.26). Pooling the two phase 3 Studies APD356-009 and APD356-011 together, the Mantel-Haenszel relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.17 with a 95% CI of (0.78, 1.75). Similar to the week 52 results, the 95% confidence interval exceeded the 1.5 non-inferiority margin for the pooled analysis.

Table 6: Incidence of FDA-Defined Valvulopathy at Week 24 by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

	Study APD356-009		Study APD356-011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing, excluding baseline valvulopathy	1089	1213	1103	1170	4575
FDA-defined Valvulopathy	21	25	20	27	93
Incidence of Valvulopathy	1.93%	2.06%	1.81%	2.31%	
Relative Risk (90% CI) [95% CI]	1.07 (0.66, 1.73) [0.60, 1.90]		1.27 (0.79, 2.06) [0.72, 2.26]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	1.17 (0.83, 1.64) [0.78, 1.75]				

Source: Created by reviewer.

In addition to using LOCF for imputing missing FDA-defined valvulopathy, a completers analysis was performed as a sensitivity analysis. Subjects are considered completers if they completed all 52 weeks of treatment. Among the 7,181 subjects in the safety population from Study APD356-009 and Study APD356-011, 3,823 (53.2%) subjects completed the full 52 weeks of study drug treatment. In this completers population, the risk of developing FDA-defined valvulopathy was also compared between the lorcaserin 10 mg BID treatment group and the placebo group. The incidence of FDA-defined valvulopathy at week 52 is presented in Table 7 for subjects in the completers population without FDA-defined valvulopathy at baseline. In Study APD356-009, the incidence was 3.38% in the lorcaserin 10 mg BID group and was 3.01% in the placebo group. The incidences in Study APD356-011 was lower, with 1.52% and 2.41% in the lorcaserin and placebo groups respectively. Based on both studies, the pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 0.90 with a 95% CI of (0.59, 1.38) for the week 52 completers analysis.

Similarly, the incidence of FDA-defined valvulopathy at week 24 is presented in Table 8 for the completers analysis. In Study APD356-009, the incidence was 3.52% in the lorcaserin 10 mg BID group and was 3.19% in the placebo group. In Study APD356-011, the incidence was 3.31% in the lorcaserin 10 mg BID group and was 2.95% in the placebo group. The pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.12 with 95% CI (0.70, 1.77).

Reviewer's comment: *The between-group comparisons shown in Table 8 were close to those shown in Table 6, suggesting that at 24 weeks, the results for FDA-defined valvulopathy in the safety population were similar to the results in the completers population. However, the Week 52 results for the safety population (Table 7) and the*

Week 52 results for the completers population (Table 5) were quite different. The reason for the discrepancy between week 24 and week 52 results is unknown.

Table 7: Incidence of FDA-Defined Valvulopathy at Week 52 by Treatment Group (Completers Population, Subjects with Baseline Valvulopathy Excluded)

	Study APD356-009		Study APD356-011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing, excluding baseline valvulopathy	698	857	790	853	3198
FDA-defined Valvulopathy	21	29	19	13	82
Incidence of Valvulopathy	3.01%	3.38%	2.41%	1.52%	2.56%
Relative Risk (90% CI) [95% CI]	1.12 (0.71, 1.79) [0.65, 1.95]		0.63 (0.35, 1.14) [0.32, 1.27]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	0.90 (0.63, 1.29) [0.59, 1.38]				

Source: Created by reviewer.

Table 8: Incidence of FDA-Defined Valvulopathy at Week 24 by Treatment Group (Completers Population, Subjects with Baseline Valvulopathy Excluded)

	Study APD356-009		Study APD356-011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing, excluding baseline valvulopathy	709	882	797	853	3251
FDA-defined Valvulopathy	14	20	17	20	71
Incidence of Valvulopathy	1.97%	3.38%	2.13%	2.32%	2.18%
Relative Risk (90% CI) [95% CI]	1.15 (0.65, 2.02) [0.58, 2.26]		1.09 (0.64, 1.86) [0.57, 2.06]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	1.12 (0.76, 1.65) [0.70, 1.77]				

Source: Created by reviewer.

3.1.6.1.2 Sensitivity Analysis for FDA-defined Valvulopathy

Among subjects in the safety population, a total of 198 subjects had FDA-defined valvulopathy at week 24 (Table 5), while a total of 175 subjects had FDA-defined valvulopathy at week 52 (Table 3). As shown in Table 9, among the 198 subjects who had FDA-defined valvulopathy at week 24, 74 subjects had no FDA-defined valvulopathy at week 52. One possible explanation for these subjects' valvulopathy to disappear was the improvement of valvular regurgitation over time; another possible reason might be caused by the discrepancy between echocardiogram readers and the fact that echocardiograms for the same subject were not consistently evaluated by the same readers over time.

Table 9: Comparison of FDA-Defined Valvulopathy Status at Week 24 versus Week 52 (Safety Population)

		Week 24 Status			Total
		Valvulopathy	Non-Valvulopathy	Unknown	
Week 52 Status	Valvulopathy	96	73	6	175
	Non-Valvulopathy	74	4169	275	4518
	Unknown	28	880	1580	2488
	Total	198	5122	1861	7181

Source: Created by reviewer.

Another way to evaluate the risk of developing FDA-defined valvulopathy from baseline to week 52 is to compare the incidence of FDA-defined valvulopathy at *either* week 24 or week 52. In this sensitivity analysis, subjects who had valvulopathy at *either* week 24 or week 52 were considered as valvulopathy cases at week 52. As shown in Table 10, the pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.11 with a 95% CI of (0.86, 1.52). Similar to results depicted in Table 4 (week 52 safety population) or Table 6 (week 24 safety population), the non-inferiority of the lorcaserin 10 mg BID regimen compared to placebo exceeded the 1.5 non-inferiority margin.

Table 10: Incidence of FDA-Defined Valvulopathy at *either* Week 24 or Week 52 by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

Worst Status at Week 24 or Week 52	Study APD356-009		Study APD356-011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing, excluding baseline valvulopathy	1191	1278	1153	1208	4830
FDA-defined Valvulopathy	38	45	34	40	157
Incidence of Valvulopathy	3.19%	3.52%	2.95%	3.31%	
Relative Risk (90% CI) [95% CI]	1.10 (0.77, 1.58) [0.72, 1.69]		1.12 (0.77, 1.64) [0.72, 1.76]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	1.11 (0.86, 1.44) [0.82, 1.52]				

Source: Created by reviewer.

Similarly, for subjects in the completers population, the comparison of incidence rates of FDA-defined valvulopathy at *either* week 24 or week 52 between lorcaserin and placebo is presented in Table 11. The pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.03 with a 95% CI of (0.73, 1.47). In this analysis, the upper limit of the 95% confidence interval of the relative risk ratio was less than 1.5 non-inferiority margin.

Table 11: Incidence of FDA-Defined Valvulopathy at *either* Week 24 or Week 52 by Treatment Group (Completers Population, Subjects with Baseline Valvulopathy Excluded)

Worst Status at Week 24 or Week 52	Study APD356-009		Study APD356-011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing, excluding baseline valvulopathy	715	883	803	867	3268
FDA-defined Valvulopathy	27	38	28	28	121
Incidence of Valvulopathy	3.78%	4.30%	3.49%	3.23%	3147
Relative Risk (90% CI) [95% CI]	1.14 (0.76, 1.71) [0.70, 1.85]		0.93 (0.60, 1.43) [0.55, 1.55]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	1.03 (0.77, 1.39) [0.73, 1.47]				

Source: Created by reviewer.

In Study APD356-009 and Study APD356-011, all the echocardiograms were read by 2 different readers. Any discrepant readings between the readers were adjudicated by a third reader. Kappa statistics were used to assess the agreement between the two readers for all paired readings (Table 12). The Kappa statistics suggested that the reader concordance for MR reading was higher in Study APD356-009 than in Study APD356-011, while the reader concordance for AR reading was higher in Study APD356-011 than in Study APD356-009. In the two studies, the Kappa statistics were comparable across treatment groups for both MR and AR reading. Overall, the Kappa statistic was 0.32 for MR reading and 0.38 for AR reading, indicating that readings from the two readers were only marginally in agreement.

Table 12: Summary Kappa Statistics for Discordance between Reader A and Reader B by Treatment Group (all paired readings from Safety Population)

Kappa (95% CI)	Study APD356-009		Study APD356-011			Overall
	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	
MR Reading	0.35 (0.33, 0.37)	0.38 (0.36, 0.40)	0.26 (0.24, 0.29)	0.30 (0.27, 0.34)	0.26 (0.24, 0.29)	0.32 (0.31, 0.33)
AR Reading	0.35 (0.31, 0.38)	0.33 (0.28, 0.36)	0.46 (0.42, 0.50)	0.39 (0.33, 0.44)	0.44 (0.41, 0.48)	0.39 (0.37, 0.40)

Source: Created by reviewer.

The echocardiograms requiring third reader adjudication for AR and MR readings with ≥ 2 grades discordance are summarized in Table 13. Overall, the adjudication rates were higher for a less severe rating in Study APD356-011 than in Study APD356-009, and were higher for a less severe rating for the mitral valve than for the aortic valve. In Study APD356-011, the adjudication rates were higher for a less severe rating in the lorcaserin 10 mg BID group than in the placebo group for both AR and MR readings. In Study APD356-009, the adjudication rates were similar in both groups. When the discrepant readings between Reader A and Reader B were ≥ 2 grades discordance, Reader C's adjudication was slightly in favor of the less severe reading. Especially for the AR

readings in Study APD356-009, Reader C chose the less severe reading between Reader A and Reader B to be the adjudicated reading for about 90% of the discrepancies with 2 grades discordance.

Table 13: Summary of Echocardiograms with Readings Discrepant by ≥ 2 Categories and Requiring Adjudication in Phase 3 Studies

Study	Placebo			Lorcaserin 10 mg BID		
	N	n (%)	% Adjudicated for reader with less severe reading	N	n (%)	% Adjudicated for reader with less severe reading
Aortic Valve						
APD356-009	4816	9 (0.2%)	8/9 (88.9%)	5322	11 (0.2%)	10/11 (90.9%)
APD356-011	3772	23 (0.6%)	11/23 (47.8%)	3927	33 (0.8%)	20/33 (66.6%)
Mitral Valve						
APD356-009	4816	53 (1.1%)	27/53 (50.9%)	5322	57 (1.1%)	28/57 (49.1%)
APD356-011	3772	64 (1.7%)	38/64 (59.4%)	3927	97 (2.5%)	50/97 (51.6%)

Source: Created by reviewer.

Reviewer's comment: *Even though all the readers should be kept blinded for the treatment assignments, it may be of concern when the adjudication results of discrepant readings were potentially in favor of the less severe readings, especially for the AR readings in Study APD356-009. This might bias the analysis results towards the alternative hypothesis that the lorcaserin 10 mg BID regimen is non-inferior to the placebo in the risk of developing FDA-defined valvulopathy.*

The results in Table 4 were based on adjudicated echocardiogram readings from both Reader A and Reader B. In order to assess the impact of the poor agreement between the two readers and the potential adjudication bias, the analysis results for FDA-defined valvulopathy based on the readings from Reader A or Reader B are shown in Table 14 and Table 15, respectively.

When only using the echocardiogram readings from Reader A (the primary reader), the pooled relative risk ratio between lorcaserin 10 mg BID regimen and placebo was 1.30 with a 95% CI of (0.92, 1.84), with respect to the risk of developing FDA-defined valvulopathy from baseline to week 52. Results are shown in Table 14.

Table 14: Incidence of FDA-Defined Valvulopathy Based on Reader A at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

LOCF Status at Week 52 Based on Reader A alone	Study APD356-009		Study APD356-011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing, excluding baseline valvulopathy	1188	1277	1153	1208	4821
FDA-defined Valvulopathy	24	35	29	38	126
Incidence of Valvulopathy	2.02%	2.74%	2.52%	3.16%	
Relative Risk (90% CI) [95% CI]	1.36 (0.88, 2.09) [0.81, 2.27]		1.25 (0.84, 1.87) [0.78, 2.02]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	1.30 (0.97, 1.74) [0.92, 1.84]				

Source: Created by reviewer.

Similar results were found when only using the readings from Reader B (the secondary reader); results are shown in Table 15. The pooled relative risk ratio between lorcaserin and placebo was 1.10 with a 95% CI of (0.75, 1.62).

Table 15: Incidence of FDA-Defined Valvulopathy Based on Reader B at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

LOCF Status at Week 52 Based on Reader B alone	Study APD356-009		Study APD356-011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing, excluding baseline valvulopathy	1178	1267	1147	1207	4799
Valvulopathy	28	28	19	27	102
Incidence of Valvulopathy	2.38%	2.21%	1.66%	2.24%	
Relative Risk (90% CI) [95% CI]	0.93 (0.60, 1.44) [0.55, 1.56]		1.35 (0.83, 2.20) [0.76, 2.42]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	1.10 (0.80, 1.52) [0.75, 1.62]				

Source: Created by reviewer.

When looking at the relative risk of FDA-defined valvulopathy for each individual reader (Table 14 and 15), the results are consistent with that reported when valvulopathy scores are adjudicated (Table 4). Each of these analysis demonstrated that the relative risk exceeded the non-inferiority margin of 1.5.

3.1.6.1.3 Individual Valvular Regurgitation

In order to evaluate the risk of increased individual valvular regurgitation between the lorcaserin groups and the placebo group, the proportions of subjects who experienced any increase in aortic (AR), mitral (MR), pulmonary (PR), or tricuspid regurgitation (TR) from baseline to week 52 are summarized in Table 16. The LOCF method was used for subjects who had data available at week 24 but not at week 52. The comparison of

proportions between the lorcaserin 10 mg BID group and the placebo group is presented in Table 17. Compared with the placebo group, the proportion of increasing pulmonary regurgitation in the lorcaserin 10 mg BID group reached the nominal $\alpha=0.05$ significance level (17.5% versus 15.3%, relative risk RR=1.14 with a 95% CI of (1.00, 1.30)). With respect to other individual valvular regurgitations including AR, MR, and TR, the proportion was consistently higher in the lorcaserin 10 mg BID group than in the placebo group. Furthermore, 46.94% of the subjects in the pooled lorcaserin 10 mg BID group experienced increase in at least one of the four individual valvular regurgitations, compared to 42.36% of the subjects in the placebo group. The pooled relative risk ratio between lorcaserin 10 mg BID regimen and placebo was 1.11 with a 95% CI of (1.04, 1.18).

Table 16: Summary of Any Increase in Valvular Regurgitation from Baseline to Week 52 (LOCF) by Treatment Group (Safety Population)

Number (%)* of subjects	Study APD356-009		Study APD356-011			Total
	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	
Aortic Valve	101 (8.5%)	128 (10.0%)	68 (5.7%)	41 (6.3%)	68 (5.3%)	406 (7.3%)
Mitral Valve	265 (22.2%)	302 (23.6%)	204 (17.0%)	113 (17.4%)	243 (19.1%)	1127 (20.1%)
Pulmonary Valve	209 (18.4%)	231 (19.3%)	148 (12.4%)	89 (13.7%)	201 (15.8%)	878 (16.1%)
Tricuspid Valve	204 (17.4%)	246 (19.6%)	183 (15.3%)	121 (18.7%)	209 (16.4%)	963 (17.3%)
Any Valve[^]	561 (47.0%)	655 (51.3%)	454 (37.8%)	268 (41.3%)	543 (42.6%)	2481 (44.3%)

* The denominator of the percentage was the number of subjects without missing values, for each individual valvular regurgitation.

[^] Subject with increase for more than one valve was only counted once.

Source: Created by reviewer.

Table 17: Proportion of Subjects with Any Increase in Valvular Regurgitation from Baseline to Week 52 (LOCF) (Safety Population)

	Pooled Placebo	Pooled Lorcaserin 10 mg BID	Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	CMH test p-value
AR	7.05%	7.68%	1.09 (0.89, 1.33)	0.405
MR	19.57%	21.36%	1.09 (0.98, 1.22)	0.123
PR	15.32%	17.48%	1.14 (1.00, 1.30)	0.042
TR	17.98%	16.30%	1.10 (0.97, 1.25)	0.121
Any Valve	42.36%	46.94%	1.11 (1.04, 1.18)	0.001

Source: Created by reviewer.

Similar as Table 16 and Table 17 for week 52, summaries of the valvular regurgitation increase from baseline to week 24 are shown in Table 18 and Table 19. The proportion of subjects with increase in at least one of the four individual valvular regurgitations was 44.81% in the pooled lorcaserin 10 mg BID group, and was 40.74% in the pooled placebo

group. The pooled relative risk ratio was 1.10 with a 95% CI of (1.03, 1.17), suggesting that the lorcaserin 10 mg BID group had statistically significantly higher risk of developing increase in at least one of the four valvular regurgitations. In addition, the proportion was always higher in the pooled lorcaserin 10 mg BID group than in the pooled placebo group, with respect to each of the individual valvular regurgitation. The differences between lorcaserin and placebo were statistically significant at the nominal $\alpha=0.05$ significance level for mitral valve and tricuspid valve.

Table 18: Summary of Any Increase in Valvular Regurgitation from Baseline to Week 24 by Treatment Group (Safety Population)

Number (%)* of subjects	Study APD356-009		Study APD356-011			Total
	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	
Aortic Valve	97 (8.9%)	125 (10.3%)	68 (5.9%)	45 (7.2%)	75 (6.1%)	410 (7.7%)
Mitral Valve	208 (19.1%)	262 (21.6%)	188 (16.4%)	102 (16.3%)	234 (19.0%)	994 (18.7%)
Pulmonary Valve	174 (17.8%)	192 (17.7%)	149 (13.1%)	90 (14.4%)	203 (16.5%)	808 (16.0%)
Tricuspid Valve	176 (16.4%)	225 (19.0%)	171 (14.9%)	103 (16.5%)	216 (17.5%)	891 (16.9%)
Any Valve[^]	476 (43.6%)	573 (47.2%)	437 (38.0%)	258 (41.2%)	524 (42.4%)	2268 (42.7%)

* The denominator of the percentage was the number of subjects without missing values, for each individual valvular regurgitation.

[^] Subject with increase for more than one valve was only counted once.

Source: Created by reviewer.

Table 19: Proportion of Subjects with Any Increase in Valvular Regurgitation from Baseline to Week 24 (Safety Population)

	Pooled Placebo	Pooled Lorcaserin 10 mg BID	Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	CMH test p-value
AR	7.36%	8.17%	1.11 (0.91, 1.35)	0.321
MR	17.67%	20.26%	1.15 (1.02, 1.29)	0.025
PR	15.23%	17.06%	1.12 (0.98, 1.28)	0.101
TR	15.64%	18.23%	1.17 (1.02, 1.32)	0.019
Any Valve	40.74%	44.81%	1.10 (1.03, 1.17)	0.005

Source: Created by reviewer.

Increase in Valvular Regurgitation Except 'Absent' to 'Trace'

The change of valvular regurgitation from 'Absent' to 'Trace' may not be clinically meaningful. Therefore, this analysis evaluates the risk of developing increases in individual valvular regurgitation except for increases of 'Absent' to 'Trace'. For subjects with any increase (except 'Absent' to 'Trace') in aortic (AR), mitral (MR), pulmonary (PR), or tricuspid regurgitation (TR) from baseline to week 52 (LOCF), the proportions in each treatment group and the comparison between lorcaserin 10 mg BID and placebo

are shown in Table 20 and Table 21. For each of the individual regurgitation in mitral, pulmonary, or tricuspid valve, the proportion of subjects with an increase except ‘Absent’ to ‘Trace’ was statistically significantly higher at the nominal $\alpha=0.05$ level in the lorcaserin 10 mg BID group than in the placebo group. However, a slightly higher proportion of subjects in the placebo group had increased aortic valvular regurgitation compared to the lorcaserin 10 mg BID group. In the pooled lorcaserin 10 mg BID group, 32.76% of the subjects had an increase except ‘Absent’ to ‘Trace’ in at least one of the four individual regurgitations, compared to 28.42% in the pooled placebo group. The relative risk ratio between lorcaserin 10 mg BID regimen and placebo was 1.15 with a 95% CI of (1.06, 1.25).

Table 20: Summary of Any Increase Except ‘Absent’ to ‘Trace’ in Valvular Regurgitation from Baseline to Week 52 (LOCF) by Treatment Group (Safety Population)

Number (%)* of subjects	Study APD356-009		Study APD356-011			Total
	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	
Aortic Valve	18 (1.5%)	18 (1.4%)	19 (1.6%)	7 (1.1%)	14 (1.1%)	76 (1.4%)
Mitral Valve	113 (9.5%)	134 (10.5%)	90 (7.5%)	58 (8.9%)	121 (9.5%)	516 (9.2%)
Pulmonary Valve	209 (18.4%)	231 (19.3%)	148 (12.4%)	89 (13.7%)	201 (15.8%)	878 (16.1%)
Tricuspid Valve	121 (10.3%)	159 (12.6%)	117 (9.8%)	86 (13.3%)	151 (11.9%)	634 (11.4%)
Any Valve	369 (30.9%)	440 (34.4%)	312 (36.0%)	188 (29.0%)	396 (31.1%)	1705 (30.5%)

Source: Created by reviewer.

Table 21: Proportion of Subjects with Any Increase Except ‘Absent’ to ‘Trace’ in Valvular Regurgitation from Baseline to Week 52 (LOCF) (Safety Population)

	Pooled Placebo	Pooled Lorcaserin 10 mg BID	Mantel-Haenszel ‘Pooled’ Relative Risk (95% CI)	CMH test p-value
AR	1.54%	1.25%	0.81 (0.51, 1.30)	0.384
MR	8.47%	9.99%	1.18 (0.99, 1.41)	0.066
PR	15.32%	17.48%	1.14 (1.00, 1.30)	0.042
TR	10.03%	12.25%	1.22 (1.04, 1.43)	0.014
Any Valve	28.42%	32.76%	1.15 (1.06, 1.25)	0.001

Source: Created by reviewer.

With respect to subjects who experienced any increase except ‘Absent’ to ‘Trace’ from baseline to week 24, the proportions and the comparisons are shown in Table 22 and Table 23. For AR, MR, PR, and TR, the proportion was consistently higher in the lorcaserin 10 mg BID group than in the placebo group. Furthermore, the proportion of increase in MR and TR was statistically significantly higher at the nominal $\alpha=0.05$ level for lorcaserin than placebo. Similar as the results for week 52 in Table 21, the proportions of subjects with any increase in valvular regurgitation from baseline to week 24 were 31.67% and 27.67%

in the lorcaserin and placebo groups respectively. The proportion was statistically significantly higher in the lorcaserin 10 mg BID group, with a relative risk ratio of 1.13 and a 95% CI of (1.04, 1.24).

Table 22: Summary of Any Increase except ‘Absent’ to ‘Trace’ in Valvular Regurgitation from Baseline to Week 24 by Treatment Group (Safety Population)

Number (%)* of subjects	Study APD356-009		Study APD356-011			Total
	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	
Aortic Valve	12 (1.1%)	19 (1.6%)	19 (1.7%)	7 (1.1%)	15 (1.2%)	72 (1.4%)
Mitral Valve	94 (8.6%)	132 (10.9%)	86 (7.5%)	52 (8.3%)	113 (9.2%)	477 (9.0%)
Pulmonary Valve	174 (17.8%)	192 (17.7%)	149 (13.1%)	90 (14.4%)	203 (16.5%)	808 (16.0%)
Tricuspid Valve	104 (9.7%)	149 (12.6%)	110 (9.6%)	74 (11.8%)	162 (13.1%)	599 (11.4%)
Any Valve[^]	320 (29.3%)	391 (32.2%)	300 (26.1%)	177 (28.2%)	377 (30.5%)	1565 (29.4%)

* The denominator of the percentage was the number of subjects without missing values, for each individual valvular regurgitation.

[^] Subject with increase for more than one valve was only counted once.

Source: Created by reviewer.

Table 23: Proportion of Subjects with Any Increase except ‘Absent’ to ‘Trace’ in Valvular Regurgitation from Baseline to Week 24 (Safety Population)

	Pooled Placebo	Pooled Lorcaserin 10 mg BID	Mantel-Haenszel ‘Pooled’ Relative Risk (95% CI)	CMH test p-value
AR	1.38%	1.39%	1.00 (0.62, 1.63)	0.99
MR	8.03%	10.01%	1.24 (1.04, 1.50)	0.019
PR	15.23%	17.06%	1.12 (0.98, 1.28)	0.101
TR	9.64%	12.86%	1.33 (1.13, 1.57)	0.0006
Any Valve	27.67%	31.37%	1.13 (1.04, 1.24)	0.006

Source: Created by reviewer.

3.1.6.2 Beck Depression Inventory

3.1.6.2.1 BDI-II Total Score

A description of the Beck Depression Inventory is provided in Section 3.1.4.2. Based on clinical input, a BDI-II total score of 0-13 is considered normal or minimal depression; 14-19 corresponds to mild depression; 20-28 corresponds to moderate depression; 29-63 corresponds to severe depression. Using the LOCF method to impute the missing scores, a categorical summary of the BDI-II total score at week 52 is presented in Table 24. At week 52, the majority of the subjects (about 90%) had a BDI-II total score of less than 14, indicating none to minimal depression. Approximately 2% of the subjects had mild

depression, while the proportion of moderate depression and severe depression was both less than one percent. The remainder of scores (around 7%) at week 52 was unknown, as these subjects did not have any post baseline assessment for the BDI-II score. Furthermore, the incidence of severe depression (BDI-II score >29) at week 52 is shown in Table 25. In Study APD356-009, the incidence was 0.27% in the lorcaserin 10 mg BID group and was 0.14% in the placebo group. In Study APD356-011, the incidence was 0.40% and 0.13% in the lorcaserin and placebo groups, respectively. Compared to the placebo group, the incidence was higher in the lorcaserin 10 mg BID group, however the difference was not statistically significant. The pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 2.44 with a 95% CI of (0.77, 7.77).

Table 24: Summary of Categorical BDI-II Total Score at Week 52 (LOCF) by Treatment Group, Safety Population

Level of Depression Based on BDI-II Total Score N (%)	Study APD356-009		Study APD356-011			Total N=7181
	Placebo (N=1584)	Lorcaserin 10 mg BID (N=1593)	Placebo (N=1601)	Lorcaserin 10 mg QD (N=801)	Lorcaserin 10 mg BID (N=1602)	
Severe Depression (score: 29 ~ 63)	2 (0.1%)	4 (0.3%)	2 (0.1%)	0 (0%)	6 (0.4%)	14 (0.2%)
Moderate Depression (score: 20 ~ 28)	19 (1.2%)	15 (0.9%)	15 (0.9%)	8 (1.0%)	9 (0.6%)	66 (0.9%)
Mild Depression (score: 14 ~ 19)	35 (2.2%)	35 (2.2%)	36 (2.3%)	19 (2.4%)	40 (2.5%)	165 (2.3%)
None to Minimal Depression (score: 0 ~ 13)	1372 (86.6%)	1423 (89.3%)	1433 (89.5%)	727 (90.8%)	1455 (90.8%)	6410 (89.3%)
Unknown (score: missing)	156 (9.9%)	116 (7.3%)	115 (7.2%)	47 (5.9%)	92 (5.7%)	526 (7.3%)

Source: Created by reviewer.

Table 25: Incidence of Severe Depression based on BDI-II Total Score at Week 52 (LOCF) by Treatment Group, Safety Population

Level of Depression Based on BDI-II Total Score	Study APD356-009		APD356-Study 011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Subjects with at least one post-baseline assessment	1428	1477	1486	1510	5901
Severe Depression	2	4	2	6	14
Incidence of Severe Depression	0.14%	0.27%	0.13%	0.40%	0.24%
Relative Risk (95% CI)	1.93 (0.36, 10.54)		2.95 (0.60, 14.60)		
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	2.44 (0.77, 7.77)				

Source: Created by reviewer.

The summaries in Tables 24 and 25 assessed the Week 52 score only. Because the BDI-II scores can vary within a subject during the trial, the highest score post baseline until

week 52 is also assessed. The summary of the highest BDI-II total score and the comparison between lorcaserin and placebo groups is presented in Table 26 and Table 27. The distribution of the highest BDI-II total score was similar to the BDI-II total score at week 52 as presented in Table 24. In Study APD356-009, the incidence was 0.68% in the lorcaserin 10 mg BID group and was 0.56% in the placebo group. In Study APD356-011, the incidence was 0.40% and 0.13% in the lorcaserin and placebo groups respectively. The pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.55 with a 95% CI of (0.71, 3.42).

Table 26: Summary of Categorical Highest BDI-II Total Score after Baseline by Treatment Group, Safety Population

Level of Depression Based on BDI-II Total Score N (%)	Study APD356-009		Study APD356-011			Total N=7181
	Placebo (N=1584)	Lorcaserin 10 mg BID (N=1593)	Placebo (N=1601)	Lorcaserin 10 mg QD (N=801)	Lorcaserin 10 mg BID (N=1602)	
Severe Depression (score: 29 ~ 63)	8 (0.5%)	10 (0.6%)	2 (0.1%)	0 (0%)	6 (0.4%)	26 (0.4%)
Moderate Depression (score: 20 ~ 28)	38 (2.4%)	35 (2.2%)	24 (1.5%)	11 (1.4%)	20 (1.3%)	128 (1.8%)
Mild Depression (score: 14 ~ 19)	84 (5.3%)	84 (5.3%)	67 (4.2%)	28 (3.5%)	60 (3.8%)	323 (4.5%)
None to Minimal Depression (score: 0 ~ 13)	1298 (81.9%)	1348 (84.6%)	1393 (87.0%)	715 (89.3%)	1424 (88.9%)	6180 (86.1%)
Unknown (score: missing)	156 (9.9%)	116 (7.3%)	115 (7.2%)	47 (5.9%)	92 (5.7%)	526 (7.3%)

Source: Created by reviewer.

Table 27: Incidence of Severe Depression based on Highest BDI-II Total Score after Baseline by Treatment Group, Safety Population

Level of Depression Based on BDI-II Total Score	Study 009		Study 011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing	1428	1477	1486	1510	5901
Severe Depression	8	10	2	6	26
Incidence of Severe Depression	0.56%	0.68%	0.13%	0.40%	0.44%
Relative Risk (95% CI)	1.21 (0.48, 3.05)		2.95 (0.60, 14.60)		
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	1.55 (0.71, 3.42)				

Source: Created by reviewer.

3.1.6.2.2 BDI-II Score for Item # 9 (Suicidal Thoughts)

In the BDI-II inventory, Item 9 of the scale addresses suicidal thoughts. An Item #9 score of 0 is considered normal or no suicidal thought, while scores of 1 to 3 correspond to having thoughts of suicide. The incidences of suicidal thoughts at week 52 are shown in Table 28. In Study APD356-009, the incidence was lower in the lorcaserin 10 mg BID

group than in the placebo group (0.41% versus 0.63%). While in Study APD356-011, the incidence was higher in the lorcaserin group (0.79%) than in the placebo group (0.40%). The pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.17 with a 95% CI of (0.59, 2.32).

Table 28: Incidence of Suicidal Thoughts based on BDI-II Item #9 at Week 52 (LOCF) by Treatment Group, Safety Population

Suicidal Thoughts Based on BDI-II Item #9	Study 009		Study 011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing	1429	1478	1486	1512	5905
Suicidal Thoughts	9	6	6	12	33
Incidence of Suicidal Thoughts	0.63%	0.41%	0.40%	0.79%	0.56%
Relative Risk (95% CI)	0.65 (0.23, 1.81)		1.97 (0.74, 5.22)		
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	1.17 (0.59, 2.32)				

Source: Created by reviewer.

Other than the score at week 52 with LOCF, the highest score of suicidal thoughts during the trial phase is evaluated. As shown in Table 29, the incidence of suicidal thoughts based on the highest score was higher in the lorcaserin 10 mg BID group than in the placebo group, in both Study APD356-009 and Study APD356-011: the incidence was 1.76% versus 1.19% in Study APD356-009, and was 1.12% versus 0.81% in Study APD356-011. The pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.44 with a 95% CI of (0.90, 2.30).

Table 29: Incidence of Suicidal Thoughts based on BDI-II Item #9 (Highest Score after Baseline) by Treatment Group, Safety Population

Suicidal Thoughts Based on BDI-II Item #9	Study 009		Study 011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing	1429	1478	1486	1512	5905
Suicidal Thoughts	17	26	12	17	72
Incidence of Suicidal Thoughts	1.19%	1.76%	0.81%	1.12%	1.22%
Relative Risk (95% CI)	1.48 (0.81, 2.71)		1.39 (0.67, 2.91)		
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	1.44 (0.90, 2.30)				

Source: Created by reviewer.

3.1.6.2.3 Other BDI-II Score Individual Item Assessment

Other than Item #9 for suicidal thoughts, it is also of clinical interest to evaluate the individual BDI-II scores for Item #18 (changes in appetite), Item #19 (concentration difficulty), and Item #20 (tiredness or fatigue). In the risk assessments that follow, the highest BID-II score from baseline to week 52 is used in the calculations.

BDI-II Score for Item #18 (Changes in Appetite)

In the BDI-II inventory, Item #18 addresses changes in Appetite. An Item #18 score of 0 is considered no appetite change, while scores of 1A to 3A correspond to losing appetite and scores of 1B to 3B correspond to having increased appetite. Subjects with score 2A or 3A were considered to have greatly lost their appetite during the trial phase. Compared to the placebo group, the incidence of losing appetite greatly was statistically significantly higher at the nominal $\alpha=0.05$ significance level in the lorcaserin 10 mg BID group, with a pooled relative risk ratio of 1.98 and corresponding 95% CI of (1.73, 2.27); results depicted in Table 30.

Table 30: Incidence of Losing Appetite Greatly based on BDI-II Item #18 (Highest Score after Baseline) by Treatment Group, Safety Population

	Study 009		Study 011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Losing Appetite Greatly Based on BDI-II Item #18					
Number without missing	1429	1478	1486	1511	5904
Losing Appetite Greatly	131	271	140	280	822
Incidence of Losing Appetite	9.17%	18.3%	9.42%	18.53%	13.9%
Relative Risk (95% CI)	2.00 (1.65, 2.43)		1.97 (1.63, 2.38)		
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	1.98 (1.73, 2.27)				

Source: Created by reviewer.

BDI-II Score for Item #19 (Concentration Difficulty)

Item #19 in the BDI-II inventory is about concentration difficulty. An Item #19 score of 0 is considered normal or no concentration difficulty, while scores of 1 to 3 correspond to having concentration difficulty. As shown in Table 31, among subjects without missing, the incidence of having concentration difficulty was higher in the lorcaserin 10 mg BID group than in the placebo group, for both Study APD356-009 and Study APD356-011. The pooled relative risk ratio was 1.14 with 95% (1.03, 1.26), indicating that the incidence of having concentration difficulty was statistically significantly higher in the lorcaserin group than in the placebo group.

Table 31: Incidence of Having Concentration Difficulty based on BDI-II Item #18 (Highest Score after Baseline) by Treatment Group, Safety Population

	Study 009		Study 011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Having Concentration Difficulty Based on BDI-II Item #19					
Number without missing	1429	1478	1486	1511	5904
Having Concentration Difficulty	303	361	276	316	1256
Incidence of Concentration Difficulty	21.20%	24.42%	18.57%	20.91%	21.3%
Relative Risk (95% CI)	1.15 (1.01, 1.32)		1.13 (0.97, 1.30)		
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	1.14 (1.03, 1.26)				

Source: Created by reviewer.

BDI-II Score for Item #20 (Tiredness or Fatigue)

Item #20 in the BDI-II inventory is focused on feeling of tiredness or fatigue. An Item #20 score of 0 is considered normal or non tiredness, while scores of 1 to 3 correspond to having tiredness or fatigue. As shown in Table 32, among subjects without missing, the incidence of tiredness or fatigue was higher in the lorcaserin 10 mg BID group than in the placebo group, for both Study APD356-009 and Study APD356-011. The pooled relative risk ratio was 1.11 with a 95% CI of (1.04, 1.19), indicating that the incidence of Tiredness or Fatigue was statistically significantly higher in the lorcaserin group than in the placebo group.

Table 32: Incidence of Tiredness or Fatigue Difficulty based on BDI-II Item #20 (Highest Score after Baseline) by Treatment Group, Safety Population

Tiredness or Fatigue Based on BDI-II Item #20	Study 009		Study 011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Number without missing	1429	1478	1486	1511	5904
Tiredness or Fatigue	558	636	487	557	2238
Incidence of Tiredness or Fatigue	39.05%	43.03%	32.77%	36.86%	
Relative Risk (95% CI)	1.10 (1.01, 1.20)		1.12 (1.02, 1.24)		
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	1.11 (1.04, 1.19)				

Source: Created by reviewer.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

In the following sections, safety results for FDA-defined valvulopathy and the BDI-II inventory are presented for specific subgroups. It should be noted that these analyses are exploratory in nature to assess general trends. No protocol-defined multiplicity adjustments were provided and as such the statistical analysis does not include a multiplicity adjustment in the results that follow.

Gender

Only considering subjects randomized to receive lorcaserin 10 mg BID or placebo, a total of 4,830 subjects in the safety population did not have FDA-defined valvulopathy at baseline, and had at least one echocardiogram data available post randomization. Among these subjects, 3,880 subjects (90%) were female, while 950 subjects (20%) were male. The incidence of FDA-defined valvulopathy at week 52 (LOCF) for female or male subjects is presented in Table 33. Among the female subjects, the incidence of FDA-defined valvulopathy at week 52 was 2.59% in the lorcaserin 10 mg BID group and 2.32% in the placebo group, for Study APD356-009. For Study APD356-011, the incidence of FDA-defined valvulopathy at week 52 was 2.28% and 1.81% in the

lorcaserin and placebo groups, respectively. The pooled Mantel-Haenszel relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 1.18 with a 95% CI of (0.78, 1.78).

In contrast, among male subjects, the incidence of FDA-defined valvulopathy was slightly higher in the lorcaserin 10 mg BID group than in the placebo group in Study APD356-009 (2.98% versus 2.49%), but was much lower in the lorcaserin group in Study APD356-011 (0.82% versus 2.60%). The pooled relative risk ratio between lorcaserin and placebo was 0.71 with a 95% CI of (0.30, 1.70).

Table 33: Incidence of FDA-Defined Valvulopathy at Week 52 (LOCF) by Gender and Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

	Study APD356-009		Study APD356-011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Females					
Number without missing, excluding baseline valvulopathy	990	1043	884	963	3880
FDA-defined Valvulopathy	23	27	16	22	88
Incidence of Valvulopathy	2.32%	2.59%	1.81%	2.28%	2.27%
Relative Risk (90% CI) [95% CI]	1.11 (0.70, 1.77) [0.64, 1.93]		1.26 (0.74, 2.16) [0.67, 2.39]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	1.18 (0.83, 1.67) [0.78, 1.78]				
Males					
Number without missing, excluding baseline valvulopathy	201	235	269	245	950
FDA-defined Valvulopathy	5	7	7	2	21
Incidence of Valvulopathy	2.49%	2.98%	2.60%	0.82%	2.21%
Relative Risk (90% CI) [95% CI]	1.20 (0.46, 3.10) [0.39, 3.71]		0.31 (0.08, 1.16) [0.07, 1.50]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	0.71 (0.34, 1.47) [0.30, 1.70]				

Source: Created by reviewer.

Subgroup analysis of the BDI-II total score at week 52 (LOCF) by gender is presented in Table 39. Among female subjects, the incidence of severe depression based on BDI-II total score was consistently higher in the lorcaserin group than in the placebo group, in both Study APD356-009 (0.33% versus 0.08%) and Study APD356-011 (0.49% versus 0.17%). The pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 3.23 with a 95% CI of (0.89, 11.70). The analysis of severe depression was not meaningful for male subjects, because there was only one case of severe depression among male subjects.

Table 34: Incidence of Severe Depression based on BDI-II Total Score at Week 52 (LOCF) by Gender and Treatment Group, Safety Population

Level of Depression Based on BDI-II Total Score	Study 009		Study 011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Female					
Number without missing	1195	1221	1166	1213	4795
Severe Depression	1	4	2	6	13
Incidence of Severe Depression	0.08%	0.33%	0.17%	0.49%	0.27%
Relative Risk (95% CI)	3.91 (0.44, 34.97)		2.88 (0.58, 14.26)		
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	3.23 (0.89, 11.70)				
Male					
Number without missing	233	256	320	297	1106
Severe Depression	1	0	0	0	1
Incidence of Severe Depression	0.43%	0%	0%	0%	0.09%

Source: Created by reviewer.

Race

Subgroup analyses for FDA-defined valvulopathy by race category are presented in Table 35. Similar as the subgroup analyses of gender, among the 4,830 subjects in the safety population for analysis, 3,396 subjects (70.3%) were White or Caucasian, 850 subjects (17.6%) were Black or African American, 484 subjects (10.0%) were Hispanic or Latino, with 100 subjects (2.1%) were of other races.

Only considering subjects randomized to receive lorcaserin 10 mg BID or placebo, a total of 4,830 subjects in the safety population did not have FDA-defined valvulopathy at baseline, and had at least one echocardiogram data available post randomization. Among these subjects, 3,880 subjects (90%) were female, while 950 subjects (20%) were male. Among Black or African American subjects, the incidence of FDA-defined valvulopathy at week 52 was consistently higher in the lorcaserin 10 mg BID group than in the placebo group, in both Studies APD356-009 and APD356-011.

Among the non-Black subjects, the incidence of FDA-defined valvulopathy in the lorcaserin group at week 52 was higher in Study APD356-009 but was lower in Study APD356-011, compared to the placebo group.

Table 35: Incidence of FDA-Defined Valvulopathy at Week 52 (LOCF) by Race Category and Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

	Study APD356-009		Study APD356-011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
White or Caucasian					
Number without missing, excluding baseline valvulopathy	835	918	794	849	3396
FDA-defined Valvulopathy	23	26	17	18	84
Incidence of Valvulopathy	2.75%	2.83%	2.14%	2.12%	2.47%
Relative Risk (90% CI) [95% CI]	1.03 (0.65, 1.64) [0.59, 1.79]		0.99 (0.57, 1.72) [0.51, 1.91]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	1.01 (0.71, 1.44) [0.66, 1.54]				
Black or African American					
Number without missing, excluding baseline valvulopathy	202	218	219	211	850
FDA-defined Valvulopathy	4	6	3	4	17
Incidence of Valvulopathy	1.98%	2.75%	1.37%	1.90%	2.00%
Relative Risk (90% CI) [95% CI]	1.39 (0.49, 3.97) [0.40, 4.85]		1.38 (0.40, 4.81) [0.31, 6.11]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	1.39 (0.62, 3.10) [0.53, 3.61]				
Hispanic or Latino					
Number without missing, excluding baseline valvulopathy	136	118	113	117	484
FDA-defined Valvulopathy	0	1	3	0	4
Incidence of Valvulopathy	0%	0.85%	2.65%	0%	0.83%
Other					
Number without missing, excluding baseline valvulopathy	18	24	27	31	100
FDA-defined Valvulopathy	1	1	0	2	4
Incidence of Valvulopathy	5.56%	4.17%	0%	6.45%	4.00%

Source: Created by reviewer.

Subgroup analysis of the BDI-II total score at week 52 (LOCF) by race category is presented in Table 41. Among Black subjects, since only 2 subjects had severe depression with BDI-II total score >28 at week 52, the comparison between lorcaserin and placebo was not conducted.

Among the non-Black subjects, the incidence of severe depression consistently higher in the lorcaserin group than in the placebo group, in both Study APD356-009 (0.33% versus 0.17%) and Study APD356-011 (0.41% versus 0.08%). The pooled relative risk ratio between the lorcaserin 10 mg BID group and the placebo group was 2.93 with a 95% CI of (0.79, 10.79).

Table 36: Incidence of Severe Depression based on BDI-II Total Score at Week 52 (LOCF) by Race Category and Treatment Group, Safety Population

Level of Depression Based on BDI-II Total Score	Study 009		Study 011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
White or Caucasian					
Number without missing	970	1025	1007	1029	4031
Severe Depression	2	4	1	3	10
Incidence of Severe Depression	0.21%	0.39%	0.10%	0.29%	0.25%
Black or African American					
Number without missing	247	266	281	290	1084
Severe Depression	0	0	1	1	2
Incidence of Severe Depression	0%	0%	0.34%	0.36%	0.18%
Hispanic or Latino					
Number without missing	187	158	156	160	661
Severe Depression	0	0	0	2	2
Incidence of Severe Depression	0%	0%	0%	1.25%	0.30%
Others					
Number without missing	28	24	40	33	125
Severe Depression	0	0	0	0	0
Incidence of Severe Depression	0%	0%	0%	0%	0%

Source: Created by reviewer.

Age

Subgroup analyses for FDA-defined valvulopathy and BDI-II total score by age category (≤ 50 years old or >50 years old) are presented in Table 42 and Table 43 respectively. Among subjects with age less than 50, the incidence of FDA-defined valvulopathy at week 52 was consistently higher in the lorcaserin 10 mg BID group than in the placebo group, in both Studies APD356-009 (2.07% versus 1.48%) and APD356-011 (1.02% versus 0.81%). The pooled relative risk ratio for FDA-defined valvulopathy was 1.36 with a 95% CI of (0.74, 2.50).

In general, the incidence of FDA-defined valvulopathy was higher among older subjects than among younger subjects given that the overall incidence was 3.86% for subjects older than 50 years and 1.36% for subjects with an age ≤ 50 years. However, for subjects older than 50 years, the incidence of FDA-defined valvulopathy at week 52 was lower in the lorcaserin 10 mg BID group than in the placebo group, in both Studies APD356-009 and APD356-011. The pooled relative risk ratio between lorcaserin and placebo was 0.94 with a 95% CI of (0.59, 1.50).

Table 37: Incidence of FDA-Defined Valvulopathy at Week 52 (LOCF) by Age Group and Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

	Study APD356-009		Study APD356-011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Age ≤ 50					
Number without missing, excluding baseline valvulopathy	744	821	745	782	3092
FDA-defined Valvulopathy	11	17	6	8	42
Incidence of Valvulopathy	1.48%	2.07%	0.81%	1.02%	1.36%
Relative Risk (90% CI) [95% CI]	1.40 (0.75, 2.63) [0.66, 2.97]		1.27 (0.52, 3.08) [0.44, 3.64]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	1.36 (0.81, 2.26) [0.74, 2.50]				
Age > 50					
Number without missing, excluding baseline valvulopathy	447	457	408	426	1738
FDA-defined Valvulopathy	17	17	17	16	67
Incidence of Valvulopathy	3.80%	3.72%	4.17%	3.76%	3.86%
Relative Risk (90% CI) [95% CI]	0.98 (0.56, 1.70) [0.51, 1.89]		0.90 (0.51, 1.58) [0.46, 1.76]		
Mantel-Haenszel 'Pooled' Relative Risk (90% CI) [95% CI]	0.94 (0.63, 1.39) [0.59, 1.50]				

Source: Created by reviewer.

Table 38: Incidence of Severe Depression based on BDI-II Total Score at Week 52 (LOCF) by Age Group and Treatment Group, Safety Population

	Study 009		Study 011		Total
	Placebo	Lorcaserin 10mg BID	Placebo	Lorcaserin 10mg BID	
Age ≤ 50					
Number without missing	942	987	987	1001	3917
Severe Depression	1	3	1	4	9
Incidence of Severe Depression	0.11%	0.30%	0.10%	0.40%	0.23%
Relative Risk (95% CI)	2.86 (0.30, 27.48)		3.94 (0.44, 35.22)		
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	3.40 (0.71, 16.33)				
Age > 50					
Number without missing	486	490	499	509	1984
Severe Depression	1	1	1	2	5
Incidence of Severe Depression	0.21%	0.20%	0.20%	0.39%	0.25%
Relative Risk (95% CI)	0.99 (0.06, 15.81)		1.96 (0.18, 21.55)		
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	1.48 (0.25, 8.83)				

Source: Created by reviewer.

4.2 Other Special/Subgroup Populations

No other subgroups or populations were assessed.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The primary safety endpoint for the echocardiogram evaluation was the proportion of subjects who developed FDA-defined valvulopathy at week 52. FDA-defined valvulopathy was defined as an echocardiographic finding of MILD or greater aortic regurgitation (AR) *or* MODERATE or greater mitral regurgitation (MR).

Once approved, a weight loss drug would be used by hundred of thousands of patients, many of whom would be at low short-term absolute risk for serious disease due to their body weight. It is clinically important to determine the excess risk acceptable for such a drug. During the development process of this NDA application, The Agency continuously emphasized that ruling out a 50% increased in the incidence of FDA-defined valvulopathy was both an important and a reasonable request for the applicant. As such, the Agency stated that data in the NDA must be able to rule out a relative risk for FDA-defined valvulopathy of at least 1.5 (powered at 80%).

The pooled relative risk ratio between lorcaserin and placebo was 1.07 with a 95% confidence interval of (0.75, 1.55). The lorcaserin 10 mg BID group failed to demonstrate the non-inferiority to the placebo group at week 52, given the upper limit of the confidence interval exceeded the pre-specified non-inferiority margin of 1.5. Similar results were shown in several sensitivity analyses for the incidence of FDA-defined valvulopathy. Therefore, the pooled data from Studies APD356-009 and APD356-011 could not robustly rule out a relative risk of 1.5 for lorcaserin 10 mg BID regimen in the risk of developing FDA-defined valvulopathy from baseline to week 52. Detailed analysis results are provided in Section 3.1.6.1.1 and Section 3.1.6.1.2.

With respect to the risk of developing increased valvular regurgitation at week 52 for at least one valve among aortic, mitral, pulmonary, and tricuspid valves, the incidence was statistically significantly higher at the nominal $\alpha=0.05$ level in the lorcaserin 10 mg BID group than in the placebo group in each study separately. Pooling Study APD356-009 and Study APD356-011 together, the pooled relative risk ratio was 1.11 with a 95% confidence interval of (1.04, 1.18), indicating that the difference between lorcaserin and placebo was statistically significant (46.94% versus 42.36%, $p=0.001$). More details of this assessment can be found in Section 3.2.3.1.2.

BDI-II total score was designed to assess the presence and severity of symptoms of depression. For the risk of developing severe depression defined as a BDI-total score greater than 28 at week 52, no statistically significant difference was found between lorcaserin and placebo. The pooled relative risk ratio between lorcaserin and placebo was

2.44 with a 95% confidence interval of (0.77, 7.77). The estimated relative risk of 2.44 and a wide confidence interval suggested that there might be a relationship between lorcaserin 10 mg BID regimen and increased risk of severe depression but the currently available data might not be powered to draw definite conclusion on it. More details of this assessment can be found in Section 3.2.3.2.1.

The BDI-II score for each individual item of the inventory corresponded to a specific category of depressive symptom or attitude. The following is a summary finding of four key items from the inventory.

- Based on BDI-II score for Item #9, there does not appear to be a significant relationship between lorcaserin and increased risk of suicidal thoughts. The pooled relative risk ratio at week 52 was 1.17 with a 95% confidence interval of (0.59, 2.32).
- Based on BDI-II score for Item #18, the lorcaserin regimen was shown to be associated with an increase in risk of losing appetite. The pooled relative risk ratio between lorcaserin and placebo was 1.98 with a 95% confidence interval of (1.73, 2.27).
- Based on BDI-II score for Item #19, the lorcaserin regimen was shown to be associated with an increase in risk of developing concentration difficulty. The pooled relative risk ratio between lorcaserin and placebo was 1.14 with a 95% confidence interval of (1.03, 1.26).
- Based on BDI-II score for Item #20, the lorcaserin regimen was shown to be associated with an increase in risk of having tiredness or fatigue. The pooled relative risk ratio between lorcaserin and placebo was 1.11 with a 95% confidence interval of (1.04, 1.19).

More details of these analysis results can be found in Section 3.2.3.2.2 and in Section 3.2.3.2.3.

5.2 Conclusions and Recommendations

Based on a non-inferiority margin of 1.5 for the relative risk ratio (see Section 1.3 for a discussion on the selection of the non-inferiority margin), the pooled analysis of two phase 3 randomized placebo-controlled clinical trials APD356-009 and APD356-011 failed to rule out that the lorcaserin 10 mg twice-a-day (BID) regimen was inferior to the placebo in the risk of developing FDA-defined valvulopathy (aortic regurgitation mild or greater, or mitral regurgitation moderate or greater) at 52 weeks.

Compared to placebo, the lorcaserin 10 mg BID regimen was found to be associated with an increase in at least one of the four valvular regurgitations (aortic valve, mitral valve, pulmonary valve, and tricuspid valve). The incidence of developing increased valvular regurgitation was statistically significantly higher at the nominal $\alpha=0.05$ level in the lorcaserin group than in the placebo group, in both Studies APD356-009 and APD356-011 separately, as well as in the pooled analysis of both studies.

Since the main focus of the pooled phase 3 studies was to evaluate FDA-defined valvulopathy, the sample sizes were not adequately powered for the assessment of the

Beck Depression Inventory. For the assessment of the Beck Depression Inventory, no statistically significant difference between lorcaserin and placebo in the BDI-II total score was found. However, the incidence of severe depression at 52 weeks, defined as the proportion of subjects with a BDI-II total score greater than 28, was noticeably higher in the lorcaserin group than in the placebo group, in both Studies APD356-009 and APD356-011 separately, as well as in the pooled analysis of both studies. The corresponding 95% confidence interval for the pooled analysis included the null value of one but had a wide range, indicating that even the pooled phase 3 studies might not be powered to draw a definite conclusion.

Based on individual BDI-II items addressing specific questions related to depression, there does not appear to be a significant association between the lorcaserin regimen and an increase in suicidal thoughts. In contrast, the lorcaserin 10 mg BID regimen was found to be associated with statistically significantly higher risk of losing appetite, developing concentration difficulty and having tiredness or fatigue.

Appendix

A.1 Supplementary Tables

A.1.1 BDI-II Item # 9, Suicidal Thoughts

A categorical summary of BDI-II score for Item #9 at week 52 is presented in Table 39, with the LOCF method to impute the missing values. At week 52, less than 1% of the subjects in Study APD356-009 and Study APD356-011 had thoughts of suicide, while more than 92% of the subjects had no suicidal thoughts. Note that about 7% of the subjects had missing value of the Item #9 score because they did not have any post baseline assessment.

Table 39: Summary of Categorical BDI-II, Item #9 at Week 52 (LOCF) by Treatment Group, Safety Population

Suicidal Thoughts Based on BDI-II Item #9 N (%)	Study APD356-009		Study APD356-011			Total N=7181
	Placebo (N=1584)	Lorcaserin 10 mg BID (N=1593)	Placebo (N=1601)	Lorcaserin 10 mg QD (N=801)	Lorcaserin 10 mg BID (N=1602)	
Suicidal Thoughts (score: 1 ~ 3)	9 (0.6%)	6 (0.4%)	6 (0.4%)	2 (0.3%)	12 (0.8%)	35 (0.5%)
Non Suicidal Thoughts (score: 0)	1420 (89.7%)	1472 (92.4%)	1480 (92.4%)	752 (93.9%)	1500 (93.6%)	6624 (92.2%)
Unknown (score: missing)	155 (9.8%)	115 (7.2%)	115 (7.2%)	47 (5.9%)	90 (5.6)	522 (7.3%)

Source: Created by reviewer.

Other than the score at week 52 with LOCF, the highest BDI-II score for Item #9 after baseline until week 52 is categorized in Table 40. Slightly more than 1% of the subjects had thoughts of suicide between baseline and week 52, compared to only 0.5% of subjects who had suicidal thoughts at week 52 (Table 39).

Table 40: Incidence of Suicidal Thoughts based on BDI-II Item #9 (Highest Score after Baseline) by Treatment Group, Safety Population

Suicidal Thoughts Based on BDI-II Item #9 n (%)	Study APD356-009		Study APD356-011			Total N=7181
	Placebo (N=1584)	Lorcaserin 10 mg BID (N=1593)	Placebo (N=1601)	Lorcaserin 10 mg QD (N=801)	Lorcaserin 10 mg BID (N=1602)	
Suicidal Thoughts (score: 1 ~ 3)	17 (1.1%)	26 (1.6%)	12 (0.8%)	6 (0.8%)	17 (1.1%)	78 (1.1%)
Non Suicidal Thoughts (score: 0)	1412 (89.1%)	1452 (91.2%)	1474 (92.1%)	748 (93.4%)	1495 (93.3%)	6581 (91.6%)
Unknown (score: missing)	155 (9.8%)	115 (7.2%)	115 (7.2%)	47 (5.9%)	90 (5.6)	522 (7.3%)

Source: Created by reviewer.

A.1.2 BDI-II Item # 18, Change in Appetite

The highest BDI-II score for Item #18 after baseline till week 52 is categorized in Table 32. About 65% of the subjects in Study APD356-009 and Study APD356-011 lost appetite to some degree, with approximately 29% of the subjects having no appetite change. Only less than 2% of the subjects gained appetite in any degree during 52 weeks. Note that about 7% of the subjects had a missing value of the Item #18 score because they did not have any post baseline assessment.

In both Study APD356-009 and Study APD356-011, the incidence of losing appetite greatly (score of 2A, or 3A) in the lorcaserin 10 mg BID group was about doubled, as compared to the placebo group.

Table 41: Summary of Categorical BDI-II, Item #18 (Highest Score after Baseline) by Treatment Group, Safety Population

Change in Appetite Based on BDI-II Item #18 N (%)	Study APD356-009		Study APD356-011			Total N=7181
	Placebo (N=1584)	Lorcaserin 10 mg BID (N=1593)	Placebo (N=1601)	Lorcaserin 10 mg QD (N=801)	Lorcaserin 10 mg BID (N=1602)	
No appetite at all (score=3A)	5 (0.3%)	3 (0.2%)	2 (0.1%)	1 (0.1%)	6 (0.4%)	17 (0.2%)
Appetite is much less (score=2A)	126 (8.0%)	268 (16.8%)	138 (8.6%)	117 (14.6%)	274 (17.1%)	923 (14.9%)
Appetite is somewhat less (score=1A)	685 (43.2%)	857 (53.8%)	760 (47.5%)	413 (51.6%)	818 (51.1%)	3533 (49.2%)
No Appetite change (score=0)	580 (36.6%)	336 (21.1%)	540 (33.7%)	210 (26.2%)	395 (24.7%)	2061 (28.7%)
Appetite is somewhat greater (score=1B)	27 (1.7%)	13 (0.1%)	42 (2.6%)	13 (1.6%)	16 (1.0%)	111 (1.6%)
Appetite is much greater (score=2B)	2 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0%)	1 (0.1%)	5 (0.1%)
Crave food all the time (score=3B)	4 (0.3%)	0 (0%)	3 (0.2%)	0 (0%)	1 (0.1%)	8 (0.1%)
Unknown (score: missing)	155 (9.8%)	115 (7.2%)	115 (7.2%)	47 (5.9%)	91 (5.7%)	523 (7.3%)

Source: Created by reviewer.

A.1.3 BDI-II Item # 19, Concentration Difficulty

The highest BDI-II score for Item #19 (concentration difficulty) after baseline until week 52 is categorized in Table 42. Approximately 20% of the subjects had concentration difficulty of different degrees during the 52 weeks trial phase, while about 73% of the subjects had no concentration difficulty. Note that about 7% of the subjects had a missing value of the Item #19 score because they did not have any post baseline assessment.

Table 42: Summary of Categorical BDI-II, Item #19 (Highest Score after Baseline) by Treatment Group, Safety Population

Concentration Difficulty Based on BDI-II Item #19 n (%)	Study APD356-009		Study APD356-011			Total N=7181
	Placebo (N=1584)	Lorcaserin 10 mg BID (N=1593)	Placebo (N=1601)	Lorcaserin 10 mg QD (N=801)	Lorcaserin 10 mg BID (N=1602)	
Can't concentrate on anything (score: 3)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0%)	4 (0.3%)	7 (0.1%)
Hard to concentrate on anything for long (score: 2)	36 (2.3%)	47 (3.0%)	32 (2.0%)	18 (2.3%)	35 (2.2%)	168 (2.3%)
Can't concentrate as well as usual (score: 1)	266 (16.8%)	313 (19.7%)	243 (15.2%)	117 (14.6%)	277 (17.3%)	1216 (16.9%)
Non Concentration Difficulty (score: 0)	1126 (71.2%)	1117 (70.1%)	1210 (75.6%)	619 (77.3%)	1195 (74.6%)	5267 (73.4%)
Unknown (score: missing)	155 (9.8%)	115 (7.2%)	115 (7.2%)	47 (5.9%)	91 (5.7)	523 (7.3%)

Source: Created by reviewer.

A.1.4 BDI-II Item # 20, Tiredness or Fatigue

The highest BDI-II score for Item #20 after baseline till week 52 is categorized in Table 43. Approximately 35% of the subjects in Study APD356-009 and Study APD356-011 got tiredness or fatigue to a certain degree during 52 weeks, while about 58% of the subjects had no tiredness or fatigue. Note that about 7% of the subjects had a missing value of the Item #19 score because they did not have any post baseline assessment.

Table 43: Summary of Categorical BDI-II, Item #20 (Highest Score after Baseline) by Treatment Group, Safety Population

Tiredness or Fatigue Based on BDI-II Item #19 n (%)	Study APD356-009		Study APD356-011			Total N=7181
	Placebo (N=1584)	Lorcaserin 10 mg BID (N=1593)	Placebo (N=1601)	Lorcaserin 10 mg QD (N=801)	Lorcaserin 10 mg BID (N=1602)	
Too tired to do most of the things (score: 3)	7 (0.4%)	6 (0.4%)	6 (0.4%)	2 (0.3%)	7 (0.4%)	28 (0.4%)
Too tired to do a lot of the things (score: 2)	52 (3.3%)	47 (3.0%)	39 (2.4%)	14 (1.8%)	36 (2.3%)	188 (2.6%)
Get more tired more easily (score: 1)	499 (31.5%)	583 (36.6%)	442 (27.6%)	229 (28.6%)	514 (32.1%)	2267 (31.6%)
Non Tiredness (score: 0)	871 (55.0%)	842 (52.9%)	999 (62.4%)	509 (63.6%)	954 (59.6%)	4175 (58.1%)
Unknown (score: missing)	155 (9.8%)	115 (7.2%)	115 (7.2%)	47 (5.9%)	91 (5.7)	523 (7.3%)

Source: Created by reviewer.

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 022529/0

Drug Name: Lorcaserin tablets

Indication(s): Weight management

Applicant: Arena Pharmaceuticals Inc

Dates: Submission date: December 22, 2009
PDUFA Goal Date: October 22, 2010
Advisory Committee Date: September 16, 2010

Review Priority: Standard

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Keywords: clinical studies, NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Efficacy Conclusions:

Confirmation of efficacy: The results of two Phase 3 studies are consistent and confirm the efficacy of lorcaserin 10 mg bid and 10 mg qd compared to placebo after 52 weeks of treatment, in the co-primary weight loss endpoints of average weight loss compared to baseline, the percentage of subjects who lost at least 5% of baseline body weight, and the percentage of subjects who lost at least 10% of baseline body weight. Results of alternate analysis models and other versions of the analysis population were consistent with the results from the primary analysis. However, the placebo-adjusted weight loss was relatively low, compared to the benchmark of 5% described in the February 2007 draft *Guidance for Industry: Developing Products for Weight Management*. The results from the primary analyses are shown below:

TABLE 1 Efficacy results from Study 009 and Study 011; primary analyses (MITT/LOCF)

1. Weight loss at week 52 as a % of baseline weight					
Treatment groups	N	Baseline mean (kg) ± SE	Adjusted mean % change from baseline at Week 52 ± SE	Difference in adjusted mean % change, Lorcaserin - Placebo (95% CI)	P-value vs. Placebo
Study APD356-009 BLOOM					
Lorcaserin 10 mg bid	1538	100.4 ± 0.4	-5.9 ± 0.2	-3.7 (-4.1, -3.3)	<0.0001
Placebo	1499	99.7 ± 0.4	-2.2 ± 0.1		
Study APD356-011 BLOSSOM					
Lorcaserin 10 mg bid	1561	100.3 ± 0.4	-5.8 ± 0.2	-3.0 (-3.4, -2.6)	<0.0001
Lorcaserin 10 mg qd	771	100.1 ± 0.6	-4.7 ± 0.2	-1.9 (-2.5, -1.4)	<0.0001
Placebo	1541	100.8 ± 0.4	-2.8 ± 0.2		
2. Percentage of subjects achieving ≥ 5% weight loss at week 52					
Treatment groups	N	Number of responders (%)	Difference in proportions (95% CI)	Odds ratio (95% CI)	p-value vs. placebo
Study APD356-009 BLOOM					
Lorcaserin 10 mg bid	1538	731 (47.5%)	27.2 (24.0, 30.5)	3.6 (3.1, 4.2)	<0.001
Placebo	1499	304 (20.3%)			
Study APD356-011 BLOSSOM					
Lorcaserin 10 mg bid	1561	737 (47.2%)	22.2 (18.9, 25.5)	2.7 (2.3, 3.1)	<0.0001
Lorcaserin 10 mg qd	771	310 (40.2%)	15.2 (11.1, 19.3)	2.0 (1.7, 2.4)	<0.0001
Placebo	1541	385 (25.0%)			
3. Percentage of subjects achieving ≥ 10% weight loss at week 52					
Study APD356-009 BLOOM					
Lorcaserin 10 mg bid	1538	347 (22.6%)	14.9 (12.4, 17.4)	3.5 (2.8, 4.4)	< 0.001
Placebo	1499	115 (7.7%)			
Study APD356-011 BLOSSOM					
Lorcaserin 10 mg bid	1561	353 (22.6%)	12.9 (10.3, 15.4)	2.7 (2.2, 3.3)	< 0.0001
Lorcaserin 10 mg qd	771	134 (17.4%)	7.6 (4.6, 10.7)	2.0 (1.5, 2.5)	< 0.0001
Placebo	1541	150 (9.7%)			

Considerations that may limit the extension of study conclusions to the intended target population are as follows:

1. A substantial percentage of randomized subjects in each study and study arm, between 40% and 55%, withdrew prior to week 52. At any given time during the study, subjects who had lost less weight were more likely to withdraw than subjects who had lost more weight.
2. Subjects in the African American/ Black and Hispanic/ Latino minority subgroups were more likely to withdraw than subjects in the majority Caucasian / White subgroup. These minority subgroups also had less average weight loss in the placebo and lorcaserin arms compared to the majority subgroup.

Other key findings are as follows:

1. The results from secondary efficacy endpoints, such as LDL-cholesterol, systolic and diastolic blood pressure, fasting plasma glucose, total body fat, and total quality of life score, supported the efficacy of lorcaserin compared to placebo.
2. Patients who withdrew early were likely to be within 5% of their baseline weight at the time of withdrawal. This is consistent with classifying early withdrawals as 5% non-responders. A reasonable measure of efficacy to extend the study conclusions to the intended target population is the placebo-adjusted odds of being classified as a 5% responder. This measure can encompass the intention-to-treat population by classifying early dropouts as 5% non-responders.
3. If a subject had not lost at least 5% of baseline body weight by week 12, they were not likely to be a 5% responder at week 52. This relationship, which has a reasonable level of sensitivity and specificity for lorcaserin 10 mg bid, may serve as an early benchmark for continued use of lorcaserin.

Safety Conclusions: A separate statistical review of specific safety issues was provided by Dr. Xiao Ding, Ph.D.

Recommendations: General recommendations for the clinical studies section in the package insert are included in this review (see part 5.3).

1.2 Brief Overview of Clinical Studies

The long-term efficacy of lorcaserin was evaluated in two Phase 3 studies: APD356-009 (BLOOM; Study 009) and APD356-011 (BLOSSOM; Study 011). Both studies enrolled adults between ages 18 and 65 years who were either obese ($\text{BMI} \geq 30 \text{ kg/m}^2$), or overweight with at least one weight related co-morbid condition ($\text{BMI} 27\text{-}30 \text{ kg/m}^2$). The two studies were designed to evaluate the effect of lorcaserin administered in conjunction with behavior

modification for 52 weeks as a primary endpoint period. Both studies were conducted at sites within the US. The mean baseline weight was approximately 100 kg in each study (TABLE 6)¹. The large majority of subjects were female (81%). The largest racial group was Caucasian/white (67%), followed by African American/ black (19%) and Hispanic/ Latino (12%). The comorbid conditions of dyslipidemia and hypertension occurred in 30% and 23% of subjects, respectively.

In Study 009, 3182 subjects were randomized in a 1:1 ratio to lorcaserin 10 mg bid: placebo. In Study 011, 4008 subjects were randomized in a ratio of 2:1:2 to lorcaserin 10 mg bid: lorcaserin 10 mg qd: placebo. Participants in both studies were treated with a behavior modification program, which was considered to be the standard of care for obese and overweight subjects.

Study 009 was continued for a second year, with a re-randomization of lorcaserin subjects to either continue with lorcaserin or to switch to placebo in a 2:1 ratio. Subjects who had been randomized to placebo in the first year were continued on placebo.

1.3 Statistical Issues and Findings

Disposition: A substantial percentage of randomized subjects in each study and study arm, between 40% and 55%, withdrew prior to week 52 (TABLE 5). This level of discontinuation is typical of weight loss studies. The efficacy of lorcaserin in the intended target population needs to be evaluated in the context of this high level of discontinuation.

Most of the subjects who withdrew early did so before the week 26 mid-point (FIGURE 4, TABLE 5). On average, subjects who withdrew early had lost less weight at the time of withdrawal, compared to the average weight loss at the same study week in subjects who completed the study (FIGURE 6). This trend was apparent in both the placebo and the lorcaserin arms. My interpretation of this finding is that at any given time throughout the study, subjects who were less successful at losing weight were more likely to drop out than subjects who were more successful. Based on this interpretation, the completers are likely to be different from the non-completers with respect to the efficacy endpoint.

Analysis of efficacy: The applicant pre-specified three co-primary efficacy endpoints, and used a gate-keeping strategy to control the overall Type I error, in the order shown below:

- (1) the proportion of subjects achieving $\geq 5\%$ reduction in body weight at the end of year 1 (“5% responders”)
- (2) the change from baseline to the end of year 1 in body weight
- (3) the proportion of subjects achieving $\geq 10\%$ reduction in body weight at the end of year 1 (“10% responders”)

In my opinion, the 5% responder endpoint is a key endpoint in these studies because of the substantial percentage of early withdrawals. It may be reasonable to extend the study results to the intended target population in terms of the percentage of subjects who could be expected to

¹ Table and figure references in the Executive Summary refer to tables and figures in the main body of this report.

lose at least 5% of their baseline body weight after 52 weeks of lorcaserin, with early withdrawals classified as non-responders. The placebo-adjusted effect of lorcaserin can be expressed as the odds of being classified as a 5% responder with lorcaserin compared to placebo, along with the 95% confidence interval.

The applicant used several versions of the analysis population and different analysis models in order to evaluate the sensitivity of estimates for each of the co-primary efficacy endpoints. The analysis models included both analysis of covariance and mixed model repeated measures for the continuous endpoint, and logistic regression for the categorical endpoints. The analysis populations included a modified intention-to-treat population, both with and without last observation carried forward, a per protocol population, a completers population, and a returning dropout population that included off-treatment weights from subjects who dropped out but returned for a final weight. On request, the applicant provided an additional sensitivity analysis with dropouts classified as non-responders for the categorical endpoint.

Efficacy at week 52: The primary results for the three co-primary endpoints are as follows:

(1) 5% responders: After 52 weeks of treatment in Study 009, 48% of subjects treated with lorcaserin 10 mg bid had lost at least 5% of their baseline body weight, compared to 20% of subjects treated with placebo (TABLE 9). The odds of being classified as a 5% responder with lorcaserin compared to placebo were 3.6 (95% CI 3.1 to 4.2).

The results for Study 011 were similar, with 47% in the lorcaserin bid arm, 40% in the lorcaserin 10 mg qd arm, and 25% in the placebo arm classified as 5% responders (TABLE 11). The odds of being classified as a 5% responder with lorcaserin compared to placebo were 2.7 (95% CI 2.3 to 3.1) for the 10 mg bid arm and 2.0 (95% CI 1.7, 2.4) for the 10 mg qd arm.

These results are based on the primary analysis of the MITT population, carrying forward the last on-study weight prior to dropout. In both studies, the majority of dropouts had lost less than 5% of their baseline body weight at the time of dropout (FIGURE 8, FIGURE 12). This means that carrying forward the last observation was reasonably close to classifying study withdrawals as non-responders. In a sensitivity analysis, which classified dropouts as non-responders in the 5% endpoint, the results were very similar to those from the primary analysis with the MITT/LOCF population (TABLE 9, TABLE 11).

Results from sensitivity analyses using the completers population and the per protocol population supported the results from the primary analysis.

(2) Change from baseline in body weight: The placebo-adjusted mean weight loss with lorcaserin 10 mg bid was 3.7% of baseline body weight (95% CI 3.3% to 4.1%) in Study 009 and 3.0% (95% CI 2.6% to 3.4%) in Study 011 (TABLE 8, TABLE 10). The placebo-adjusted mean weight loss with lorcaserin 10 mg qd was 1.9 (95% CI 1.4% to 2.5%) in Study 011. These estimates are from the primary analysis of the MITT population with last observation carried forward. Results from different versions of the analysis population and different analysis methods were reasonably consistent in both studies. The primary analysis and several supportive analyses resulted in placebo-adjusted effects that were statistically significantly less than 5% of baseline body weight. Because a weight loss of 5% is a benchmark described in the weight loss

guidance, the clinical review division should evaluate whether or not the weight loss associated with lorcaserin is clinically significant.

(3) *10% responders*: In both studies, the results for the 10% weight loss responders were consistent with the results for the 5% weight loss responders, with a smaller overall percentage of subjects in this category compared to 5% responders (TABLE 8, TABLE 10).

Subgroups:

Sex: Males and females were fairly similar in the mean placebo-adjusted effect of lorcaserin 10 mg bid in Study 009. However, results from Study 011 suggested that males may not show additional benefit with the 10 mg bid dose compared to the 10 mg qd dose, whereas females did have a greater mean weight loss with the higher dose compared to the lower dose (TABLE 20, FIGURE 22).

Race: The placebo-adjusted effect of lorcaserin 10 mg bid in the two minority subgroups African American/ Black and Hispanic/ Latino was fairly similar to the majority subgroup Caucasian/ White. However, the unadjusted mean weight loss in the placebo and lorcaserin arms was less in the minority subgroups compared to the majority subgroup (TABLE 21, FIGURE 23). This finding corresponds to a lower retention of subjects in the minority subgroups compared to the majority subgroup (TABLE 22). In addition, subjects in the Hispanic/ Latino subgroup in Study 011 did not appear to respond to the lower lorcaserin dose, but did have a response to the higher dose.

Age: The enrollment criteria in both studies excluded subjects who were over 65 years old, and so the comparative effect of lorcaserin in this older age group could not be evaluated in these studies.

Baseline co-morbidities: The placebo-adjusted effect of lorcaserin 10 mg bid on the proportion of 5% responders was fairly similar among subgroups defined either by baseline BMI, baseline dyslipidemia or baseline hypertension in each study (TABLE 23 - TABLE 28).

Other efficacy endpoints: The results from secondary efficacy endpoints supported the efficacy of lorcaserin compared to placebo. In general, the mean difference between lorcaserin and placebo was relatively small but statistically significant. This review provides summaries for LDL-cholesterol, systolic and diastolic blood pressure, fasting plasma glucose, total body fat, and total quality of life score (TABLE 12 - TABLE 17). These were pre-specified as key secondary efficacy endpoints in one or both studies.

Year 2 of Study 009: More 5% responder subjects from year 1 remained as 5% responders when maintained for a second year on lorcaserin (67.9%) than when switched to placebo for the second year (50.3%; TABLE 19). However, these results should be described carefully with respect to the following limitations of inference to the intended target population:

1. Subjects who were randomized in year 2 were more likely to lose weight than the overall target population. Only 50% of the initially randomized population completed year 1 and

participated in year 2. The retention of subjects in the study was related to their ongoing experience of weight loss.

2. The subgroup of 5% responders to lorcaserin from year 1 represents subjects who are more likely to lose weight than the overall target population.
3. The longitudinal profile of weight change in the lorcaserin and placebo arms in years 1 and 2 may invite comparisons between lorcaserin and placebo in year 2 (FIGURE 17). However, these comparisons are difficult to interpret because (a) the lorcaserin arm was re-randomized at the start of year 2 and the placebo arm was not; and (b) although we prefer to depict longitudinal profiles in the completer population, we also recognize that the relationship between weight loss and tendency to remain in the study confounds the comparison between lorcaserin and placebo arms over time.

Predicting 5% non-responder status at week 52 from weight change at week 12: If a subject had not lost at least 5% of baseline body weight by week 12, they were not likely to be a 5% responder at week 52 (FIGURE 18). This relationship is fairly similar for Study 009 and Study 011, and for the lorcaserin 10 mg bid and placebo arms. The high sensitivity and specificity of this relationship in the lorcaserin 10 mg bid arm of each study suggests that it may be reasonable to recommend to physicians that a patient who has not lost at least 5% of baseline body weight after taking lorcaserin for 3 months is not likely to benefit from the drug and should be discontinued in order to avoid further exposure to the risks associated with lorcaserin (FIGURE 18).

2. INTRODUCTION

2.1 Overview

Lorcaserin hydrochloride in tablet form is intended for weight management, including weight loss and maintenance of weight loss in obese subjects ($\text{BMI} \geq 30 \text{ kg/m}^2$), or overweight subjects ($\text{BMI} \geq 27\text{-}30 \text{ kg/m}^2$) who have one or more weight-related co-morbid medical conditions. The dosage is 10 mg twice a day.

Lorcaserin is a selective serotonin 2C receptor agonist. Serotonin and certain serotonin agonists decrease food intake and reduce body weight through activation of centrally located 5-HT_{2C} receptors. The applicant developed lorcaserin with the intention of activating 5-HT_{2C} receptors without initiating the heart valve toxicity seen in the historical weight management products fenfluramine and dexfenfluramine. These products enhanced serotonin release and blocked its reuptake, leading to activation of multiple serotonin receptor subtypes with toxicity that included cardiac valvular regurgitation. The manufacturers of fenfluramine and dexfenfluramine voluntarily withdrew these drugs from the marketplace in 1997 after numerous reports revealed that subjects who had taken the drugs experienced serious adverse cardiovascular effects. The applicant also developed lorcaserin with the intent to minimize its effect on mood and perception².

2.2 Scope of Statistical Review: Pivotal Efficacy and Safety Studies

In this submission, the applicant describes the results from five controlled studies to support the efficacy and safety of lorcaserin. One Phase 1 study involved a single 10 mg dose of lorcaserin given to 20 healthy male volunteers two hours prior to a meal (Study APD356-001C). Each volunteer received each of four study treatments as single oral doses: lorcaserin 0.1 mg, 1 mg, 10 mg and placebo. Dosing days were separated by a washout period of 7 days. Phase 2 Study APD356-003 enrolled 352 obese subjects and randomized them to one of four arms: lorcaserin 1 mg, 5 mg, 15 mg or placebo, for 4 weeks. Phase 2 Study APD356-004 enrolled 469 obese subjects and randomized them to one of four arms: lorcaserin 10 mg once daily, 15 mg once daily, 10 mg twice daily, or placebo, for 12 weeks. The applicant evaluated the long-term efficacy of lorcaserin in two Phase 3 studies: APD356-009 (BLOOM) and APD356-011 (BLOSSOM). The focus of the statistical review of efficacy is on Studies 009 and 011.

2.2.1 Phase 3 Studies 009 and 011

Studies 009 and 011 both included adults between ages 18 and 65 years who were either obese ($\text{BMI} \geq 30 \text{ kg/m}^2$), or overweight with at least one weight related co-morbid condition ($\text{BMI} 27\text{-}30 \text{ kg/m}^2$). The highest allowable BMI was 45 kg/m^2 at screening. Pregnant or lactating women were excluded from enrollment, as were subjects who had undergone prior bariatric surgery.

² The source of this paragraph (paraphrased) is part 2.2 (Introduction) of the submission.

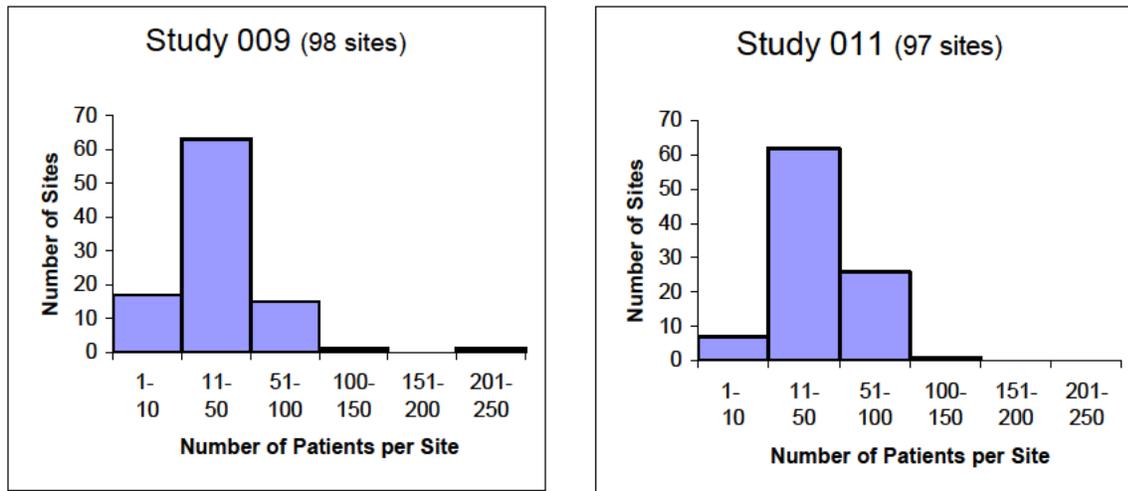
Study 009 was conducted from November 2006 (first subject enrolled) to February 2009 (last subject completed). Study 011 was conducted from January 2008 to July 2009.

The two Phase 3 studies were designed to evaluate the effect of lorcaserin administered in conjunction with behavior modification for 104 weeks (Study 009) and 52 weeks (Study 011). In Study 009, 3182 subjects were randomized in a 1:1 ratio to lorcaserin 10 mg bid: placebo. In Study 011, 4008 subjects were randomized in a ratio of 2:1:2 to lorcaserin 10 mg bid: lorcaserin 10 mg qd: placebo. In both studies, the primary efficacy endpoint was evaluated after 52 weeks. Study 009 was continued for a second year, with a re-randomization of lorcaserin subjects to either continue with lorcaserin or to switch to placebo in a 2:1 ratio. Subjects who had been randomized to placebo in the first year were continued on placebo. The design of this second year is described in more detail in Part 3.1.7.2 of this review.

Participants in both studies were treated with a behavior modification program, which was considered to be the standard of care for obese and overweight subjects. The Arena Healthy Lifestyle Program included bi-weekly counseling sessions with a trained counselor/dietician during the initial month of treatment, followed by monthly sessions for the remainder of the study. The prescribed diet consisted of approximately 600 kilocalories less per day than the subject's calculated Estimated Energy Requirement (calculated using WHO criteria with an activity factor of 1.3. For subjects who engage in ≥ 1 hour/day of aerobic exercise, an activity factor of 1.4 was used. Subjects were also encouraged to engage in 30 minutes of moderate exercise per day.

Study 009 was conducted at 98 sites and Study 011 was conducted at 97 sites. All sites in both studies were in the US. The majority of sites in each study (65%) enrolled between 11 and 50 subjects (FIGURE 1). There was a substantial overlap in sites for the two studies. I made an informal tally and identified 70 sites that were shared between the two studies.

FIGURE 1 Number of subjects per site in Studies 009 and 011



Source: Analysis by this reviewer

Number of subjects in each study:

The applicant planned to enroll 3100 subjects in Study 009 and 3000 subjects in Study 011, making the assumption that 60% would complete year 1 (TABLE 2). The number of subjects who were projected to complete year 1 served as the basis for calculating the size of each study.

TABLE 2 Number of subjects planned for Study 009 and Study 011

Year 1 Treatment	No. of subjects randomized	Projected number of subjects (60%) completing Year 1	Year 2 Treatment (Study 009 only)	Projected number of subjects re-randomized	Projected number of subjects (60%) completing Year 2
Study 009					
Placebo	1550	930	Placebo	930	558
Lorcaserin 10 mg bid	1550	930	Placebo	310	186
			Lorcaserin 10 mg bid	620	372
Study 011					
Placebo	1200	720			
Lorcaserin 10 mg qd	600	360			
Lorcaserin 10 mg bid	1200	720			
Study 009 and 011 combined					
Placebo	2750	1650			

Year 1 Treatment	No. of subjects randomized	Projected number of subjects (60%) completing Year 1	Year 2 Treatment (Study 009 only)	Projected number of subjects re-randomized	Projected number of subjects (60%) completing Year 2
Lorcaserin 10 mg qd	600	360			
Lorcaserin 10 mg bid	2750	1650			
Lorcaserin (both dosages)	3350	2010			

Source: Study 009 protocol, Table 6, and Study 011 protocol, Table 1

The applicant developed the size of each study from several considerations: (1) a specific evaluation of the occurrence of cardiac valvulopathy; (2) a general evaluation of safety; and (3) the evaluation of efficacy from three co-primary endpoints. A key resource was the February 2007 draft *Guidance for Industry: Developing Products for Weight Management*. As part of my review, I also evaluated the size of each study with respect to the criteria for clinical significance, as described in the weight management guidance. I used a statistical interpretation of these criteria, and I note that this interpretation is my own and does not reflect explicit statements in this guidance.

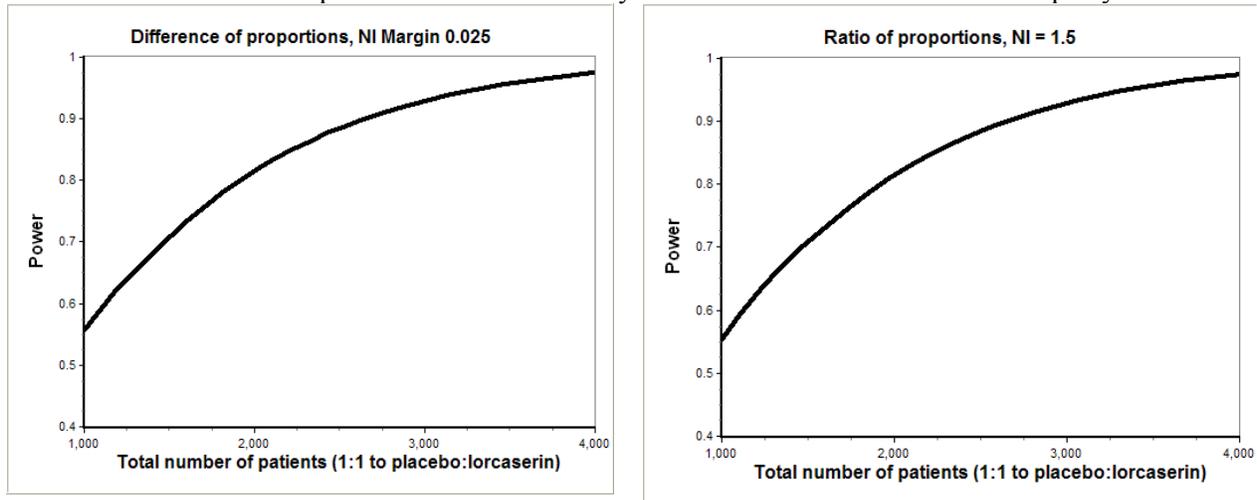
(1) Sufficient exposure to evaluate the occurrence of cardiac valvulopathy

The applicant noted that the echocardiographic safety endpoint was the primary determinant of sample size in Study 009. The primary analysis of echocardiographic safety data would consider the proportion of subjects who develop “FDA-defined valvulopathy.” Based on the results of the 12-week study APD356-004, the applicant estimated that the proportion of subjects who would develop FDA-defined valvulopathy in the placebo group would be approximately 5% per year. The applicant used a non-inferiority margin of 2.5%, corresponding to an incidence of 7.5% in the lorcaserin group. Using this non-inferiority margin on the difference in incidence between the lorcaserin group and the placebo group, along with a one-sided alpha of 0.05, the applicant calculated the total sample size required to provide 80% power to be 1879 subjects. Adjusting for the 40% dropout rate produces a total of 3100 subjects to be randomized, or 1550 subjects per treatment group (FIGURE 2).

I confirmed the calculations for study power. The noninferiority margin of 2.5% on the difference scale corresponds to a margin of 1.5 on the risk ratio scale ($7.5\%/5\% = 1.5$). The non-inferiority margin of 1.5 was recommended by the Division at the preNDA meeting on 8/12/09. The Division also agreed that a one-sided alpha of 0.05 was acceptable for this evaluation. At the estimated incidence rates of 5% and 7.5% for the placebo arm and the non-inferiority margin, respectively, the results for statistical power for the risk ratio are very similar to the results for the risk difference (FIGURE 2).

The applicant noted that Study 011 was not powered to detect meaningful differences in the incidence of FDA valvulopathy. Instead, they planned to combine the echocardiographic safety data with those from other trials for an integrated safety analysis.

FIGURE 2 Statistical power for a non-inferiority evaluation of FDA-defined valvulopathy



Notes:

Assumptions used in calculations: The incidence in the placebo group is 0.05/year; one-tailed α of 0.05; 1:1 allocation between lorcaserin and placebo, and a non-inferiority (NI) margin of 0.025 for the risk difference or, equivalently, 1.5 for the risk ratio (i.e. the incidence in the lorcaserin group at the NI margin is 0.075/year). The results are very similar for the difference of proportions and the ratio of proportions at this level of incidence. 80% power is achieved for approximately 1860 subjects total (i.e., 930 per arm); 90% power is achieved for a total of approximately 2700 subjects total.

Methods: Difference of proportions (exact), and ratio of proportions (exact), using East 5.2.

Source: Analysis by this reviewer

(2) Sufficient exposure to the product to support a general assessment of safety: The weight management guidance suggests that “A reasonable estimation of the safety of a weight-management product upon which to base approval generally can be made when a total of approximately 3,000 subjects are randomized to active doses of the product and no fewer than 1,500 subjects are randomized to placebo for 1 year of treatment.”

The total number of subjects who were projected to complete one year in Studies 009 and 011 met the criterion for exposure to placebo but was less than recommended for exposure to lorcaserin for one year (TABLE 2). However, these estimates were very conservative. An evaluation of the safety of lorcaserin, including an assessment of the exposure of subjects to lorcaserin, is included in the clinical review by Dr. Julie Golden, M.D.

(3) Adequate statistical power to assess the efficacy of lorcaserin after one year of treatment: Following the weight management guidance, a subject’s body weight after one year of treatment in relation to baseline body weight is expressed in two different ways, as co-primary endpoints:

Continuous endpoint: *the average weight loss at one year, expressed as a percentage change from baseline*

Categorical endpoint: *the percentage of subjects who lost at least 5% of their baseline body weight at one year*

The efficacy of lorcaserin in comparison to placebo was evaluated from these two co-primary endpoints. The applicant also used a third co-primary endpoint, the percentage of subjects who lost at least 10% of their baseline body weight at one year. However, for purposes of evaluating the clinical significance of lorcaserin from a statistical perspective, I will focus on the two co-primary endpoints that are described in the weight management guidance.

The applicant used the categorical endpoint for a calculation of statistical power. They assumed that 15% to 20% of subjects in the placebo arm would meet this endpoint at one year, based on results from previous studies. Studies 009 and 011 had adequate statistical power to detect a placebo-adjusted effect of 5% or greater in this endpoint. These studies are “overpowered” with respect to a statistical comparison between lorcaserin and placebo. Based on the number of subjects needed to support an evaluation of safety, the studies are large enough to detect an effect that is smaller than a clinically significant effect. This is the basis for the comment in the guidance that “*the number of subjects necessary to demonstrate the efficacy of a weight-management product will be smaller than the number needed to adequately assess safety.*”

However, in my opinion, a larger study supports a useful statistical interpretation of the criteria for clinical significance that are described in the weight management guidance. Under the topic “Efficacy benchmarks,” the guidance recommends:

In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

- *The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant*
- *The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.*

In my opinion, in order for the criteria to be interpretable, they need to be applied to the target population, rather than to the observed results of a study. For example, suppose the observed difference between lorcaserin and placebo in a clinical study were 5.1%. Based on the observed difference, we would conclude in favor of lorcaserin. But suppose instead that the observed difference between means were 4.9%. Would we conclude against lorcaserin, or would this difference be close enough to 5% to decide in favor of lorcaserin? What would our conclusion be if the observed difference were 4.5%, or 4.0%, or 3.0%? Without understanding the variability of the difference observed from the study, it is difficult to decide. Without projecting the observed result onto the target population as a confidence interval, I believe that these observed differences between means are arbitrary and not interpretable.

For this reason, I believe that it is much clearer to conclude in favor of lorcaserin if the 95% confidence interval of the difference between means excludes values less than 5%. This interprets the criterion for clinical significance from the perspective of the target population. A larger study will have greater statistical power than a smaller study, with respect to meeting this criterion when the population effect is close to 5%. For example, a smaller study, with 150 subjects per arm, could meet this criterion with adequate statistical power if the effect in the target population were 6.1% or greater (TABLE 3, *criterion a*). A larger study, with 1500 subjects per arm, could meet this criterion if the effect in the target population were 5.3% or greater.

With respect to the categorical endpoint, applying a statistical interpretation to the criteria for clinical significance is more complicated. The description actually covers three different ways to express and evaluate the endpoint: as a single percentage (with a benchmark of 35%), as a comparison of the ratio of active product to placebo (with a benchmark of 2), and as a comparison of the difference between active product and placebo (with a benchmark of 0). I believe that the intention behind these criteria is to make sure that a reasonable percentage of subjects are 5% responders with the active product, compared to placebo. However, they seem unnecessarily complicated when comparing the percentage of 5% responders between active drug and placebo in the target population.

I believe it is more useful to express the desired benchmarks in the target population in terms of the odds ratio. For example, when the percentage of active product responders is 35% and is twice that of the placebo group, the odds ratio is 2.5 (FIGURE 3). When the percentage of active product responders is 50% and is twice that of the placebo group, the odds ratio is 3.0. This may define a reasonable working range for weight management products, from which to develop benchmarks. The odds ratio and confidence interval can be calculated from a logistic regression model that includes the main features of the study design, such as the treatment group assignment, stratification factors, and baseline covariates.

I believe that the criteria for clinical significance would benefit from further consideration and development in the weight management guidance. In my opinion, applying the benchmarks to the target population rather than to the observed results of a study provides a clear interpretation of the meaning of the benchmark.

FIGURE 3 Criterion for clinical significance in the categorical endpoint; the relationship between the ratio and the odds ratio of active group to placebo group responders

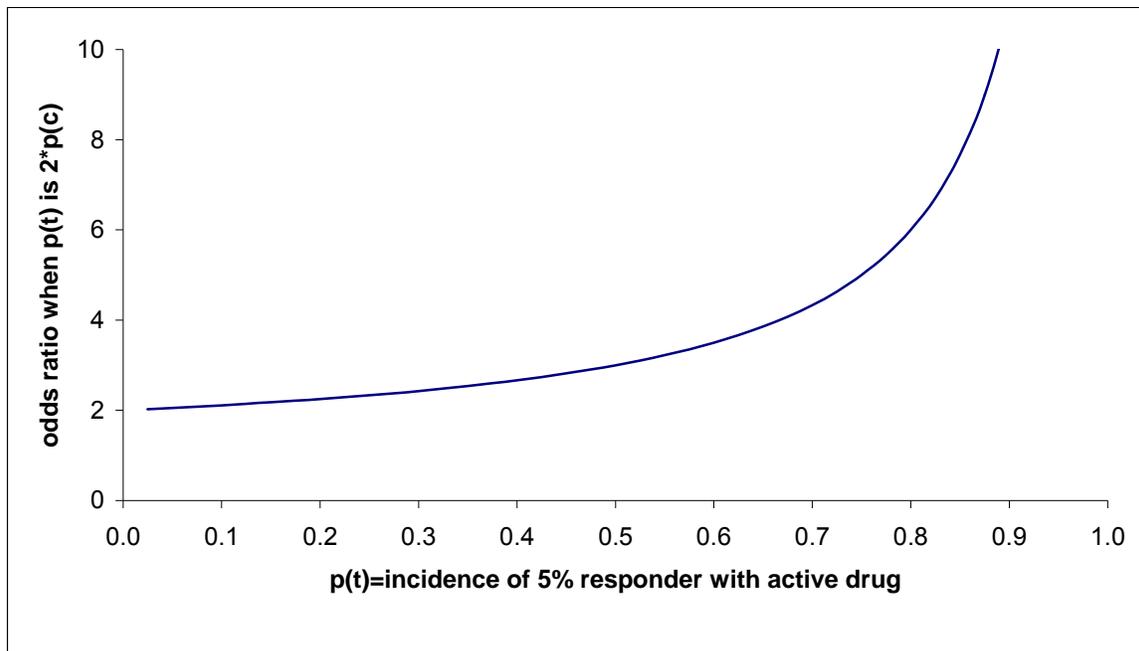


TABLE 3 Statistical interpretation of criteria for clinical significance of the continuous weight loss endpoint from the February 2007 draft *Guidance for Industry: Developing Products for Weight Management*.

Criterion from weight loss guidance	Statistical interpretation of the criterion	Inference about Lorcaserin in the target population based on meeting this criterion ¹ :	
		With n=150 subjects per arm	With n=1500 subjects per arm
<i>The difference in mean weight loss between the active-product and placebo-treated groups is:</i>			
<i>(a) at least 5 percent</i>	The 95% confidence interval (CI) of Lorcaserin – Placebo should exclude values < 5%	Lorcaserin – Placebo ≥ 6.1%	Lorcaserin – Placebo ≥ 5.3%
<i>(b) and the difference is statistically significant</i>	The 95% CI of Lorcaserin – Placebo should exclude values ≤ 0%	Lorcaserin – Placebo ≥ 1.1%	Lorcaserin – Placebo ≥ 0.3%

Notes:

¹ 90% power and two-tailed α of 0.05 or one-tailed α of 0.025 were used throughout these calculations. Bullet points 1(a) and (b): I used an estimate of standard deviation of 2.8, in units of percentage change from baseline. I obtained this estimate from Phase 2 Study 004, which reported 2.8 kg as the standard deviation of the average change from baseline after 85 days of treatment with 10 mg BID lorcaserin (n=77; see Table 7 in the report for Study 004). Although 2.8 was based on kg rather than percentage change, I reasoned that the average baseline weight was close to 100 kg, so that it might be reasonable to use 2.8 as an estimated standard deviation on the scale of percentage change from baseline. Minimum effect sizes were calculated from the two-group t-test (nQuery Advisor 7.0).

2.2.2 Other studies

BLOOM-DM is the third Phase 3 study in the lorcaserin program, and is evaluating the safety and efficacy of lorcaserin in patients with type 2 diabetes. However, because of difficulties with enrollment, the division agreed that the NDA could be submitted prior to the completion of this study.

2.3 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown in (TABLE 4). Individual study reports were submitted for each study.

TABLE 4 Data sources for studies

Document: NDA 022529.0 CDER EDR link: \\CDSESUB1\N022529 Company: Arena Pharmaceuticals, Inc. Drug: Lorcaserin Submission date: December 22, 2009

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1. Subject disposition

A substantial percentage of randomized subjects in each study and study arm, between 40% and 55%, withdrew prior to week 52 (TABLE 5A). A large percentage of early withdrawal is typical of weight loss studies. Investigators in this field have proposed and evaluated different ways to evaluate weight loss programs and/or drugs, given that a large percentage of subjects are likely to discontinue before the primary endpoint period³. The weight management guidance recommends estimating the effect of a drug by several different methods. This sensitivity analysis should reflect the time dynamics and reasons for early discontinuation.

The percentage of subjects who withdrew prior to week 52 was somewhat greater in the placebo group in each study than in the lorcaserin arm(s) (TABLE 5A). In all study arms, the reason for early withdrawal given by the greatest percentage of subjects was “withdrawal of consent,” followed by “lost to follow-up.” A summary of attempts to reach subjects who were lost to follow-up was included in the disposition database. I reviewed a selection of these summaries to gain an appreciation of the several failed attempts to reach these subjects by phone and registered

³ For example, see Gadbury, GL, CS Coffee and DB Allison, 2003: Modern statistical methods for handling missing repeated measurements in obesity trial data: beyond LOCF. Obesity Reviews 4: 175-184.

letter. Early withdrawal due to an adverse event accounted for less than 10% of randomized subjects in each study arm.

Subjects who withdrew early were more likely to do so before the week 26 mid-point of the study (TABLE 5B). This pattern is also illustrated in (FIGURE 4). The shortest average time on study was in subjects who were lost to follow-up. Subjects with higher BMI at baseline were somewhat more likely to withdraw early from the study than subjects with a lower baseline BMI (FIGURE 5). This effect was small but consistent between the studies and across study arms. However, the correlation between baseline BMI and number of weeks on the study was low (-0.02 in the lorcaserin arm and -0.07 in the placebo arm of Study 009), suggesting that baseline BMI may not contribute substantially to a subject's decision to withdraw.

On average, subjects who withdrew early had lost less weight at the time of withdrawal, compared to the average weight loss at the same study week in subjects who completed the study. To assess this pattern, I created five subgroups of subjects, according to their last week on the study, as follows:

- week 0-6 subgroup: dropped out on or before week 6
- week 6-12 subgroup: dropped out after week 6, up to and including week 12
- week 12-24 subgroup: dropped out after week 12, up to and including week 24
- week 24-52 subgroup: dropped out after week 24 but before week 52
- completers: completed the study

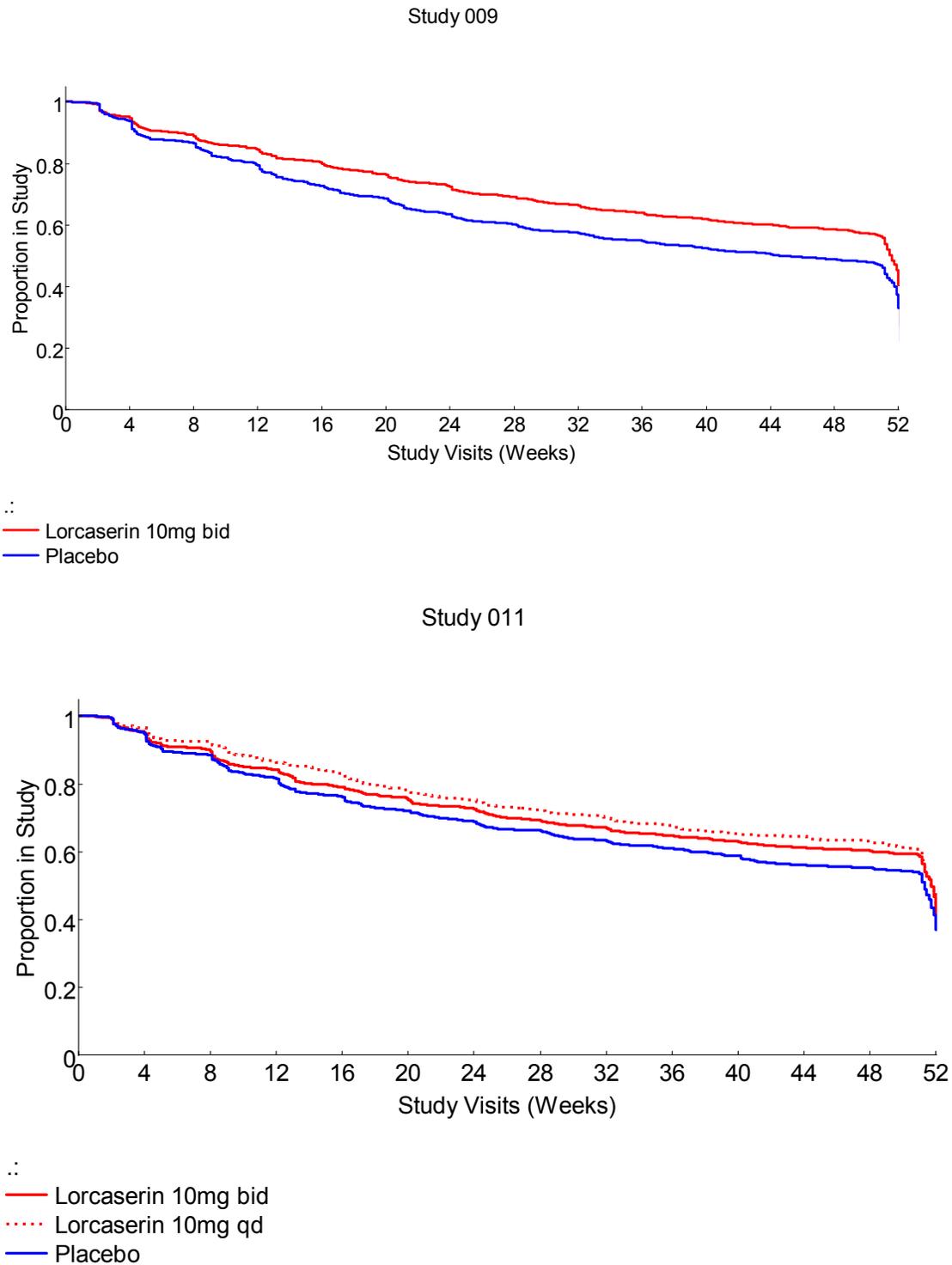
The time course of average weight loss in each dropout subgroup and in the completers is depicted in FIGURE 6. The average weight loss at weeks 4, 12, 24 and 52 is also tabulated for each cohort and study arm. The average weight loss in dropout cohort 6 is less than the average weight loss in the completers at week 4, for both the lorcaserin and placebo arms (FIGURE 6; week 4 is the final visit for this dropout subgroup). This finding is consistent across the final visits for dropout cohorts 12, 24 and 52 compared to the completers at the same visit. My interpretation of this finding is that subjects who are less successful at losing weight at any given time throughout the study are more likely to drop out than subjects who are more successful. Based on this interpretation, the completers may be different from the non-completers with respect to the efficacy endpoint.

Subjects who withdrew early from the study had the opportunity to return for a weight measurement at week 52. These weights were not used in the primary efficacy analysis, but they were used in one of the sensitivity analyses. The largest percentage of subjects returning for a week 52 weight had withdrawn because of an adverse event, and, perhaps not surprisingly, the smallest percentage came from subjects who were lost to follow-up (TABLE 5C).

TABLE 5 Disposition of subjects in Study 009 and Study 011 at week 52

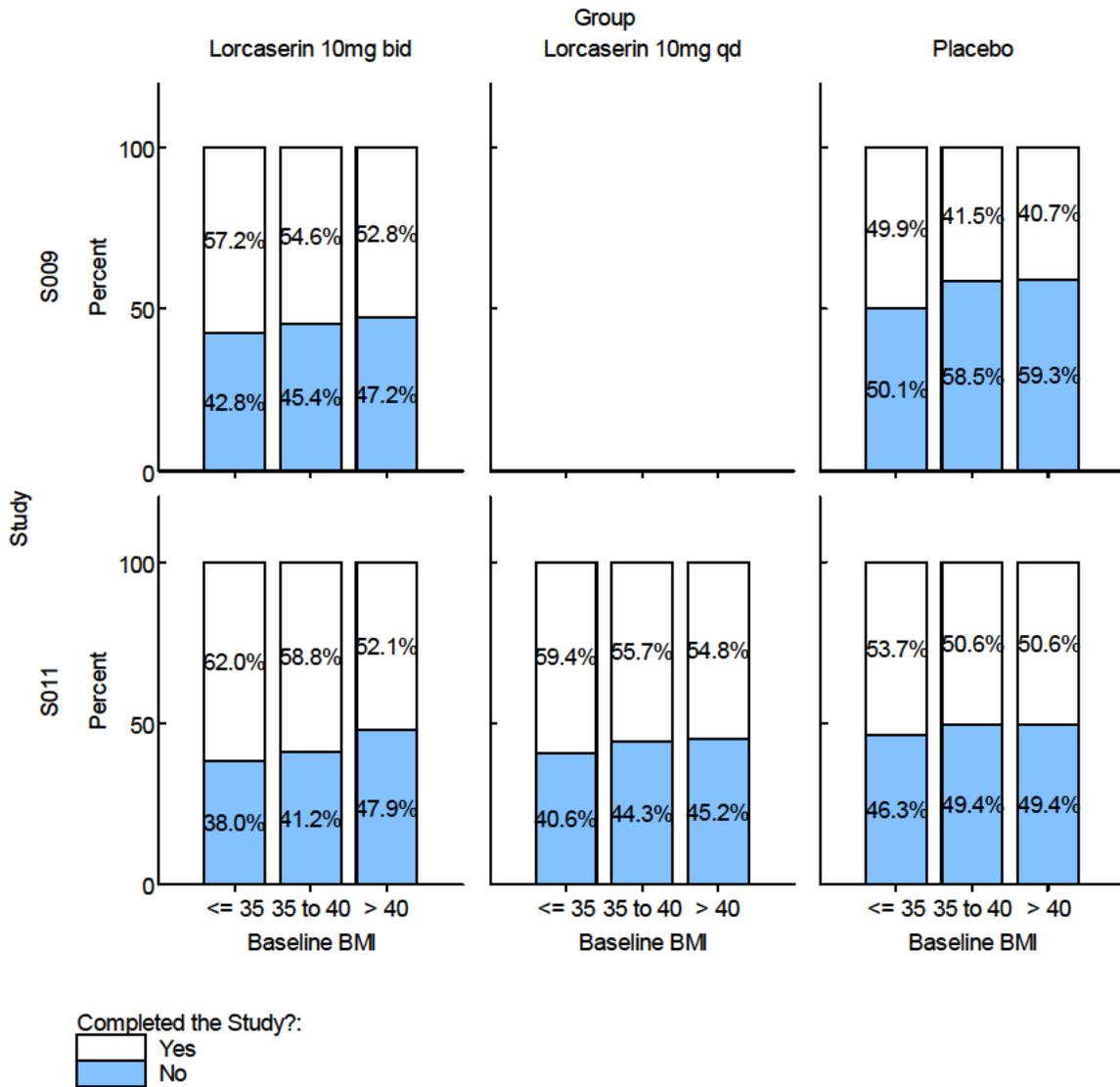
	Study 009		Study 011		
	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Lorcaserin 10 mg QD	Placebo
A. Disposition¹					
Number randomized	1595	1587	1603	802	1603
No. (%) who completed	883 (55.4)	715 (45.1)	917 (57.2)	473 (59.0)	834 (52.0)
No. (%) who withdrew prior to week 52	712 (44.6)	872 (54.9)	686 (42.8)	329 (41.0)	769 (48.0)
Reason for withdrawal:					
Withdrawal of consent	307 (19.2)	439 (27.7)	293 (18.3)	162 (20.2)	376 (23.5)
Lost to follow-up	191 (12.0)	226 (14.2)	198 (12.4)	83 (10.3)	234 (14.6)
Adverse event	113 (7.1)	106 (6.7)	115 (7.2)	50 (6.2)	74 (4.6)
Combined other reasons ²	101 (6.3)	100 (6.3)	80 (5.0)	34 (4.2)	85 (5.3)
B. Average time on study (weeks) prior to withdrawal					
Reason for withdrawal:					
Withdrawal of consent	20.0	18.8	17.7	16.9	17.3
Lost to follow-up	12.7	11.2	14.0	17.1	12.7
Adverse event	17.4	17.1	19.7	18.0	15.9
Combined other reasons ²	21.2	15.8	23.8	27.7	27.3
C. Returning dropouts: Subjects who withdrew but returned for a final weight					
No. (%) of returning dropouts	154 (9.7)	191 (12.0)	114 (7.1)	54 (6.7)	119 (7.4)
Reason for withdrawal n (%):					
Withdrawal of consent	76 (4.8)	128 (8.1)	46 (2.9)	26 (3.2)	66 (4.1)
Lost to follow-up	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Adverse event	51 (3.2)	37 (2.3)	42 (2.6)	20 (2.5)	30 (1.9)
Combined other reasons ²	26 (1.6)	26 (1.6)	26 (1.6)	8 (1.0)	22 (1.4)
<i>Notes</i>					
¹ For percentages, the number of subjects randomized was used as the denominator.					
² For "Combined other reasons," the following discontinuation categories were combined: Protocol deviation / noncompliance, Sponsor decision, PI decision and Other discontinuation reason					
<i>Source:</i> Integrated Summary of Efficacy, Table 4, and additional analysis by this reviewer.					

FIGURE 4 Disposition of subjects in Study 009 and Study 011 by week 52



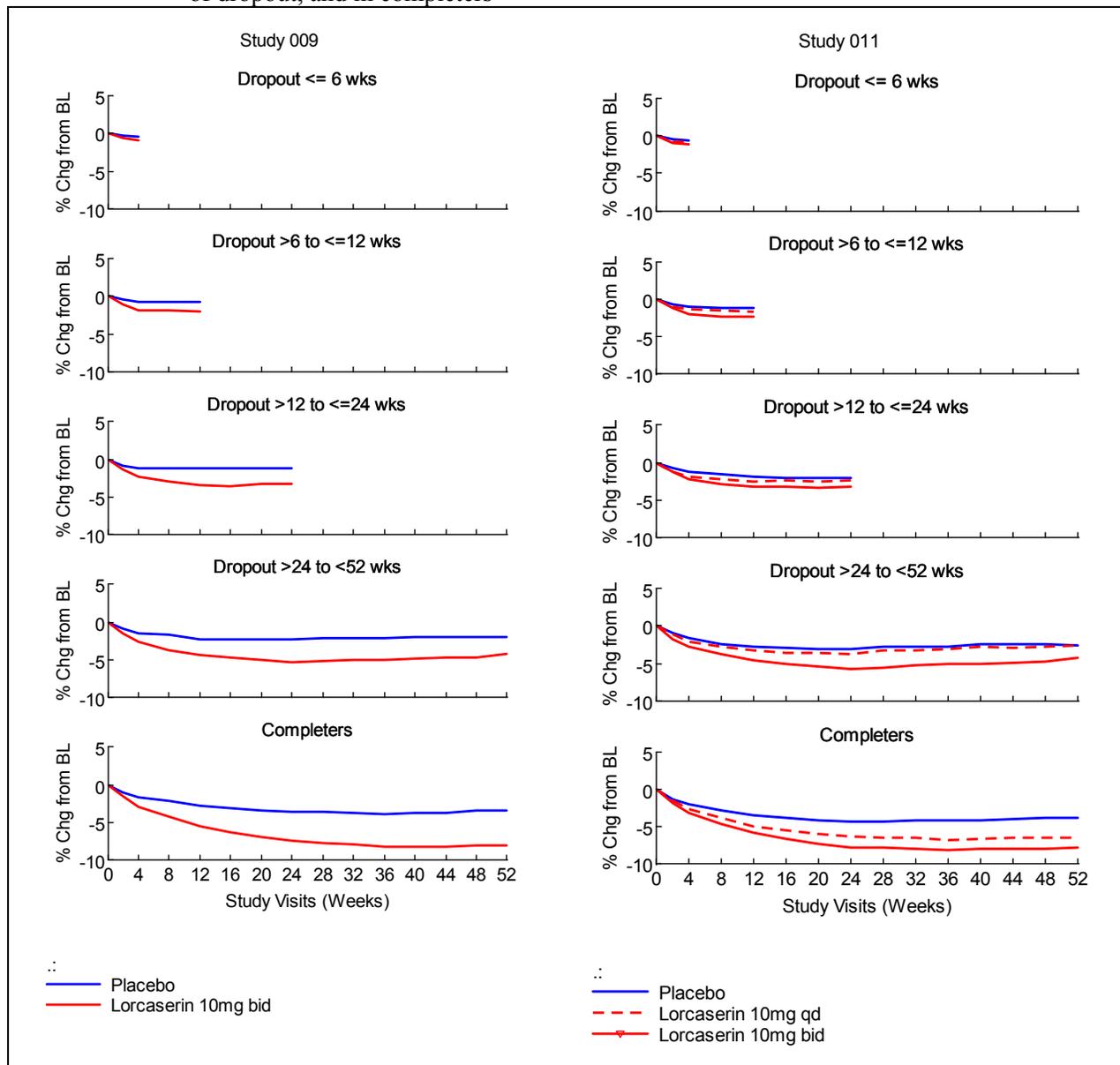
Source: Analysis by this reviewer

FIGURE 5 Percentage of early withdrawals (before week 52) in Study 009 and 011, and the relationship to baseline BMI



Source: Analysis by this reviewer

FIGURE 6 Body weight, mean percent change from baseline (MITT) in subgroups defined by week of dropout, and in completers



		Average % change from baseline in body weight in final visit for each dropout subgroup, and comparable visit for completers subgroup								
		Study 009				Study 011				
		Visit (week)	4	12	24	52	4	12	24	52
Subgroups by final visit before dropping out	Placebo		-0.4	-0.7	-1.2	-2.0	-0.6	-1.2	-2.0	-2.5
	Lorcaserin 10mg qd						-0.8	-1.7	-2.3	-2.5
	Lorcaserin 10mg bid		-0.8	-2.0	-3.2	-4.2	-1.1	-2.4	-3.2	-4.2
Completers	Placebo		-1.6	-2.7	-3.6	-3.3	-2.0	-3.5	-4.3	-3.9
	Lorcaserin 10mg qd						-2.7	-4.9	-6.4	-6.5
	Lorcaserin 10mg bid		-2.9	-5.4	-7.4	-8.0	-3.1	-5.8	-7.8	-7.9

Notes: Within each subgroup, the weight at the subject's final visit before dropping out was carried forward to the final visit for that subgroup.

Source: Analysis by this reviewer.

3.1.2. Subject demographic and baseline characteristics

Studies 009 and 011 were fairly similar in the distribution of subject demographic and baseline characteristics (TABLE 6). The enrollment criteria of both studies excluded subjects over 65 years of age. The large majority of subjects (approximately 80%) were female. Approximately two-thirds of the subjects were Caucasian. The average baseline weight was approximately 100 kg, and the distribution of subjects across obesity categories defined by levels of body mass index was fairly similar between the two studies and among the arms within each study (TABLE 6).

TABLE 6 Subject demographic and baseline characteristics in the randomized subjects in Study 009 and Study 011

Number of randomized subjects (n)	Study 009		Lorcaserin 10mg qd n=802	Study 011	
	Lorcaserin 10mg bid n=1595	Placebo n=1587		Lorcaserin 10mg bid n=1603	Placebo n=1603
Age (years)					
Mean ± SD	43.7 ± 11.3	44.4 ± 11.1	43.7 ± 11.7	43.8 ± 11.8	43.7 ± 11.8
Median	44.0	45.0	44.0	44.0	44.0
Range	18 to 66	18 to 66	18 to 65	18 to 65	18 to 65
Sex					
Female (n, %)	1323 (82.9%)	1334 (84.1%)	657 (81.9%)	1290 (80.4%)	1251 (78.0%)
Male (n, %)	272 (17.1%)	253 (15.9%)	145 (18.1%)	313 (19.5%)	352 (22.0%)
Race ¹					
Caucasian/White	1081 (67.8%)	1048 (66.0%)	539 (67.2%)	1081 (67.4%)	1066 (66.5%)
African American/ Black	300 (18.8%)	299 (18.8%)	160 (20.0%)	306 (19.1%)	319 (19.9%)
Hispanic/Latino	181 (11.3%)	213 (13.5%)	86 (10.7%)	174 (10.9%)	181 (11.3%)
Asian	12 (0.8%)	9 (0.6%)	3 (0.4%)	12 (0.7%)	10 (0.6%)
Native Hawaiian / Pacific Islander	1 (0.0%)	1 (0.0%)	4 (0.5%)	10 (0.6%)	6 (0.4%)
American Indian / Alaska Native	11 (0.7%)	4 (0.3%)	7 (0.9%)	7 (0.4%)	10 (0.6%)
Other	9 (0.6%)	11 (0.7%)	3 (0.4%)	13 (0.8%)	11 (0.7%)
Baseline comorbid conditions					
Dyslipidemia	534 (33.5%)	525 (33.1%)	218 (27.2%)	455 (28.4%)	439 (27.4%)
Hypertension	335 (21.0%)	342 (21.6%)	175 (21.8%)	388 (24.2%)	383 (23.9%)
Sleep apnea	72 (4.5%)	55 (3.5%)	27 (3.4%)	72 (4.5%)	73 (4.6%)
Glucose intolerance	18 (1.1%)	14 (0.9%)	15 (1.9%)	29 (1.8%)	18 (1.1%)
Weight (kg)					
Mean ± SD	100.4 ± 15.7	99.7 ± 15.6	100.1 ± 16.7	100.5 ± 15.6	100.8 ± 16.2
Median	99.0	98.3	97.5	99.1	99.0
Range	62.6 to 156.9	62.7 to 156.0	64.9 to 185.4	64.1 to 159.3	63.9 to 165.9
BMI (kg/m ²)					
Mean ± SD	36.2 ± 4.3	36.1 ± 4.3	35.9 ± 4.3	36.1 ± 4.3	36.0 ± 4.2
Median	35.8	35.7	35.2	35.6	35.5
Range	26.8 to 46.2	26.7 to 46.5	26.4 to 46.8	26.7 to 52.5	27.1 to 46.6
BMI categories					
< 30	75 (4.7%)	65 (4.1%)	30 (3.7%)	75 (4.7%)	66 (4.1%)

Number of randomized subjects (n)	Study 009		Lorcaserin 10mg qd n=802	Study 011	
	Lorcaserin 10mg bid n=1595	Placebo n=1587		Lorcaserin 10mg bid n=1603	Placebo n=1603
≥ 30 to ≤ 35	615 (38.6%)	653 (41.1%)	362 (45.1%)	649 (40.5%)	664 (41.4%)
> 35 to ≤ 40	570 (35.7%)	537 (33.8%)	243 (30.3%)	549 (34.2%)	557 (34.7%)
> 40	335 (21.0%)	332 (20.9%)	167 (20.8%)	330 (20.6%)	316 (19.7%)

Source: Analysis by this reviewer, from 0000\...\ISS-ISE\Analysis\DM.xtp for randomized subjects

3.1.3. Analysis populations

The applicant used the same definitions in the analysis of each study separately. Differences in terminology pertain to the distinction between year 1 and year 2 for Study 009. These definitions are as follows:

Modified Intent-to-Treat (MITT) Population: The MITT population consisted of all randomized subjects who had a baseline measurement, who received at least one dose of study medication, and who had a post-randomization measurement. Subject data was analyzed according to the treatment assigned at randomization, regardless of the treatment received during the course of the trial. Data collected after subjects discontinued from treatment was not included in the primary analysis. The last observation on or prior to discontinuation (LOCF) was carried forward and used in the analysis. At least 95% of randomized subjects were in the MITT populations (TABLE 7).

In Study 009, the MITT1 population for Year 1 was as defined above. The MITT2 population for Year 2 consisted of all randomized subjects who completed Year 1, were re-randomized at week 52, took at least one dose of study medication after re-randomization, and had at least one weight measurement post re-randomization. The last post re-randomization observation on or prior to discontinuation was carried forward and used in the analysis.

Week 52 (W52) Population: The W52 population included all randomized subjects who had a post-baseline body weight recorded within 2 weeks of the scheduled 52-week visit. This included subjects who withdrew from the study prior to week 52, and returned for a body weight measurement within 2 weeks of their scheduled week 52 visit. Approximately 60% of randomized subjects were in the W52 population (TABLE 7).

Per-Protocol Population: The PP population excluded subjects and/or data points with clinically important protocol deviations based on a set of pre-specified criteria. The PP population did not include estimates for missing data. Study 009 had a PP1 population for Year 1 and a PP2 population for Year 2. The per-protocol criteria were similar in both studies, and in both years of Study 009, and included the following:

- The subject had a baseline body weight measurement recorded.
- The subject had a body weight recorded within 2 weeks (days 357-371) of the scheduled 52-week visit.
- If the subject was a tobacco user at baseline, he/she did not stop tobacco use at week 52.
- The subject's compliance in taking study medication over 52 weeks of the study was 80-120%.
- The subject provided body weights for at least 10 of the 14 scheduled visits during year 1.

Safety Analysis Population: The safety population included all subjects who were randomized and received at least one dose of study drug. Missing or invalid data was not imputed.

The combined analysis of Study 009 and Study 011 used the same definition of the MITT population at year 1 as in the separate analyses. In addition, the applicant defined an MITT2 population. The MITT2 population included all subjects in the MITT population. However, if subjects who had withdrawn early returned for a week 52 weight measurement, this value was used instead of the LOCF value. Subjects who did not return for a week 52 weight did have the LOCF value used to estimate their final weight. The term "MITT2" was used differently in the combined analysis than it was in the analysis of year 2 data from Study 009.

In the combined analysis of the two studies, the applicant defined the Returning Dropout Population (RDP) instead of using the Week 52 Population. The two definitions are very similar, but the criteria for including week 52 weights from "returning dropouts" was specified to be within 2 weeks (days 357-371) of the scheduled 52-week visit. This excluded a small number of subjects in Study 009 who were in the W52 population but not the RDP (TABLE 7). The applicant also defined a Completers Population (CP) to include all subjects who had completed the study at year 1. The analyses of the CP population and RDP population did not estimate missing data.

As an additional sensitivity analysis, I used the following approach to estimating week 52 weight for study dropouts: (1) if a subject dropped out but returned for a final weight, I used this weight for week 52; (2) if a subject dropped out and did not return for a final weight, I estimated the week 52 weight by adding 0.3 kg per month to the last measured weight, based on the number of months between the drop-out date and week 52. This method incorporates the rate of regain that is expected after discontinuation of a weight loss effort, as described in Fabricatore et al. (2009)⁴.

On request, the applicant did an additional sensitivity analysis of the 5% and 10% responder endpoints, using a non-responder imputation for study dropouts. This analysis was applied to the intention-to-treat population (ITT), that is, all randomized patients.

⁴ Fabricatore, A.N., T.A. Wadden, R.H. Moore, M.L. Butryn, S.B. Heymsfield and A.M. Nguyen, 2009. Predictors of attrition and weight loss success: Results from a randomized controlled trial. *Behaviour Research and Therapy* 47: 685-691.

TABLE 7 Analysis populations defined for Study 009 and Study 011, primary endpoint (Year 1 for Study 009)

	Study 009		Study 011		
	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Lorcaserin 10 mg QD	Placebo
Number randomized	1595	1587	1603	802	1603
Safety population, n (%)	1593(99.9)	1584 (99.8)	1602 (99.9)	801 (99.9)	1601 (99.9)
Separate analysis of each study¹					
MITT population, n (%)	1538 (96.5)	1499 (94.5)	1561 (97.4)	771 (96.1)	1541 (96.1)
Week 52 population, n (%)	1031 (64.6)	901 (56.8)	1028 (64.1)	524 (65.3)	951 (59.3)
Per Protocol population, n (%)	737 (46.2)	583 (36.7)	846 (52.8)	418 (52.1)	764 (47.7)
Combined analysis of Study 009 and Study 011					
Returning Dropout population, n (%)	1015 (63.6)	888 (56.0)	1028 (64.1)	524 (65.3)	951 (59.3)
Completers population, n (%)	883 (55.4)	716 (45.1)	917 (57.2)	473 (59.0)	834 (52.0)
MITT2 population, n (%) ²	1538 (96.5)	1499 (94.5)	1561 (97.4)	771 (96.1)	1541 (96.1)
<i>Notes</i>					
¹ Study 009, the Year 1 terms for the MITT and PP analysis populations are MITT1 and PP1					
² For the combined analysis, MITT2 refers to an analysis population, as described in Part 3.1.3 of this review. Note that for the separate analysis of Study 009, MITT2 refers to the MITT population in Year 2.					
<i>Sources:</i> Study 009 report, Figure 2; Study 011 report, Table 5; and analysis by this reviewer					

3.1.4. Co-primary efficacy endpoints

For both Study 009 and Study 011, the sponsor defined three co-primary efficacy endpoints in the following order: (1) the proportion of subjects achieving $\geq 5\%$ reduction in body weight at the end of year 1 (“5% responders”); (2) the change from baseline to the end of year 1 in body weight; and (3) the proportion of subjects achieving $\geq 10\%$ reduction in body weight at the end of year 1 (“10% responders”). This order is important in the approach to controlling Type I error (described at the end of this section).

This set of co-primary endpoints is somewhat different from those recommended in the 2007 weight management guidance. The continuous endpoint is the absolute change in body weight from baseline rather than the percentage change as described in the guidance. The 5% responder endpoint is the same as is described in the guidance. The applicant also included a 10% responder endpoint. In my opinion, the differences are not substantial enough to cause discrepancies in study conclusions based on the applicant’s endpoints compared to the guidance’s endpoints. This is due to several considerations: (1) the third endpoint, the 10% responder endpoint, is evaluated at the end of the closed testing procedure (see below) and therefore does not influence gate-keeping decisions from the first two endpoints; (2) the 10% responder endpoint is obtained from a subset of subjects who are 5% responders, and so statistical conclusions about both categorical endpoints are likely to be similar; (3) in these study

populations where the average baseline weight is approximately 100 kg, the continuous endpoint may be fairly similar when expressed either as an absolute change or as a percentage change. However, for extension of inference to the target population, it is important to know whether the drug effect is best expressed as a percentage change or an absolute change. The results of these studies should inform subjects in the target population about the weight loss they can expect after one year of treatment. The weight management guidance expresses the continuous endpoint as a percentage change in part because the health effects of a 5% or greater weight loss from baseline have been described in the literature: “In overweight and obese individuals, particularly individuals with comorbidities such as hypertension, dyslipidemia, and type 2 diabetes, long-term weight loss greater than or equal to 5 percent following diet, exercise, and in some cases, drug treatment, is associated with improvement in various metabolic and cardiovascular risk factors (Douketis and Macie et al. 2005)”⁵. For this reason, I evaluated the continuous endpoint as a percentage change from baseline in this review.

Approach to multiplicity: Control of Type I error in the co-primary endpoints: Based on the 2007 guidance, the efficacy of lorcaserin would be supported if either one or both of the co-primary endpoints described in the guidance were statistically significant. The guidance does not comment on the control of Type I error in the co-primary endpoints. However, the ICH-E9 guidance advises that in the event that a protocol identifies more than one primary endpoint, “the effect on the Type I error should be explained because of the potential for multiplicity problems ...; the method of controlling Type I error should be given in the protocol.”⁶

The protocols for studies 009 and 011 describe a gate-keeping strategy to control the Type I error for three co-primary endpoints. This strategy also gives priority to the continuous endpoint and to the 5% responder endpoint, which are either similar (in the case of the continuous endpoint) or the same as (in the case of the 5% responder endpoint) the two endpoints described in the weight management guidance. The gate-keeping strategy is a closed testing procedure, with the following steps:

- Step 1: Test the proportion of 5% responders at a two-tailed α of 0.05. If the result is significant, conclude that the results support the efficacy of lorcaserin compared to placebo. Continue to step 2.
- Step 2: Test the change from baseline to the end of year 1 in body weight at a two-tailed α of 0.05. If the result is significant, continue to step 3.
- Step 3: Test the proportion of 10% responders at a two-tailed α of 0.05.

⁵ Douketis, JD, C Macie, L Thabane, and DF Williamson, 2005, Systematic Review of Long-Term Weight Loss Studies in Obese Adults: Clinical Significance and Applicability to Clinical Practice, *International Journal of Obesity*, 29:1153-1167; the quotation is from Part IIIA of the weight management guidance (2007 draft).

⁶ Part II.B.5., *Guidance for Industry, E9 Statistical Principles for Clinical Trials*, September 1998

3.1.5. Statistical analysis methods for primary efficacy endpoint

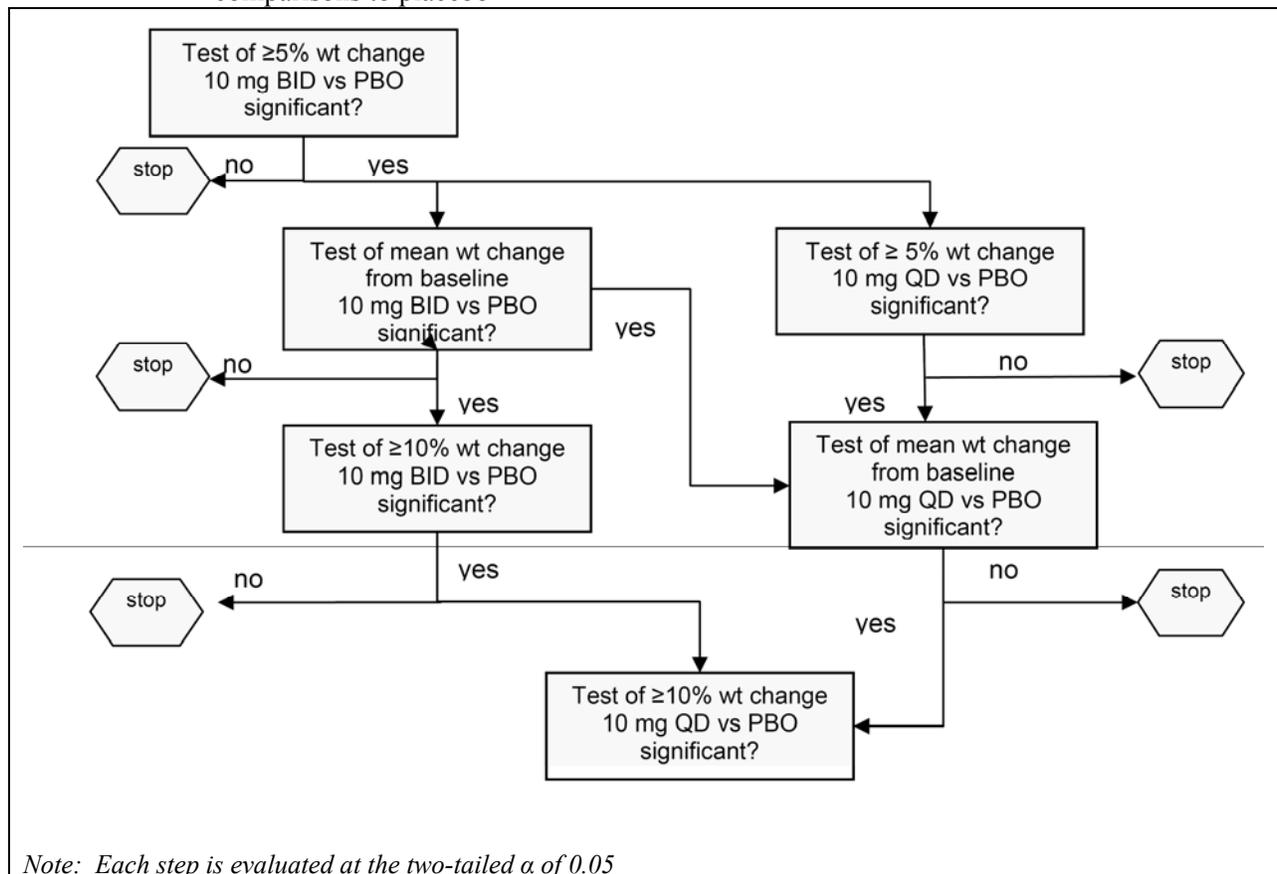
Continuous endpoint: Change in weight was analyzed with analysis of covariance (ANCOVA) models with treatment and gender as the factors, and baseline body weight as covariate. The primary analysis for year 1 used the MITT1 population with LOCF estimation for subjects who dropped out before the end of year 1. The applicant also analyzed the percent change from baseline with the same analysis model.

Categorical endpoints: The yes/no occurrence of a 5% responder was analyzed with a logistic regression model with effects for treatment, gender and baseline body weight (kg). The same approach was used to analyze the 10% responder endpoint.

Approach to multiplicity: Control of Type I error between dose levels of lorcaserin (Study 011):

The applicant described a closed testing procedure that included the three co-primary efficacy endpoints and the comparisons of two lorcaserin dose arms against placebo. This process is depicted in FIGURE 7.

FIGURE 7 Study 011; closed testing procedure for 3 co-primary endpoints and 2 dose level comparisons to placebo



Source: Study 011 Statistical Methods, Figure 2

3.1.6. Results of the statistical analysis of efficacy: Weight endpoints

Study 009

Continuous endpoint: After 1 year of treatment with lorcaserin 10 mg bid, subjects lost a statistically significant amount of weight. Expressed as a % change from baseline, the placebo-adjusted average weight loss was 3.7%, with a 95% confidence interval of 3.3% to 4.1% (TABLE 8, result 1). I confirmed this result. Expressed as weight loss in kg, the placebo-adjusted average weight loss was 3.6 kg, with a 95% confidence interval of 3.2 to 4.0. These two expressions are similar (with a correlation of 0.98) because the average baseline was close to 100 kg in each arm. Because of this similarity, I will use the “% change from baseline” expression in further review comments about the continuous endpoint. This result was consistent across different versions of the analysis population and different methods of analysis (TABLE 8).

This result supports the criterion for statistical significance as described in the weight management guidance, but it does not provide statistical support to the criterion that the difference in mean weight loss between the active product and the placebo should be at least five percent. This is because the placebo-adjusted result was statistically significantly less than 5%.

The majority of subjects who dropped out prior to the end of the study remained within $\pm 5\%$ of their baseline body weight (FIGURE 8; top two portions of each bar). These are the subjects whose final weight was estimated by LOCF in the primary analysis. Some of these subjects returned for a final week 52 weight (“returning dropouts”; FIGURE 8, middle portion of each bar). Using the week 52 weight of the returning dropouts instead of LOCF did not appreciably affect the distribution of weight change (FIGURE 9) or the results of the statistical analysis (TABLE 8, result 9). Estimating the final weight of non-returning dropouts by a weight gain algorithm also did not greatly affect the percentage of subjects who had gained more than 5% of their baseline weight (FIGURE 10), and did not greatly affect the results of the statistical analysis (TABLE 8, result 8). A longitudinal profile of weight change from baseline in the completers population is given in FIGURE 11.

Categorical endpoints: After one year of treatment with lorcaserin 10 mg bid, a statistically significantly greater percentage of subjects lost at least 5% of their baseline body weight, compared to placebo (TABLE 9). Expressed as a difference in percentages, the percentage of 5% weight loss responders was 27.2% greater (absolute) in the lorcaserin arm than in the placebo arm (TABLE 9). The results from the analysis of the MITT population are supported by the results of the analyses of the per protocol population (PP) and the completers population (CP).

Subjects who dropped out were more likely to stay within $\pm 5\%$ of their baseline body weight compared to subjects who completed the study (FIGURE 8; the blue portion of the bottom of each bar represents the completers). For this reason, a sensitivity analysis that classified dropouts as non-responders produced results that were similar to the primary analysis (TABLE 9).

This result supports the criterion for statistical significance in the 5% responder endpoint, as described in the weight management guidance. The odds ratio of lorcaserin to placebo was at least 3 in all analyses, based on the lower 95% confidence bound (TABLE 9). An odds ratio of 3 corresponds to a ratio of 2 when the proportion of weight loss responders is 0.50 in the active drug.

The results for the 10% weight loss responders were consistent with the results for the 5% weight loss responders, with a smaller overall percentage of subjects in this category compared to 5% weight loss responders (TABLE 9).

TABLE 8 Study 009; Weight as a % change from baseline at year 1; results from primary and supportive analyses

Study 009 Treatment groups	N	Baseline mean (kg) ± SE	Adjusted mean % change from baseline at Week 52 ± SE ¹	Difference in adjusted mean % change, Lorcaserin - placebo (95% CI)	P-value vs. placebo
Analyses with MITT1 population					
Lorcaserin 10 mg bid	1538	100.4 ± 0.4			
Placebo	1499	99.7 ± 0.4			
1. Primary analysis: LOCF estimation for dropouts; primary ANCOVA model; sponsor’s analysis					
Lorcaserin 10 mg bid			-5.9 ± 0.2	-3.7 (-4.1, -3.3)	<0.0001
Placebo			-2.2 ± 0.1		
2. MITT1 population with no estimation for missing data; MMRM model; sponsor’s analysis					
Lorcaserin 10 mg bid			-6.8 ± 0.1	-4.2 (-4.6, -3.8)	<0.001
Placebo			-2.6 ± 0.1		
3. MITT1 population with LOCF estimation for dropouts; ANCOVA model including factor for site; this reviewer’s analysis					
			-5.9 ± 0.2	-3.6 (-4.1, -3.2)	<0.0001
			-2.3 ± 0.2		
Analysis with PP1 population					
4. no LOCF estimation (dropouts were not included in this population); primary ANCOVA model; sponsor’s analysis					
Lorcaserin 10 mg bid	737	100.7 ± 0.6	-8.2 ± 0.3	-4.9 (-5.7, -4.2)	<0.001
Placebo	583	99.0 ± 0.7	-3.3 ± 0.3		
Analysis with Completers population					
5. no LOCF estimation (dropouts were not included in this population); primary ANCOVA model; sponsor’s analysis					
Lorcaserin 10 mg bid	861	100.6 ± 0.5	-8.0 ± 0.3	-4.8 (-5.4, -4.1)	<0.001
Placebo	697	99.3 ± 0.6	-3.2 ± 0.3		
Other Analyses					
6. Returning dropouts and completers (non-returning dropouts were not included in this population); primary ANCOVA model; this reviewer’s analysis ^A					
Lorcaserin 10 mg bid	1015	100.2 ± 0.5	-6.9 ± 0.3	-4.0 (-4.7, -3.4)	<0.0001

Placebo	888	99.1 ± 0.5	-2.9 ± 0.3		
7. MITT1 population with (a) weight regain estimation for non-returning dropouts; (b) week 52 weights for returning dropouts; primary ANCOVA model; this reviewer's analysis ^A					
Lorcaserin 10 mg bid	1569	100.4 ± 0.4	-4.9 ± 0.2	-3.6 (-4.1, -3.1)	<0.0001
Placebo	1517	99.7 ± 0.4	-1.3 ± 0.2		
8. MITT1 population with (a) LOCF imputation for non-returning dropouts and (b) week 52 weight for returning dropouts; this reviewer's analysis ^A					
Lorcaserin 10 mg bid	1569	100.4 ± 0.4	-5.6 ± 0.2	-3.4 (-3.8, -2.9)	<0.0001
Placebo	1517	99.7 ± 0.4	-2.2 ± 0.2		
<i>Notes:</i>					
^A The group totals in this analysis represent a small percentage of cases with duplicate records in the analysis database; this analysis database represented a combination of variables from several databases provided by the applicant. I was not able to fully resolve this issue, but I do not believe that the inaccuracies that resulted from the analysis of this database affected the interpretation of results.					
<i>Sources:</i>					
1. Study report, Table 11, which references Tables 14.2.1.1 and 14.2.3, and Table E4.0 submitted 4/2/2010 (0008)					
2. Table E4.10 submitted 4/2/2010 (0008)					
3. Analysis by this reviewer					
4. Table E4.11 submitted 4/2/10 (0008)					
5. Table E4.1 submitted 4/2/10 (0008)					
6, 7, 8. Analysis by this reviewer					

TABLE 9 Study 009; 5% and 10% weight loss responders; results from primary and supportive analyses

Treatment groups	N	Number of responders (%)	Difference in proportions ¹ (95% CI)	Odds ratio ² (95% CI)	p-value ² vs. placebo
% of subjects achieving \geq 5% weight loss at week 52					
1. Primary analysis: MITT1; LOCF					
Lorcaserin 10 mg bid	1538	731 (47.5%)	27.2 (24.0, 30.5)	3.6 (3.1, 4.2)	<0.001
Placebo	1499	304 (20.3%)			
2. Supportive analysis: PP; LOCF					
Lorcaserin 10 mg bid	737	489 (66.4%)	34.2 (29.2, 39.4)	4.2 (3.3, 5.3)	< 0.001
Placebo	583	187 (32.1%)			
3. Supportive analysis: Completers					
Lorcaserin 10 mg bid	861	567 (65.9%)	33.9 (29.2, 38.6)	4.0 (3.3, 5.0)	< 0.001
Placebo	697	223 (32.0%)			
4. Supportive analysis: ITT (all randomized patients) with Non-responder imputation					
Lorcaserin 10 mg bid	1595	567 (35.6%)	21.4 (18.5, 24.3)	3.4 (2.8, 4.0)	<0.001
Placebo	1587	225 (14.2%)			
% of subjects achieving \geq 10% weight loss at week 52					
5. Primary analysis: MITT1; LOCF					
Lorcaserin 10 mg bid	1538	347 (22.6%)	14.9 (12.4, 17.4)	3.5 (2.8, 4.4)	< 0.001
Placebo	1499	115 (7.7%)			
6. Supportive analysis: PP; LOCF					
Lorcaserin 10 mg bid	737	267 (36.2%)	22.7 (18.2, 27.1)	3.7 (2.8, 4.9)	< 0.001
Placebo	583	79 (13.6%)			
7. Supportive analysis: Completers					
Lorcaserin 10 mg bid	861	303 (35.2%)	21.6 (17.5, 25.6)	3.5 (2.7, 4.5)	< 0.001
Placebo	697	95 (13.6%)			
8. Supportive analysis: ITT (all randomized patients) with Non-responder imputation					
Lorcaserin 10 mg bid	1595	303 (19.0%)	13.1 (10.8, 15.3)	3.8 (2.9, 4.8)	< 0.001
Placebo	1587	94 (5.9%)			
<i>Notes:</i>					
¹ The difference in proportions and 95% CI were calculated using normal approximation.					
² The odds ratios and p-values were calculated by using the logistic regression model specified for the primary analysis, with effects for treatment, gender and baseline body weight.					
<i>Sources:</i>					

Treatment groups	N	Number of responders (%)	Difference in proportions ¹ (95% CI)	Odds ratio ² (95% CI)	p-value ² vs. placebo
<ol style="list-style-type: none"> 1. Study 009 Clinical Report, Table 10 (references Tables 14.2.1 and 14.2.1.2) 2. Study 009 Clinical Report, Table 14.2.73 3. Study 009 Table E72.10 (submitted 4/2/10 under 0008) 4. Study 009 Response to 8/18/10 request, Table 5 (received 8/26/10 under 0028). These results are different from those reported in Table 24 of the applicant's briefing document for the Advisory Committee meeting 9/16/10. 5. Study 009 Clinical Report, Table 12 (references Table 14.2.5.1); and Response to 8/18/10 request, Table 1 (received 8/26/10 under 0028) 6. Study 009 Clinical Report, Table 14.2.5.1; and Response to 8/18/10 request, Table 2 (received 8/26/10 under 0028) 7. Study 009 Table E73.10 (received 4/2/10 under 0008) and Response to 8/18/10 request, Table 3 (received 8/26/10 under 0028) 8. Study 009 Response to 8/18/10 request, Table 6 (received 8/26/10 under 0028). These results are different from those reported in Table 25 of the applicant's briefing document for the Advisory Committee meeting 9/16/10. 					

FIGURE 8 Study 009; Distribution of weight change at week 52; MITT population with primary imputation method (LOCF)

Study 009 Week 52 Weight as % Change from Baseline; MITT Population

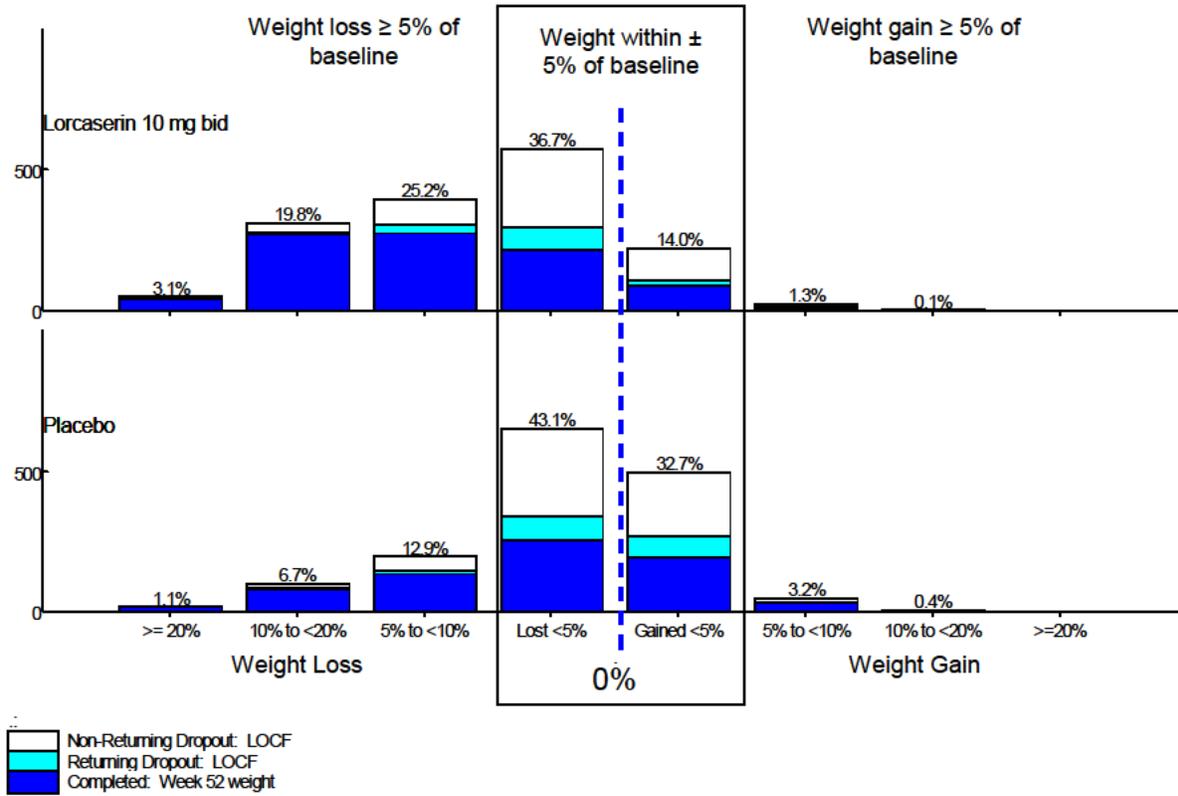


FIGURE 9 Study 009; Distribution of weight change at week 52; MITT population with week 52 weights for returning dropouts

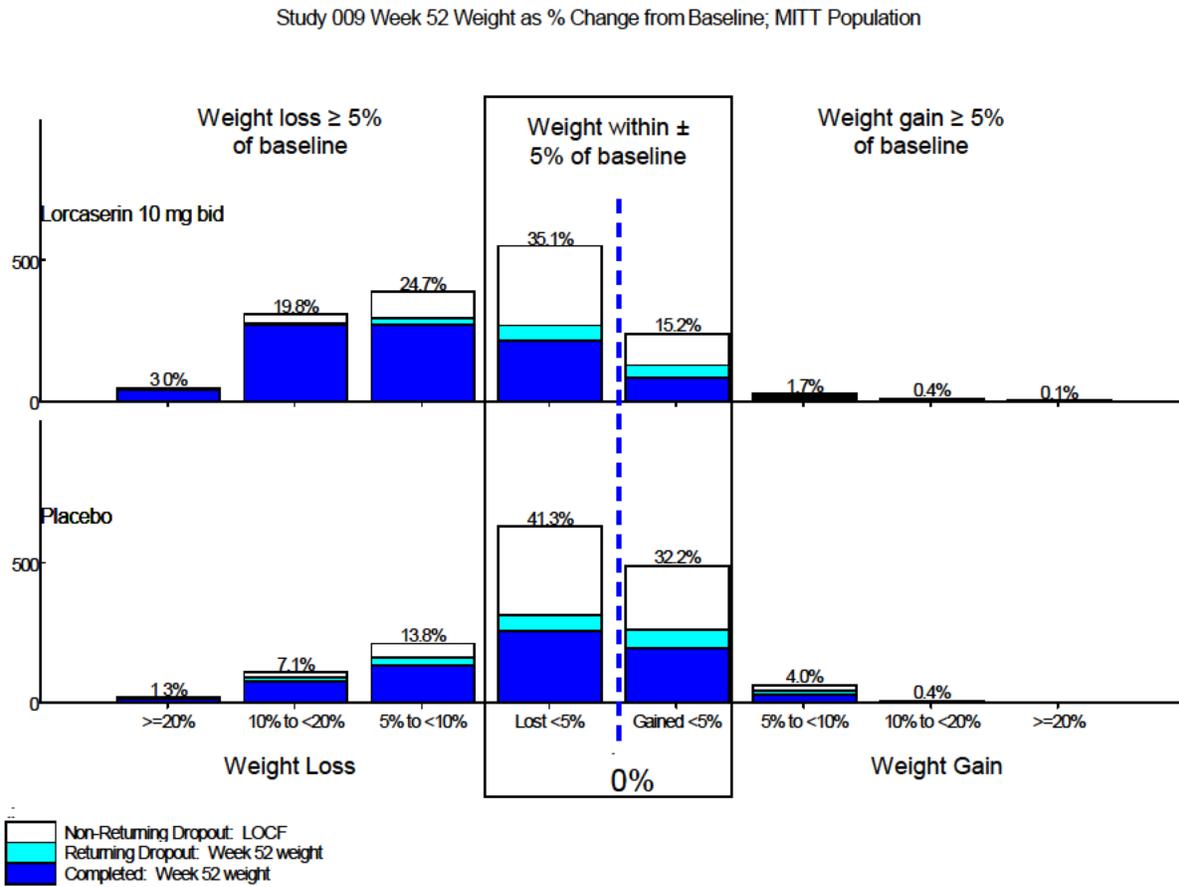


FIGURE 10 Study 009; Distribution of weight change at week 52; MITT population with week 52 weights for returning dropouts and weight regain estimation for non-returning dropouts

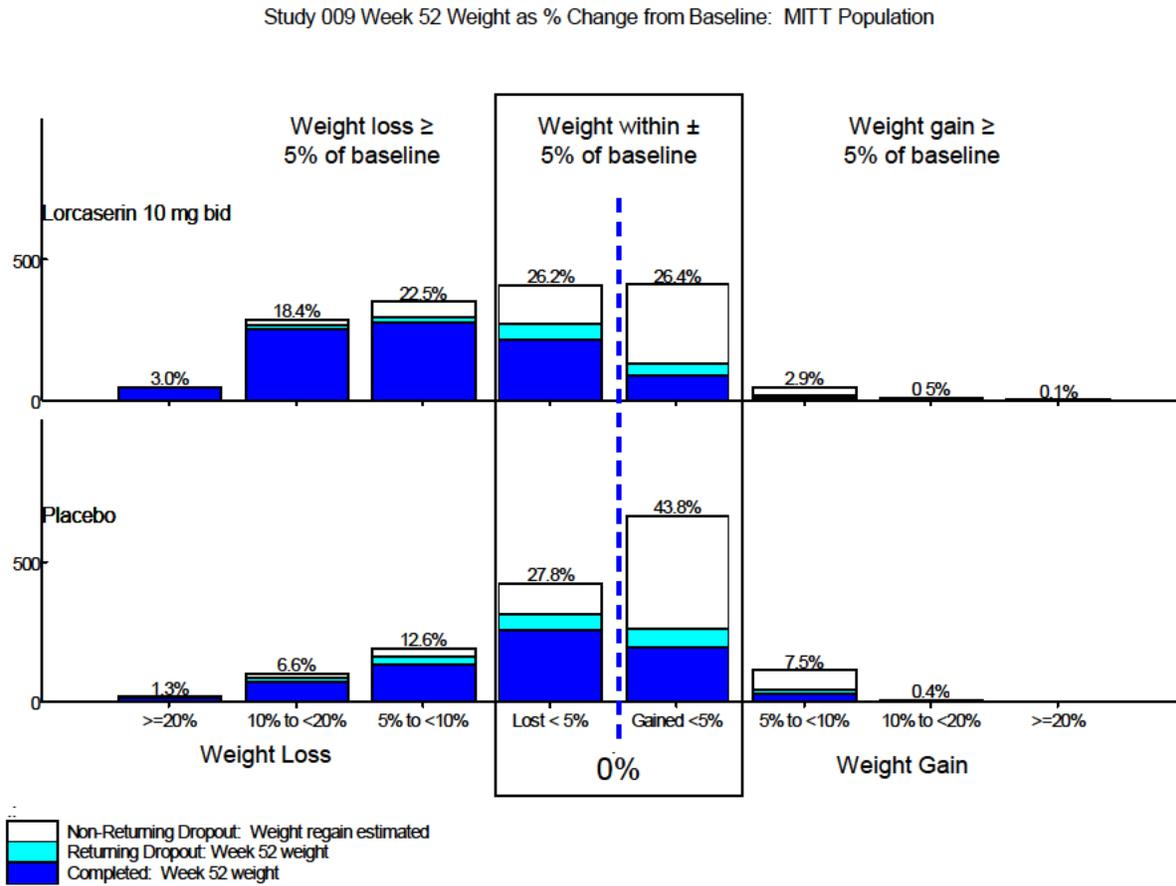
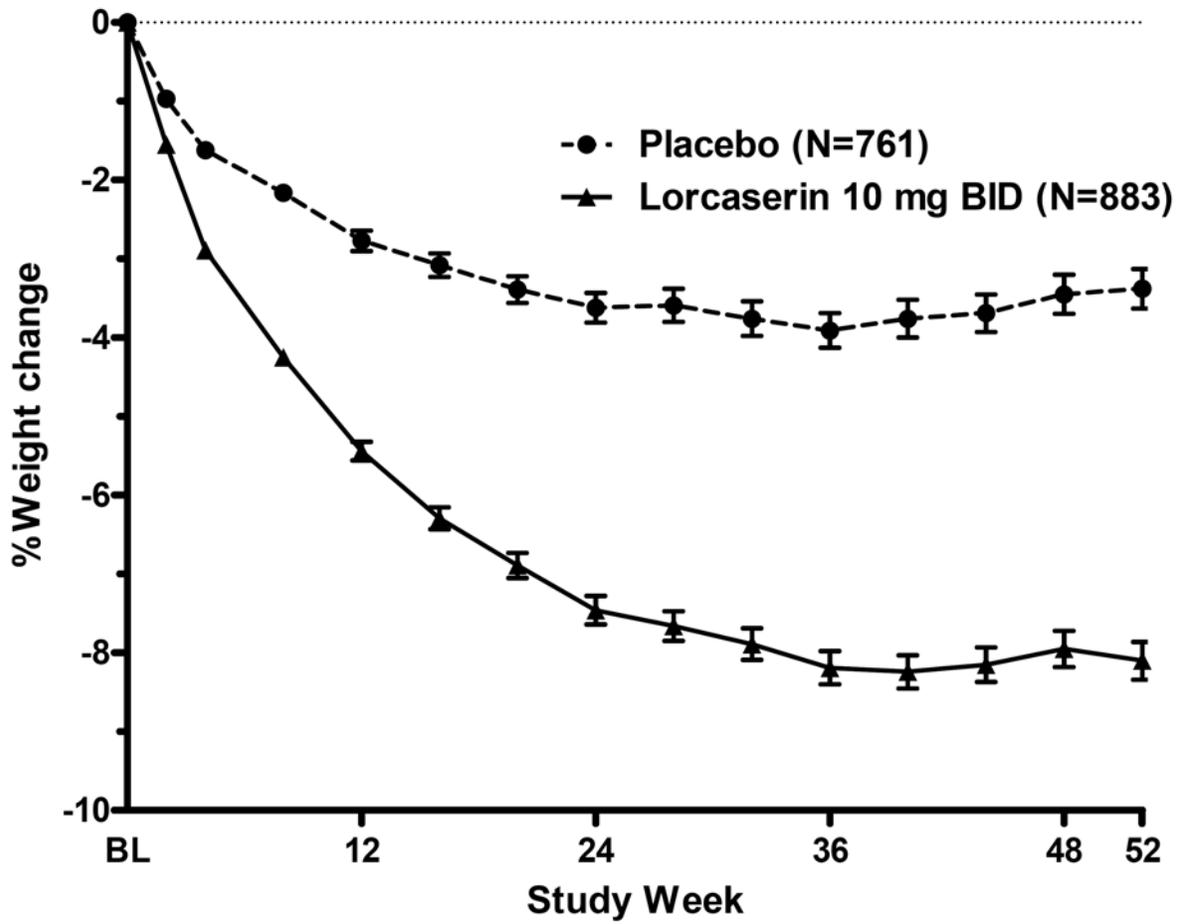


FIGURE 11 Study 009; Mean percent change of body weight from baseline during year 1; Completers



Source: Response to 8/18/10 request, Figure 1B (received 8/26/10 under 0028)

Study 011

Continuous endpoint: After 1 year of treatment with either lorcaserin 10 mg bid or 10 mg qd, subjects lost a statistically significant amount of weight (TABLE 10). I confirmed this result. Results from different versions of the analysis population and different methods of analysis were consistent. The average amount of weight lost in the lorcaserin 10 mg bid arm was greater than the average weight loss in the lorcaserin 10 mg qd (TABLE 10). This result supports a dose-response relationship between these two dosages.

This finding meets the criterion for statistical significance described in the weight management guidance. However, as in Study 009, the average weight loss was statistically significantly less than 5%. Expressed as a % change from baseline, the placebo-adjusted average weight loss with lorcaserin 10 mg bid was 3.0%, with a 95% confidence interval of 2.6% to 3.4% (TABLE 10, result 1).

Many subjects who remained within $\pm 5\%$ of their baseline body weight dropped out prior to the end of the study (FIGURE 12; top two portions of each bar). A small percentage of these dropouts returned for a week 52 weight. Using the week 52 weight of the returning dropouts instead of LOCF did not appreciably affect the distribution of weight change (FIGURE 13) or the results of the statistical analysis (TABLE 10, result 9). Estimating the final weight of non-returning dropouts by a weight gain algorithm did not greatly affect the percentage of subjects who had gained more than 5% of their baseline weight (FIGURE 14), and did not greatly affect the results of the statistical analysis (TABLE 10, result 8). A longitudinal profile of weight change over time is shown in FIGURE 15.

Categorical endpoints: After one year of treatment with lorcaserin 10 mg bid, a statistically significantly greater percentage of subjects lost at least 5% of their baseline body weight, compared to placebo (TABLE 11). This result is supported by results from analyses of the per protocol population and the completers population. The lower 95% confidence bound of the odds ratio of lorcaserin to placebo was 2.5 or greater in most of the analyses (TABLE 11). This is within the range of 2.5 to 3.0 that I have suggested for the odds ratio. Another sensitivity analysis, which classified dropouts as non-responders, produced results that are similar to the primary analysis with the MITT/LOCF population (TABLE 11).

The percentage of 5% weight loss responders in the lorcaserin 10 mg qd arm was lower than in the 10 mg bid arm (TABLE 11). This finding supports the dose-response relationship between the two dosages.

The results for the 10% weight loss responders were consistent with the results for the 5% weight loss responders, with a smaller overall percentage of subjects in this category compared to 5% weight loss responders (TABLE 11).

TABLE 10 Study 011; Weight as a % change from baseline at year 1; results from primary and supportive analyses

Study 011 Treatment groups	N	Baseline mean (kg) ± SE	Adjusted mean % change from baseline at Week 52 ± SE ¹	Difference in adjusted mean % change, Lorcaserin - placebo (95% CI)	P-value vs. placebo
Analyses with MITT1 population					
Lorcaserin 10 mg bid	1561	100.3 ± 0.4			
Lorcaserin 10 mg qd	771	100.1 ± 0.6			
Placebo	1541	100.8 ± 0.4			
1. Primary analysis: LOCF estimation for dropouts; primary ANCOVA model					
Lorcaserin 10 mg bid			-5.8 ± 0.2	-3.0 (-3.4, -2.6)	<0.0001
Lorcaserin 10 mg qd			-4.7 ± 0.2	-1.9 (-2.5, -1.4)	<0.0001
Placebo			-2.8 ± 0.2		
2. MITT1 population with no estimation for missing data; MMRM model					
Lorcaserin 10 mg bid			-6.7 ± 0.1	-3.4 (-3.8, -3.1)	<0.001
Lorcaserin 10 mg qd			-5.3 ± 0.2	-2.1 (-2.5, -1.6)	<0.001
Placebo			-3.2 ± 0.1		
Analysis with PP1 population					
3. primary ANCOVA model					
Lorcaserin 10 mg bid	846	100.2 ± 0.5	-7.8 ± 0.2	-3.9 (-4.6, -3.2)	<0.0001
Lorcaserin 10 mg qd	418	99.3 ± 0.8	-6.5 ± 0.3	-2.5 (-3.4, -1.7)	<0.0001
Placebo	764	101.3 ± 0.6	-4.0 ± 0.3		
Analysis with Completers population					
4. no LOCF estimation (dropouts were not included in this population); primary ANCOVA model; sponsor's analysis					
Lorcaserin 10 mg bid	1050	100.4 ± 0.5	-7.1 ± 0.2	-3.7 (-4.3, -3.0)	<0.001
Lorcaserin 10 mg qd	534	99.3 ± 0.7	-5.6 ± 0.3	-2.1 (-2.9, -1.4)	<0.001
Placebo	832	100.9 ± 0.5	-3.4 ± 0.3		
Other Analyses					
5. Returning dropouts and completers (non-returning dropouts were not included in this population); primary ANCOVA model; this reviewer's analysis ^A					
Lorcaserin 10 mg bid	1030	100.4 ± 0.5	-6.6 ± 0.2	-3.3 (-3.9, -2.7)	<0.0001
Lorcaserin 10 mg qd	576	99.3 ± 0.7	-5.1 ± 0.3	-1.8 (-2.5, -1.1)	<0.0001
Placebo	1064	100.8 ± 0.5	-3.3 ± 0.3		
6. MITT1 population with (a) weight regain estimation for non-returning dropouts; (b) week 52 weights for returning dropouts; primary ANCOVA model; this reviewer's analysis ^A					
Lorcaserin 10 mg bid	1579	100.3 ± 0.4	-5.0 ± 0.2	-3.1 (-3.6, -2.6)	<0.0001
Lorcaserin 10 mg qd	777	100.0 ± 0.6	-3.9 ± 0.3	-2.0 (-2.3, -1.6)	<0.0001
Placebo	1558	100.7 ± 0.4	-1.9 ± 0.2		
7. MITT1 population with (a) LOCF imputation for non-returning dropouts and (b) week 52 weight for returning dropouts ^A					
Lorcaserin 10 mg bid	1579	100.3 ± 0.4	-5.8 ± 0.2	-3.0 (-3.4, -2.5)	<0.0001
Lorcaserin 10 mg qd	777	100.0 ± 0.6	-4.6 ± 0.2	-1.8 (-2.3, -1.2)	<0.0001
Placebo	1558	100.7 ± 0.4	-2.9 ± 0.2		

Notes:

^A The group totals in this analysis represent a small percentage of cases with duplicate records in the analysis database; this analysis database represented a combination of variables from several databases provided by the applicant. I was not able to fully resolve this issue, but I do not believe that the inaccuracies that resulted from the analysis of this database affected the interpretation of results.

Sources:

1. Study 011 report, Table 11
2. Study 011 Table E4.10 submitted 4/2/2010 (0008)
3. Study 011 report, Table 14.2.3.1
4. Study 011 Table E2.1 submitted 4/2/10 (0008)
- 5, 6, 7 Analysis by this reviewer

TABLE 11 Study 011; 5% and 10% weight loss responders; results from primary and supportive analyses

Treatment groups	N	Number of responders (%)	Difference in proportions vs. placebo ¹ (95% CI)	Odds Ratio vs. placebo (95% CI) ²	p-value vs. placebo ²
% of subjects achieving ≥ 5% weight loss at week 52					
1. Primary analysis: MITT1; LOCF					
Lorcaserin 10 mg bid	1561	737 (47.2%)	22.2 (18.9, 25.5)	2.7 (2.3, 3.1)	<0.0001
Lorcaserin 10 mg qd	771	310 (40.2%)	15.2 (11.1, 19.3)	2.0 (1.7, 2.4)	<0.0001
Placebo	1541	385 (25.0%)			
2. Supportive analysis: PP; LOCF					
Lorcaserin 10 mg bid	846	535 (63.2%)	28.3 (23.6, 33.0)	3.2 (2.6, 3.9)	< 0.0001
Lorcaserin 10 mg qd	418	222 (53.1%)	18.2 (12.3, 24.0)	2.1 (1.6, 2.7)	<0.0001
Placebo	764	267 (34.9%)			
3. Supportive analysis: Completers					
Lorcaserin 10 mg bid	914	568 (62.1%) ³	27.4 (22.9, 31.9)	3.1 (2.5, 3.8)	<0.001
Lorcaserin 10 mg qd	470	247 (52.6%) ³	17.8 (12.3, 23.4)	2.1 (1.6, 2.6)	<0.001
Placebo	832	289 (34.7%)			
4. Supportive analysis: ITT (all randomized patients) Non-responder imputation					
Lorcaserin 10 mg bid	1603	582 (36.2%)	18.0 (15.0, 22.0)	2.5 (2.2, 3.0)	<0.001
Lorcaserin 10 mg qd	802	248 (30.9%)	12.6 (8.0, 16.4)	2.0 (1.6, 2.4)	<0.001
Placebo	1603	293 (18.3%)			
% of subjects achieving ≥ 10% weight loss at week 52					
5. Primary analysis: MITT1; LOCF					
Lorcaserin 10 mg bid	1561	353 (22.6%)	12.9 (10.3, 15.4)	2.7 (2.2, 3.3)	< 0.0001
Lorcaserin 10 mg qd	771	134 (17.4%)	7.6 (4.6, 10.7)	2.0 (1.5, 2.5)	< 0.0001
Placebo	1541	150 (9.7%)			
6. Supportive analysis: PP; LOCF					
Lorcaserin 10 mg bid	846	297 (35.1%)	19.0 (14.9, 23.2)	2.8 (2.2, 3.6)	< 0.0001
Lorcaserin 10 mg qd	418	110 (26.3%)	10.2 (5.3, 15.2)	1.9 (1.4, 2.5)	< 0.0001

Treatment groups	N	Number of responders (%)	Difference in proportions vs. placebo ¹ (95% CI)	Odds Ratio vs. placebo (95% CI) ²	p-value vs. placebo ²
Placebo	764	123 (16.1%)			
7. Supportive analysis: Completers					
Lorcaserin 10 mg bid	914	313 (34.3%)	18.7 (14.8, 22.7)	2.8 (2.2, 3.6)	< 0.001
Lorcaserin 10 mg qd	470	122 (26.0%)	10.5 (5.8, 15.1)	1.9 (1.4, 2.5)	< 0.001
Placebo	832	129 (15.5%)			
8. Supportive analysis: ITT (all randomized patients), Non-responder imputation					
Lorcaserin 10 mg bid	1603	319 (19.9%)	11.7 (9.4, 14.1)	2.8 (2.3, 3.5)	<0.001
Lorcaserin 10 mg qd	802	123 (15.3%)	7.2 (4.3, 10.0)	2.0 (1.6, 2.7)	<0.001
Placebo	1603	131 (8.2%)			
<i>Notes:</i>					
¹ The difference in proportions and 95% CI were calculated using normal approximation.					
² The odds ratios and p-values were calculated by using the logistic regression model specified for the primary analysis, with effects for treatment, gender and baseline body weight.					
<i>Sources:</i>					
1. Study 011 Clinical Report, Table 9			5. Study 011 Clinical Report, Table 12		
2. Study 011 Clinical Report, Table 14.2.1			6. Study 011 Clinical Report, Table 14.2.5		
3. Study 011 Table E72.10 (received 4/2/10 0008)			7. Study 011 Table E73.11 (received 4/2/10 0008)		
4. Study 011 Response to 8/18/10 request, Table 7 (received 8/26/10 under 0028). These results are different from those reported in Table 24 of the applicant's briefing document for the Advisory Committee meeting 9/16/10.			8. Study 011 Response to 8/18/10 request, Table 8 (received 8/26/10 under 0028) These results are different from those reported in Table 25 of the applicant's briefing document for the Advisory Committee meeting 9/16/10.		

FIGURE 13 Study 011; Distribution of weight change at week 52; MITT population with week 52 weights for returning dropouts

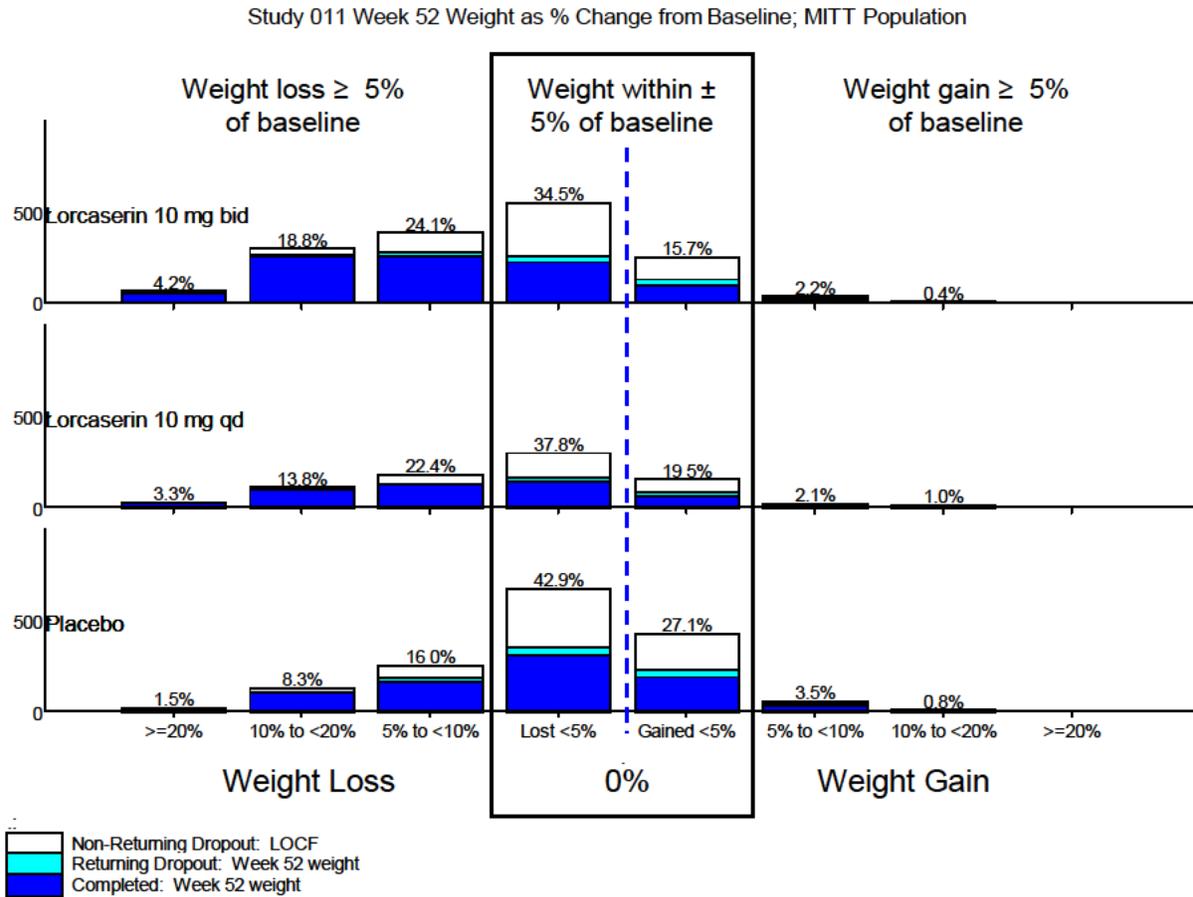


FIGURE 14 Study 011; Distribution of weight change at week 52; MITT population with week 52 weights for returning dropouts and weight regain estimation for non-returning dropouts

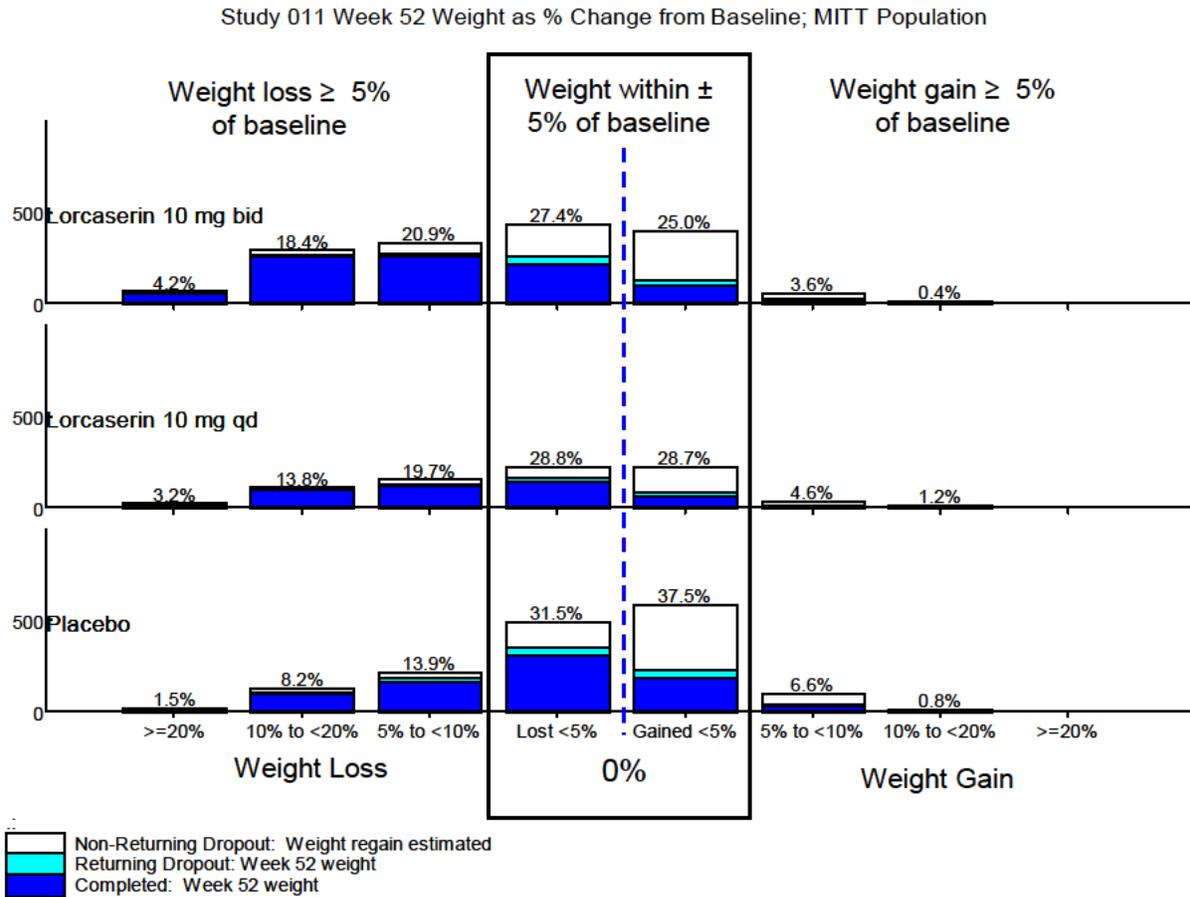
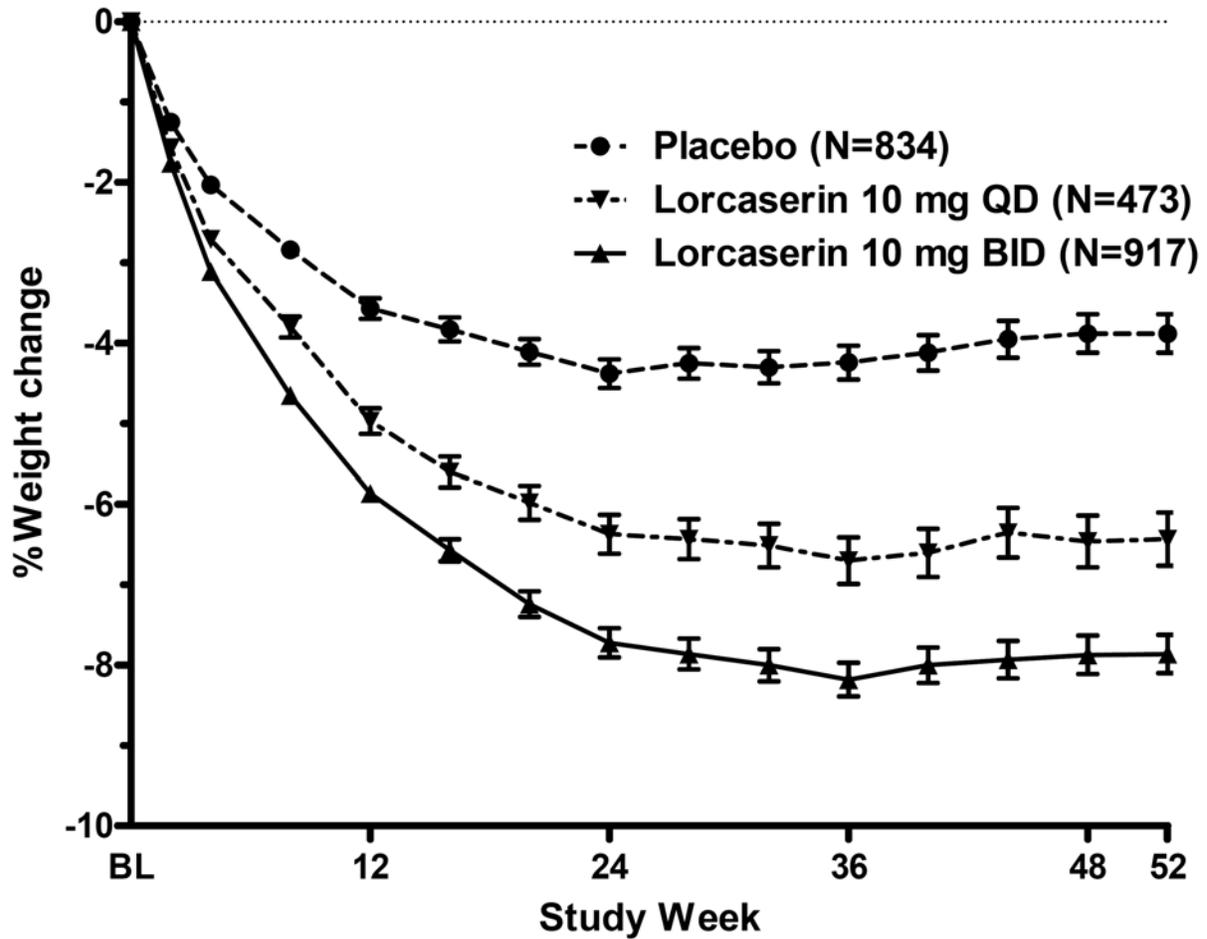


FIGURE 15 Study 011; Mean change from baseline (%) over time (mean \pm SE) by treatment group; Completer population



Source: Response to 8/18/10 request, Figure 3B (received 8/26/10 under 0028)

3.1.7. Other Efficacy Endpoints

3.1.7.1. Key secondary efficacy endpoints

For each study, the statistical analysis plan identified groups of key secondary efficacy endpoints. Within each group, endpoints were prioritized in pre-specified order. Each group of endpoints was evaluated only if the primary comparison of the proportion of 5% weight loss responders was significant.

Both studies identified a group of lipid profile variables and a group of blood pressure variables. Within the lipid group, both studies identified LDL-cholesterol as the key variable or first variable to be evaluated. Within the blood pressure group, both studies identified systolic (SBP) and diastolic blood pressure (DBP) as key variables. Because both studies had a similar approach to the analysis of the lipid group and the blood pressure group, this review includes the results from the applicant's analysis of LDL-cholesterol, SBP and DBP from the data pooled across studies. For the pooled analysis, the applicant used an analysis of covariance model, with baseline value of the endpoint as a covariate, treatment arm and study as factors. Only the lorcaserin 10mg arm and the placebo were included as treatment arms in these pooled analyses.

The statistical analysis plan for Study 009 identified one additional group, consisting of glycemic control variables, in which fasting glucose was specified as the key variable. The statistical analysis plan for Study 011 identified two additional groups, one group consisting of body composition endpoints, in which body fat was identified as the key variable, and the other group consisting of quality of life endpoints, in which the total score was identified as the key variable. this review includes the results from the applicant's analysis of these endpoints from their respective studies.

The results from the secondary efficacy endpoints supported the efficacy of lorcaserin compared to placebo. In general, the mean difference between lorcaserin and placebo was relatively small, but the mean difference was statistically significant.

LDL-Cholesterol (pooled analysis): The mean difference in change in LDL-cholesterol from baseline at week 52 was relatively small (-1.30 mg/dL with 95% confidence interval of -2.4 to -0.3) between the lorcaserin 10 mg bid arm and the placebo arm, but in the direction of an improved level of LDL-cholesterol in the lorcaserin arm compared to placebo (TABLE 12).

SBP and DBP (pooled analysis): The mean difference in change in SBP and DBP was also relatively small, but the difference was in the direction of lowered blood pressure in the lorcaserin arm compared to placebo (TABLE 13, TABLE 14).

Fasting Plasma Glucose (analysis from Study 009): The mean difference in change in fasting plasma glucose (FPG) was relatively small, but the difference was in the direction of lowered FPG in the lorcaserin arm (TABLE 15).

Total body fat (analysis from Study 011): Both lorcaserin groups and the placebo group had an average reduction in body fat by a small amount between week 52 and baseline. The two lorcaserin dose groups had a greater average reduction than placebo (TABLE 16).

Quality of life (analysis from Study 011): The lorcaserin groups had an average increase in total quality of life score and the placebo group had an average decrease between week 52 and baseline (TABLE 17).

TABLE 12 Analysis of percent change from baseline in LDL (mg/dL) at week 52 (MITT/LOCF), pooled data from Study 009 and Study 011

Treatment	N	Mean (SD)		Percent Change from Baseline (%)			
		Baseline	Week 52	Mean (SE)	Median	Min	Max
Pooled Placebo	2764	114.14 (29.71)	115.46 (30.82)	2.96 (0.40)	1.18	-82.95	209.76
Pooled Lorcaserin 10 mg BID	2869	114.25 (31.17)	113.93 (32.23)	1.63 (0.40)	-0.75	-72.65	217.86
Percent Change from Baseline (%)							
Treatment	LS Mean (SE)	95% CI for LS Mean		p-Value			
Pooled Placebo	2.92 (0.38)	(2.17, 3.67)		<0.001			
Pooled Lorcaserin 10 mg BID	1.62 (0.38)	(0.88, 2.35)		<0.001			
Between Treatment Difference							
Lorcaserin 10 mg BID vs. Placebo		Difference in LS Means (95% CI) (%)			p-Value		
		-1.30 (-2.35, -0.25)			0.015		
p-Value for ANCOVA Effects							
Baseline Value					<0.001		
Treatment					0.015		
Protocol					<0.001		
Root Mean Square Error of Change = 20.10							
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error							

Source: ISE-Statistical-Report, Table E6.0

TABLE 13 Analysis of change from baseline in systolic blood pressure (mmHg) at week 52 (MITT/LOCF), pooled data from Study 009 and Study 011

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 52	Mean (SE)	Median	Min	Max
Pooled Placebo	3039	121.51 (11.74)	120.46 (12.46)	-1.05 (0.21)	-1.00	-58.00	51.00
Pooled Lorcaserin 10 mg BID	3096	121.39 (11.86)	119.66 (12.66)	-1.73 (0.22)	-2.00	-59.00	58.00
Change from Baseline							
Treatment	LS Mean (SE)		95% CI for LS Mean		p-Value		
Pooled Placebo	-1.02 (0.20)		(-1.41, -0.64)		<0.001		
Pooled Lorcaserin 10 mg BID	-1.76 (0.19)		(-2.14, -1.38)		<0.001		
Between Treatment Difference		Difference in LS Means (95% CI)			p-Value		
Lorcaserin 10 mg BID vs. Placebo		-0.74 (-1.27, -0.20)			0.007		
p-Value for ANCOVA Effects							
Baseline Value					<0.001		
Treatment					0.007		
Protocol					0.966		
Root Mean Square Error of Change = 10.77							
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error							

Source: ISE-Statistical Report, Table E11.0

TABLE 14 Analysis of change from baseline in diastolic blood pressure (mmHg) at week 52 (MITT/LOCF), pooled data from Study 009 and Study 011

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 52	Mean (SE)	Median	Min	Max
Pooled Placebo	3039	77.71 (8.09)	76.67 (8.75)	-1.04 (0.16)	-1.00	-44.00	48.00
Pooled Lorcaserin 10 mg BID	3096	77.44 (8.05)	75.94 (8.70)	-1.50 (0.16)	-2.00	-40.00	50.00
Change from Baseline							
Treatment	LS Mean (SE)		95% CI for LS Mean		p-Value		
Pooled Placebo	-0.97 (0.14)		(-1.24, -0.69)		<0.001		
Pooled Lorcaserin 10 mg BID	-1.57 (0.14)		(-1.84, -1.29)		<0.001		
Between Treatment Difference		Difference in LS Means (95% CI)			p-Value		
Lorcaserin 10 mg BID vs. Placebo		-0.60 (-0.99, -0.21)			0.003		
p-Value for ANCOVA Effects							
Baseline Value					<0.001		
Treatment					0.003		
Protocol					0.340		
Root Mean Square Error of Change = 7.83							
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error							

Source: ISE-Statistical-Report, Table E12.0

TABLE 15 Study 009; Summary of change from baseline in fasting plasma glucose (mg/dL) at week 52: MITT population

Treatment	N	Fasting Plasma Glucose (mg/dL) Mean (SEM)			p-Value
		Baseline	Week 52	Change from Baseline at Week 52	
Lorcaserin	1538	94.3 (0.26)	93.5 (0.26)	-0.8 (0.27)	< 0.0001
Placebo	1499	94.1 (0.27)	95.3 (0.28)	1.1 (0.26)	

Source: Study 009 report, Table 26

TABLE 16 Study 011; Summary of change from baseline in total body fat (%) at week 52: MITT population

Treatment	N	n ^a	Mean (SD)		Change from Baseline			p-value
			Baseline	Week 52	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	
Lorcaserin 10 mg BID	1561	85	46.73 (5.744)	44.40 (6.483)	-2.33 (0.380)	-2.335 (0.332)	(-2.99, -1.68)	<0.0001
Lorcaserin 10 mg QD	771	35	47.06 (6.349)	45.78 (7.479)	-1.28 (0.565)	-1.284 (0.517)	(-2.30, -0.26)	0.0139
Placebo	1541	69	45.61 (5.761)	44.44 (6.448)	-1.16 (0.261)	-1.153 (0.369)	(-1.88, -0.42)	0.0021
Between Treatment Difference			Difference in LS Means (95% CI)			p-value		
Lorcaserin 10 mg BID vs. Placebo			-1.183 (-2.16, -0.20)			0.0184		
Lorcaserin 10 mg QD vs. Placebo			-0.131 (-1.39, 1.12)			0.8368		
Lorcaserin 10 mg QD vs. Lorcaserin 10 mg BID			1.051 (-0.16, 2.26)			0.0886		
p-value for ANCOVA Effects								
Baseline Value							0.7867	
Treatment							0.0409	
Root Mean Square Error of Change=3.06								

Source: Study 011 report, Table 28

TABLE 17 Study 011; Change from baseline in overall converted score of the quality of life questionnaire at week 52: MITT population

Treatment	N	n ^a	Mean (SD)		Change from Baseline			
			Baseline	Week 52	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-value
Lorcaserin 10 mg BID	1561	1291	74.7 (16.07)	86.7 (12.77)	12.0 (0.36)	11.82 (0.28)	(11.26, 12.37)	<0.0001
Lorcaserin 10 mg QD	771	658	75.5 (15.98)	86.6 (13.38)	11.1 (0.49)	11.32 (0.40)	(10.54, 12.10)	<0.0001
Placebo	1541	1217	75.3 (15.58)	85.1 (13.60)	9.9 (0.36)	9.96 (0.29)	(9.38, 10.53)	<0.0001
Between Treatment Difference			Difference in LS Means (95% CI)				p-value	
Lorcaserin 10 mg BID vs. Placebo			1.86 (1.06, 2.66)				<0.0001	
Lorcaserin 10 mg QD vs. Placebo			1.37 (0.40, 2.33)				0.0057	
Lorcaserin 10 mg QD vs. Lorcaserin 10 mg BID			-0.49 (-1.45, 0.47)				0.3146	
p-value for ANCOVA Effects								
Baseline Value							<0.0001	
Treatment							<0.0001	
Root Mean Square Error of Change=10.21								

Source: Study 011 report, Table 30

3.1.7.2. Year 2 of Study 009

Study 009 extended into a second year. Subjects who completed the initial 52 weeks of treatment (n=1599) were eligible to continue the second year. The start of the second year included a randomization, stratified according to whether or not the subject had been classified as a 5% responder at the end of year 1. Subjects who received placebo during year 1 remained on placebo for year 2. Subjects who received lorcaserin during year 1 were re-randomized within each of the two strata in a 2:1 ratio to either remain on lorcaserin 10 mg bid or switch to placebo, respectively for year 2 (FIGURE 16). The percentage of subjects who completed the second year was 72.6% overall, and was relatively similar among groups (TABLE 18). This percentage is higher than the completion percentage from the first year, which was 50.1% overall (TABLE 5). Subjects who completed the first year appeared to be more likely to remain in the study for the entire second year as well.

On average, subjects in all randomized arms gained weight in year 2 (FIGURE 17). However, even with these weight gains during year 2, each group had an average weight loss over the two year period. The lorcaserin→lorcaserin group had a greater average weight loss than the lorcaserin→placebo group or the placebo→placebo group (TABLE 18).

The applicant pre-specified the primary endpoint, restricting it to the stratum of subjects who entered year 2 as 5% responders in year 1 (groups C and D in FIGURE 16). In this stratum, lorcaserin subjects from year 1 who were randomized to remain on lorcaserin in year 2 were compared to the lorcaserin subjects from year 1 who were randomized to switch to placebo in

year 2. The modified intention-to-treat population, MITT2, was defined as all randomized subjects who completed year 1, were re-randomized at week 52, took at least one dose of study medication after re-randomization, and had at least one weight measurement post re-randomization. The last post re-randomization observation on or prior to discontinuation was carried forward and used in the analysis. An additional analysis population was the per-protocol population for year 2 (PP2), which excluded subjects and/or data points with clinically important protocol deviations. Additional analyses also used the weight at the start of year 2 as the reference baseline for the weight endpoint. However, the applicant did not provide summaries for all groups.

Based on the pre-specified endpoint, the applicant concluded that more 5% responder subjects from year 2 remained as 5% responders when maintained for a second year on lorcaserin (67.9%) than when switched to placebo for the second year (50.3%; TABLE 19). This can be interpreted as retention of effect. A formal comparison between lorcaserin and placebo responder subgroups is difficult to interpret because: (1) the subgroups are defined within each arm by the weight response at the end of year 1, and for this reason are not comparable; and (2) the lorcaserin group was re-randomized at the start of Year 2 and the placebo group was not. Nevertheless, it is interesting to note informally that 69% of the placebo responders from year 1 remained as placebo responders in year 2 (TABLE 19).

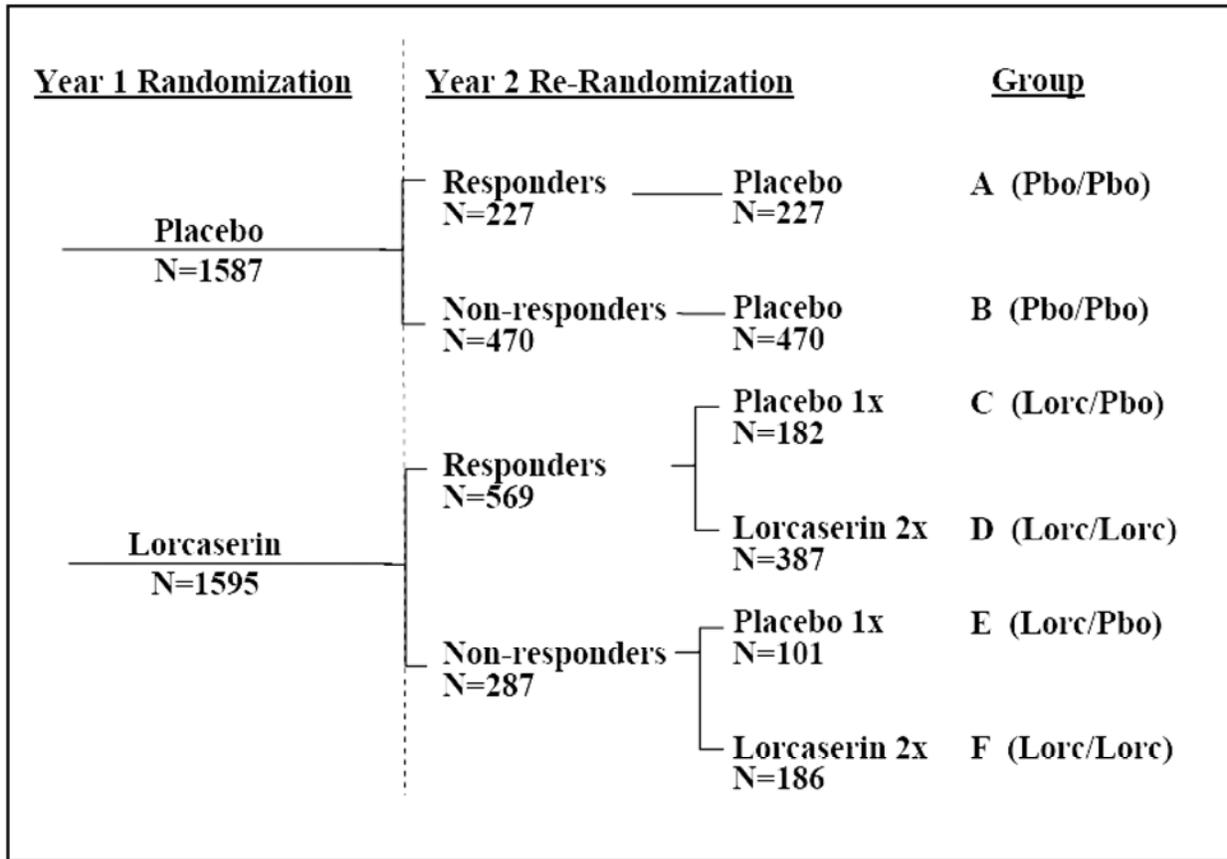
I believe that the results from year 2 of Study 009 are difficult to interpret with respect to the intended target population of lorcaserin, for the following reasons:

- (1) Only 50% of the initially randomized population completed year 1 and participated in year 2. As I have discussed in other parts of this review, the tendency to complete year 1 of the study was related at least in part to a subject's ongoing experience of weight loss. This means that subjects who were randomized in year 2 were likely to be different from the target population in terms of tendency to lose weight.
- (2) The applicant focused attention on the 5% responders to lorcaserin from year 1. This subgroup is based on the response to treatment in year 1. For this reason, this subgroup is one more step removed from the target population. However, I note that the comparison between lorcaserin→lorcaserin and lorcaserin→placebo was not greatly different when combined across responders and non-responders (TABLE 19).

In addition, although the applicant was careful not to make formal statistical comparisons between the lorcaserin responder subgroup and the placebo responder subgroup, less careful readers may not realize that these two subgroups are not comparable, because responder status was based on the weight endpoint at the end of year 1.

For these reasons, I believe that claims based on the results from year 2 of Study 009, if included in the label at all, need to be very carefully expressed in order to avoid over-generalization to the intended target population of lorcaserin.

FIGURE 16 Study 009 design, showing year 1 and year 2 randomizations



Source: Study 009 report, Figure 1

TABLE 18 Study 009; Disposition in year 2

Year 1 randomization	Lorcaserin n=1595				Placebo n=1587
Week 52 primary outcome (in Week 52 completers)	Lorcaserin Responders ¹ (C and D) n=856		Lorcaserin Non-Responders (E and F) n=287		Placebo Responders and Non- Responders n=697
	Group C Lorcaserin → Placebo	Group D Lorcaserin → Lorcaserin	Group E Lorcaserin → Placebo	Group F Lorcaserin → Lorcaserin	Group A+B Placebo → Placebo
Year 2 randomization ²	182	387	101	186	697
No. (%) in MITT2 population	175 (96.2)	380 (98.2)	100 (99.0)	184 (98.9)	684 (98.1)
No. (%) who completed	128 (70.3)	304 (78.6)	67 (66.3)	122 (65.6)	507 (72.7)
No. (%) in PP2 population	93 (51.1)	221 (57.1)	47 (46.5)	87 (46.8)	344 (49.4)
No. (%) who withdrew prior to week 104	54 (29.7)	83 (21.4)	34 (33.7)	64 (34.4)	190 (27.3)
Reason for withdrawal:					
Withdrawal of consent	31 (17.0)	44 (11.4)	23 (22.8)	30 (16.1)	105 (15.1)
Lost to follow-up	14 (7.7)	25 (6.5)	9 (8.9)	17 (9.1)	37 (5.3)
Adverse event	7 (3.8)	10 (2.6)	2 (2.0)	7 (3.8)	21 (3.0)
Combined other reasons ³	2 (1.1)	4 (1.0)	0 (0.0)	10 (5.4)	27 (3.9)
<i>Notes</i>					
¹ Responders were subjects who lost ≥ 5% of baseline body weight by week 52.					
² For percentages, the number of subjects randomized in year 2 was used as the denominator.					
³ For “Combined other reasons,” the following discontinuation categories were combined: Protocol deviation / noncompliance, Sponsor decision, PI decision and Other discontinuation reason					
<i>Source:</i> Study 009 report, Table 14.1.2					

Statistical review of NDA 022529/0 Lorcaserin for weight management

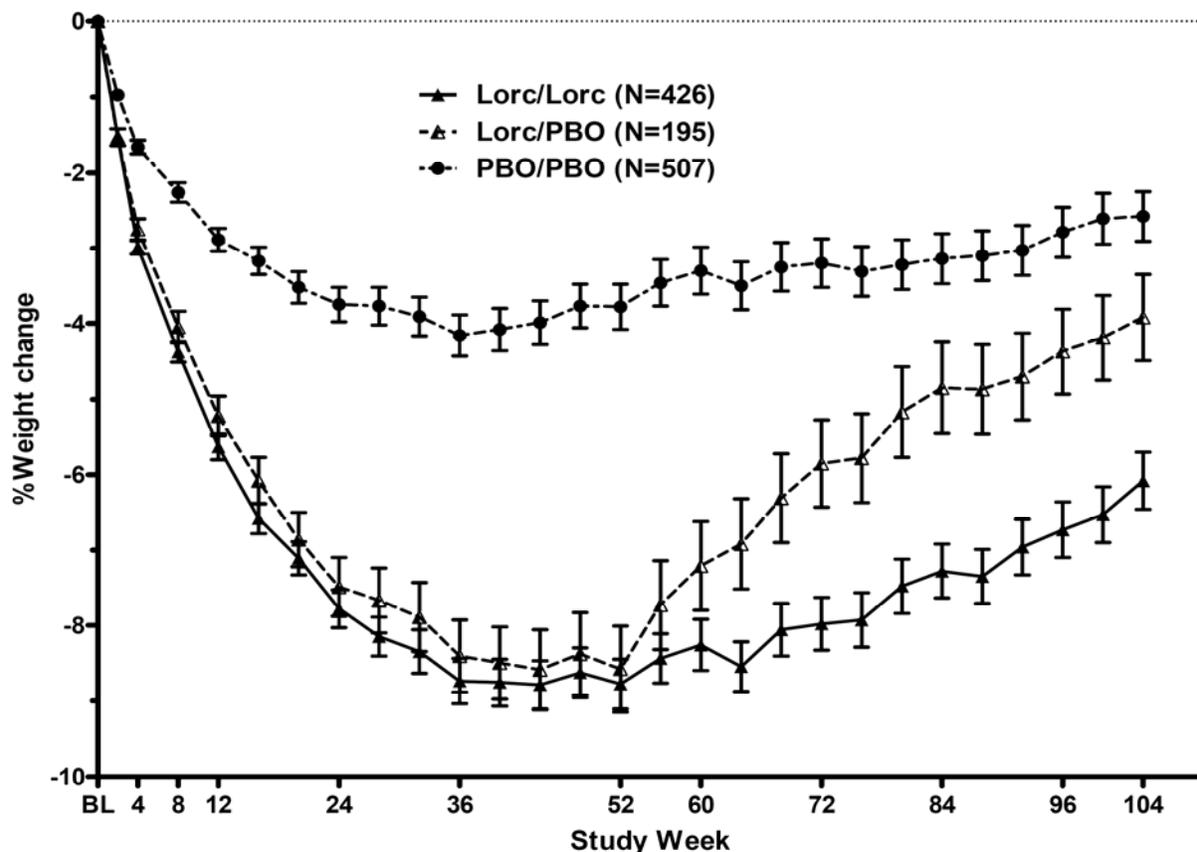
TABLE 19 Study 009; Year 2 results for MITT2/LOCF analysis population

Year 1 randomi- zation	Year 1 5% responder status	Year 2 re- randomization	Group code	Year 1 Baseline mean ± SD	Week 104 endpoints			
					LS Mean change from baseline ± SEM	L→L vs. L→P LS Mean Diff. (95% CI)	n (%)	L→L vs. L→P Odds Ratio (95% CI)
Placebo N=1587	Responder N=227	Placebo N=227	A P→P	99.2 ± 15.1	-9.1 ± 0.4 N=225		156 (69.3%)	
	Non-responder N=470	Placebo N=470	B P→P	99.4 ± 16.0	0.6 ± 0.3 N=459		48 (10.5%)	
Lorcaserin N=1595	Responder N=569	Placebo N=182	C L→P	98.8 ± 15.1	-6.5 ± 0.5 N=175	-2.1 ¹ (-3.2, -1.1)	88 (50.3%)	2.1 (1.5, 3.0)
		Lorcaserin N=387	D L→L	99.6 ± 15.3	-8.6 ± 0.3 N=380		258 (67.9%)	
	Non-responder N=287	Placebo N=101	E L→P	103.7 ± 18.0	1.7 ± 0.6 N=100	-1.4 (-2.9, 0.0)	8 (8.0%)	1.8 (0.8, 4.1)
		Lorcaserin N=186	F L→L	102.6 ± 16.3	0.2 ± 0.5 N=184		25 (13.6%)	
Combined groups	Responders and Non-Responders	Placebo→ Placebo N=697	A+B P→P	99.3 ± 15.7	-2.4 ± 0.3 N=684		204 (29.8%)	
		Lorcaserin → Placebo N=283	C+E L→P	100.6 ± 16.4	-3.4 ± 0.5 N=275	-2.2 (-3.3, -1.1)	96 (34.9%)	1.9 (1.4, 2.5)
		Lorcaserin → Lorcaserin N=573	D+F L→L	100.6 ± 15.7	-5.6 ± 0.4 N=564		283 (50.2%)	

Notes: ¹Primary analysis pre-specified by applicant (5% responders from Year 1: Lorcaserin→Lorcaserin vs Lorcaserin→Placebo, or, Group D vs Group C)

Sources: ISE report, Tables 61 and 62; and Response to 8/18/10 request, Tables 11 and 12 (received 8/26/10 under 0028)

FIGURE 17 Study 009; change in body weight (%) from baseline to week 104; Completers population



Source: Response to 8/18/10 request, Figure 2B (received 8/26/10 under 0028)

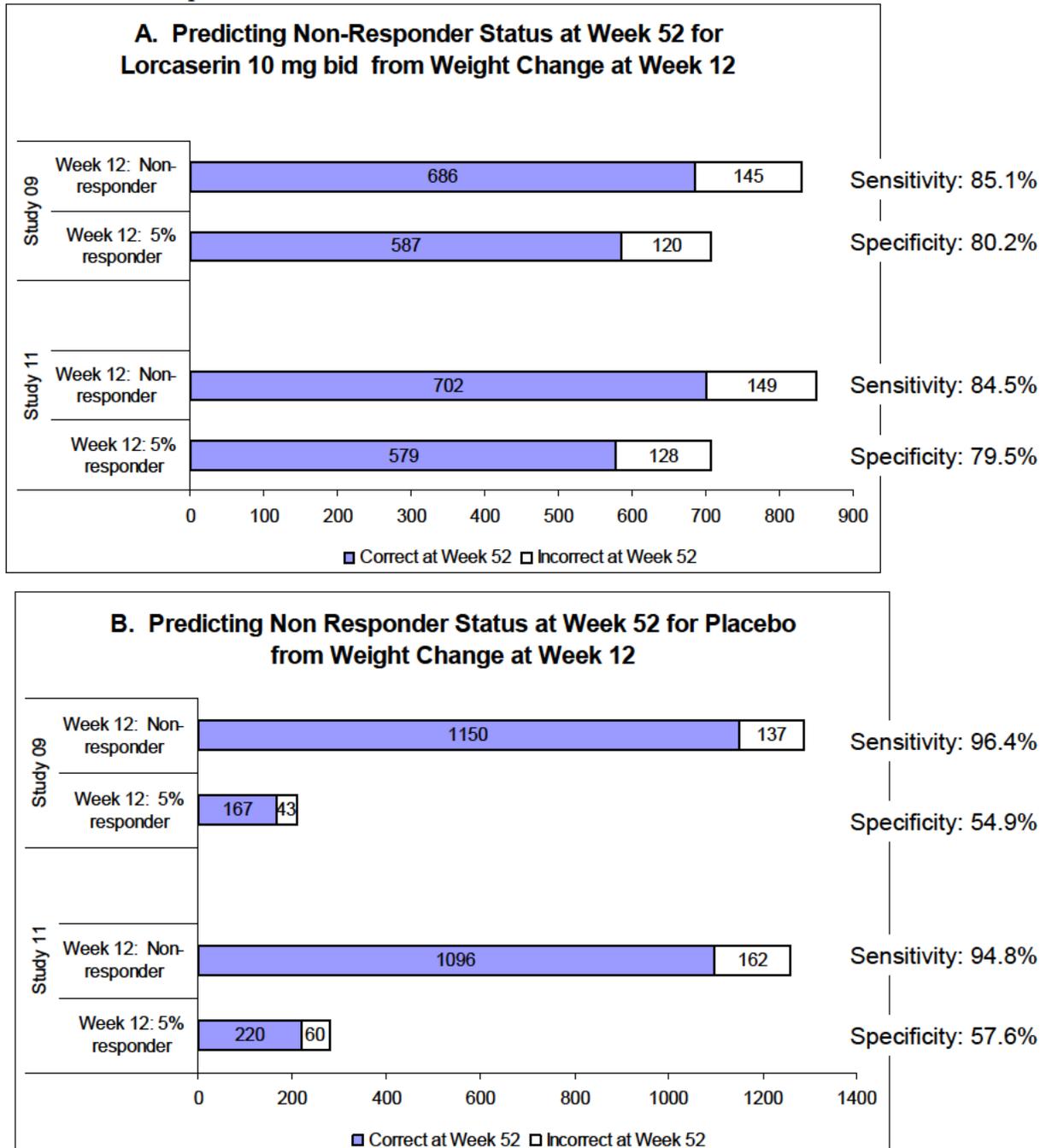
3.1.8. Predicting Non-Responders from Change in Weight at Week 12

If a subject had not lost at least 5% of baseline body weight by week 12, they were not likely to be a 5% responder at week 52 (FIGURE 18). This relationship is fairly similar for Study 009 and Study 011, and for the lorcaserin 10 mg bid and placebo arms. The high sensitivity and specificity of this relationship in the lorcaserin 10 mg bid arm of each study suggests that it may be reasonable to recommend to physicians that a patient who has not lost at least 5% of baseline body weight after taking lorcaserin for 3 months is not likely to benefit from the drug and should be discontinued in order to avoid further exposure to the risks associated with lorcaserin (FIGURE 18).

I selected week 12 after evaluating results from weeks 4, 12 and 26. At week 12, there appeared to be a reasonable separation between 5% responders and non-responders (FIGURE 19, FIGURE 20). I selected 5% weight loss at week 12 as the decision point, because the logistic regression models for each study and study arm were fairly similar in identifying a weight loss close to 5%

as the point at which the probability of being a 5% responder at week 52 was 50% (FIGURE 21). I chose 50% as the cut-point for classifying subjects as being a 5% responder at week 52 from week 12 results because this cut-point had a reasonable balance of sensitivity and specificity for each study and study arm (results not shown in this review). I believe it is reasonable to calculate sensitivity and specificity from the proportion of responders in these clinical studies because: (1) subjects were assigned at random to treatments; and (2) the intention of the enrollment criteria was to represent the target population of lorcaserin. However, this prediction of the 52-week outcome from week 12 results may have a different sensitivity and specificity in actual use.

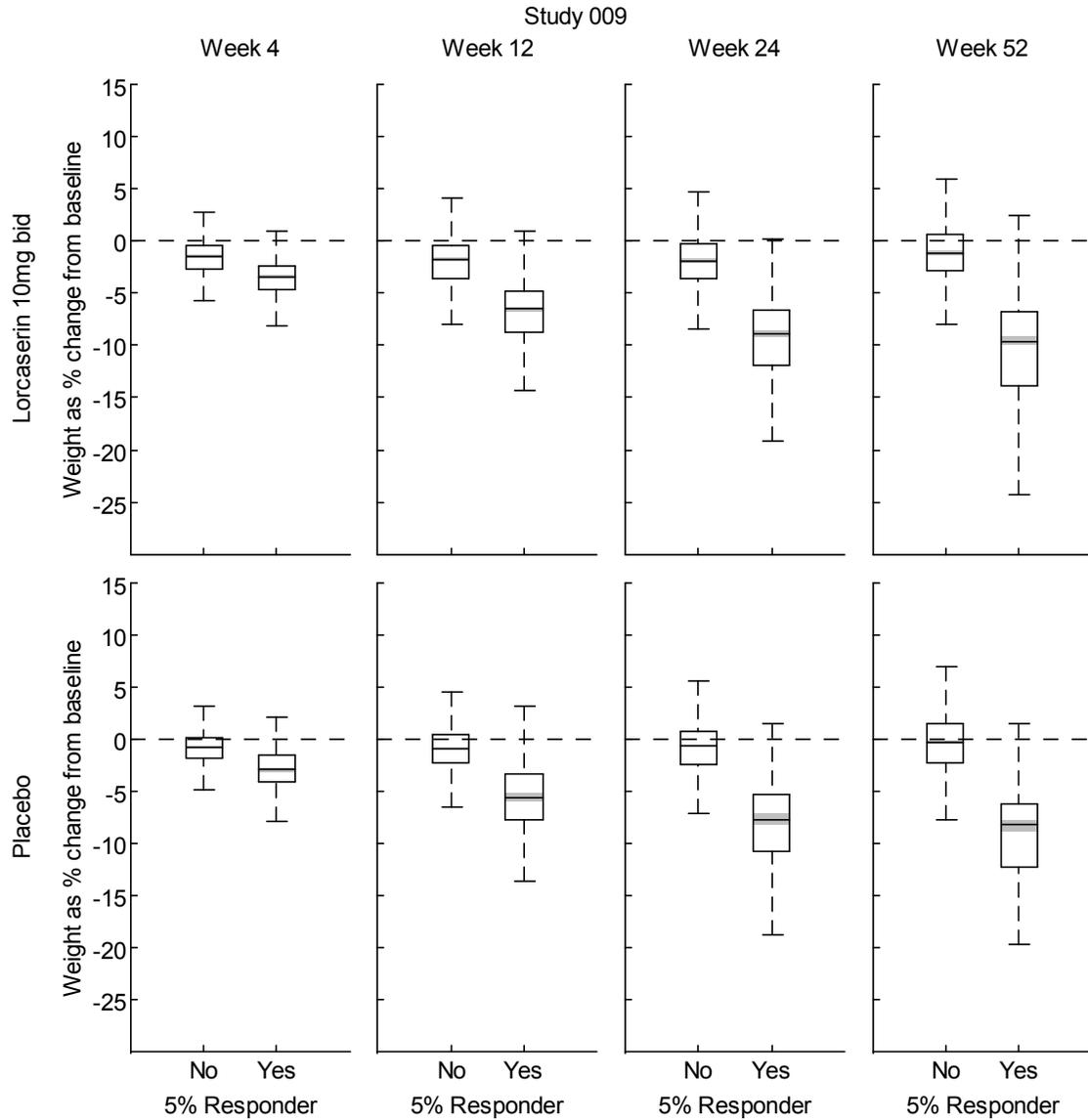
FIGURE 18 Predicting non-responder status at week 52 from weight change at week 12 in lorcaserin and placebo arms



Note: The MITT/LOCF population was used in this analysis

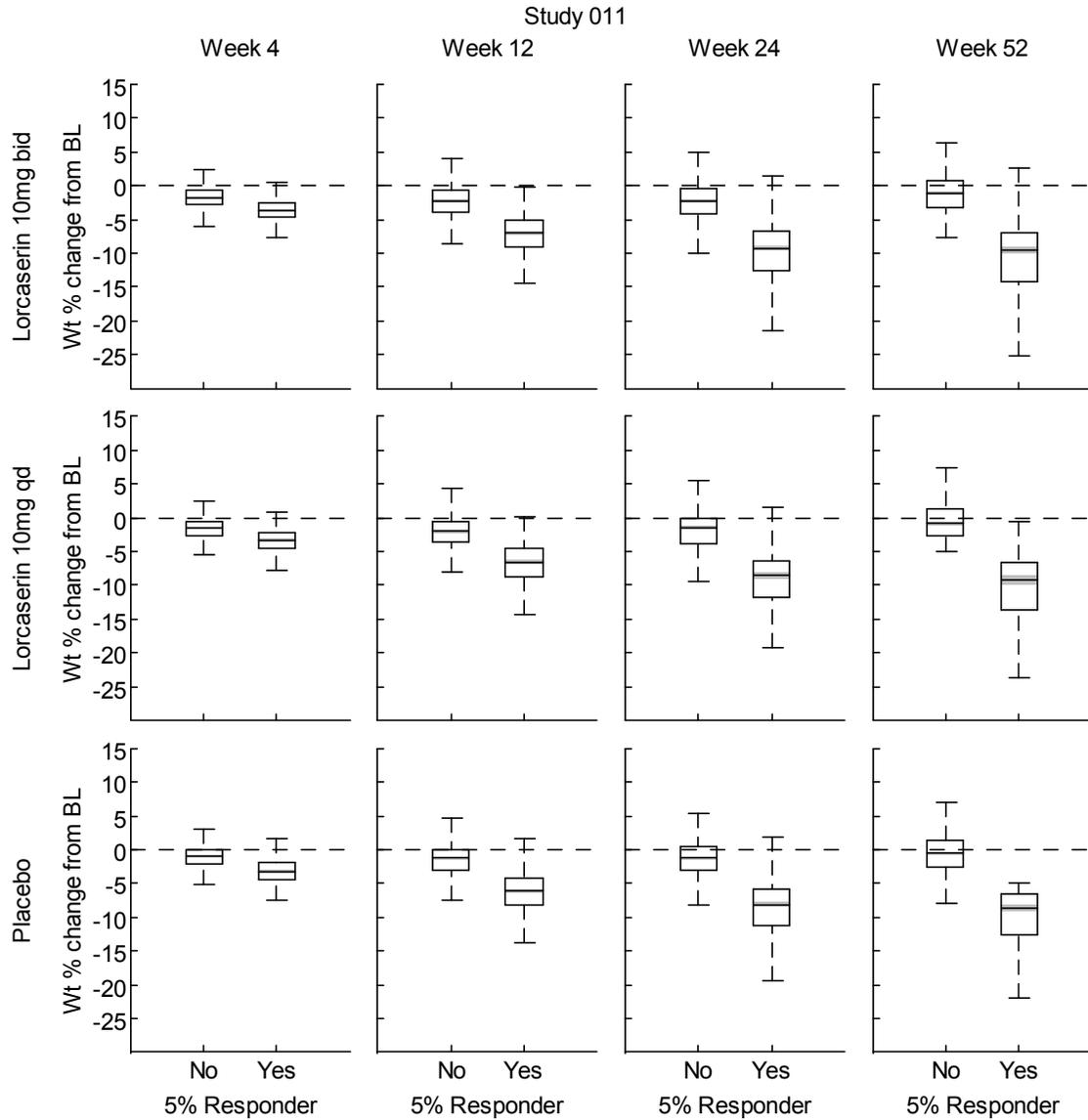
Source: Analysis by this reviewer

FIGURE 19 Study 009; 5% responder status at 52 weeks and the distribution of weight change at weeks 4, 12, 24 and 52 (MITT/LOCF)



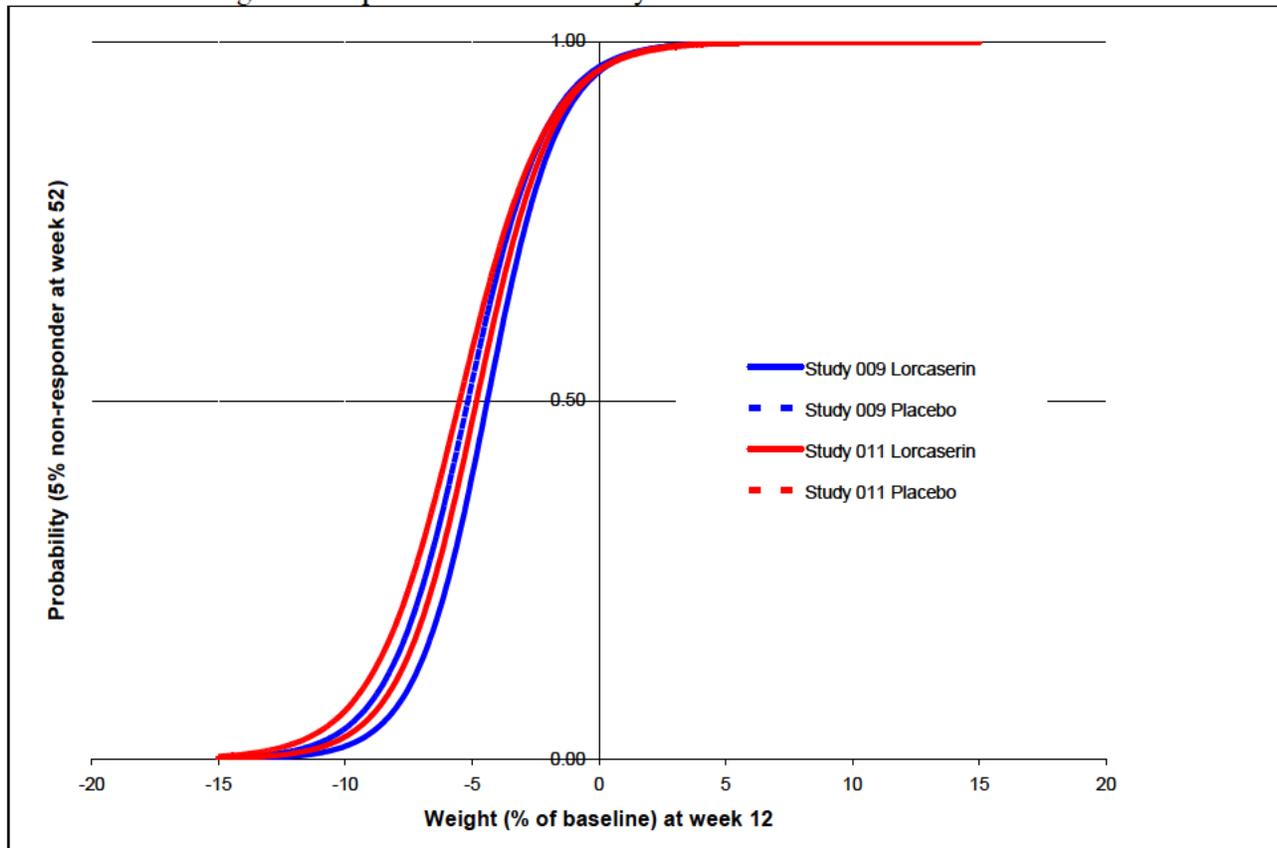
Source: Analysis by this reviewer

FIGURE 20 Study 011; 5% responder status at 52 weeks and weight change at weeks 4, 12, 24 and 52 (MITT/LOCF)



Source: Analysis by this reviewer

FIGURE 21 Predicting 5% non-responders at week 52 from weight change at week 12; logistic regression equations from each study and arm



Notes: The form of the logistic regression equation is: $\log_e(5\% \text{ non-responder at week 52} / 5\% \text{ responder}) = \beta_0 (\text{sem}) + \beta_1 (\text{sem}) [\% \text{ weight change from baseline at week 12}]$

The logistic regression coefficients for each model are as follows:

- Study 009 Lorcaserin: 3.12 (0.16) + 0.71 (0.04)
- Study 009 Placebo: 3.30 (0.15) + 0.64 (0.04)
- Study 011 Lorcaserin: 3.18 (0.17) + 0.66 (0.03)
- Study 011 Placebo: 3.18 (0.15) + 0.58 (0.03)

Source: Analysis by this reviewer

3.2 Evaluation of Safety

An evaluation of the safety of lorcaserin is included in the clinical review by Dr. Julie Golden, M.D., and in the statistical review of specific safety issues by Dr. Xiao Ding, Ph.D.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Race and Age

Sex: Females made up the large majority of each study (about 80%). However, the studies were large enough to evaluate the placebo-adjusted effect of lorcaserin in males and females. In Study 009, males and females were fairly similar in the mean placebo-adjusted effect of lorcaserin 10 mg bid (FIGURE 22, TABLE 20). In Study 011, males and females were relatively similar in the effect of lorcaserin 10 mg qd; however, in the higher dose arm, the two sexes were different. The effect of both dose levels was relatively similar in males, while females had a greater average weight loss at the higher dose (FIGURE 22, TABLE 20).

A larger percentage of males completed each study compared with females, although the difference is not very great (FIGURE 22, TABLE 22). For this reason, it does not appear that the different response of males to the two dose arms compared with females in Study 011 was related to differential retention in the study.

Race: Subjects in the Caucasian/White subgroup made up the large majority of each study (about 66%). However, the studies were large enough to evaluate the placebo-adjusted effect of lorcaserin in African American/Black and Hispanic/Latino subgroups. In Study 009, the three subgroups were relatively similar in the mean placebo-adjusted effect of lorcaserin 10 mg qd (FIGURE 23, TABLE 21). However, the unadjusted mean weight loss in the placebo and the lorcaserin arms was less in the African American/Black and the Hispanic/Latino subgroups compared to the Caucasian/White subgroup (FIGURE 23, TABLE 21). This finding corresponds to a lower retention of subjects in the African American/Black and the Hispanic/Latino subgroups (FIGURE 23, TABLE 22). The applicant, in describing these findings, noted “These data indicate that the phase 3 behavior modification program was less effective in Black and Hispanic subjects than in White subjects. This program, in either design or administration, may be inherently more effective in certain ethnic groups.”⁷

This pattern is also apparent in the results from Study 011, with additional information concerning response of racial subgroups to the 10 mg qd dose of lorcaserin. Subjects in the Caucasian/White subgroup had a dose-response relationship between the two dose arms of lorcaserin and placebo (FIGURE 23, TABLE 21). Subjects in the African American/Black subgroup had a relatively similar response to each dose (FIGURE 23, TABLE 21). Subjects in the Hispanic/Latino subgroup did not appear to respond to the lower dose compared to placebo, but did have a response to the higher dose (FIGURE 23, TABLE 21).

Age: The enrollment criteria in both studies excluded subjects who were over 65 years old, and so the comparative effect of lorcaserin in this older age group could not be evaluated in these studies.

⁷ ISE-Report, Part 5.1.1, p. 103/174

FIGURE 22 Weight loss at week 52: Interaction with sex, Study 009 and Study 011: MITT/LOCF

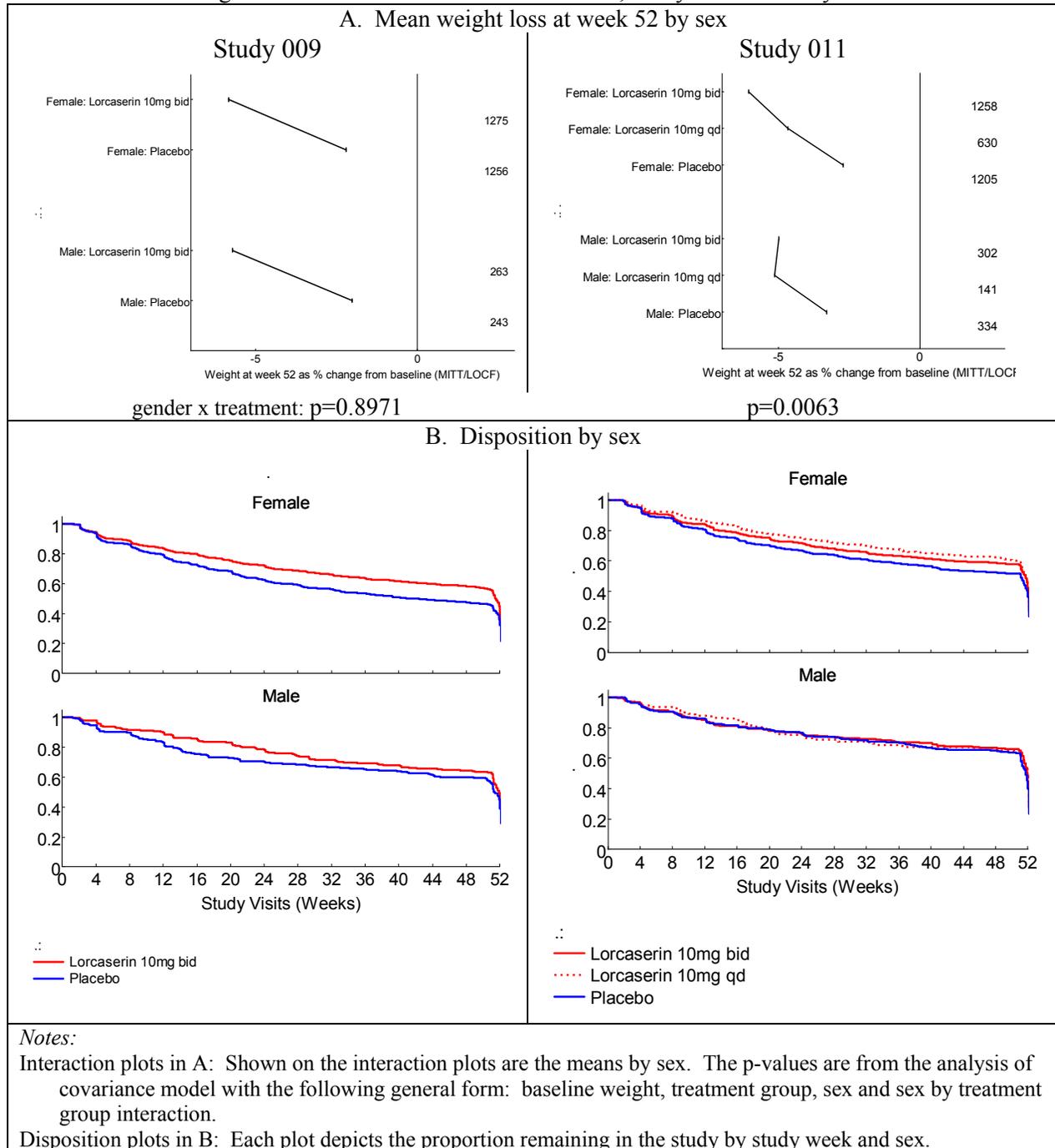
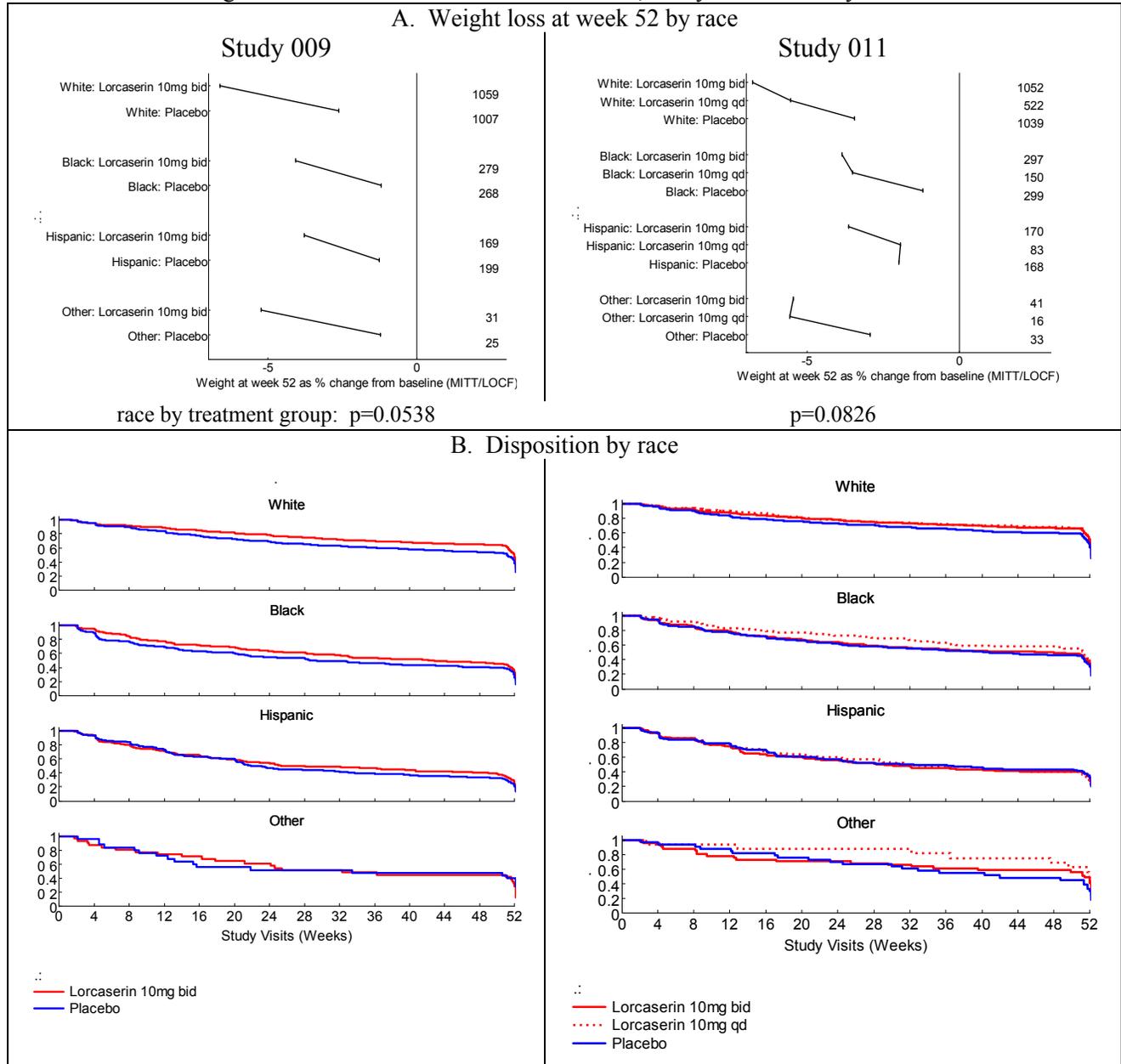


FIGURE 23 Weight loss at week 52: Interaction with race, Study 009 and Study 011: MITT/LOCF



Notes:

Interaction plots in A: Shown on the interaction plots are the means for each race category. The p-values are from the analysis of covariance model with the following general form: baseline weight, treatment group, race and race by treatment group interaction. The race category of “other” includes subgroups with small numbers of subjects as well as the “other” category designated by the applicant.

Disposition plots in B: Each plot depicts the proportion remaining in the study by study week and race.

TABLE 20 Mean weight loss in MITT population by sex; Study 009 and 011

	Treatment Arm	Sex	LS Mean change Baseline ± SE	Lorcaserin – Placebo LS Mean (95% CI)
Study 009	Lorcaserin 10mg bid	Female	-5.8 ± 0.2	-3.6 (-4.1, -3.2)
		Male	-6.0 ± 0.4	-3.7 (-4.7, -2.7)
	Placebo	Female	-2.1 ± 0.2	
		Male	-2.2 ± 0.4	
Study 011	Lorcaserin 10mg bid	Female	-6.0 ± 0.2	-3.3 (-3.8, -2.8)
		Male	-5.3 ± 0.4	-1.7 (-2.7, -0.7)
	Lorcaserin 10 mg qd	Female	-4.6 ± 0.3	-2.0 (-2.6, -1.3)
		Male	-5.5 ± 0.5	-2.0 (-3.1, -0.6)
	Placebo	Female	-2.6 ± 0.2	
		Male	-3.6 ± 0.4	

Source: Analysis by this reviewer

TABLE 21 Mean weight loss in MITT population by race; Study 009 and 011

Study	Treatment Arm	Race	LS Mean change from baseline ± SE	Lorcaserin – Placebo LS Mean (95% CI)
Study 009	Lorcaserin 10mg bid	White	-6.6 ± 0.2	-4.0 (-4.5, -3.5)
		Black	-4.1 ± 0.3	-2.9 (-3.9, -1.9)
		Hispanic	-3.7 ± 0.4	-2.5 (-3.7, -1.3)
		Other	-5.1 ± 1.0	-3.8 (-6.9, -0.8)
	Placebo	White	-2.6 ± 0.2	
		Black	-1.2 ± 0.4	
		Hispanic	-1.2 ± 0.4	
		Other	-1.2 ± 1.2	
Study 011	Lorcaserin 10mg bid	White	-6.8 ± 0.2	-3.3 (-3.9, -2.8)
		Black	-3.9 ± 0.4	-2.7 (-3.7, -1.7)
		Hispanic	-3.5 ± 0.5	-1.5 (-2.9, -0.2)
		Other	-5.4 ± 1.0	-2.6 (-5.4, 0.3)
	Lorcaserin 10 mg qd	White	-5.5 ± 0.3	-2.1 (-2.7, -1.4)
		Black	-3.6 ± 0.5	-2.3 (-3.6, -1.1)
		Hispanic	-1.8 ± 0.7	0.1 (-1.5, 1.8)
		Other	-5.5 ± 1.5	-2.6 (-6.3, 1.0)
	Placebo	White	-3.5 ± 0.2	
		Black	-1.2 ± 0.4	
		Hispanic	-1.9 ± 0.5	
		Other	-2.8 ± 1.1	

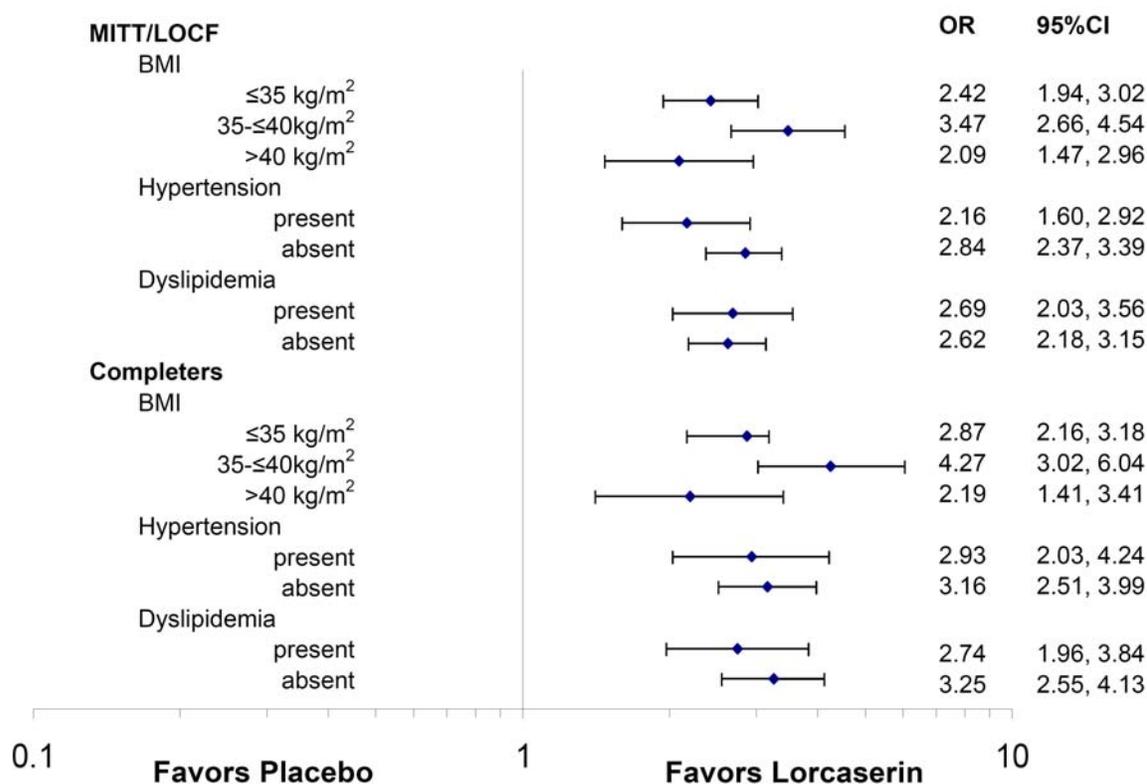
Source: Analysis by this reviewer

TABLE 22 Study completion in MITT population by sex and by race; Study 009 and 011

Treatment Arm	Sex	Study 009	Study 011
		N completed in MITT (%)	N completed in MITT (%)
Lorcaserin 10mg bid	Female	717/1275 (56.2%)	718/1258 (57.1%)
	Male	166/263 (63.1%)	199/302 (65.9%)
Lorcaserin 10 mg qd	---		381/630 (60.4%)
	---		92/141 (65.2%)
Placebo	Female	572/1256 (45.5%)	622/1205 (51.6%)
	Male	144/243 (59.3%)	212/334 (63.5%)
Treatment Arm	Race	N completed in MITT (%)	N completed in MITT (%)
Lorcaserin 10mg bid	White	674/1059 (63.6%)	688/1052 (65.4%)
	Black	129/279 (46.2%)	141/297 (47.5%)
	Hispanic	66/169 (39.1%)	66/170 (38.8%)
	Other	14/31 (45.2%)	22/41 (53.7%)
Lorcaserin 10 mg qd	---		346/522 (66.3%)
	---		83/150 (55.3%)
	---		33/83 (39.8%)
	---		11/16 (68.8%)
Placebo	White	534/1007 (53.0%)	611/1039 (58.8%)
	Black	107/268 (39.9%)	137/299 (45.8%)
	Hispanic	64/199 (32.2%)	71/168 (42.3%)
	Other	11/25 (44.0%)	15/33 (45.5%)

Source: Analysis by this reviewer

FIGURE 25 Study 011; Odds ratio for the proportion of subjects achieving $\geq 5\%$ reduction from baseline in body weight by subgroup; Lorcaserin 10 mg bid vs. placebo



Source: Response to 8/18/10 request, Figure 5 (received 8/26/10 under 0028), Figure 7

TABLE 23 Study 009; Subgroup analysis of 5% responders by BMI category at baseline; MITT/LOCF; analysis results

Treatment	N	n (%)	Difference in Proportion (%) (95% CI)	Odds-Ratio (95% CI) ^a
BMI $\leq 35 \text{ kg/m}^2$				
Placebo	686	148 (21.57)	---	---
Lorcaserin 10 mg BID	671	342 (50.97)	29.39 (24.52, 34.27)	3.78 (2.99, 4.79)
BMI $> 35 - \leq 40 \text{ kg/m}^2$				
Placebo	507	96 (18.93)	---	---
Lorcaserin 10 mg BID	547	247 (45.16)	26.22 (20.83, 31.61)	3.55 (2.68, 4.70)
BMI $> 40 \text{ kg/m}^2$				
Placebo	306	60 (19.61)	---	---
Lorcaserin 10 mg BID	320	143 (44.69)	25.08 (18.05, 32.11)	3.36 (2.34, 4.81)
p-Value for Treatment by Subgroup Interaction is = 0.835				
^a From the logistic regression model, adjusting for baseline body weight and gender.				

Source: Response to 8/18/10 request, Table E72.16 (received 8/26/10 under 0028)

TABLE 24 Study 011; Subgroup analysis of 5% responders by BMI category at baseline; MITT/LOCF; analysis results

Treatment	N	n (%)	Difference in Proportion (%) (95% CI)	Odds-Ratio (95% CI) ^a
BMI ≤35 kg/m²				
Placebo	701	196 (27.96)	---	---
Lorcaserin 10 mg QD	383	165 (43.08)	15.12 (9.15, 21.09)	1.94 (1.49, 2.52)
Lorcaserin 10 mg BID	706	342 (48.44)	20.48 (15.52, 25.44)	2.42 (1.94, 3.02)
BMI >35 - ≤40 kg/m²				
Placebo	535	115 (21.50)	---	---
Lorcaserin 10 mg QD	228	96 (42.11)	20.61 (13.32, 27.90)	2.66 (1.90, 3.71)
Lorcaserin 10 mg BID	536	261 (48.69)	27.20 (21.72, 32.68)	3.47 (2.66, 4.54)
BMI >40 kg/m²				
Placebo	303	72 (23.76)	---	---
Lorcaserin 10 mg QD	160	48 (30.00)	6.24 (-2.33, 14.80)	1.37 (0.89, 2.11)
Lorcaserin 10 mg BID	318	125 (39.31)	15.55 (8.35, 22.74)	2.09 (1.47, 2.96)
p-Value for Treatment by Subgroup Interaction is = 0.069				
^a From the logistic regression model, adjusting for baseline body weight.				

Source: Response to 8/18/10 request, Table E72.16 (received 8/26/10 under 0028)

TABLE 25 Study 009; Subgroup analysis of 5% responders by baseline dyslipidemia (absent, present); MITT/LOCF; analysis results

Treatment	N	n (%)	Difference in Proportion (%) (95% CI)	Odds-Ratio (95% CI) ^a
Absent				
Placebo	992	188 (18.95)	---	---
Lorcaserin 10 mg BID	1022	450 (44.03)	25.08 (21.18, 28.98)	3.43 (2.80, 4.19)
Present				
Placebo	507	116 (22.88)	---	---
Lorcaserin 10 mg BID	516	282 (54.65)	31.77 (26.13, 37.41)	4.08 (3.11, 5.34)
p-Value for Treatment by Subgroup Interaction is = 0.301				
^a From the logistic regression model, adjusting for baseline body weight and gender.				

Source: Response to 8/18/10 request, Table E72.15 (received 8/26/10 under 0028)

TABLE 26 Study 011; Subgroup analysis of 5% responders by baseline dyslipidemia (absent, present); MITT/LOCF; analysis results

Treatment	N	n (%)	Difference in Proportion (%) (95% CI)	Odds-Ratio (95% CI) ^a
Absent				
Placebo	565	189 (33.45)	---	---
Lorcaserin 10 mg QD	321	167 (52.02)	18.57 (11.87, 25.28)	2.15 (1.62, 2.85)
Lorcaserin 10 mg BID	594	368 (61.95)	28.50 (22.99, 34.01)	3.25 (2.55, 4.13)
Present				
Placebo	267	100 (37.45)	---	---
Lorcaserin 10 mg QD	149	80 (53.69)	16.24 (6.35, 26.13)	1.87 (1.24, 2.81)
Lorcaserin 10 mg BID	320	200 (62.50)	25.05 (17.18, 32.91)	2.74 (1.96, 3.84)
p-Value for Treatment by Subgroup Interaction is = 0.712				
^a From the logistic regression model, adjusting for baseline body weight.				

Source: Response to 8/18/10 request, Table E72.18 (received 8/26/10 under 0028)

TABLE 27 Study 009; Subgroup analysis of 5% responders by baseline hypertension (absent, present) MITT/LOCF; analysis results

Treatment	N	n (%)	Difference in Proportion (%) (95% CI)	Odds-Ratio (95% CI) ^a
Absent				
Placebo	1171	229 (19.56)	---	---
Lorcaserin 10 mg BID	1214	553 (45.55)	26.00 (22.39, 29.60)	3.50 (2.91, 4.21)
Present				
Placebo	328	75 (22.87)	---	---
Lorcaserin 10 mg BID	324	179 (55.25)	32.38 (25.31, 39.45)	4.22 (3.00, 5.93)
p-Value for Treatment by Subgroup Interaction is = 0.319				
^a From the logistic regression model, adjusting for baseline body weight and gender.				

Source: Response to 8/18/10 request, Table E72.14 (received 8/26/10 under 0028)

TABLE 28 Study 011; Subgroup analysis of 5% responders by baseline hypertension (absent, present) MITT/LOCF; analysis results

Treatment	N	n (%)	Difference in Proportion (%) (95% CI)	Odds-Ratio (95% CI) ^a
Absent				
Placebo	1168	272 (23.29)	---	---
Lorcaserin 10 mg QD	600	234 (39.00)	15.71 (11.12, 20.31)	2.11 (1.70, 2.61)
Lorcaserin 10 mg BID	1181	545 (46.15)	22.86 (19.12, 26.60)	2.84 (2.37, 3.39)
Present				
Placebo	371	111 (29.92)	---	---
Lorcaserin 10 mg QD	171	75 (43.86)	13.94 (5.16, 22.72)	1.81 (1.24, 2.63)
Lorcaserin 10 mg BID	379	183 (48.28)	18.37 (11.51, 25.22)	2.16 (1.60, 2.92)
p-Value for Treatment by Subgroup Interaction is = 0.313				
^a From the logistic regression model, adjusting for baseline body weight.				

Source: Response to 8/18/10 request, Table E72.14 (received 8/26/10 under 0028)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

A key issue in the clinical studies of lorcaserin was the substantial percentage of randomized subjects in each study and study arm, between 40% and 55%, who withdrew prior to week 52. At any given time during the study, subjects who had lost less weight were more likely to withdraw than subjects who had lost more weight. The extent of dropout, and the relationship between ongoing weight loss and tendency to drop out, focuses the analysis on the categorical version of the weight endpoint. Patients who withdrew early were likely to be within 5% of their baseline weight at the time of withdrawal. This is consistent with classifying early withdrawals as 5% non-responders. A reasonable measure of efficacy to extend the study conclusions to the intended target population is the placebo-adjusted odds of being classified as a 5% responder. This measure can encompass the intention-to-treat population by classifying early dropouts as 5% non-responders.

If a subject had not lost at least 5% of baseline body weight by week 12, they were not likely to be a 5% responder at week 52. This relationship, which has a reasonable level of sensitivity and specificity for lorcaserin 10 mg bid, may serve as an early benchmark for continued use of lorcaserin.

5.2 Conclusions

The results of two Phase 3 studies are consistent and confirm the efficacy of lorcaserin 10 mg bid and 10 mg qd compared to placebo after 52 weeks of treatment, in the co-primary weight loss endpoints of average weight loss compared to baseline, the percentage of subjects who lost at least 5% of baseline body weight, and the percentage of subjects who lost at least 10% of baseline body weight. Results of alternate analysis models and other versions of the analysis population were consistent with the results from the primary analysis. The results from secondary efficacy endpoints, such as LDL-cholesterol, systolic and diastolic blood pressure, fasting plasma glucose, total body fat, and total quality of life score, supported the efficacy of lorcaserin compared to placebo. However, the placebo-adjusted weight loss was relatively low, compared to the benchmark of 5% described in the February 2007 draft *Guidance for Industry: Developing Products for Weight Management*. For this reason, it may be useful to recommend that patients who have not lost at least 5% of baseline body weight by week 12 should stop taking lorcaserin. They may not experience the weight loss benefits of lorcaserin and so should not continue to be exposed to the risks associated with the drug.

5.3 Recommendations for Labeling

I have the following general recommendations for part 14 (Clinical Studies) of the package insert, based on the version that the applicant submitted with the NDA/0:

1. The applicant proposes [REDACTED] (b) (4). The Division may want to consider whether the [REDACTED] (b) (4) of this study limits its usefulness in the package insert.
2. The applicant refers to Study 009 as [REDACTED] (b) (4) and Study 011 as [REDACTED] (b) (4) throughout this section. The Division may want to recommend more neutral names such as Study 1 and Study 2.
3. The applicant claims in the text that [REDACTED] (b) (4). However, we typically do not describe the [REDACTED] (b) (4) that are not part of the primary endpoint.
4. The results of both studies should clearly describe the extent of study dropout prior to week 52, in the text and in tables and figures.
5. The applicant reports the combined results of Study 009 and Study 011 (see Table 3). However, I believe the results from each study should be reported separately. Baseline body weight should also be reported in these summary tables.
6. The applicant reports results [REDACTED] (b) (4) and the completers (see Table 3). However, I believe that the results should be summarized for the ITT/LOCF population only.
7. Section 14.1.2 describes the [REDACTED] (b) (4).
[REDACTED] (b) (4)
8. Figure 1 in part 14 shows the longitudinal profile of weight changes during Years 1 [REDACTED] (b) (4) of Study 009. This figure, if it is included, should represent the [REDACTED] (b) (4) population. The figure legend should clarify the percentage of originally randomized subjects are represented by the completers population, and the relationship between the completers population and the originally randomized population, with respect to tendency to lose weight.
9. The label can include a recommendation to physicians that patients who have not lost at least 5% of their starting body weight after three months may not benefit from lorcaserin.

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

/s/

JANICE A DERR
09/22/2010

JON T SAHLROOT
09/22/2010

THOMAS J PERMUTT
09/22/2010
concur



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

CLINICAL STUDIES

NDA/Serial Number: 22529
Drug Name: Lorquess (lorcaserin HCl)
Indication(s): Anti-obesity
Applicant: Arena Pharmaceuticals, Inc.
Date(s): Filing Mtg: 02/17/2010
PDUFA date: 08/22/2010
Completion date: 07/13/2010
Review Priority: S
Biometrics Division: DB VI
Statistical Reviewer: Ling Chen, Ph.D., Mathematical Statistician, Special Project Team.
Concurring Reviewers: Stella Machado, Ph.D., Acting Team Leader, Division Director
Medical Division: Controlled Substance Staff
The CSS Team: Katherine Bonson, Ph.D., Pharmacologist, OD/CSS
Project Manager: Corinne P. Moody, OD/CSS
Keywords: Crossover design; Drug abuse potential study; Self-reported endpoint; Multiple endpoints

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1. Executive Summary

Study APD356-013 was a randomized, double-blind, double-dummy, placebo- and active-controlled, 7-way crossover study to evaluate the abuse potential of single doses of lorcaserin compared to placebo, zolpidem (a schedule IV drug), and ketamine (a schedule III drug), in healthy male and female recreational polydrug users. The study included qualification phase and treatment phase.

There were 7 treatments in the study. These treatments were placebo, ketamine 100 mg, zolpidem 15 mg and 30 mg, and lorcaserin 20 mg, 40 mg and 60 mg. A 7x7 modified Williams design was used. A total of 29 subjects completed the study, one of which (Subject 9079) discontinued at the last treatment period due to emesis experienced during administration of the 60 mg lorcaserin treatment.

The primary objectives of the study were 1) to evaluate the abuse potential of lorcaserin compared to placebo as measured by Drug Liking visual analog scale (VAS); 2) to evaluate the abuse potential of lorcaserin compared to zolpidem as measured by Drug Liking VAS; 3) to confirm the abuse potential of zolpidem compared to placebo as measured by Drug Liking VAS, in order to confirm study validity. Besides the primary measure Drug Liking VAS, there were 26 secondary abuse potential measures (some of measures were on a bipolar scale) in the study. These measures were classified into 7 categories: Balance effects, Positive effects, Negative effects, Sedative effects, Perceptual/Dissociative effects, Other drug effects, and Objective measures of drug effects. In this reviewer's secondary analysis, Balance effects, Positive effects, and Sedative effects were used.

The results from this reviewer's primary and secondary analyses show that

- Both positive control drugs zolpidem and ketamine validated the study on the primary measure Drug Liking VAS and all positive measures from both balance effects and positive effects.
- Ketamine had drug disliking, bad effects and drowsiness similar to placebo, while zolpidem had drug disliking and bad effects similar to placebo.
- Compared to two positive control drugs, all doses of lorcaserin showed significantly lower drug liking.
- Compared to zolpidem, lorcaserin had significantly higher bad effects and drug disliking except for lorcaserin 20 mg vs. zolpidem 15 mg. Compared to ketamine, lorcaserin had significantly higher drug disliking.
- The positive effects of lorcaserin are lower than that of zolpidem. Some of these comparisons were statistically significant.
- Lorcaserin had significantly lower good effects, euphoria effects and high than ketamine. Subjects clearly like ketamine more than lorcaserin, which can be seen from significant difference between lorcaserin and ketamine on Overall Drug Liking VAS, and Take Drug Again VAS.
- Compared to zolpidem, lorcaserin had lower sedative effects. Except for lorcaserin 60 mg on ARCI PCAG, all differences were statistically significant.
- Even though the results showed that there was no significant difference between lorcaserin 60 mg and zolpidem on Good Effects VAS (bipolar scale) and High VAS, lorcaserin 60 mg had significantly lower Good Effects VAS than zolpidem on a

- unidirectional scale, and significantly lower response to Overall Drug Liking VAS and Take Drug Again VAS.
- Lorcaserin 40 mg and 60 mg had significantly higher Good Effects VAS (in both bipolar and unidirectional scales) and High VAS than placebo while lorcaserin 40 mg and 60 mg had significantly higher Drug Disliking VAS and Bad Effects VAS than placebo in a bipolar scale.
 - Lorcaserin 20 mg appears similar to placebo for all abuse measures except bad effects and drug disliking in a bipolar scale, in which lorcaserin had significantly higher bad effects and drug disliking.

Per pharmacologist reviewer, Dr. Katherine Bonson's request, this reviewer also provided descriptive statistics for Emax of Hallucination VAS in this report. The interpretation of the results for Hallucinations VAS and conclusion from this study may be found in Dr. Bonson's report.

2. Review Report on Study APD356-013 (UPN1230A)

2.1 Overview

2.1.1 Objectives of the study

Primary objectives:

- To evaluate the abuse potential of lorcaserin compared to placebo as measured by Drug Liking visual analog scale (VAS);
- To evaluate the abuse potential of lorcaserin compared to zolpidem as measured by Drug Liking VAS;
- To confirm the abuse potential of zolpidem compared to placebo as measured by Drug Liking VAS, in order to confirm study validity.

Secondary objectives:

- To evaluate the abuse potential of lorcaserin compared to zolpidem as assessed by measures of positive, negative, perceptual, sedative, and other subjective effects;
- To confirm the abuse potential of zolpidem compared to placebo as assessed by measures of positive, negative, perceptual, sedative, and other subjective effects in order to confirm measure/endpoint sensitivity to zolpidem;
- To evaluate the abuse potential of lorcaserin compared to ketamine and placebo as assessed by measures of positive, negative, perceptual, sedative, and other subjective effects;
- To confirm the abuse potential of ketamine compared to placebo as assessed by measures of positive, negative, perceptual, sedative and other subjective effects in order to confirm/measure endpoint sensitivity to ketamine;
- To evaluate the safety and tolerability of lorcaserin.

Reviewer's Comment: This reviewer focuses on the primary objective, and also considers several abuse potential measures mentioned in the sponsor's secondary objectives, which are often interest to the Controlled Substance Staff (CSS). The summaries of descriptive statistics for all secondary measures are presented in Appendix.

2.1.2 Study design

This was a randomized, double-blind, double-dummy, placebo- and active-controlled, 7-way crossover study to evaluate the abuse potential of single doses of lorcaserin compared to placebo, zolpidem and ketamine in healthy male and female recreational polydrug users.

There were seven treatments in the study. These treatments were

P - placebo

Z15 – zolpidem 15 mg

Z30 – zolpidem 30 mg

K100 – ketamine 100 mg

L20 – lorcaserin 20 mg

L40 – lorcaserin 40 mg

L60 – lorcaserin 60 mg

The study included a qualification phase and a treatment phase. Qualified subjects were randomized to 1 of 14 treatment sequences. In the treatment phase, subjects received all 7 treatments in the order specified by treatment sequence according to a modified two 7x7 Williams Squares design. The sequences were partially fixed such that subjects did not receive the 60 mg dose of lorcaserin prior to having received the 40 mg dose (i.e., 40 mg and 60 mg/placebo period could occur at any time throughout the study, as long as the 40 mg treatment period occurred prior to the 60 mg/placebo period). This was for the safety concern of the 60 mg lorcaserin.

Reviewer's Comments: modified 7x7 Williams design lost the property of the original Williams design: balancing the first order carryover effects.

Based on the half-life ($t_{1/2}$) of lorcaserin (approximately 10 to 11 hours), as well as that of zolpidem and ketamine (each approximately 2.5 hours), a 7-day washout for each period is considered acceptable.

Data were collected at -0.5, 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, 12 and 24.0 hours except Overall Drug Liking VAS, Take Drug Again VAS, and Drug Familiarity Similarity VAS. Data for Overall Drug liking VAS and Take Drug Again VAS were collected at hours 8 and 24, and Data for Drug Familiarity Similarity VAS was collected only at hour 24.

Reviewer's Comments: In general, sponsors collects data at -0.5, 1.0 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12, 24) hours during each treatment period. The sponsor did not collect data at hours 1.5, 5, and 6.

This reviewer found that for some abuse potential measures data were collected at hour 0 (planning time). For example, Drug Liking VAS, Good Effect VAS and Bad Effect VAS. The actual collecting time for planned hour 0 was around hour 0.25.

2.1.3 Abuse Potential Measures in the Study

There were many abuse potential measures in the study. There measures are classified as follows:

Primary measure: Drug Liking VAS (“at the moment”)

Secondary measures:

- Balance effects
 - Overall Drug Liking VAS
 - Take Drug Again VAS
 - Good and Bad Drug Effects VAS
 - Subjective Drug Value

- Positive effects
 - High VAS
 - Good Drug Effects VAS
 - ARCI Morphine Benzedrine Group [MBG]

- Negative effects
 - Bad Drug Effects VAS
 - Feeling Sick VAS
 - ARCI Lysergic Acid Diethylamide [LSD]
- Sedative effects
 - ARCI Pentobarbital and Chlorpromazine Group [PCAG]
 - Alertness/Drowsiness VAS
- Perceptual/Dissociative effects
 - Spaced Out VAS
 - Floating VAS
 - Detached VAS
 - Hallucinations VAS
 - Sounds Louder VAS
 - Vision Crisp Clear VAS
- Other drug effects
 - Any Drug Effects VAS
 - Drug Similarity VASs
 - Dizziness VAS

Objective measures of drug effects

- Choice Reaction Time [CRT]:
 - i. Total Reaction Time (TRT)
 - ii. Recognition Reaction Time (RRT)
 - iii. Motor Reaction Time (MRT)
 - iv. Percentage Correct Responses

The primary endpoints were the peak scores (Emax or Emin for some variables) for all measures (primary and secondary variables). Partial time-weighted means from 0 to 4 hours post-dose (TWM (0-4h)) and 0 to 24 hours post-dose (TWM (0-24h)) were also calculated for each variable and considered as supportive endpoints.

Reviewer's Comments: The endpoint of interest to the CSS is Emax (or Emax of change from predose response) during 8 hours after dosing. The sponsor used Emax at any time during 24 hours after dosing. Because the data at hours 1.5, 3, 4 and 5 were not collected, even though the Sponsor used Emax during 24 hours, they might still miss the peak responses of subjects reached at hour 1.5 and between hour 4.0 and hour 6.0.

In this reviewer's analysis, maximum of responses at hour 8 and 24 for Overall Drug Liking VAS and Take Drug Again VAS, and response at hour 24 for Drug Familiarity Similarity VAS are considered as endpoints for these measures.

Because Subjective Drug Value has not been validated, this measure is not included in this review's analysis.

2.1.4 Number of Subjects:

Healthy male and female subjects aged 18 to 55 (inclusive), who were recreational polydrug users with a history of psychedelic and central nervous system (CNS) depressant drug use, and who passed pharmacologic qualification criteria. Subjects with a history or presence of drug or alcohol dependence were excluded.

Thirty five qualified subjects were randomized to the treatment phase. Twenty nine subjects completed 6 study treatments (not including 60 mg lorcaserin), had no major protocol deviations and were included in the analyses of the abuse potential measures.

2.1.5 Statistical Methodologies used in the Sponsor's analyses

Primary endpoints (Emax and/or Emin) and scores for the primary and secondary measures were analyzed using a mixed-effect model for a crossover study. The mixed-effect model had treatment, period, and sequence as fixed effects; baseline (pre-dose) measurement as a covariate, where applicable, and subject nested within sequence as a random effect. Time-weighted mean (TWM) values (from 0 to 4 hours post-dose and from 0 to 24 hours post-dose) were also calculated for each variable and considered as supportive endpoints and analyzed using a mixed effect model. The primary contrasts consisted of comparisons of each dose of lorcaserin to placebo, each dose of lorcaserin and zolpidem, and each dose of zolpidem to placebo (study validity), while the secondary contrasts consisted of comparisons of each dose of lorcaserin to ketamine and ketamine compared to placebo. The point estimates, associated 95% confidence intervals (CIs), and p-values were derived from the mixed-effects model for all contrasts (if the measure was normally distributed and for ratios if it was log-normal). The residuals from the mixed-effect model were investigated for centrality of distribution. Measures not centrally distributed were investigated for centrality of log-transformed data (natural log) using the same mixed-effect model. Measures not fitting either condition were analyzed non-parametrically for overall treatment effect using the Kruskal-Wallis test. If there was an overall treatment effect, measures analyzed non-parametrically were compared pair-wise using the Wilcoxon Sign-Rank test.

2.1.6 Sponsor's results and conclusion

Results

- Validity of the current study was confirmed by demonstrating that Emax for Drug Liking was significantly higher for 15 mg and 30 mg zolpidem compared to placebo. In support of this, the secondary active comparator, ketamine, also showed significantly higher Emax for Drug Liking compared to placebo.
- Evaluation of balance measures (Drug Liking VAS, Overall Drug Liking VAS, Take Drug Again VAS, Good and Bad Effects VAS and Subjective Drug Value) indicate that at supratherapeutic doses, lorcaserin is associated with significant disliking compared to placebo, zolpidem and ketamine. At the total daily therapeutic dose, lorcaserin was not different from placebo on these measures. Based on the time course profile and analysis

of derived parameters (Emax and TWM variables), on balance, negative effects outweighed the positive effects over the assessment period.

- Ketamine and zolpidem, 30 mg in particular, demonstrated significant positive responses on balance of effects measures compared to placebo, indicating that for these active comparators the positive effects outweighed the negative effects.
- Lorcaserin was associated with significant responses on most “at the moment” positive effects measures (Good Effects VAS, High VAS and ARCI MBG) compared to placebo. However, these responses were lower than those observed for zolpidem and ketamine; these differences were significant on most but not all endpoints.
- Analysis of negative effects (Bad Drug Effects VAS, Feeling Sick VAS and ARCI LSD scale) showed that lorcaserin has significant negative effects at supratherapeutic doses compared to placebo and to the weak negative effects of ketamine. The duration of these negative effects was considerably longer than any seen with zolpidem.
- Sedative effects results (Alertness/Drowsiness VAS and ARCI PCAG) showed that lorcaserin at supratherapeutic doses may have modest sedative effects compared to placebo; however, these were significantly lower than those observed with 30 mg zolpidem and 100 mg ketamine (the latter for 60 mg lorcaserin only).
- On all measures of perceptual/dissociative effects, ketamine and zolpidem were observed to be significantly different from placebo. In contrast, lorcaserin did not show consistent effects. Significant increases in Floating VAS, Detached VAS and Spaced Out VAS Emax were observed compared to placebo, but in most cases, these were lower than Emax for zolpidem, particularly at 30 mg.
- The Drug Similarity VAS show that most subjects could correctly identify ketamine and related the effects of zolpidem most closely to those of benzodiazepines; subjects were generally also able to identify placebo. For lorcaserin, the 20 mg dose was most similar to placebo, whereas 40 mg lorcaserin was not associated with any previously experienced drug. The highest lorcaserin dose, 60 mg showed weak similarity to Ecstasy or LSD (mean or median values <40) but to no other drugs.
- In general, subjective effects were near maximal at 40 mg lorcaserin, with only a few measures showing further increases at 60 mg lorcaserin (e.g., Any Effects VAS, Spaced Out VAS, Feeling Sick VAS, and Bad Effects VAS). The near maximal responses on Any Effects VAS confirm that an appropriate range of lorcaserin doses was evaluated.
- Based on the objective measure (CRT) lorcaserin did not have marked effects on reaction time or accuracy. Some decrements in performance were observed at the 60 mg lorcaserin dose; however, these were generally lower than those seen following administration of zolpidem, which showed the expected impairments in reaction time.
- Examination of the time course of lorcaserin’s effects on CRT indicates that the decrements in performance (e.g., Emax observed for TRT) were not observed at the expected time of peak concentrations of lorcaserin but were mainly observed around 12 hours post-dose.

Conclusion

The Sponsor concluded that while lorcaserin had modest “at the moment” positive effects compared to placebo, at suprathreshold doses, lorcaserin was significantly disliked compared to placebo, zolpidem and ketamine, and was associated with prominent negative effects and little sedative or perceptual/dissociative effects. Furthermore, subjects, selected based on their recreational drug use experience and subjective responses to zolpidem and ketamine, showed no willingness to take lorcaserin again and ascribed it and placebo the lowest perceived value possible.

The Sponsor also stated that based on the overall pattern of responding on the subjective measures evaluated in this study, it is evident that lorcaserin is disliked and does not have reinforcing effects across the range of doses tested nor is it associated with notable perceptual or dissociative effects. Furthermore, the AEs reported in the current study demonstrated that suprathreshold doses are associated with negative side effects that would mitigate the risk of abuse. Therefore, it can be concluded that the risk for abuse associated with lorcaserin would be lower than both ketamine, a Schedule III drug, and zolpidem, a Schedule IV drug.

2.2 Data Location

The dataset qsmsdeep.xpt used in the reviewer’s analysis is listed in Section 5.3.5.4.25.2.1 Data Listing Dataset at the original submission from the Sponsor dated 12/18/2009.

2.3 Reviewer’s Primary Analysis

2.3.1 Descriptive statistics on primary measure Drug Liking VAS

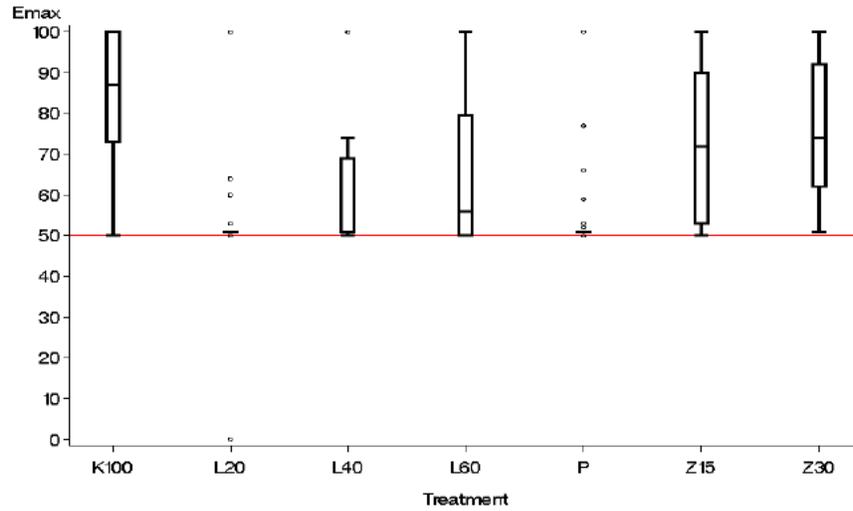
Tables 1 summarizes the mean, standard error, minimum, the first quartile (Q₁), median, the third quartile (Q₃), and maximum for Emax of Drug Liking VAS.

Table 1: Summary Statistics for Emax of Drug Liking VAS

Treatment	N	Mean	StdErr	Min	Q1	Med	Q3	Max
K100	29	83.86	3.11	50	73	87	100	100
L20	29	54.03	1.83	50	51	51	51	100
L40	29	63.62	3.44	50	51	51	70	100
L60	28	66.07	3.78	50	50	56	84.75	100
P	29	56.10	2.49	50	51	51	51.5	100
Z15	29	74.17	3.60	51	52.5	72	94	100
Z30	29	77.03	3.18	51	62.5	74	92.5	100

The distributions of the Emax of Drug Liking VAS by treatments are described by boxplots in Figures 1, where the middle line in each boxplot is the median response to the treatment.

Figure 1: Boxplots for Emax of Drug Liking VAS



Drug Liking VAS was defined on a bipolar scale. The red line on Figure 1 indicates the neutral response. From Figure 1, one may notice that all the peak responses for each treatment were greater than or equal to 50, the neutral response. The distribution of L20 was very similar to that of placebo. The median response to L40 and the 25th percentile of L60 were very close to 50. However, 25% of study subjects responded to L60 greater than 80. In terms of median that of L60 is still greatly below those of Z15, Z30 and K10.

Similarly, Table 2 summarizes the mean, standard error, minimum, the first quartile (Q_1), median, the third quartile (Q_3), and maximum for Emin of Drug Liking VAS, where Emin is the minimum response during 8 hours after dosing.

Table 2: Summary Statistics for Emin of Drug Liking VAS

Treatment	N	Mean	StdErr	Min	Q1	Med	Q3	Max
K10	29	49.69	2.41	0	50	50	50	90
L20	29	34.34	4.13	0	0	50	50	50
L40	29	18.97	3.85	0	0	11	41.5	50
L60	28	13.32	2.90	0	0	8	22.75	50
P	29	42.41	2.92	0	47.5	50	50	50
Z15	29	40.83	3.18	0	36.5	50	50	51
Z30	29	40.11	3.16	0	31	49	50	59

Emin of Drug Liking VAS presents the maximum drug disliking by a subject. Thus, the lower the response to Drug Liking VAS, the higher the drug disliking. For L40 and L60 approximately 75 percent of subjects had Emin of Drug Liking VAS below 50. Twenty five percent of subjects had strong drug disliking to lorcaserin with a score 0 from the 25% percentiles for all doses of lorcaserin. Compared to both positive control drugs, it appears that lorcaserin was more disliked.

The distributions of the Emin of Drug Liking VAS by treatments are described by boxplots in Figures 2.

Figure 2: Boxplots for Emin of Drug Liking VAS

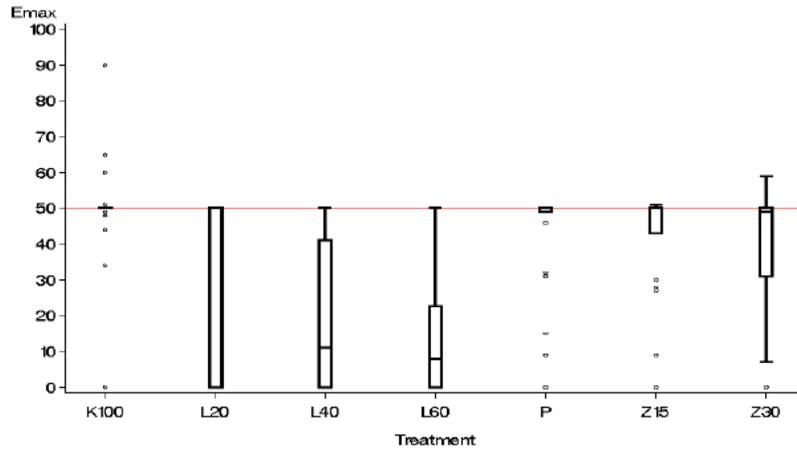
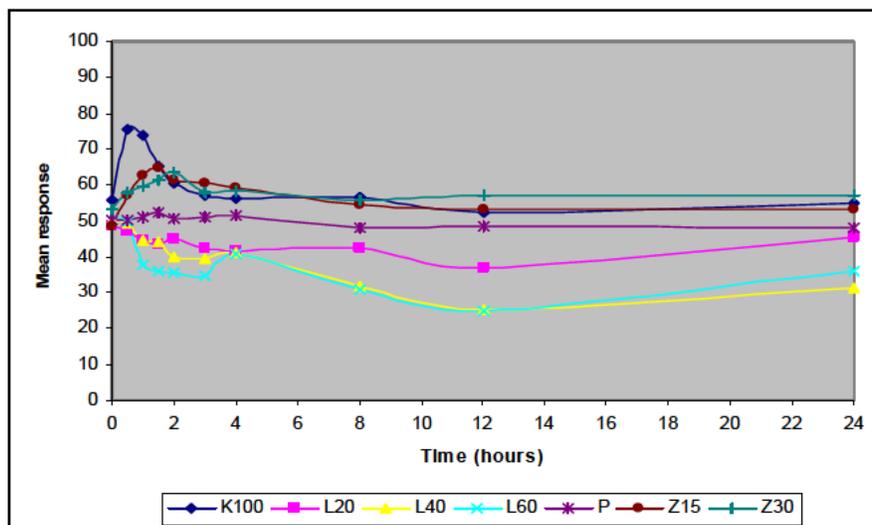


Figure 3 shows the mean time course profiles for Drug Liking VAS. Each point on the graph was calculated by averaging responses to Drug Liking VAS by treatment at a particular time point. This is the graph that most sponsors like to present to the FDA. The disadvantage of the graph is that each subject may reach the highest response at different time point. By averaging responses at each time point by treatment, the peak value of the mean responses for each treatment may be substantially lower than the mean of Emax of the treatment, which is the main interest of the CSS. Nevertheless, this graph, for the primary measure Drug Liking VAS, shows that the mean time course profiles from all three doses of lorcaserin were below 50. This indicates on the average at each time point, the study subjects appear to dislike the drug.

Figure 3: Mean Time Course Profiles for Drug Liking VAS



Notice that the summary statistics and the graphics did not take into account the possible effects due to treatment periods and sequences used in the crossover design study.

2.3.2 Statistical testing

2.3.2.1 Study model and statistical methodologies

The statistical model used in the reviewer’s primary analysis includes sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. The model assumption of the normality of error terms was checked using Shapiro-Wilk W-test on the residuals. If the normal assumption was not satisfied, the rank data (ranking responses within subject) were used to obtain the p-value of the test for difference in medians between two treatments.

2.3.2.2 Results

Table 3 lists the least square means and corresponding standard errors of the estimated means for Emax of Drug Liking VAS by treatment.

Table 3: Estimation of Emax of Drug Liking VAS for Individual Treatments

Statistic \ Treatment	K100	L20	L40	L60	P	Z15	Z30
N	29	29	29	28	29	29	29
LSmean	83.86	53.77	62.78	66.47	55.66	73.28	76.76
StdErr	3.32	3.33	3.37	3.43	3.32	3.33	3.32

Table 4 lists the treatment comparisons from the reviewer’s primary analysis on Emax of Drug Liking VAS. Because the p-value of the Shapiro-Wilk W-test on residuals is 0.0029, a rank analysis was performed by this reviewer. Thus, the difference of the least square means, standard error, and p-value of the rank-test are listed in Table 3. The least square means and standard errors are on the original scales.

The statistical analysis results on Emax of Drug Liking VAS show that at $\alpha=0.05$ (two-sided)

- ketamine 100 mg and two doses of zolpidem had significantly higher median response than placebo. That is, both positive control drugs validated the study;
- the medians of three doses of lorcaserin were significantly lower than that of ketamine 100 mg and that of any dose of zolpidem;
- the medians of lorcaserin 40 mg and lorcaserin 60 mg were higher than that of placebo, and the median of lorcaserin 20 mg was less than that of placebo, however, those differences were not statistically significant.

Table 4: Treatment Comparisons for Emax of Drug Liking VAS

TRT1	TRT2	N	LSmean Diff	StdErr	p-value (Rank)	Comments
K100	P	29	28.20	4.004	<.0001	Validation Tests
Z15	P	29	17.62	3.999	<.0001	
Z30	P	29	21.10	3.999	<.0001	
K100	L20	29	30.08	4.013	<.0001	Compare the new drug with a Schedule III drug
K100	L40	29	21.08	4.032	<.0001	
K100	L60	28	17.39	4.088	<.0001	
Z15	L20	29	19.51	4.000	<.0001	Compare the new drug with two doses of a schedule IV drug
Z30	L20	29	22.99	4.021	<.0001	
Z15	L40	29	10.50	4.017	0.0011	
Z30	L40	29	13.98	4.053	<.0001	
Z15	L60	28	6.81	4.142	0.0054	
Z30	L60	28	10.30	4.075	0.0001	
L20	P	29	-1.89	4.001	0.4975	Compare the new drug with placebo
L40	P	29	7.12	4.036	0.3025	
L60	P	28	10.80	4.102	0.1529	

Table 5 lists the least square means and corresponding standard errors of the estimated means on Emin of Drug Liking VAS by treatment.

Table 5: Estimation of Emin of Drug Liking VAS for Individual Treatments

Statistic \ Treatment	K100	L20	L40	L60	P	Z15	Z30
N	29	29	29	28	29	29	29
LSmean	83.86	53.77	62.78	66.47	55.66	73.28	76.76
StdErr	3.32	3.33	3.37	3.43	3.32	3.33	3.32

Table 6 lists the treatment comparisons from the reviewer's primary analysis on Emin of Drug Liking VAS. Because p-value of Shapiro-Wilk W-test on residuals is 0.3010, the difference of the least square means, standard error and p-value of the t-test are listed.

The study results on Emin of Drug Liking VAS show that at $\alpha=0.05$ (two-sided)

- no significant difference in mean was found between any positive control drug and placebo;
- means of three doses of lorcaserin were lower than that of any positive control drug. The differences were statistically significant except in comparison of lorcaserin 20 mg vs. each dose of zolpidem;
- means of lorcaserin 40 mg and 60 mg were significantly lower than that of placebo.

Table 6: Treatment Comparisons for Emin of Drug Liking VAS

TRT1	TRT2	N	LSmean Diff	StdErr	p-value	Comments
K100	P	29	7.98	4.199	0.0593	Positive control drugs compare to placebo
Z15	P	29	-2.10	4.195	0.6175	
Z30	P	29	-0.94	4.281	0.8273	
K100	L20	29	16.42	4.210	0.0001	Compare the new drug to a Schedule III drug
K100	L40	29	31.60	4.230	<.0001	
K100	L60	28	35.31	4.290	<.0001	
Z15	L20	29	6.34	4.195	0.1327	Compare the new drug to two doses of a schedule IV drug
Z30	L20	29	7.50	4.304	0.0833	
Z15	L40	29	21.52	4.214	<.0001	
Z30	L40	29	22.69	4.361	<.0001	
Z15	L60	28	25.24	4.346	<.0001	
Z30	L60	28	26.40	4.343	<.0001	
L20	P	29	-8.44	4.197	0.046	Compare the new drug to placebo
L40	P	29	-23.62	4.235	<.0001	
L60	P	28	-27.34	4.303	<.0001	

Overall, the study subjects appeared to dislike lorcaseerin.

2.4 Reviewer’s Secondary Analysis

The abuse potential measures considered in this reviewer’s secondary analysis are balance effects, positive effects and sedative effects. The summary statistics on Emax (or Emin) for all secondary abuse potential measures used in the Sponsor’s analysis are presented as Tables 14-20 in Appendix.

The statistical methodologies used in this reviewer’s secondary analysis are the same as those in the primary analysis.

Tables 4 and 5 list the least square means and the standard errors, and treatment comparisons, respectively, for balance effects.

Table 7: Estimation for Emax (or Emin) of Balance Effects for Individual Treatments

TRT	Bad Effect VAS		Good Effect VAS		Overall Liking VAS		Take Drug Again VAS	
	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr
K100	47.79	3.31	84.57	3.16	72.25	4.56	75.01	5.36
L20	33.97	3.32	53.05	3.17	42.48	4.57	28.82	5.37
L40	21.11	3.37	61.88	3.22	31.21	4.65	27.47	5.46
L60	14.70	3.44	69.51	3.28	36.41	4.75	23.50	5.59
P	46.16	3.31	53.62	3.16	48.91	4.56	42.09	5.36
Z15	42.22	3.32	76.51	3.17	61.47	4.57	62.08	5.38
Z30	41.03	3.43	76.61	3.17	68.27	4.56	68.74	5.36

Table 8: Treatment Comparisons for Balance Effects

Abuse Potential Measure	Bad Effects VAS		Good Drug Effects VAS		Overall Liking VAS		Take Drug Again VAS	
	LSm diff	p-Value	LSm diff	p-Value	LSm diff	p-Value	LSm diff	p-Value
K100 vs P	1.63	0.4934	30.95	<.0001	23.34	0.0002	32.92	<.0001
Z15 vs P	-3.94	0.3677	22.89	<.0001	12.56	0.0447	19.99	0.0079
Z30 vs P	-5.13	0.3874	23.00	<.0001	19.36	0.0022	26.64	0.0004
K100 vs L20	13.82	0.0003	31.52	<.0001	29.77	<.0001	46.19	<.0001
K100 vs L40	26.69	<.0001	22.69	<.0001	41.04	<.0001	47.53	<.0001
K100 vs L60	33.09	<.0001	15.06	0.0003	35.84	<.0001	51.51	<.0001
L20 vs P	-12.18	0.0028	-0.57	0.885	-6.43	0.3022	-13.28	0.0762
L40 vs P	-25.05	<.0001	8.27	0.039	-17.70	0.0053	-14.62	0.0531
L60 vs P	-31.46	<.0001	15.90	0.0001	-12.50	0.0513	-18.59	0.0158
L20 vs Z15	-8.25	0.0346	-23.46	<.0001	-18.99	0.0026	-33.26	<.0001
L20 vs Z30	-7.06	0.0375	-23.57	<.0001	-25.79	<.0001	-39.92	<.0001
L40 vs Z15	-21.12	<.0001	-14.62	0.0003	-30.26	<.0001	-34.60	<.0001
L40 vs Z30	-19.92	<.0001	-14.73	0.0003	-37.06	<.0001	-41.26	<.0001
L60 vs Z15	-27.52	<.0001	-6.99	0.0883	-25.07	0.0001	-38.58	<.0001
L60 vs Z30	-26.33	<.0001	-7.10	0.0787	-31.86	<.0001	-45.23	<.0001

Note: Bad Effects is Emin of Good and Bad Effects. Good Effects is Emax of Good and Bad Effects.

Good and Bad Effects VAS were measured on a VAS bipolar scale. Thus, the evaluation of Bad Effects VAS and Good Effects VAS were based on Emin of Good and Bad Effects VAS and Emax of Good and Bad Effects VAS, respectively. The study results show that

- two positive control drugs, ketamine and zolpidem, had significantly higher mean (or median) response than placebo for Good Effects VAS on a bipolar scale, Overall Liking VAS and Take Drug Again VAS. Thus, the positive control drugs validated the study for balance effects;
- three doses of lorcaserin had significantly lower mean (or median) responses than placebo on Bad Effects VAS on a bipolar scale. Lorcaserin also had lower mean (or median) responses than zolpidem on Bad Effects. The differences were statistically significant except for the low dose of lorcaserin;
- for Good Effects on a bipolar scale, L20 and L40 had significantly lower mean (or median) response than both positive control drugs, and L60 had significantly lower mean (or median) response than K100, but had no significant difference with any dose of zolpidem. When compared to placebo, L40 and L60 had significantly higher mean (or median) response, but L20 did not show the difference to be significant;
- For Overall Drug Liking, three doses of lorcaserin had significantly lower mean (or median) responses than both positive control drugs. The differences in mean responses between three doses of lorcaserin and placebo were negative. That means overall the study subjects like placebo more than lorcaserin. But, the differences in mean (or median) responses were not statistically significant for L20 and L60;
- For Take Drug Again VAS, three doses of lorcaserin had lower mean (or median) responses to both ketamine and zolpidem. Lorcaserin had lower mean (or median) than placebo. This difference for L60 was statistically significant.

Tables 9 and 10 list the least square means and corresponding standard errors, and treatment comparisons for positive effects, respectively.

Table 9: Estimation for Emax of Positive Effects for Individual Treatments

TRT	ARCI MBG		Good Effects		High VAS	
	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr
K100	5.18	0.87	85.76	5.89	92.61	6.08
L20	1.16	0.87	23.56	5.91	22.98	6.10
L40	2.40	0.88	45.57	5.98	57.62	6.18
L60	2.84	0.90	57.73	6.09	74.21	6.30
P	1.22	0.87	27.74	5.89	21.61	6.08
Z15	3.67	0.87	76.69	5.91	72.07	6.10
Z30	5.29	0.87	82.90	5.90	80.06	6.09

Table 10: Treatment Comparisons for Positive Effects

Abuse Potential Measure	ARCI MBG		Good Effects VAS		High VAS	
	LSm diff	p-Value	LSm diff	p-Value	LSm diff	p-Value
K100 vs P	3.96	<.0001	58.02	<.0001	70.99	<.0001
Z15 vs P	2.45	0.0124	48.95	<.0001	50.45	<.0001
Z30 vs P	4.07	<.0001	55.15	<.0001	58.45	<.0001
K100 vs L20	4.01	<.0001	62.20	<.0001	69.63	<.0001
K100 vs L40	2.77	0.0051	40.19	<.0001	34.99	<.0001
K100 vs L60	2.34	0.0194	28.03	0.0002	18.40	0.0184
L20 vs P	-0.06	0.9520	-4.18	0.5641	1.36	0.8571
L40 vs P	1.18	0.2281	17.83	0.0156	36.01	<.0001
L60 vs P	1.62	0.1054	29.99	<.0001	52.60	<.0001
L20 vs Z15	-2.51	0.0105	-53.13	<.0001	-49.09	<.0001
L20 vs Z30	-4.13	<.0001	-59.33	<.0001	-57.08	<.0001
L40 vs Z15	-1.27	0.1949	-31.12	<.0001	-14.44	0.0589
L40 vs Z30	-2.89	0.0037	-37.33	<.0001	-22.44	0.0039
L60 vs Z15	-0.83	0.4088	-18.96	0.0123	2.15	0.7844
L60 vs Z30	-2.45	0.0139	-25.16	0.0008	-5.85	0.4486

Note: Good Effects in this table is on a unidirectional scale.

For the positive effects in Table 9-10, the results are summarized below:

- Both positive control drugs had significantly higher mean responses than placebo on any of positive effects in the table. Thus, the positive control drugs validated the study on positive effects.
- The mean (median) response of K100 was significantly higher than that of any dose of lorcaserin.
- There was no significant difference in mean (or median) response between L20 and placebo, and the mean (or median) responses of L20 were significantly lower than that of each dose zolpidem on all positive effects;

- The mean (or median) responses of L40 and L60 were significantly lower than that of each dose of zolpidem on Good Effect VAS. This significance was also showed between L40 and Z30 on ARCI MBG and High VAS, and between L60 and Z30 on ARCI MBG;
- There was no significant difference in mean (or median) responses between L40 and Z15, and between L60 and Z15 on ARCI MBG, and between L40 and Z15, between L60 and each dose of zolpidem on High VAS.

This reviewer also analyzed the responses to Sedative Effects. Tables 11 and 12 present the results of estimation for Emax and comparisons between treatments.

Table 11: Estimation for Emaxs of Sedative Effects for Individual Treatments

TRT	ARCI PCAG		Drowsiness VAS	
	LSmean	StdErr	LSmean	StdErr
K100	3.12	0.57	-16.27	4.24
L20	1.60	0.57	-5.54	4.25
L40	3.55	0.58	-9.75	4.30
L60	4.26	0.59	-18.47	4.38
P	1.70	0.57	-9.59	4.24
Z15	5.38	0.57	-31.65	4.25
Z30	6.73	0.57	-39.85	4.37

The statistical analysis results from sedative effects are summarized below:

- Compared to placebo, K100 had barely significantly higher mean (or median) response on ARCI PCAG and no significant differences in mean (or median) on Drowsiness VAS.
- When comparing mean response of K100 to that of lorcaserin, no significant results were found for sedative effects except between K100 and L20, where K100 had significantly higher sedative effects on both ARCI PCAG and Drowsiness VAS.
- Compared to placebo, significantly higher mean responses were found for L40 and L60 on ARCI PCAG.
- Lorcaserin had lower mean response than zolpidem on ARCI PCAG. The differences are statistically significant except between L60 and Z15. Lorcaserin had significantly higher mean response than zolpidem on Drowsiness VAS.

Note that Emin of Alertness/Drowsiness VAS presented as Drowsiness VAS, the lower response was the higher drowsiness. Therefore, lorcaserin had less sedative effects than both zolpidem and ketamine.

Table 12: Treatment Comparisons for Sedative Effects

Abuse Potential Measure	ARCI PCAG		Drowsiness VAS	
	LSm diff	p-Value	LSm diff	p-Value
K100 vs P	1.42	0.0458	-6.68	0.2376
Z15 vs P	3.67	<.0001	-22.06	0.0001
Z30 vs P	5.02	<.0001	-30.26	<.0001
K100 vs L20	1.51	0.0334	-10.73	0.0078
K100 vs L40	-0.43	0.543	-6.51	0.3901
K100 vs L60	-1.15	0.1128	2.20	0.758
L20 vs P	-0.10	0.8906	4.05	0.1311
L40 vs P	1.85	0.01	-0.16	0.7534
L60 vs P	2.56	0.0005	-8.88	0.145
L20 vs Z15	-3.77	<.0001	26.12	<.0001
L20 vs Z30	-5.12	<.0001	34.32	<.0001
L40 vs Z15	-1.83	0.0106	21.90	0.0004
L40 vs Z30	-3.17	<.0001	30.10	<.0001
L60 vs Z15	-1.11	0.1289	13.18	0.018
L60 vs Z30	-2.46	0.0008	21.39	0.003

2.5 Descriptive analysis for Emax of Hallucination VAS

Per Dr. Katherine Bonson’s request, this reviewer did some descriptive statistics for Emax of Hallucination (See Table 19 in Appendix). Table 13 gives the study subjects who had scores 50 or more to L40 and L60 on Emax of Hallucination VAS.

Table 13: Subjects Had Hallucination Score Higher than 50

Subject	TRT	Emax
9004	L60	65
9006	L40	66
9006	L60	70
9009	L60	51
9024	L40	77
9024	L60	69
9039	L40	51
9042	L60	58
9043	L40	51
9072	L40	100
9072	L60	81
9104	L60	65

The mean time course profiles for Hallucinations VAS are presented in Figure 4. The peak mean responses to K100, Z15 and Z30 for Hallucinations VAS were reached at hours 0.5, 0.5 and 1.5 with scores approximately 20, 14, and 30, respectively. Although the peak mean responses of lorcaserin was lower than that of ketamine and zolpidem from Figure 4, the mean responses of L40 and L60 were increasing during the first 4 hours. Because the Sponsor did not collect the data at hours 5, 6, and 7 for Hallucinations VAS, the peak mean response to lorcaserin may be even higher than what was observed, and the peaks may be reached at a later time than hour 4.

Figure 4: Mean Time Course Profiles for Hallucinations VAS

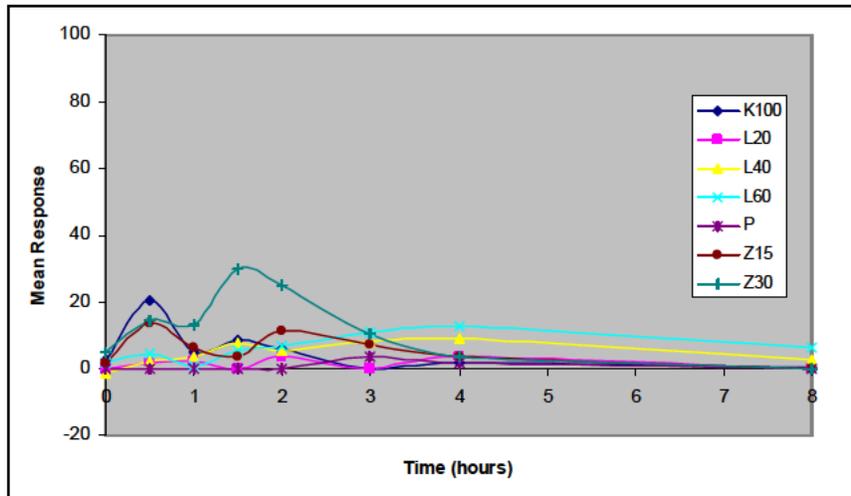


Figure 5: Boxplots for Emax of Hallucinations VAS

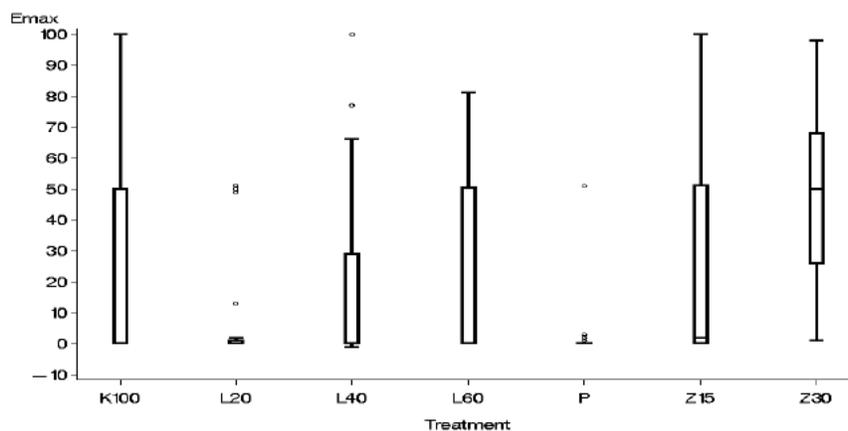


Figure 5 presents the distributions of Emax of Hallucinations by treatment. The distribution of L20 is very similar to that of placebo. As was shown in Table 19, 50% of study subjects had score 0 to three doses of lorcaserin on Emax of Hallucinations VAS. The differences between two doses of lorcaserin, 40 mg and 60 mg, and placebo on this measure are evident.

3. Conclusion

Table 10 summarizes the results from this reviewer’s primary and secondary analysis.

Table 14: Summary for Comparisons among Treatments ($\alpha=0.05$, two-sided)

Abuse Potential Measure	K100 vs P	Z15 vs P	Z30 vs P	K100 vs L20	K100 vs L40	K100 vs L60	L20 vs P	L40 vs P	L60 vs P	L20 vs Z15	L20 vs Z30	L40 vs Z15	L40 vs Z30	L60 vs Z15	L60 vs Z30	Measure
Drug Liking	S	S	S	S	S	S	NS-	NS	NS	S-	S-	S-	S-	S-	S-	Primary
Drug Disliking	NS	NS-	NS-	S	S	S	S-	S-	S-	NS-	NS-	S-	S-	S-	S-	Balance Effects
Bad Effects	NS	NS-	NS-	S	S	S	S-	S-	S-	S-	S-	S-	S-	S-	S-	
Good Effects	S	S	S	S	S	S	NS-	S	S	S-	S-	S-	S-	NS-	NS-	
Overall Drug Liking	S	S	S	S	S	S	NS-	S-	NS-	S-	S-	S-	S-	S-	S-	
Take Drug Again	S	S	S	S	S	S	NS-	NS-	S-	S-	S-	S-	S-	S-	S-	
ARCI MBG	S	S	S	S	S	S	NS-	NS	NS	S-	S-	NS-	S-	NS-	S-	Positive Effects
Good Effects	S	S	S	S	S	S	NS-	S	S	S-	S-	S-	S-	S-	S-	
High	S	S	S	S	S	S	NS	S	S	S-	S-	NS-	S-	NS	NS-	
ARCI PCAG	S	S	S	S	NS-	NS-	NS-	S	S	S-	S-	S-	S-	NS-	S-	Sedative Effects
Drowsiness	NS-	S-	S-	S-	NS-	NS	NS	NS-	NS-	S	S	S	S	S	S	

Note:

S – Significant.

NS – Not Significant.

The negative sign with the S or NS shows the sign of mean (or median) difference (the first treatment – the second treatment).

When Emin is used for endpoint, the lower mean (or median) is the higher drug disliking, bad effects or drowsiness.

This reviewer summarizes the study findings as follows:

- Both positive control drugs zolpidem and ketamine validated the study on the primary measure Drug Liking VAS and all positive measures from both balance effects and positive effects.
- Ketamine had drug disliking and bad effects and drowsiness similar to placebo, while zolpidem had drug disliking and bad effects similar to placebo.
- Compared to two positive control drugs, all doses of lorcaserin showed significantly lower drug liking.
- Lorcaserin had significantly higher bad effects and drug disliking when compared to zolpidem except lorcaserin 20 mg vs. zolpidem 15 mg, and had significantly higher drug disliking, compared to ketamine.
- The positive effects of lorcaserin are lower than those of zolpidem. Some of these comparisons were statistically significant.
- Lorcaserin had significantly lower good effects, euphoria effects and high than ketamine. Subjects clearly like ketamine more than lorcaserin, which can be seen from significant difference between lorcaserin and ketamine on Overall Drug Liking VAS, and Take Drug Again VAS.
- Compared to zolpidem, Lorcaserin had lower sedative effects. Except for lorcaserin 60 mg on ARCI PCAG, all differences were statistically significant.

- Even though the results showed that there was no significant difference between lorcaserin 60 mg and zolpidem on Good Effects VAS (bipolar scale) and High VAS, lorcaserin 60 mg had significantly lower Good Effects VAS than zolpidem on a unidirectional scale, and significantly lower response to Overall Drug Liking VAS and Take Drug Again VAS.
- Lorcaserin 40 mg and 60 mg had significantly higher Good Effects VAS (in both bipolar and unidirectional scales) and High VAS than placebo while lorcaserin 40 mg and 60 mg had significantly higher Drug Disliking VAS and Bad Effects VAS than placebo in a bipolar scale.
- Lorcaserin 20 mg appears similar to placebo in all abuse measures except bad effects and drug disliking in a bipolar scale, in which lorcaserin had significantly higher bad effects and drug disliking.

For Hallucinations VAS, Dr. Bonson will give comments in her review report.

Appendix

Table 15: Summary Statistics for Emax (or Emin) of Balance Effects

Abuse Potential Measure	TRT	N	Mean	StdErr	Min	Q1	Med	Q3	Max
Overall Drug Liking VAS (Emax)	K100	29	72.31	3.74	49	51	70	94.5	100
	L20	29	43.45	4.18	0	49.5	50	50.5	100
	L40	29	33.24	6.05	0	0	23	50.5	100
	L60	28	34.86	5.67	0	7.25	30	51	100
	P	29	49.76	3.51	0	50	50	51	100
	Z15	29	63.45	4.26	0	50	58	82	100
	Z30	29	68.28	3.67	37	51	61	92	100
Take Drug Again VAS (Emax)	K100	29	74.90	4.69	11	56.5	79	100	100
	L20	29	30.00	5.31	0	0	49	51	100
	L40	29	29.00	6.20	0	0	17	51	100
	L60	28	22.18	6.18	0	0	3.5	42	100
	P	29	42.90	4.75	0	25.5	50	51	100
	Z15	29	64.10	5.03	0	50	64	90	100
	Z30	29	68.52	4.39	23	50.5	59	96	100
Good and Bad Effects VAS (Emax)	K100	29	84.34	3.15	50	70	93	100	100
	L20	29	52.79	1.28	49	50	51	51	81
	L40	29	62.66	3.22	50	50	51	68	100
	L60	28	68.50	4.09	37	50	61.5	89	100
	P	29	53.48	1.82	50	51	51	51	100
	Z15	29	76.90	3.61	50	58.5	79	100	100
	Z30	29	76.48	3.18	51	60	76	92.5	100
Good and Bad Effects VAS (Emin)	K100	29	47.07	1.83	0	49.5	50	50	51
	L20	29	33.41	4.01	0	5	49	50	50
	L40	29	21.52	3.81	0	0	25	40	50
	L60	28	13.18	3.41	0	0	0	30.25	56
	P	29	46.07	1.85	3	49	50	50	50
	Z15	29	42.31	3.06	0	45.5	50	50	56
	Z30	29	40.33	3.75	0	32	49	50	79
Drug Liking VAS (Emin)	K100	29	49.69	2.41	0	50	50	50	90
	L20	29	34.34	4.13	0	0	50	50	50
	L40	29	18.97	3.85	0	0	11	41.5	50
	L60	28	13.32	2.90	0	0	8	22.75	50
	P	29	42.41	2.92	0	47.5	50	50	50
	Z15	29	40.83	3.18	0	36.5	50	50	51
	Z30	29	40.11	3.16	0	31	49	50	59

Table 16: Summary Statistics for Emax of Positive Effects

Abuse Potential Measure	TRT	N	Mean	StdErr	Min	Q1	Med	Q3	Max
High VAS	K100	29	92.034	3.70	0.00	91.5	100	100	100
	L20	29	21.345	7.33	-55.00	0	0	54.5	100
	L40	29	55.586	7.50	-49.00	19.5	56	94.5	100
	L60	28	74.679	6.66	0.00	63	95.5	100	100
	P	29	19.655	5.61	-50.00	0	3	50.5	79
	Z15	29	69.828	5.04	1.00	56	69	92.5	100
	Z30	29	79.276	4.47	0.00	70.5	85	99	100
Good Effect VAS	K100	29	85.83	4.33	0	78	98	100	100
	L20	29	23.62	6.04	0	0	0	55	100
	L40	29	45.86	6.81	0	1	51	75.5	100
	L60	28	58.54	6.65	0	25.25	67.5	87.75	100
	P	29	27.59	6.06	0	0	4	51	100
	Z15	29	77.34	4.24	0	64	82	96.5	100
	Z30	29	83.10	2.99	49	72	83	100	100
ARCI Morphine Benezdrine Group	K100	29	5.21	1.03	0	0	4	10	16
	L20	29	1.21	0.56	-1	0	0	1	12
	L40	29	2.41	0.80	0	0	1	2	16
	L60	28	3.00	0.79	0	0	1	5.5	16
	P	29	1.17	0.43	0	0	0	1	10
	Z15	29	3.72	0.93	-1	0	2	6	16
	Z30	29	5.31	0.98	0	0.5	3	10	15

Table 17: Summary Statistics for Emax of Negative Effects

Abuse Potential Measure	TRT	N	Mean	StdErr	Min	Q1	Med	Q3	Max
Bad Effect VAS	K100	29	25.03	5.73	0	0	7	55.5	100
	L20	29	35.83	7.38	0	0	9	74.5	100
	L40	29	75.41	5.76	0	61.5	85	100	100
	L60	28	88.82	3.33	40	85.5	100	100	100
	P	29	29.90	6.22	0	0	2	51	100
	Z15	29	34.17	6.35	0	0	31	58.5	100
	Z30	29	52.59	5.83	0	29	51	79	100
Feeling Sick VAS	K100	29	9.62	4.47	0	0	0	1	100
	L20	29	24.59	6.41	-3	0	0	58.5	100
	L40	29	61.97	6.94	0	16	73	94	100
	L60	28	73.50	6.14	0	51.25	89	100	100
	P	29	18.90	5.40	-1	0	0	50.5	100
	Z15	29	16.41	5.78	-50	0	1	49.5	100
	Z30	29	35.17	6.87	0	0.5	28	62.5	100
ARCI Lysergic Acid Diethylamide	K100	29	3.38	0.44	0	1	4	5.5	7
	L20	29	1.48	0.35	0	0	1	2.5	7
	L40	29	3.45	0.47	-1	1.5	4	5	8
	L60	28	4.71	0.52	0	2.25	5	7	10
	P	29	0.52	0.21	-2	0	0	1	4
	Z15	29	1.97	0.35	0	0.5	1	3	8
	Z30	29	3.00	0.47	0	1	2	5	9

Table 18: Summary Statistics for Emax of Sedative Effects

Abuse Potential Measure	TRT	N	Mean	StdErr	Min	Q1	Med	Q3	Max
ARCI Pent. Chlorpromazine Alcohol Group	K100	29	3.28	0.56	0	0	3	5.5	9
	L20	29	1.59	0.36	0	0	1	3	7
	L40	29	3.86	0.68	0	1	3	5	13
	L60	28	4.11	0.52	0	2	3	6.75	9
	P	29	1.79	0.49	-1	0	1	2	9
	Z15	29	5.48	0.56	1	3	6	8	10
	Z30	29	6.90	0.64	1	5	7	9	13
Alertness /Drowsiness VAS (Emin)	K100	29	-17.31	4.16	-61	-38	-9	0	14
	L20	29	-5.48	2.49	-50	-4	0	0	15
	L40	29	-12.83	3.91	-66	-19.5	-4	0	17
	L60	28	-17.11	4.97	-92	-21.5	-6	0	8
	P	29	-10.52	3.42	-66	-9.5	-1	0	0
	Z15	29	-32.93	5.39	-91	-52	-18	-12.5	0
	Z30	29	-41.00	5.43	-94	-50	-43	-23	0

Table 19: Summary Statistics for Emax of Perceptual/Dissociative Effects

Abuse Potential Measure	TRT	N	Mean	StdErr	Min	Q1	Med	Q3	Max
Hallucinations VAS	K100	29	21.14	6.03	0	0	0	50	100
	L20	29	9.14	3.54	0	0	0	1.5	51
	L40	29	17.14	5.33	-1	0	0	39.5	100
	L60	28	20.68	5.63	0	0	0	50.75	81
	P	29	3.90	2.43	0	0	0	0.5	51
	Z15	29	25.10	6.17	0	0	2	51	100
	Z30	29	48.83	5.65	1	22.5	50	69.5	98
Detached VAS	K100	29	41.52	6.94	0	0	50	73	100
	L20	29	11.90	4.38	0	0	0	3.5	79
	L40	29	23.62	6.19	-50	0	2	51	100
	L60	28	25.82	6.40	0	0	0	59.25	95
	P	29	11.69	4.19	0	0	0	5	66
	Z15	29	29.79	5.63	0	0.5	22	56.5	80
	Z30	29	43.14	5.76	0	5.5	50	57	100
Floating VAS	K100	29	55.97	6.86	0	16.5	59	87.5	100
	L20	29	12.97	4.37	0	0	0	25	68
	L40	29	28.83	5.28	0	0	22	51	81
	L60	28	29.29	6.54	0	0	4	63	100
	P	29	14.86	4.68	-6	0	0	49.5	75
	Z15	29	37.24	6.50	0	1	49	69.5	95
	Z30	29	52.31	5.73	0	35.5	52	77	97
Sounds Louder VAS	K100	29	11.38	3.08	0	0	1	24.5	50
	L20	29	1.17	0.55	-1	0	1	1	16
	L40	29	7.10	3.07	-26	0	1	7.5	50
	L60	28	7.71	2.72	0	0	1	8.25	49
	P	29	2.07	1.32	0	0	1	1	39
	Z15	29	5.31	1.92	-1	0.5	1	2	35
	Z30	29	9.55	2.49	0	0.5	2	16	50
Spaced Out VAS	K100	29	53.52	7.17	0	2.5	64	87.5	100
	L20	29	17.62	5.22	0	0	0	49.5	82
	L40	29	33.24	6.83	-5	0	12	65.5	100
	L60	28	48.25	7.40	0	0	50.5	83.5	100
	P	29	17.14	4.81	0	0	0	50	73
	Z15	29	48.62	6.73	0	6.5	61	78	100
	Z30	29	65.10	5.29	0	49.5	72	84	100
Vision Clear Crisp VAS	K100	29	4.69	2.35	-19	0	1	1	50
	L20	29	3.31	1.92	-1	0	0	1	46
	L40	29	4.62	2.34	-7	0	1	1	50
	L60	28	6.86	2.62	-4	0	0.5	2.75	48
	P	29	1.03	0.32	0	0	0	1.5	8
	Z15	29	5.59	2.76	-15	0	0	2.5	50
	Z30	29	7.86	2.68	0	0	1	11	50

Table 20: Summary Statistics on Other Drug Effects

Abuse Potential Measure	TRT	N	Mean	StdErr	Min	Q1	Med	Q3	Max
Any Effect VAS	K100	29	92.90	3.77	0	94	100	100	100
	L20	29	47.86	7.88	0	0	53	93.5	100
	L40	29	87.00	4.82	0	84	100	100	100
	L60	28	95.43	2.04	51	100	100	100	100
	P	29	33.69	6.87	0	0	27	58.5	100
	Z15	29	85.90	4.38	0	77	99	100	100
	Z30	29	91.34	3.23	30	94	100	100	100
Dizziness VAS	K100	29	37.07	7.48	-24	0	23	72.5	100
	L20	29	11.83	3.83	0	0	0	19.5	51
	L40	29	34.24	5.85	0	0	39	60.5	94
	L60	28	34.29	6.63	-3	0	41.5	64.75	100
	P	29	12.55	4.74	0	0	0	3.5	100
	Z15	29	32.59	7.48	-49	0	3	69	100
	Z30	29	59.00	6.79	0	24	71	88.5	100
Overall Familiarity Similarity VAS	K100	29	76.31	4.56	13	60.5	78	100	100
	L20	29	54.62	5.89	0	39.5	51	76.5	100
	L40	29	50.83	7.04	0	5.5	52	85.5	100
	L60	28	49.75	7.30	0	0.25	61	82.75	100
	P	29	54.38	5.88	0	49	50	79	100
	Z15	29	67.24	4.87	0	54.5	73	86	100
	Z30	29	69.24	4.32	0	54.5	70	85	100

Table 21: Summary statistics for Emax of objective measures of drug effects (Choice Reaction Time [CRT])

Abuse Potential Measure	TRT	N	Mean	StdErr	Min	Q1	Med	Q3	Max
Motor Reaction Time (MRT) (ms)	K100	29	28.34	7.94	-36	-6.5	18	60	124
	L20	29	24.59	9.45	-96	-1	23	53.5	147
	L40	29	37.55	9.83	-52	13.5	36	54	261
	L60	28	48.07	7.74	-27	24.25	46.5	63.75	162
	P	29	27.31	7.75	-61	-3.5	31	43	114
	Z15	29	131.14	12.43	37	73	109	195	255
	Z30	29	198.52	18.48	41	136.5	182	259.5	418
Percent Correct Responses	K100	29	1.11	0.42	0	0	0	1.65	9.1
	L20	29	1.03	0.55	-1.8	0	0	1.8	14.8
	L40	29	1.14	0.38	0	0	0	1.8	7.3
	L60	28	1.14	0.35	0	0	0	1.8	7.3
	P	29	1.31	0.51	-3.4	0	0	1.8	13
	Z15	29	0.39	0.34	-1.8	-0.65	0	1.8	5.5
	Z30	29	0.66	0.46	-4.3	-1.65	0	1.8	7.1
Recognition Reaction Time (RRT) (ms)	K100	29	18.24	5.59	-30	-3.5	12	37	104
	L20	29	16.45	8.40	-82	-7.5	10	48	134
	L40	29	40.90	9.46	-5	11	27	58.5	264
	L60	28	41.39	6.73	1	19	34	54.25	154
	P	29	27.76	5.83	-31	3.5	26	61	90
	Z15	29	55.90	6.86	-10	25	52	76	162
	Z30	29	66.41	9.80	-50	37.5	66	90	187
Total Reaction Time (TRT) (ms)	K100	29	42.97	13.09	-70	-11	17	86	220
	L20	29	38.69	17.16	-178	-6	47	81.5	255
	L40	29	75.34	18.67	-43	28.5	53	106.5	525
	L60	28	86.00	13.14	3	36.75	80.5	114	292
	P	29	53.03	12.96	-93	-1.5	44	99.5	187
	Z15	29	178.59	17.26	34	106.5	160	270	333
	Z30	29	257.86	23.90	-1	183.5	252	328.5	483

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

LING CHEN
07/13/2010

STELLA G MACHADO
07/13/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 022529 **Applicant:** Arena Pharmaceuticals **Received:** December 22, 2009
Drug Name: Lorcaserin tablets **NDA/BLA Type:** standard **Filing date:** February 19, 2010
Date of Statistical filing checklist: 2/16/10

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	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			Enrollment age was limited to < 65 in both Phase 3 studies.
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			Additional analysis files for Study 009 were received on 2/10/10 in response to a request from the Division. Data files for Study 011 are acceptable.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

Note: With the additional analysis files for Study 009 that were received on 2/10/10 in response to a request from the Division, the statistical section of the application is fileable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. See comments at the end of this review.

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	

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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)			This is a review issue, not a filing issue.

Additional request for the 74-day letter (This is not a filing issue)

1. At the pre-NDA meeting on August 12, 2009, we requested additional statistical analyses of certain efficacy endpoints from Study 009 and Study 011. While we did locate the results of the completers analysis for the two studies combined, we did not locate results of the other analyses that we requested. For this reason, we request that you conduct the following analyses separately for Study 009 and Study 011: a) for the co-primary endpoints, use the completers population and the primary efficacy analysis models; and b) for the percent change in body weight from baseline, use the MITT1 and PP1 populations and a mixed-model-repeated measures (MMRM) analysis model. If you have already conducted and reported these analyses, please indicate their location in the submitted materials.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

JANICE A DERR
02/17/2010

JON T SAHLROOT
02/17/2010