FDA Briefing Document

NDA 22529

Lorcaserin Hydrochloride Tablets, 10 mg

Sponsor: Arena Pharmaceuticals

Endocrinologic and Metabolic Drugs Advisory Committee Meeting – May 10, 2012

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Section:

Discussion Points for Advisory Committee

1. Discuss whether the sponsor has provided an adequate response regarding diagnostic uncertainty for mammary tumors – i.e., adenocarcinomas versus fibroadenomas - in rats treated with lorcaserin.

2. Discuss whether the sponsor has provided an adequate response regarding the potential clinical risk associated with lorcaserin-induced mammary adenocarcinoma in rats (e.g., a sufficient safety margin).

3. Discuss whether the sponsor has provided sufficient evidence to conclude that elevation in plasma prolactin is the primary mode of action for the mammary tumors observed in rats.

4. Discuss whether the sponsor has provided an adequate response regarding the potential clinical risk associated with lorcaserin-induced astrocytoma in rats (e.g., a sufficient safety margin).

5. Taking into account the new in-vitro 5HT2 receptor potency data, discuss whether the phase 3 echocardiography data are sufficient to rule out a clinically meaningful increase in the risk for valvular heart disease in patients treated with lorcaserin.

6. Taking into account the March 28 and 29, 2012 advisory committee meeting on cardiovascular risk assessment of obesity drugs, discuss the available data to assess for excess risk for major adverse cardiovascular events in patients treated with lorcaserin.

7. Do the available data demonstrate that the potential benefits of lorcaserin outweigh the potential risks when used long-term in a population of overweight and obese individuals?

   If 'Yes', please provide your rationale and comment on the need for and approach to patient monitoring and risk management.

   If 'No', please provide your rationale and comment on what additional preclinical or clinical information should be required to potentially support approval.

Advisory Committee Nonclinical Briefing Document

Application: Lorcaserin hydrochloride, NDA 22-529
Drug Class: 5HT2c Receptor Agonist
Clinical Indication: Obesity
Reviewer: Todd Bourcier, Ph.D., Division of Metabolism and Endocrinology Products

Re: Receptor pharmacology studies included in Complete Response Resubmission for lorcaserin

Summary
Lorcaserin is a new molecular entity that targets activation of the serotonin 5HT2C receptor and is intended to promote weight loss in an obese population. Agonism at the intended target, 5HT2C, has been reasonably demonstrated to underlie the anorexigenic effect of lorcaserin. An important aspect of the non-clinical development program for lorcaserin was the assessment of receptor selectivity for 5HT2C relative to other serotonin receptor subtypes, particularly other members of the 5HT2 receptor family 5HT2A and 2B. Relative to drug action, the 5HT2A and 2B receptors are implicated in contributing to the hallucinogenic and addictive responses to drugs of abuse (5HT2A) and to drug-induced cardiac valvulopathy including that associated with use of dexfenfluramine in humans (5HT2B).

The selectivity of lorcaserin for 5HT2C was assessed by a series of *in vitro* and *in vivo* pharmacology studies and by toxicological assessments of neurobehavioral and cardiac/valvular histological endpoints.

Lorcaserin preferentially activates 5HT2C with 8- to 15-fold greater potency compared to 5HT2A, and 45- to 90-fold greater potency compared to 5HT2B. Depending on the studies one considered in the original NDA submission, off-target activation of 5HT2A and 2B appeared unlikely (2002/04 data) or possible (2009 data) when compared to clinically relevant plasma levels of lorcaserin due to differing *in vitro* estimates of receptor potency.

In their resubmission, Arena presents additional studies to clarify discrepancies in the receptor potency data reported in the original NDA. The new studies were designed to address potential receptor reserve effects in the *in vitro* assay systems that may have overestimated receptor potency of lorcaserin in the prior studies.

The new studies (referred to as 2011 data) reduced receptor density to levels more consistent with expression levels reported in the literature for 5HT2 receptors in human neurological and cardiovascular tissues. The 2011 data show that lorcaserin is at least 3- to 5-fold less potent than originally reported at all three 5HT2 receptor subtypes. Based on the new estimates of receptor potency, maximal concentrations of lorcaserin (free fraction) observed in human plasma and anticipated in human brain tissue is notably lower than the EC50 for activation of 5HT2A and 2B, while remaining above the EC50

for activation of 5HT2C *in vitro*. Plasma concentrations of lorcaserin at the therapeutic dose are thus expected to remain within the selective range for activation of 5HT2C.

Arena additionally demonstrated that based on functional activity across four *in vitro* assay platforms, lorcaserin grouped with low-potency 5HT2B agonists that are not known to be associated with clinical valvulopathy. By comparison, compounds known to cause clinical valvulopathy such as nordexfenfluramine and pergolide showed substantially higher 5HT2B receptor potency in these assays.

The 2011 receptor potency data provides supportive evidence that off-target activation of the 5HT2A or 2B receptors is unlikely at the proposed clinical dose of lorcaserin (10mg bid). This is consistent with neurological and cardiac assessments in animals which did not identify major toxicities that would be anticipated if 5HT2A and 2B were activated by lorcaserin. However, limitations in neurological assessments and the lack of validated models for drug-induced valvulopathy in animals preclude a definitive prediction that lorcaserin will be devoid of such toxicities should it be approved for marketing.

Serotonin receptor selectivity profile of Lorcaserin

Background

The original NDA submission included two sets of studies which addressed the binding affinity and receptor activation kinetics for lorcaserin against the human 5HT2A, 2B, and 2C receptors. The first set of studies was conducted in 2002/04 in support of early clinical trials, and the second was conducted in 2009 in the course of characterizing metabolites of lorcaserin. The 2009 data resulted in ~10-fold greater potency at all three receptor subtypes compared to the 2002/04 data. When compared to clinically relevant plasma drug levels, 'off-target' activation of 5HT2A and 2B appeared either plausible or unlikely, depending on which dataset one considered. The sponsor stated that the discrepant potency data was likely due to higher expression of the 5HT2 receptors by the transfected HEK293 cells used in the 2009 study which left-shifted the dose response and overestimated lorcaserin's potency. It is a known phenomenon that higher receptor density in transient expression systems may result in greater ligand potency without a substantial change in binding affinity[1], but the studies conducted by the sponsor did not control for potential effects of receptor reserve. Although this issue was not a Complete Response item, the Sponsor after consultation with the Division undertook additional studies to further characterize the functional potency of lorcaserin for human 5HT2 receptors under assay conditions that controlled for receptor reserve.

Human 5HT2 Receptor Binding Affinity

Receptor binding affinity of lorcaserin to the 5HT2A, 2B, and 2C receptors was reported in the original NDA and was not re-examined in the new pharmacology studies submitted in the Complete Response. Receptor binding affinity was similar in the 2002/04 and 2009 studies despite ~10-fold differences in receptor activation (i.e., potency) between the assays, and would not be expected to differ substantially in the 2011 studies that

[1] Jerman JC et al (2001) Eur J Pharmacol 414:23

controlled for receptor reserve. Binding affinities for lorcaserin combined from the 2002/04 and 2009 studies and expressed as Ki values were 92, 147, and 13nM for 5HT2A, 2B, and 2C, respectively (**Table 1**). Lorcaserin's affinity for 5HT2C was within 7- to 10-fold the affinity for 5HT2A and 2B.

Table 1: Lorcaserin binding affinity (Ki) for human serotonin receptors 5HT2A, 2B, and 2C *in vitro*.

	5HT2A	**5HT2B**	**5HT2C**
Binding Affinity[1,2] (Ki, nM)	92	147	13

[1]Competitive binding with ^{125}I-DOI (Ki for DOI: 0.57, 5, 0.87nM for human 5HT2A, B, C).
[2]Ki values reflect average from studies conducted in 2002 and 2009

Human 5HT2 Receptor Activation Studies

Potency of lorcaserin at the human 5HT2A, 2B, and 2C receptors was assessed by measuring downstream events in the phospholipase C pathway, specifically the accumulation of ^{3}H-inositol phosphate and release of calcium in HEK293 cells expressing the recombinant human 5HT2 receptors. Potency was determined at various levels of receptor density in an effort to eliminate the potential effects of receptor reserve. This was accomplished by assays that used the alkylating agent phenoxybenzamine to reduce 5HT2 receptor density. Additionally, some assays titrated the amount of transfected cDNA to yield low levels of receptor expression as an alternate means to eliminate receptor reserve. The maximal response of lorcaserin relative to serotonin was also assessed to distinguish partial from full agonist activities.

Table 2a lists the potency of lorcaserin in the inositol phosphate assays from the prior studies submitted in the original NDA and the 2011 study submitted in the Complete Response. Eliminating receptor reserve in the 2011 assays shows that lorcaserin is 3- to 5-fold *less* potent than reported in the 2002/04 study and ~30-fold less potent than reported in the 2009 study at all three 5HT2 receptor subtypes. Despite the shifts in potency across the studies, the relative selectivity of lorcaserin for 5HT2C remains within the range of 8x-15x for 2A, and 45x-90x for 2B (**Table 2b**).

Table 2a: Potency of lorcaserin in inositol phosphate assays
(Data from 2002/04, 2009, 2011 studies)

	Lorcaserin, EC50, nM		
Study date	**5HT2A**	**5HT2B**	**5HT2C**
2002/04	133	811	9
2009	14	82	1.8
2011	**553**	**2380**	**39**

Table 2b: Fold Selectivity of Lorcaserin for 5HT2C receptor activation[1]		
Study data	**vs. 5HT2A**	**vs. 5HT2B**
2002/04	15x	90x
2009	8x	45x
2011	**14x**	**61x**

[1]Fold selectivity determined by dividing the PI hydrolysis EC50 value for 5HT2C by the EC50 value for 5HT2A or 2B from the 2002/04, 2009, and 2011 studies.

Table 3 lists the potency of lorcaserin in the calcium release assays conducted in 2002/04 and again in 2011 under conditions that eliminated receptor reserve. Calcium release was not assessed in the 2009 studies. Lorcaserin was ~20-fold less potent at the 5HT2A and 2C receptors and ~3-fold less potent at the 5HT2B receptor compared to the potencies reported in 2002/04.

Table 3: Potency of lorcaserin in calcium release assays (Data from 2002/04 and 2011 studies)			
	Lorcaserin, EC50, nM		
Study date	**5HT2A**	**5HT2B**	**5HT2C**
2002/04	52	350	6
2011	**948**	**1040**	**146**

The maximal response of lorcaserin relative to serotonin was also assessed to distinguish partial from full agonist activities. Based on the 2011 assays that eliminated receptor reserve, lorcaserin displayed partial agonist activity at 5HT2A and partial to full agonist activity at 5HT2A and 2B (**Table 4**).

Table 4: Efficacy data for lorcaserin in 5HT2 receptor activation assays[1]			
	5HT2A	**5HT2B**	**5HT2C**
Percent activity vs. serotonin	25%	67- 151%	81 – 86%

[1]Efficacy data from inositol phosphate and calcium release assays conducted in 2011

Results from the 2011 studies are consistent with our prior observation that the selectivity of lorcaserin for 5HT2C versus 2A and 2B is driven by the functional receptor activation assays rather than the binding assays.

5HT2 receptor expression levels in potency assays compared to human tissues

Because potency of lorcaserin increases as 5HT2 receptor expression increases, it can be of interest to compare levels of receptor expression in the potency assays to potential target tissues of interest *in vivo*, particularly the heart and central nervous system tissues. **Table 5** lists the expression levels of 5HT2 receptors as measured by radioligand binding studies in the potency assays from 2011 and 2009, and from selected human tissues as reported in the literature. The range listed for the 2011 studies indicates the range of receptor expression where potency of lorcaserin was observed to be stable. By design, receptor expression in the 2011 assays was lower than in the 2009 assays, correlating with lower potency in cells expressing fewer 5HT2 receptors. Receptor expression in human tissues more closely aligns with expression levels achieved in 2011, suggesting that the potency data from the 2011 study is the more appropriate dataset to consider in extrapolating to the potential potency of lorcaserin *in vivo*.

Table 5: Expression level of 5HT2 receptors in potency assays and in human tissues (Bmax, fmol/mg protein)

	5-HT2A[2]	**5-HT2B**[3]	**5-HT2C**[b]
2009 assays	7400	1100	750
2011 assays	220 – 1200	10 – 300	14 – 750
Human tissues	Cortex Frontal : 93 – 258 PreFrontal : 70 – 137 Temp/Parietal : 45 - 232	Left ventricle : 25 LV with CHF : 120	Hypothalamus : 13 Substantia Nigra : 35 Choroid Plexus : 625

Radioligands included ^{125}I-DOI for 2009/2011 assays, ^{3}H-ketanserin or ^{125}I-LSD for 5HT2A, ^{3}H-LY266097 for 5HT2B, and ^{3}H-mesulergine for 5HT2C in human tissues

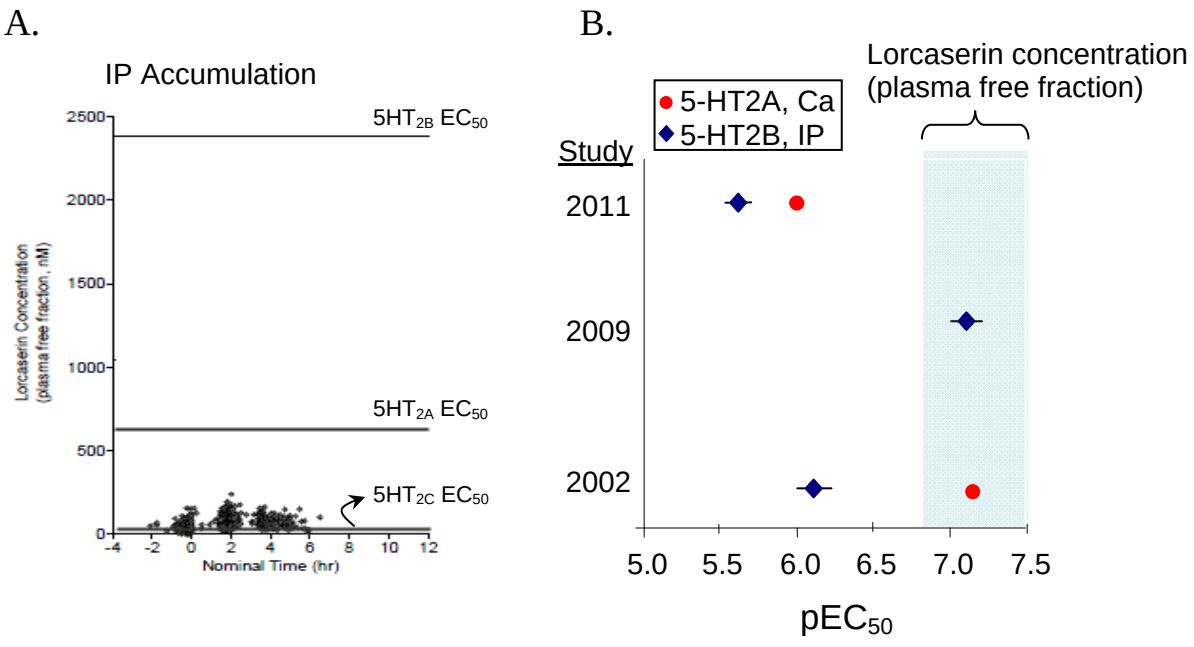
[2] Maraazziti D et al (1999) Eur Neuropshychopharm 10:21-26; Marazziti D et al (2003) Neruochem Int 42 :511-516; Huot P et al (2010) Movement Disor 25(10):1399-1408);

[3] Jaffre F et al (2008) Circ Res 104:113-123.

5HT Receptor Selectivity compared to clinical exposure to lorcaserin

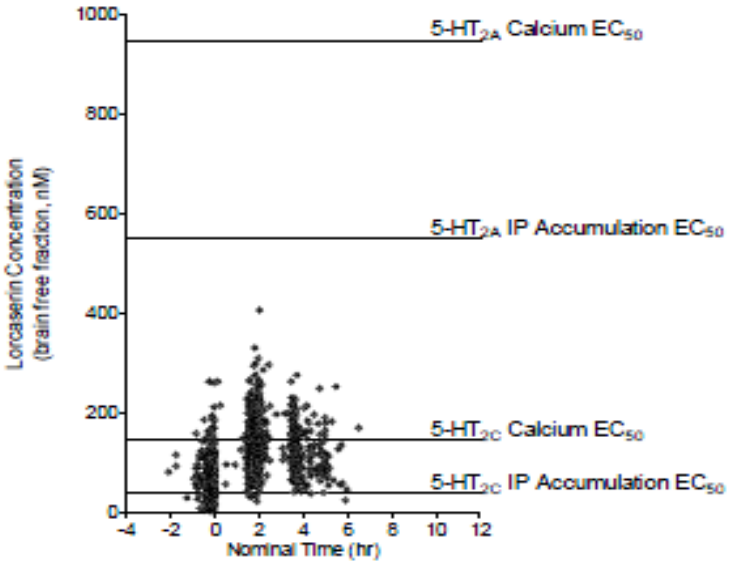
Selectivity of lorcaserin for 5HT2C is advantageous provided that plasma drug levels fall within a selective concentration range, which can be first estimated by *in vitro* EC50 values for receptor activation. Functional selectivity would be lost, for example, if the free drug concentration *in vivo* exceeds the EC50 for all three 5HT2 receptor subtypes, which could reasonably result in partial or full receptor activation. **Figure 1** compares the observed plasma lorcaserin concentration in obese/overweight subjects to *in vitro* 5HT2 receptor activation data. **Figure 1A** (on left) shows that the plasma levels of lorcaserin at the clinical dose of 10mg bid is substantially below the EC50 for activation of 5HT2A and 2B based on estimates of potency from the 2011 study. **Figure 1B** (on right) charts the change in reported potency for lorcaserin from the three studies and their relationship to the range of lorcaserin plasma concentration at the clinical dose. Whereas the reported EC50 values from 2002/04 and 2009 suggested that activation of the 2A and 2B receptors was plausible, the revised EC50 values from 2011 indicate that off-target activation of these receptors is unlikely at therapeutic exposure.

Figure 1: Lorcaserin concentration in human plasma compared to *in vitro* 5HT2 receptor potency data: **(a)** EC50 (nM) for inositol phosphate accumulation (2011 study) superimposed on scatter plot of lorcaserin plasma concentration from clinical study APD356-011. **(b)** Change in potency data (pEC50, nM) for calcium release and IP accumulation studies from 2002/04, 2009, and 2011 relative to lorcaserin plasma concentration from clinical study APD356-011.



Lorcaserin's intended pharmacological target, 5HT2C, is expressed by hypothalamic nuclei within the CNS. In addition to their expression by peripheral tissues, 5HT2A and 2B are also expressed in the CNS where they have a role in regulating aspects of behavior, including responses to hallucinogenic agents[4]. Under the Complete Response, Arena conducted studies to clarify the degree to which lorcaserin partitions to the CNS in human subjects. This new clinical data indicates that levels of lorcaserin are approximately 1.7-fold higher in the CNS compared to systemic blood levels. By comparison, lorcaserin was present in brain tissue an average of 25-fold and 10-fold higher than systemic levels in rodents and monkeys, respectively. **Figure 2** demonstrates that predicted brain levels of lorcaserin in human subjects aligns well with the EC50 for activation of 5HT2C, but falls substantially below the EC50 for activation of 5HT2A at the proposed clinical dose of 10mg bid.

Figure 2: Lorcaserin free fraction predicted in human brain compared to functional potency at the human 5-HT2A and 5-HT2C receptors. (Figure adapted from Arena's Complete Response submission)



Neurological effects in Animals

The neurobehavioral studies conducted with lorcaserin in rats and monkeys did not identify any major adverse neurological effect considered clinically prohibitive. The most likely adverse neurological effect predicted from the rat and monkey studies would be somnolence or lethargy, particularly early after initiation of dosing. Lorcaserin did not clearly elicit 5HT2A-related behavior in rats but did elicit 5HT2C-related behaviors in a dedicated neurological studies submitted in the original NDA and in the Complete Response submission. These data suggest that neurological adverse events observed in clinical studies with lorcaserin at therapeutic exposure are likely initiated by activation of central 5HT2C receptors.

[4] Filip M & Bader M (2009) Pharm Reports 61:761-777; Giorgetti M & Tecott LH (2004) Eur J Pharmcol, 488: 1-9.

Assessment of Valvulopathy in Animals

Several lines of evidence persuasively argue that among the 5HT2 receptors, activation of 5HT2B is the culprit mechanism underlying drug-induced valvular heart disease (VHD), such as that associated with dexfenfluramine[15]: 1) Cardiac valves express 5HT2A & B but very little or no 5HT2C, 2) Drugs associated with clinical VHD activate 5HT2B with high potency (e.g., methysergide, methylergonovine, ergotamine, MDMA); 3) Parkinsonian drugs pergolide and cabergoline associated with clinical VHD also activate 5HT2B, whereas structurally similar drugs (e.g., lisuride) void of 5HT2B activity are not associated with VHD; 4) Fenfluramines and serotonin are mitogenic for human cardiac valve tissue *in vitro*, an effect inhibited by a 5HT2A/B antagonist.

Huang et al[5] reported that functional profiling of pharmaceuticals for 5HT2B activity using a multi-readout platform identified known valvulopathogens as high-potency 5HT2B agonists. The authors state that such functional profiling might be useful in identifying compounds 'likely to induce valvular heart disease'. Arena adapted Huang's approach and compared the 5HT2B receptor potency of lorcaserin to two sets of reference compounds: Compound set 1 is associated with clinical VHD and are known to activate 5HT2B with high potency, and Compound set 2 are not associated with clinical valvulopathy but activate 5HT2B with low potency. Potency of all compounds was assessed in four *in vitro* assays that measure separate signaling events downstream of 5HT2B activation.

Table 6 shows that lorcaserin grouped with Compound set 1 which are not known to be associated with clinical valvulopathy and have comparatively low potency for activating 5HT2B. By comparison, Compound set 2, which are known to cause valvulopathy, showed substantially higher potency for 5HT2B in these assays. The functional profile of lorcaserin suggests a low risk of this compound acting as a valvulopathogen like dexfenfluramine, though it must be noted that no single functional profile can conclusively predict whether a 5HT2B agonist will act as a valvulopathogen *in vivo*.

[5] Huang X et al (2009) Molec Pharm 76(4):71-722

Table 6: Potency data for lorcaserin and selected reference compounds across in vitro assay platforms (Table source: NDA 22529 CR submission)

	Calcium EC_{50}	IP Accumulation EC_{50}	β-Arrestin EC_{50}	pERK EC_{50}
Compounds Associated with Valvulopathy				
Serotonin	1.8 nM	9.3 nM	263 pM	2.7 nM
Pergolide	63 nM[a]	6.3 nM	912 pM	63 nM[b]
Cabergoline	209 nM[a]	759 pM	3.0 nM	110 nM[b]
Nordexfenfluramine	18 nM	26 nM	1.9 nM	158 nM
Methylergonovine	NR	63 pM	871 pM	79 nM[b]
Drugs with Lower 5-HT_{2B} Agonist Activity Identified in the Roth Study and Not Associated with Valvulopathy				
Fenoldopam	331 nM	204 nM	129 nM	331 nM
Guanfacine	776 nM	631 nM	759 nM	1.07 µM
Oxymetazoline	331 nM	676 nM	141 nM	933 nM
Quinidine	794 nM	1.20 µM	166 nM	1.55 µM
Ropinirole	NR	14.4 µM	2.82 µM	14.1 µM
Xylometazoline	1.32 µM	4.07 µM	427 nM	3.5 µM
Lorcaserin	1.04 µM	2.38 µM	119 nM	1.82 µM

NR = no response

[a] Potencies likely to be significantly underestimated in the calcium assay.

[b] Potencies potentially underestimated to varying degrees in the pERK assay.

Nonclinical assessment of valvular heart disease is limited in that a reproducible and robust animal model to screen for drug-induced VHD is lacking. However, there are reports in the literature that cardiac alterations suggestive of VHD were produced in rats administered serotonin[6], pergolide[7], and the experimental 5HT2C agonist RO3013[8]. Results with serotonin in rats have been criticized as being consistent with spontaneous age-related cardiac disease[9], and have not been uniformly reproduced in the literature[10]. Also, the FDA is unaware of any prospective toxicology study that persuasively demonstrates cardiac findings consistent with VHD in adult animals administered dexfenfluramine.

Extensive echocardiographic monitoring was conducted in the course of clinical studies with lorcaserin. For the nonclinical assessment, a comprehensive histological evaluation of cardiac tissue from preclinical species was submitted. The histological assessment included evaluation of chordae tendineae, cardiac and valve tissue, with reporting of the incidence and severity of any changes in the histopathology of these tissues.

Lorcaserin binds to human, rat, and monkey 5HT2B with similar affinity, and activates human and monkey 5HT2B with reasonably similar potency. Lorcaserin was tested over a concentration range that substantially exceeded the *in vitro* activation potency for

[6] Gustafsson BI et al. (2005) Circulation. 111: 1517-1522.
[7] Droogmans S et al. (2007) Eur Heart J. 28:2156-2162.
[8] Fielden MR et al (2010) Exp Toxicol Path 62:607-613
[9] Donnelly KB (2008) Toxicol Path 36: 204-217
[10] Hauso O et al (2007) Reg Peptides 143: 39-46

5HT2B in rats and monkeys, so there was a reasonable expectation that cardiac lesions might be observed at the highest doses. Histological evaluations were conducted after dosing rats for 1, 3, 6, and 24 months and in monkeys after dosing for 1, 3, and 12 months with lorcaserin.

The histological appearance of the heart, endocardium, cardiac valves, and the chordae tendineae were described by the examining veterinary pathologists as within normal limits for the species examined and at all doses of lorcaserin evaluated. This result appears reassuring, but it is noteworthy that cardiac lesions were not observed at the highest concentrations of lorcaserin, which substantially exceeded the *in vitro* potency data for activation of 5HT2B. The sponsor suggests that still higher drug levels would be required to elicit activation of 5HT2B because the potency of lorcaserin *in vivo* may still be less than that predicted by the *in vitro* activation studies. However, other limitations may be more significant. For example, the ability to detect drug-induced VHD in any one of these experiments was not demonstrated by use of a positive control such as serotonin or pergolide. Thus, inherent insensitivity of the animal model is a more likely explanation that cannot be excluded. Additionally, published studies that detected drug-induced VHD in animals included evaluation of proliferative markers and echocardiography in addition to standard histology, whereas the studies done with lorcaserin were limited to evaluation of standard histology. Thus, insufficiently sensitive detection methods also cannot be excluded.

Given the experimental limitations with the toxicological data, the more appropriate data in considering the VHD risk of lorcaserin is the receptor pharmacology data described above and the echocardiography data collected in the clinical trials with lorcaserin.

Table 7: Lorcaserin activation of human, rat, and monkey 5HT2B receptors (EC50, nM)

	Binding, Ki (nM)	**EC50 (nM)**		**Plasma lorcaserin concentration achieved in toxicology studies**
		Ca	**IP**	
Human	147	1040	2380	na
Rat	114	1170	195	150 to 20,000 nM
Monkey	127	2360	725	400 to 20,000 nM

Receptor binding data from 2002/04 study
Potency data (EC50 for Calcium and IP accumulation) from 2011study.

Advisory Committee Nonclinical Briefing Document

Application: Lorcaserin hydrochloride, NDA 22-529
Drug Class: 5HT2c Receptor Agonist
Clinical Indication: Obesity
Reviewer: Fred Alavi, Ph.D. and Todd Bourcier, Ph.D.
Division of Metabolism and Endocrinology Products

Re: Carcinogenicity Assessment of Lorcaserin in Rodents

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Executive Summary

Investigational drugs intended for chronic clinical use are evaluated for their potential to be carcinogenic in two species of rodents that are administered the drug for two years, roughly approximating a lifetime exposure. Lorcaserin was identified as a non-genotoxic carcinogen in the two-year bioassay in Sprague-Dawley rats. The incidence of multiple tumor types increased in response to lorcaserin, including mammary neoplasms in males and females, and neoplasms of the brain, peripheral nerves, skin, subcutis, and liver and thyroid gland of males. The Endocrine Advisory Committee convened in September 2010 in part to discuss the impact of these findings on the overall clinical risk/benefit for lorcaserin. Among the tumor types discussed, the occurrence of mammary and brain neoplasms were of most concern regarding human risk assessment because no safety margin was identified for the former, and the safety margin was uncertain for the latter. Also, the imbalanced reclassification of mammary neoplasms reduced confidence in the final incidence data for benign and malignant tumor types. The Agency did not agree that the Sponsor provided adequate information regarding lorcaserin's tumorigenic mode of action, which is critical for evaluating human risk when safety margins are absent or are uncertain.

The Complete Response Letter issued by the Agency in October 2010 directed the sponsor to resolve the diagnostic uncertainty in the classification of mammary masses in female rats and re-address the exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma. Also, the sponsor was directed to either establish a tumorigenic mode of action for lorcaserin-induced increases in astrocytoma or clarify the safety margin to the tumorigenic dose of lorcaserin.

The sponsor convened a pathology working group (PWG) to readjudicate all mammary and lung masses from female rats. Several changes were made to the dataset, and the re-adjudicated tumor incidence data is considered definitive based on the high degree of diagnostic consensus reached by the PWG in the blinded slide evaluation. Lorcaserin increased the incidence, tumor onset and multiplicity, and lethality of mammary adenocarcinoma with a reassuring safety margin of 24-fold to the clinical dose. Lorcaserin also increased the incidence, tumor onset and multiplicity, and lethality of benign fibroadenoma at all doses without a safety margin (≤ 7-fold) to the clinical dose. Lorcaserin minimally effected plasma and tissue prolactin and differentiation of mammary lobular structures in female rats in mechanistic studies up to three months duration, but the changes that were observed are consistent with hormonal action on mammary tissue. No pattern of change was observed for estrogen, progesterone, or luteinizing hormone, and the Agency is not aware of a threshold of prolactin beyond which mammary tumors emerge. Given the high sensitivity of SD rats to prolactin and the absence of changes in other hormones, it is plausible that minimal increases in prolactin induced by lorcaserin contributed to the emergence of fibroadenoma in female rats.

The sponsor chose to clarify the safety margin for lorcaserin-induced astrocytoma in rats rather than establish a tumorigenic mode of action. Clinical data was submitted indicating that partitioning of lorcaserin to the CNS in human subjects is substantially lower than predicted by nonclinical studies in rats and non-human primates. A safety margin of 70-fold for astrocytoma in rats, based on estimated brain levels of lorcaserin, presents a negligible clinical risk and obviates the need for mode-of-action data.

Background

Carcinogenic Assessment of Investigational Pharmaceutical Compounds

Investigational drugs intended for chronic (≥ 6 months) use in human subjects are evaluated for their potential to be carcinogenic. Because genotoxic compounds are closely associated with carcinogenicity, the potential genotoxicity of pharmaceutical compounds and associated metabolites is also assessed in a standard battery of studies. Carcinogenesis is formally evaluated in two species of rodents that receive the drug for two years, roughly approximating lifetime exposure to drug. The two-year 'bioassay' is designed to detect drug-induced tumors that arise from genotoxic as well as non-genotoxic mechanisms of action.

Lorcaserin Genotoxicity Assessment

Lorcaserin and its major sulfated metabolite (APD244208) showed no evidence of genotoxic effects in a standard battery of bacterial and mammalian systems. Non-genotoxic mechanisms are therefore thought to underlie lorcaserin-induced tumors observed in the rat carcinogenicity study (described below). Examples of non-genotoxic mechanisms of neoplasia include direct or indirect promotion of cell growth or survival and persistent perturbation of hormone status.

Toxicological Findings in Short-Term Studies Pertinent to Assessment of Carcinogenicity

Toxicity of lorcaserin was tested in standard 3- and 6-month studies in Sprague Dawley rats. Doses were tolerated up to 100 mg/kg in the 3 month study, and doses up to 50mg/kg were evaluated in the 6-month study. The final report for both studies stated that the principle test article-related effect was hepatocellular centrilobular hypertrophy (minimal to moderate) and red cell turnover with splenic extramedullary hematopoeisis. Reproductive organ weight and histology of other organs, including the mammary, skin, and nervous system tissues, were reported as being within the range commonly seen in rats of this strain and age.

Summary of Carcinogenicity Studies Submitted in Original NDA

Mouse Carcinogenicity study

The carcinogenicity study in mice was completed with doses of 5, 25 and 50 mg/kg. These doses were tolerated and survival in lorcaserin-dosed groups was similar to the control group at the end of the 2 year study period. Review of the results by the Agency and the FDA's Executive Carcinogenesis Assessment Committee is consistent with the Sponsor's conclusion that no drug-related tumors were observed in mice (**Appendix A**). Exposure to lorcaserin at the No-Observed Adverse Effect (NOAEL) of 50mg/kg is 4- to 7-times higher than exposure at the clinical dose of 10mg BID, based on AUC.

Rat Carcinogenicity Study

The carcinogenicity of lorcaserin was assessed at 10, 30 and 100 mg/kg of lorcaserin in seven-week old male and female Sprague-Dawley (SD) rats. Lorcaserin was prepared in water and administered daily by gavage to rats. Note that the doses and exposure to lorcaserin in rats (**Table 1**) was substantially greater than that achieved in mice (≤ 7x clinical exposure).

Table 1: Lorcaserin doses and multiples of clinical exposure achieved in 2yr rat study				
	Dose, mg/kg	Rats/sex/group	Male	Females
104-week Rat Carcinogenicity Study	**0 (C)**	**65**	-	-
	10 (LD)	**65**	5x	7x
	30 (MD)	**65**	17x	24x
	100 (HD)	**75**	55x	82x
Exposure multiples calculated as plasma AUC exposure in rats divided by average AUC exposure of the clinical dose of lorcaserin, 10mg BID, 1.02 ug*h/ml AUC				

In May 2007, the sponsor submitted a safety report informing the Agency of increased mortality of female rats due to mammary adenocarcinoma and fibroadenoma at all doses of lorcaserin by week 55 of the ongoing study. Additionally, the sponsor described a higher incidence of astrocytoma in a few mid- and high-dose males and females, but none in the control or low dose groups. In response, the Agency requested that the sponsor provide bi-monthly updates on survival and tumor incidence, along with data to support the sponsor's suggestion that prolactin dysregulation may be causative of the mammary neoplasms in rats. These bi-monthly updates were reviewed and the findings were periodically consulted with the FDA's Executive Carcinogenicity Assessment Committee (eCAC), and considered consequential for the ongoing phase 3 clinical studies. By week 96 of the rat study, the number of deaths and the incidence of malignant and benign mammary tumors were reportedly increased at all doses of lorcaserin (**Table 2a**). The Agency requested that the sponsor meet with the Agency in April 2008 to discuss the tumor findings in rats and the potential safety implications for the ongoing clinical studies. At that meeting, the sponsor reported that the incidence of malignant adenocarcinoma in the mid- and high-dose females at week 104 was in fact notably lower than reported at the week 96 update (**Table 2a**), and that the incidence of benign fibroadenoma was notably higher than previously reported (**Table 2b**). This pattern of tumor reclassification was imbalanced and favored lorcaserin by reducing the malignancies at the low and mid-doses. Reasons for the apparent diagnostic uncertainty between the primary and peer-reviewing pathologists were not documented and therefore not available. Continuation of clinical studies was considered appropriate because: 1) the rat study was not yet complete and tumor incidence could change further, 2) the reclassified interim tumor data suggested that malignancies were confined to the highest dose of lorcaserin, 3) preliminary data in male rats suggested that lorcaserin may modestly increase prolactin, and prolactin would be monitored in the ongoing clinical trials. Investigator brochure and patient informed consent documents were updated to include the tumor findings in rats.

Table 2a: Mammary Adenocarcinoma Incidence in Female Rats from Bi-Monthly Updates (# positive / # examined)				
Data Update (Week)	Control	10 mg/kg	30 mg/kg	100 mg/kg
Week 55	0/1	2 / 4	5 / 7	13 / 15
Week 68	2 / 5	6/6	16 / 18	45 / 46
Week 88	16 / 28	27 / 38	36 / 45	72 / 74
Week 96	20 / 39	34 / 50	43 / 57	72 / 75
Week 104	30 / 65	35 / 65	35 / 65	63 / 75
Final update	29 / 65	35 / 65	36 / 65	62 / 75
Original NDA	28 / 65	34 / 65	35 / 65	60 / 75

Table 2b: Mammary Fibroadenoma Incidence in Female Rats from Bi-Monthly Updates (# positive / # examined)				
Data Update (Week)	Control	10 mg/kg/d	30 mg/kg/d	100 mg/kg/d
Week 88	4/28	16/38	24/45	35/74
Week 96	10 / 39	27 / 50	36 / 57	36 / 75
Week 104	20 / 65	47 / 65	60 / 65	53 / 75
Final update	20 / 65	48 / 65	56 / 65	51 / 75
Original NDA	20 / 65	47 / 65	53 / 65	45 / 75

The final rat carcinogenicity report was submitted with the lorcaserin NDA in Dec 2009. The incidence of mammary neoplasms was further revised from week 104, generally favoring lorcaserin. In females, adenocarcinoma was numerically increased at the low- and mid-doses, reaching statistical significance at the high-dose. Fibroadenoma was increased at all doses of lorcaserin. In males, there were numerical increases in mammary adenocarcinoma and fibroadenoma at the mid- and high-doses of lorcaserin. Lorcaserin was also found to increase multiple tumor types in male rats. These included tumors of the brain, peripheral nerves (Schwannoma), skin and subcutis, liver, and thyroid. The incidence and statistical significance of the tumors identified in female and male SD rats are listed in **Tables 3a, b**, and **c**. Conclusions of the FDA's Executive Carcinogenesis Assessment Committee are attached as **Appendix A**, noting concern regarding the conduct and evaluation of the rat study due to diagnostic

uncertainty apparent in classifying mammary neoplasms. Discussion of survival and body weight data are attached as **Appendix B**.

Table 3a: Neoplastic Findings in Female Rats from 2 year study submitted with NDA in 2009
(n= 65/sex for Control, 10, 30mg/kg and n=75/sex for 100mg/kg)

Incidence of tumors in females		**Lorcaserin dose, mg/kg/day**			
		Control	**10**	**30**	**100**
Brain	astrocytoma	0	2	0	1
Mammary	adenocarcinoma	28	34 NS	35 NS	60 SS
	fibroadenoma	20	47 SS	53 SS	45 SS
Pituitary	adenoma	50	46	31	20

NS = not significant; SS = Statistical significance ($p \leq 0.05$ rare tumor; $p \leq 0.01$ common tumor; pairwise comparison)

Table 3b: Non-neoplastic Findings in Mammary Gland of Female Rats

Incidence of non-neoplastic findings in mammary gland of female rats				
	Lorcaserin dose, mg/kg/day			
	Control	10	30	100
Lobular hyperplasia	24	23	22	26
Lobular hyperplasia w/ Atypia	18	17	26	22

Table 3c: Neoplastic Findings in Male Rats from 2 year study submitted with NDA in 2009
(n= 65/sex for Control, 10, 30mg/kg and n=75/sex for 100mg/kg)

Incidence of tumors in males		**Lorcaserin dose, mg/kg/day**			
		Control	**10**	**30**	**100**
Brain	astrocytoma	1	0	4 NS	8 SS
Mammary	adenocarcinoma	0	0	2	2 NS
	fibroadenoma	0	1	4 NS	6 NS
Skin, subcutis	benign fibroma	3	7 NS	11 SS	17 SS
Skin	squamous carcinoma	0	0	4 NS	5 SS
Nerve Sheath	Schwannoma, all sites	0	0	2 NS	9 SS
Liver	hepatocellular carcinoma	1	3	2	4
	hepatocellular adenoma	1	1	2	6 SS
	combined	**2**	**4**	**4** NS	**10** SS
Thyroid	follicular cell adenoma	0	5	4 NS	8 SS

NS = not significant; SS = Statistical significance ($p \leq 0.05$ rare tumor; $p \leq 0.01$ common tumor; pairwise comparison)

Summary of 2010 Advisory Committee Meeting and Complete Response Letter

Lorcaserin was identified as a non-genotoxic carcinogen inducing multiple tumor types in rats. Among the tumor types observed, the occurrence of mammary and brain neoplasms were of most concern regarding human risk assessment because no safety margin was identified for the former, and the safety margin was uncertain for the latter. Also, the imbalanced reclassification of mammary neoplasms reduced confidence in the final incidence data for benign and malignant tumor types. Importantly, the Agency did not agree that the Sponsor provided adequate information regarding lorcaserin's tumorigenic mode of action, which is critical for evaluating human risk when safety margins are absent or are uncertain.

Discussion of neoplasms found in organs other than the mammary gland and CNS is attached as **Appendix C**.

Mammary Tumor Incidence and Mode of Action

The final tumor incidence data showed that lorcaserin increased benign fibroadenoma at all doses and adenocarcinoma only at the high dose with statistical significance. The numerical increase in fibroadenoma and adenocarcinoma in mid- and high-dose males exceeded concurrent

and historical control values, but did not reach statistical significance unless combined. The sponsor's NDA included a statistical analysis of adenocarcinoma and fibroadenoma evaluated both separately and combined and the outcome of their analysis was confirmed by the FDA statistician. However, at the Advisory Committee meeting, the sponsor argued that the incidence of mammary adenocarcinoma and fibroadenoma should in fact not be combined for statistical purposes based of the distinct cellular lineage of these tumor types, and that fibroadenoma is not a precursor to adenocarcinoma. Because lorcaserin increased adenocarcinoma only at the high dose, it was argued that the resulting safety margin of 24-fold presents little risk of breast cancer to human subjects. While it recognized that fibroadenoma and adenocarcinoma are distinct tumor types that present appreciably different levels of clinical risk, the Agency cited several lines of evidence that raised concern about the mammary tumor data in rats regardless of whether the tumor types were combined or not. This included the imbalanced pattern of tumor reclassification favoring lorcaserin which, at the least, indicates a degree of diagnostic uncertainty from the primary and peer-reviewing pathologists. After reclassification, the incidence of adenocarcinoma remained numerically higher than the concurrent and historical controls in the low and mid-dose groups. Lorcaserin also appeared to reduce latency and increase aggressiveness of adenocarcinoma in the low and mid-doses, an effect that would not be obvious from final tumor incidence data. For example, mammary adenocarcinoma metastasized to the lung in groups administered lorcaserin but not in control, with a reported incidence of 0, 2, 7, and 6 for the control, low, mid, and high doses, respectively. Also, reduced latency of tumor emergence was suggested by palpable nodules detected earlier and in greater numbers in the dosed groups. Tumor multiplicity (as opposed to a single mass) of adenocarcinoma also appeared to be higher in groups dosed with lorcaserin: 9, 21, 13, and 33 at the control, low, mid, and high doses, respectively.

The sponsor argued that prolactin was the probable primary driver of mammary tumors in rodents administered lorcaserin, a mechanism similar to that demonstrated for dopamine antagonists used to treat psychiatric conditions. Suppression of dopamine with these agents strongly promotes the release of prolactin from the pituitary, a hormone which is a primary driver of mammary development and tumorigenesis in rodents but of unresolved /unsettled significance to human breast cancers. However, evidence supporting this pathway for lorcaserin was unpersuasive. Lorcaserin repeatedly failed to cause a robust and sustained increase in serum or tissue prolactin in rats, and the marginal increases that were observed occurred under experimental conditions that bear little resemblance to the rats used in the formal carcinogenicity study. Comparison of lorcaserin to the dopamine antagonist haloperidol and the serotonergic agent dexfenfluramine in the mechanistic studies further eroded support of an intermediary role of prolactin.

To resolve theses issues, the Agency required the sponsor to address the following two items in the Complete Response Letter, summarized here:

1. *Resolve diagnostic uncertainty in the classification of mammary masses in female rats*
    a. Account for the change in diagnoses made by the primary and subsequent pathologists from the interim updates to the final study report.
    b. In consultation with the Agency, identify an independent pathologist or group of pathologists to re-adjudicate all mammary and lung tissues from all female rats. Re-adjudication should be conducted in a blinded manner.

2. Clarify the exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma

a. Demonstrate that the apparent increase in aggressiveness of adenocarcinoma in rats administered lorcaserin is reasonably irrelevant to human risk assessment.

Safety Margin and Mode of Action to Lorcaserin-Emergent Astrocytoma

Lorcaserin increased the incidence of brain astrocytoma in male rats in a dose-dependent manner (**Table 4**). The numerical increase at the mid-dose and the statistically significant increase at the high dose are both considered related to lorcaserin treatment. The incidence of astrocytoma in males exceeded the historical control range (0-5%, mean 2.7%) for the study site. As submitted, astrocytoma emerged at exposure 17-fold higher than clinical exposure, with a safety margin of 5-fold based on plasma drug levels. Because astrocytomas are located in the CNS, which is also the site of lorcaserin's pharmacodynamic action, comparison of drug levels in the CNS across species would be a more appropriate analysis for calculating a safety margin. Lorcaserin preferentially partitions to brain tissue in monkeys and rats, but brain levels in human subjects required assumptions because distribution of lorcaserin to the CNS was not assessed in clinical studies. If one assumed that brain partitioning in humans resembles rats, then the safety margin remained unchanged (5-fold). But if monkeys are more predictive, then the safety margin increased to a more reassuring ~14-fold. A plausible tumorigenic mode-of-action for the emergence of astrocytoma with lorcaserin was absent, so risk assessment necessarily relied on the exposure difference between animals and humans, and the existing animal data yielded meaningfully different estimates of a safety margin.

Table 4: Incidence of brain astrocytoma in male rats

Lorcaserin dose, mg/kg			
Control n=65	**10** n=65	**30** n=65	**100** n=75
1 (1.5%)	0	4 (6.1%) NS	8 (10.7%) SS

Historical control range: 0-5%, mean 2.7%

To resolve this issue, the Agency required the sponsor to address the following item in the Complete Response Letter, summarized here:

1. Address the unidentified mode of action and unclear safety margin for lorcaserin-emergent brain astrocytoma

a. Provide additional data/information regarding the distribution of lorcaserin to the CNS in animals and human subjects that would clarify or provide a better estimate of exposure margins.
b. Demonstration of a substantial margin to clinical exposure is unnecessary if key events in the tumorigenic mode of action are identified and reasonably shown to be irrelevant to human risk.

NDA Resubmission and Responses to Complete Response Letter

This section summarizes the Agency's review of the new data provided in the sponsor's NDA resubmission that included responses to the CRL items discussed above.

CRL Item #1: ***Resolve diagnostic uncertainty in the classification of mammary masses in female rats***

Under this item, the sponsor was tasked with accounting for the change in mammary tumor diagnoses from the interim updates to the final study report and with having all mammary and lung tissues (for metastases) re-adjudicated by an independent pathologist(s). The sponsor informed the Agency that the contracting lab that conducted the rat study had not kept records of diagnostic changes for rats in the course of submitting the bimonthly updates, despite the fact that such updates were being used by the Agency in making regulatory decisions. This information is therefore unattainable. While such information may have shed light on the reasons for the prior diagnostic changes, the Agency agrees that re-adjudication of slides by independent pathologists would provide the definitive tumor incidence data necessary for re-assessing risk.

In consultation with the Agency, the sponsor convened a five member pathology working group (PWG) to re-adjudicate all mammary and lung tissues from female animals of all dose groups from the 2yr study. In addition, all subcutaneous tumors were submitted for re-adjudication. Mammary slides were blinded for animal ID and prior diagnosis. After each pathologist had diagnosed each slide, the PWG was convened to produce a consensus diagnosis for each slide and animal. The animal ID and prior diagnoses were then unblinded to document the diagnostic changes made by the PWG from the original study report. The PWG issued separate blinded and unblinded reports discussing the results. Members of the PWG are identified in **Appendix D**.

The PWG reached a high degree of consensus in accurately diagnosing mammary adenocarcinoma and fibroadenoma in the blinded assessment (**Table 5**). There was complete agreement on diagnosing metastatic mammary adenocarcinoma in lung tissue. The diagnostic certainty reported by the PWG in distinguishing benign from malignant mammary tumors contrasts sharply with the diagnostic uncertainty apparent in the original study report. Therefore, the Agency considers the results of the PWG as the definitive dataset for mammary tumor incidence in female rats for this study.

Table 5
Degree of Consensus for Neoplastic Lesions among PWG Group Members

Diagnosis	Number of consensus by 3/5 on PWG	Number of consensus by 4/5 on PWG	Number of consensus by 5/5 on PWG	% Unanimous Consensus
Adenocarcinoma	1	12	160	92.5%
Adenoma	2	2	15	78.9%
Fibroadenoma	7	14	715	97.1%
Fibroma	3	1	9	69.2%
Mammary Adenocarcinoma (metastatic)	0	0	21	100%
Carcinoma (metastatic, not mammary origin)	0	3	11	78.6%

The PWG reduced the incidence of adenocarcinoma particularly in the lorcaserin-dosed groups, while increasing the incidence of fibroadenoma more consistently across all groups including the control group. The number of adenocarcinoma in the vehicle, LD, MD and HD groups were reduced by 1, 13, 11 and 9, respectively. Fibroadenoma was diagnosed more frequently by the PWG and the incidence increased by 4, 7, 2 and 6 in the control, LD, MD and HD groups, respectively (**Table 6**).

Table 6
Re-adjudicated incidence of mammary tumors compared to incidences reported in the original study report.

Re-Adjudicated Mammary Tumors in Female SD Rats		**Lorcaserin dose, mg/kg**			
		0	**10**	**30**	**100**
Number of female rats/group		**65**	**65**	**65**	**75**
Adenocarcinoma	Original study	28	34	35	60
	PWG	**26**	**21**	**24**	**51***
Fibroadenoma	Original study	20	47	53	45
	PWG	**24**	**54***	**55***	**51***
Adenoma	Original study	0	0	0	0
	PWG	**1**	**2**	**5**	**4**
Lung metastases from primary mammary adenocarcinoma	Original study	0	2	7	6
	PWG	**0**	**1**	**5**	**5**

*statistical significance by trend and pair-wise comparison
Historical range for female rats from study site for last 5yrs:
Adenocarcinoma: 8.3 – 37%, mean 24%
Fibroadenoma: 22 – 54%, mean 36%

The diagnostic certainty expressed by the PWG members allows adenocarcinoma and fibroadenoma to now be evaluated separately with confidence. Statistical analysis of re-adjudicated incidence data demonstrated that adenocarcinoma increased with statistical significance at 100mg/kg lorcaserin. The numerical increase at the low and mid-doses of lorcaserin seen in the prior data is now absent, with the incidence of adenocarcinoma in these groups now similar to the concurrent and historical controls. A No-Observed-Adverse-Effect-Level (NOAEL) for adenocarcinoma is confidently identified at 30mg/kg lorcaserin. This NOAEL provides a safety margin of 24-fold to the clinical dose of 10mg BID, based on AUC exposure.

The re-adjudicated incidence data demonstrated that benign mammary fibroadenoma increased at all doses with statistical significance, with no safety margin identified (safety margin is less than 7-fold the clinical dose).

CRL Item #2: ***Clarify the exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma***

Under this item, the Sponsor was tasked with demonstrating that the apparent increase in the aggressiveness of adenocarcinoma at all doses of lorcaserin was reasonably irrelevant to human risk assessment. This item was based on several observations in the low- and mid-dose lorcaserin groups, particularly the numerical increase in adenocarcinoma, the higher incidence of lung metastases originating from mammary tissue, and the apparent decrease in tumor latency and increase in tumor multiplicity that could not be clearly ascribed to benign or malignant tumor types.

As discussed under CRL Item #1, the PWG reduced the number of adenocarcinoma in the low- and mid-dose groups such that the numerical increase reported in the original NDA was no longer present. As stated, the Agency accepts the PWG findings as definitive based on the degree of consensus reached among the five PWG members.

In consultation with the PWG, the Sponsor provided new analyses pertinent to metastases, onset, and multiplicity of adenocarcinoma in female rats.

Metastases

In the original report, mammary adenocarcinoma metastasized to the lung in groups administered lorcaserin but not in control, with an incidence of 0, 2, 7, and 6 for the control, low, mid, and high doses, respectively. The PWG lowered the incidence of lung metastases that originated from mammary adenocarcinoma to 0, 1, 5, and 5 for the control, mid, and high doses (**Table 7**).

Table 7. Re-adjudicated lung metastases of mammary and non-mammary origin in female SD rats.

Lung Tumors in female rats		**Lorcaserin dose, mg/kg**			
		0	10	30	100
Mammary Adenocarcinoma/number of rats		26/65	21/65	24/65	51/75
Adenocarcinoma, secondary *(mammary origin)*	Original Study	0	2	7	6
	PWG	**0**	**1 (5%)**	**5 (21%)**	**5 (10%)**
Carcinoma, secondary *(Non-mammary origin)*	Original Study	0	2	2	0
	PWG	0	3	4	2

The historical incidence for lung metastases among female rats that have spontaneous mammary adenocarcinoma ranges from 0% to 12.5% for the facility that conducted the rat carcinogenicity study (**Table 8**). The incidence of 5% and 10% noted for the low and high doses falls within this historical range, but the 21% incidence for the mid-dose group notably exceeds the highest historical incidence of 12.5%. Also of note, all lung metastases were observed in the groups dosed with lorcaserin; none were reported in the concurrent control group. The Agency agrees with the PWG's interpretation that the increased incidence of lung metastases in the mid and high dose groups is equivocal, with no difference noted between the control and low dose group.

Table 8. Historical Range of Lung Metastases during the Last Five Years from the 2yr rat carcinogenicity study site (derived from 40 control female SD rats, 2006-2011)

Historical Control Range	**Relative to control group**	**Relative to females with mammary adenocarcinoma**
Mean	1.1%	3.6%
Range	0 to 5%	0 to 12.5%

Tumor Onset and Multiplicity

Higher mortality in dosed groups and individual rat-level data in the original study report suggested that tumor onset and multiplicity was increased at all doses of lorcaserin, but the data was not adequate to distinguish between benign and malignant mammary neoplasms with confidence.

Tumor onset and multiplicity for fibroadenoma and adenocarcinoma was re-evaluated based on the re-adjudicated dataset from the PWG. Multiplicity refers to the number of female rats found to have more than one neoplastic mass upon histological examination. Tumor onset is estimated by the time to first palpation or by verification of the tumor's presence upon necropsy. For animals found without the predicted tumor at necropsy, the final study day was used.

For malignant adenocarcinoma, the time to tumor onset decreased and the multiplicity of tumors increased at the 100mg/kg dose (**Table 9 and Fig 1**). Both measures for the lower 10 and 30mg/kg dose groups were similar to the control group. In an additional analysis (not shown),

early deaths due to verified adenocarcinoma were significantly increased in the 100mg/kg dose group.

For benign fibroadenoma, all doses of lorcaserin were associated with a decreased time of tumor onset and notably increased multiplicity of tumor masses (**Table 9 and Fig 1**). Early deaths due to verified or suspected fibroadenoma were significantly increased at all doses of lorcaserin compared to the control group.

Table 9

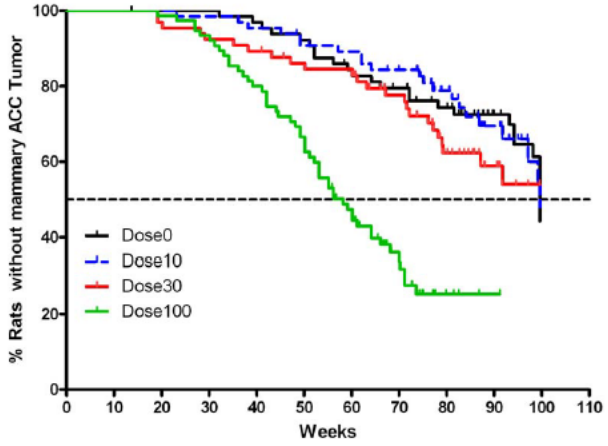
Multiplicity of Mammary Adenocarcinoma and Fibroadenoma in Female SD Rats

	Lorcaserin dose, mg/kg			
	0	**10**	**30**	**100**
Adenocarcinoma incidence	26	21	24	51
Multiplicity incidence	7	6	6	17
% Multiplicity incidence	10.8%	9.2%	9.2%	22.7%
Fibroadenoma incidence	24	54	55	51
Multiplicity incidence	7	39	51	41
% Multiplicity incidence	10.8%	60%	78.5%	54.7%

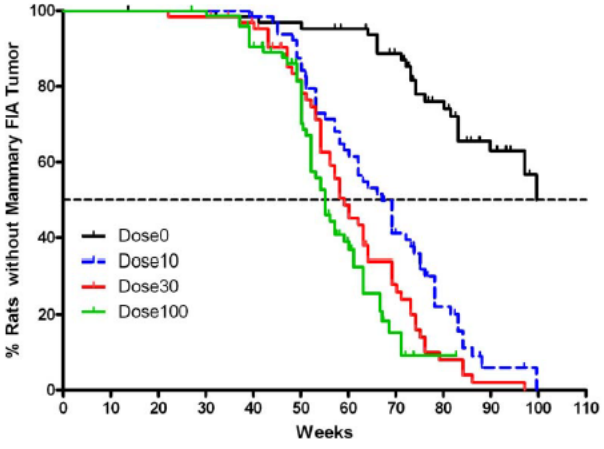
Figure 1

Time to First Detection (Tumor Onset) Analysis

Adenocarcinoma



Fibroadenoma



These new data clarify that the increased incidence and aggressiveness of adenocarcinoma is restricted to the 100mg/kg dose group. The low- and mid-dose groups were no different than control.

Consistent with an increased incidence at all doses of lorcaserin, the reduced time to tumor onset, increased tumor multiplicity, and increased lethality of fibroadenoma clearly indicates a treatment-related effect of lorcaserin without a safety margin to the clinical dose.

Tumorigenic Mode of Action Data

Summary

Readjudication by the PWG allowed identification of a 24-fold safety margin for mammary adenocarcinoma relative to the clinical dose of 10mg bid lorcaserin. In general, the Agency interprets a 24-fold safety margin to a non-genotoxic carcinogen in rodents as indicative of negligible risk to human subjects. Therefore, identifying a tumorigenic mode of action is not necessary to re-assess risk when a sufficient safety margin has been confidently established, as is now the case with lorcaserin.

Benign fibroadenoma, however, increased at all doses of lorcaserin and no safety margin to the clinical dose was identified. The clinical risk presented by benign fibroadenoma in SD rats is appreciably less than for malignant adenocarcinoma, whether or not a tumorigenic mode of action has been identified. Nevertheless, in an effort to further characterize the clinical risk presented by fibroadenoma in female rats, the Sponsor submitted a series of studies that addressed the potential role of prolactin as the tumorigenic mode of action for lorcaserin.

Sprague Dawley rats spontaneously develop mammary and pituitary tumors with age, and pituitary-derived prolactin is known to be the primary hormone that drives mammary development in rodents. Anti-dopaminergic drugs (anti-psychotics and anti-emetics) result in persistent hyperprolactinemia in rodents that eventually lead to benign and malignant mammary neoplasms in 2yr bioassays. The SD rat is considered very sensitive to prolactin-induced mammary tumorigenesis, but this pathway is not considered a rodent-specific response. The clinical relevance of prolactin-induced mammary neoplasia in rodents remains unsettled, but the current literature points to an association of high prolactin, including that induced by dopamine antagonists, with human breast cancers in women[1].

Lorcaserin minimally effected plasma and tissue prolactin levels and resulted in minimal differentiation of mammary lobular structures and increased secretory product in studies up to three months duration in female rats. By comparison, the dopamine antagonist perphenazine resulted in unequivocal and robust increases in plasma and tissue prolactin and resulted in clear differentiation of mammary lobular structures and secretory product in the same studies. In the Agency's opinion, experimental efforts to block the effect of prolactin yielded equivocal results as a consequence of the small prolactin signal generated by lorcaserin and by the dose/duration limitations encountered in the studies. No clear pattern of change was noted in the level of other hormones including estrogen, progesterone, and luteinizing hormone. Despite the minimal prolactin signal generated by lorcaserin, the equally minimal histological changes in the mammary tissue are consistent with the hormonal effect of prolactin on these tissues. To the Agency's knowledge, there is no threshold of exposure to prolactin identified in the literature beyond which results in mammary neoplasms after chronic exposure in SD rats. Given the high sensitivity of SD rats to prolactin and the absence of changes in other hormones, it is plausible that the minimal increase in exposure to prolactin induced by lorcaserin contributes to the emergence of fibroadenoma in female rats.

[1] Tworoger & Hankinson (2008) J Mamm Gland Biol Neoplas. 13(1):41-53; Harvey PW et al (2008) J Pshychopharmacol. 22:20-27; Wang et al (2002) Arch Gen Psychiatry. 59(12): 1147-1154

The following section summarizes the key findings in the mode-of-action studies submitted by the sponsor.

Effect of Lorcaserin on Plasma Prolactin

To summarize this section, a single dose of lorcaserin acutely but modestly increases plasma prolactin which changes to a delayed and modest increase during the first 10 days of dosing. Beyond 10 days of dosing, lorcaserin appears to result in episodic increases in prolactin that, over time, results in a greater proportion of animals experiencing hyperprolactinemic events. This clearly differs from a dopamine antagonist, where increases in prolactin are robust and sustained regardless of dosing duration.

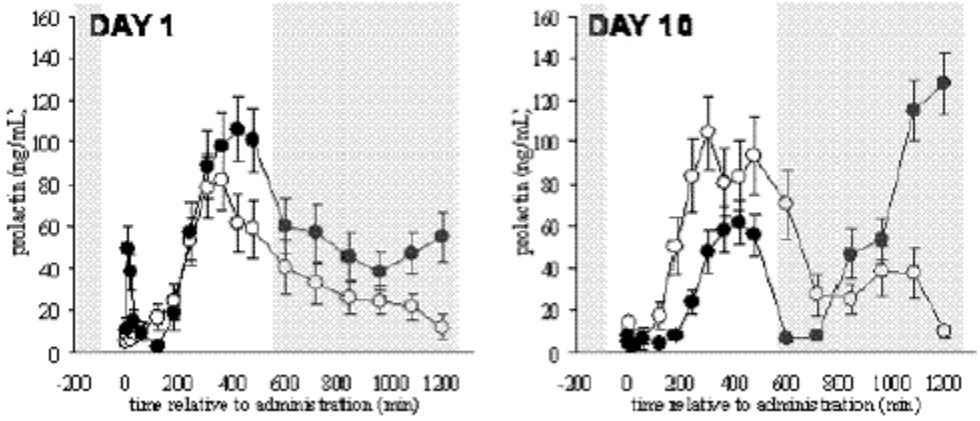
Plasma prolactin levels were followed after single and repeated doses in male and female rats.

In males, a single dose of 30 and 100mg/kg lorcaserin increased plasma prolactin by ~3-5-fold within 15 minutes of dosing. The prolactin level returned to baseline by 2 hours post-dose. There is no reliable data for repeated doses of lorcaserin in male rats, so only data in female rats will be discussed hereafter.

In females, a single dose of 10, 30, and 100mg/kg increased plasma prolactin 2- to 10-fold by 15 min post-dose. This increase in intact female rats was not observed in similar studies submitted with the original NDA. The sponsor explains that critical changes in experimental methodology, particularly animal handling and blood collection, reduced fluctuations in background prolactin and thus allowed detection of drug-induced changes in the hormone. Of note, the background level of prolactin in the new studies is notably lower than in the original study, supporting the sponsor's argument that suboptimal methodology precluded demonstration of prolactin elevations in intact female rats in the original NDA submission.

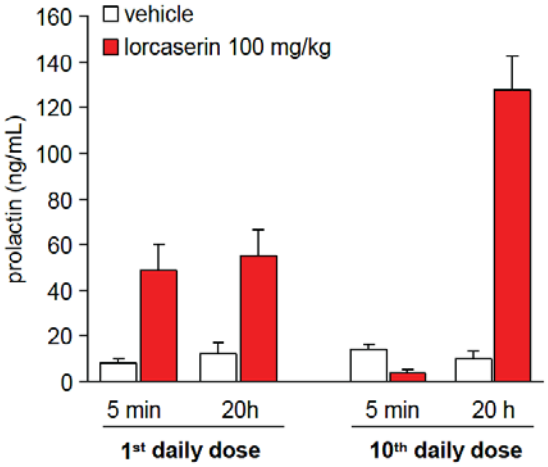
The profile of prolactin elevation changed substantially after repeated doses of lorcaserin. **Figure 2** shows that lorcaserin increased prolactin levels over the circadian pattern at most time points during the first day of dosing, but by day 10 the only time point showing a prolactin elevation is at ~20h post-dose.

Figure 2: Plasma prolactin time course after one or ten daily doses of lorcaserin (100mg/kg, closed symbols) or vehicle (open symbols).



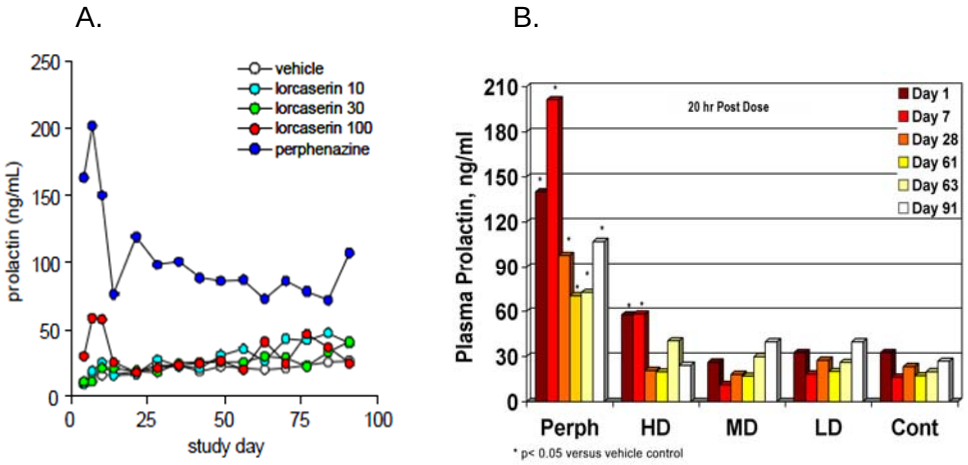
This change in profile is more readily seen at the 5 min and 20 h post-dose time points highlighted in **Figure 3**, where the acute increase in plasma prolactin after the first daily dose is lost after 10 daily doses, whereas the delayed increase at 20h post-dose remains. The reason for the delayed increase in prolactin after multiple doses of lorcaserin is uncertain.

Figure 3: Plasma prolactin after one or ten daily doses of lorcaserin at 5min and 20h post-dose timepoints.



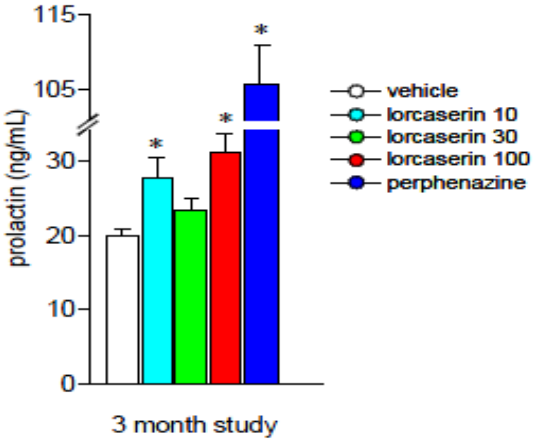
Based on the preliminary dose response and time course studies, the Sponsor followed plasma prolactin levels for 13 weeks in female rats dosed lorcaserin at 10, 30, or 100mg/kg (n=12 to 60 rats/group). Perphenazine, a dopamine receptor antagonist, was included as a positive control. Blood samples were collected at 1h and 20h time points post-dose. The sponsor states that lorcaserin did not increase plasma prolactin at 1h post-dose at any point in the study. However, an increase was observed at 20h post-dose during the first ten days of dosing (**Figures 4a & b**), being most apparent at 100mg/kg lorcaserin. Thereafter, plasma prolactin appears to return to baseline at all doses of lorcaserin. Perphenazine markedly and persistently increased plasma prolactin at all time points (1h and 20h) throughout the 13 week study.

Figure 4: Plasma prolactin time course at 20h post-dose in female SD rats, expressed as (A) line plot and (B) bar chart.



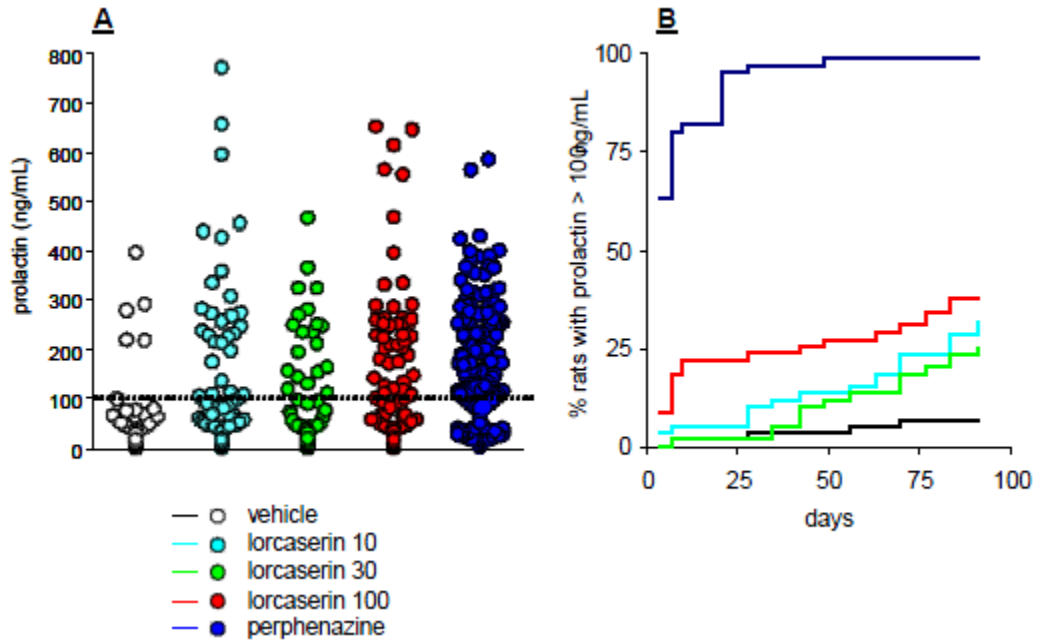
Starting around day 50 of the 13 week study, variation appears to increase in the mean level of prolactin in lorcaserin-treated groups compared to the vehicle control. Suspecting that this variation may in fact reflect an overall increase in prolactin exposure in lorcaserin-dosed groups, the sponsor provided three different analyses of the data in **Figure 4a**. In the first analysis, (**Figure 5**), the sponsor plotted the average prolactin level from all time points for each experimental group across the 13 week period. This analysis shows an overall 30%- 50% increase in prolactin in the lorcaserin groups, though a dose dependence is not seen. Perphenazine results in a 500% increase compared to control.

Figure 5: Averaged 20h prolactin levels from 13wk study in female SD rats



In **Figure 6A**, the Sponsor plotted all 20h plasma prolactin reads for each animal across all dose groups. Each point in the scatterplot represents a prolactin value which was obtained from one animal at one time point in the course of the 13 week study. The horizontal line drawn at 100ng/ml represents an upper bound that captures most of the plasma prolactin reads for the control group. This analysis shows a pattern of higher prolactin reads in all the lorcaserin dose groups compared to control. The more robust response in the 100mg/kg lorcaserin dose group likely reflects the higher prolactin values during the first 10 days of dosing, as apparent in **Figure 4** above. In **Figure 6B**, the sponsor presents a 'time to event' analysis that shows the cumulative percentage of rats that experienced at least one data point with a plasma prolactin value above 100ng/ml. The analysis shows that a greater proportion of females dosed lorcaserin experienced at least one 'high prolactin event' in the course of the 13 week study compared to the control group. All females exposed to perphenazine experienced substantial elevations in prolactin.

Figure 6: Plasma prolactin from 13 week study in SD female rats. A) scatterplot of all prolactin reads during study, B) 'time to event' analysis of the proportion of rats experiencing plasma prolactin above 100ng/ml.



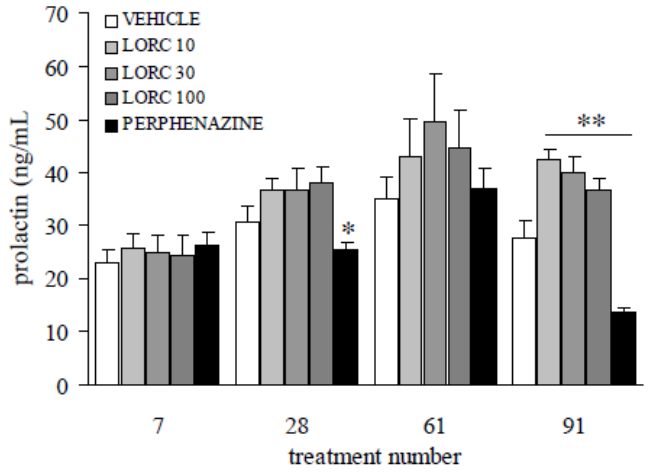
Estradiol, luteinizing hormone, and progesterone levels were also measured at Days 1, 7, 28, 60, and 90 in the 13 week study. No consistent pattern of change was observed in any hormone at any time point.

Effect of Lorcaserin on Pituitary and Mammary Prolactin

Immunohistochemical staining was performed to estimate the level of prolactin in the pituitary and mammary tissues from female rats at pre-specified time points in the 13 week study. To summarize, lorcaserin had unremarkable effects on prolactin immunostaining in the mammary endothelium, epithelium, and mast cells. However, lorcaserin modestly increased the pituitary content of prolactin, though without an apparent dose-response.

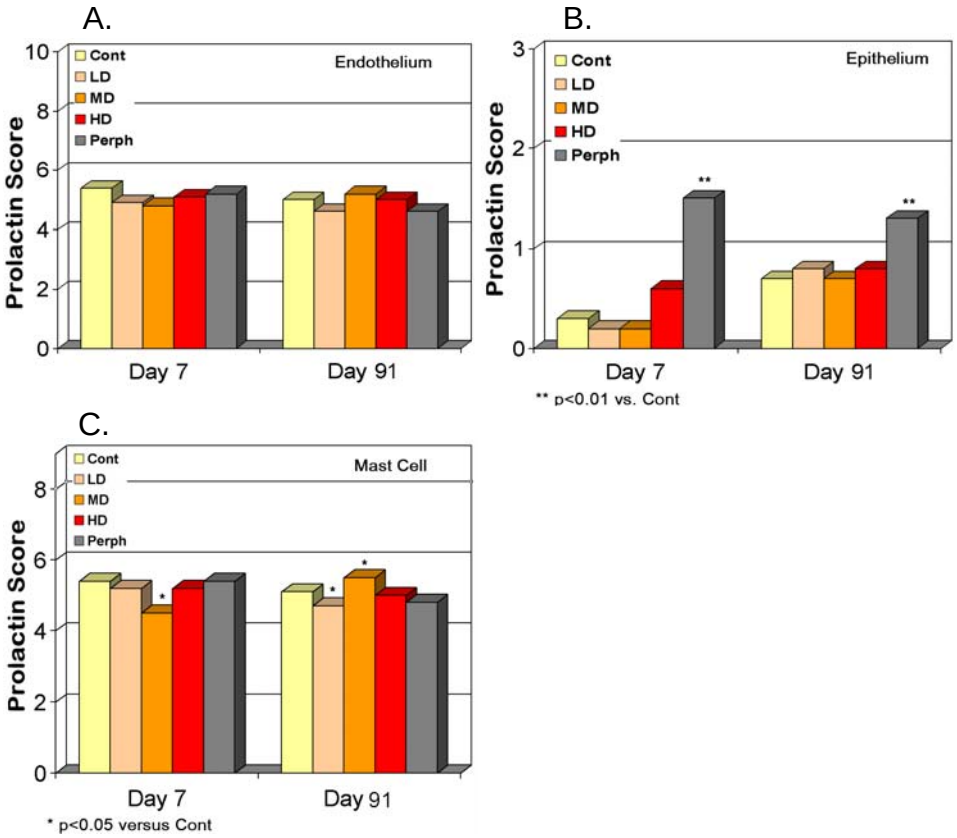
Figure 7 shows a gradual rise in pituitary prolactin in the lorcaserin dose groups over the concurrent control group, reaching statistical significance by day 91. Consistent with the robust and persistent stimulation of prolactin release, perphenazine eventually lead to depletion of pituitary prolactin. In the 2yr bioassay, lorcaserin increased the incidence of pituitary hypertrophy/hyperplasia but substantially reduced the incidence of pituitary neoplasms.

Figure 7: Prolactin immunostaining in pituitary of female SD rats



Figures 8a, **b**, and **c** show prolactin immunostaining of the endothelium, epithelium, and mast cells in mammary tissue from the female rats after 7 and 91 days of dosing with lorcaserin. Lorcaserin had unremarkable effects on the three cell types evaluated. Perphenazine increased staining consistently in the epithelium, but not in the other two cell types.

Figure 8: Prolactin immunohistochemical staining of mammary endothelium (A), epithelium (B), and mast cells (C) in female rats at days 7 and 91 in response to control, lorcaserin, or perphenazine.



Effect of Lorcaserin on Mammary Histopathology in 13wk Study in Female Rats

The Sponsor hypothesized that changes in prolactin exposure with lorcaserin, even if minimal, would result in histological changes consistent with known hormonal effects on the mammary tissue. At pre-specified time points, mammary tissues were collected and subjected to 'standard' hematoxylin & eosin examination or were sent to the laboratory of Dr. Jose Russo (Fox Chase Center) for evaluation by a whole mounting method. The latter method allows for more precise evaluation of terminal end buds and structures and of the differentiation status of lobular structures in mammary tissue.[2]

To summarize these results, lorcaserin minimally promoted differentiation of mammary lobular structures demonstrated primarily by an increase in secretory product and a higher frequency of lobular 1 & 2-type differentiation status after 28 or 91 days of dosing. Perphenazine strongly promoted lobular differentiation and hyperplasia. Despite the stark difference in the degree of response to lorcaserin versus the positive control, the minimal effects of lorcaserin are nonetheless consistent with the minimal increase in prolactin levels and with known hormonal effects on differentiation of mammary structures.

Standard histological examination of the mammary tissue at days 28 and 91 are shown in **Table 10**. Of note, lorcaserin increased secretory products in the tissue (an indicator of hormonal action) on day 28 and to a lesser degree on day 91. Lorcaserin had an equivocal effect on lobular hyperplasia, which was numerically increased but the incidence was low and did not follow a dose response. All thirty animals dosed with perphenazine showed lobular hyperplasia at both time points.

Table 10: Standard H&E evaluation of mammary tissue in female SD rats
(n=60/group for vehicle and lorcaserin; 30/group for perphenazine)

n(%) of animals with finding	Vehicle	Lorcaserin Dose Group			Perphenazine
		10 mg/klg/day	30 mg/kg/day	100 mg/kg/day	
Day 28					
Secretory products	5 (8.3)	--	10 (17.2)	15 (26.3)[a]	0
Lobular hyperplasia	0	--	0	3 (5.3)	30 (100)[a]
Hyperplasia w/atypia	0	--	0	0	0
Perialveolar hemorrhage	2 (3.3)	--	3 (5.2)	3 (5.3)	18 (60)
Day 91					
Secretory products	1 (1.7)	5 (8.3)	2 (3.3)	2 (3.6)	0
Lobular hyperplasia	1 (1.7)	3 (5.0)	0	2 (3.6)	30 (100)[a]
Hyperplasia w/atypia	0	0	1 (1.7)	1 (1.8)	1 (3.3)
Perialveolar hemorrhage	5 (8.3)	9 (15.0)	6 (10.0)	12 (21.4)	14 (46.7)[a]

Note: At Day 28 the lorcaserin 10 mg/kg group was not analyzed.

[a] P<0.05 compared to vehicle control

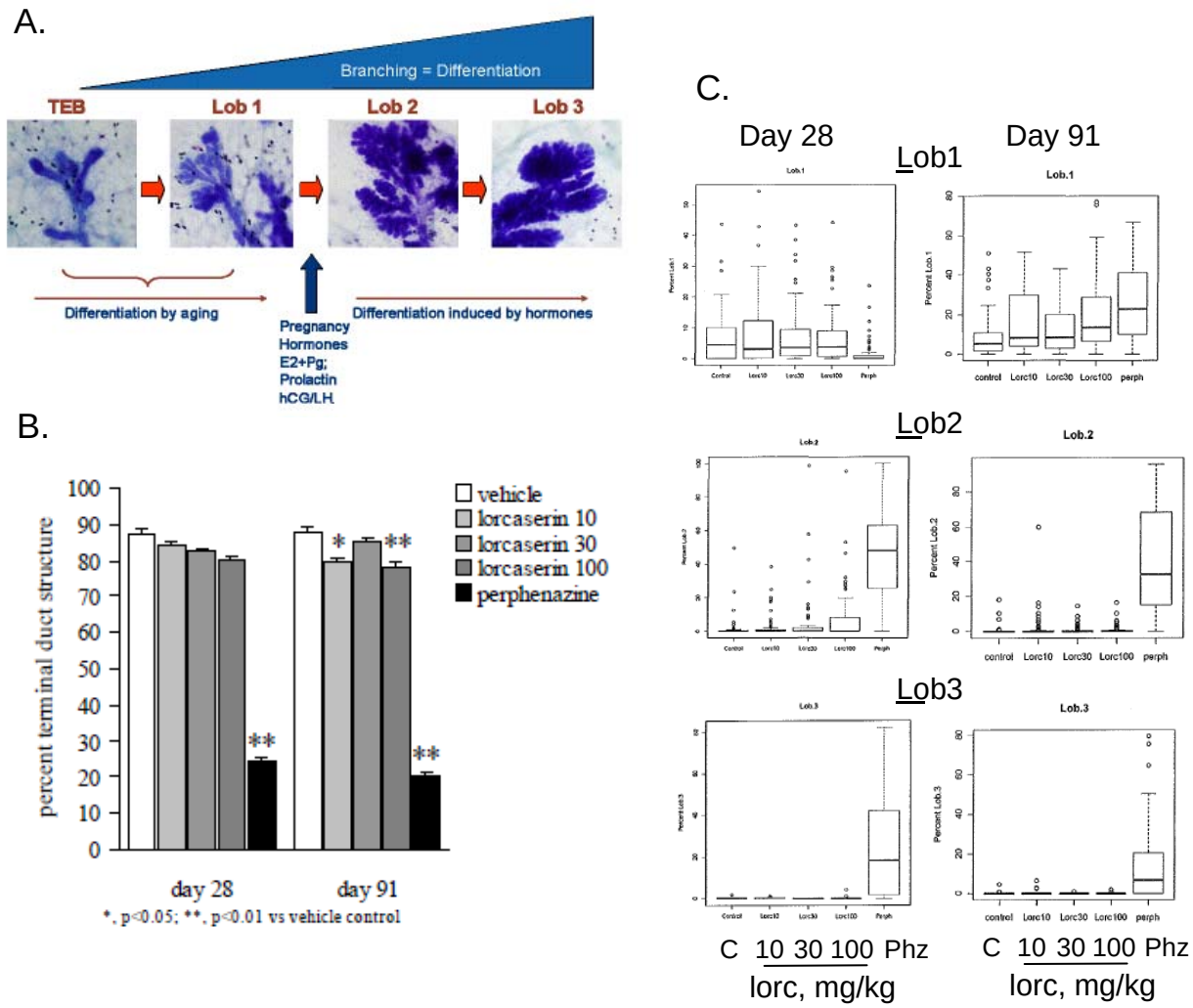
Note: Secretory product is listed as '0' for perphenazine as only the most differentiated state (hyperplasia) was recorded for each animal.

Figure 9A presents a schematic from Russo and Russo[2] that summarizes the progression of differentiation of mammary structures from terminal end buds and terminal ducts to more hyperplastic and hypertrophic structures (denoted Lob1, 2, 3) with age and in response to hormonal stimulation. Histopathological evaluation by Dr. Russo's laboratory found a small decrease in the percentage of terminal duct structures (TD) in female rats treated with 10 and 100

[2] Russo and Russo (1996) Environ Health Persp. 104(9):938-967

mg/kg lorcaserin (**Figure 9B**). Consistent with the small decrease in TD structures, Dr. Russo concluded that lorcaserin shifted more mammary tissues to the lobular 1 and 2 differentiation state (**Figure 9C**). The apparent minimal effect of lorcaserin is consistent with a hormonal effect on mammary tissue commensurate with minor increases in plasma prolactin. Consistent with robust prolactin stimulation, perphenazine markedly reduced TD structures and strongly promoted lobular differentiation at both time points.

Figure 9: A) Schematic of mammary structure differentiation.[3] Terminal end structures (B) and lobular differentiation state (C) in female SD rats in response to lorcaserin or perphenazine for 28 and 91 days.



Immunostaining of the mammary tissues for the proliferative marker PCNA (proliferative cell nuclear antigen) did not show a persuasive signal in the lorcaserin-dosed groups, but approximately doubled in response to perphenazine (**Table 11**). The minimal histological change apparent with lorcaserin after 3 months dosing likely precludes detection of a proliferative signal with this methodology.

[3] Russo and Russo (1996) Environ Health Persp. 104(9):938-967

Table 11. PCNA staining of mammary gland in female rats treated with lorcaserin and positive control, perphenazine. An increase in PCNA score suggests early signs of glandular cell hyperplasia.

PCNA Staining in the Mammary Gland after 28 or 91 Days of Treatment

Treatment	Day 28[a]	Day 91[a]
Vehicle	6.7 ± 3.0	8.01 ± 3.8
Lorcaserin 10 mg/kg	-	10.3 ± 4.7[c]
Lorcaserin 30 mg/kg	8.3 ± 3.6[b]	9.1 ± 3.5
Lorcaserin 100 mg/kg	5.8 ± 3.3	8.1 ± 3.0
Perphenazine 5 mg/kg	15.9 ± 6.7[c]	16.6 ± 5.2[c]

[a] Mean ± standard deviation [b] P < 0.05 versus vehicle control; [c]P < 0.01 versus vehicle control

Prolactin Interventional Studies

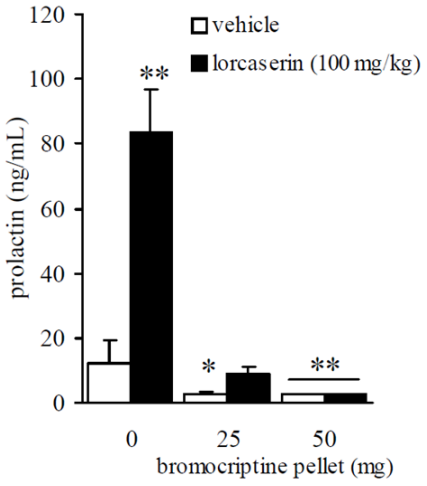
The Agency discussed experimental approaches with the sponsor intended to test the hypothesis that intervening in prolactin release or activity would ablate lorcaserin-induced preneoplastic changes in mammary tissue. Such studies, if successful, would provide the most persuasive evidence that prolactin is the primary intermediate in lorcaserin's mode of tumorigenic action. Unfortunately, none of the interventional approaches were found suitable to address this hypothesis. Studies with bromocriptine (a dopamine receptor agonist) were sufficient to demonstrate that the acute increase in prolactin with lorcaserin involves hormone release from the pituitary. However, this study involved a single dose as toxicity limited the duration of dosing, so histological endpoints could not be addressed. Dosing of hypophysectomized rats was limited to a 10 day duration and a 30mg/kg dose due to severe toxicity, and was confounded by an unusually high incidence of mammary hyperplasia in sham-operated control animals. Also, lorcaserin did not increase plasma prolactin in either sham or hypophysectomized female rats. A prolactin receptor antagonist (S179D) was better tolerated and dosing could be extended to 28 days; however, the antagonist failed to prevent perphenazine from increasing mammary hyperplasia, an event clearly related to prolactin, and is therefore not a reliable study.

These prolactin interventional studies are briefly summarized and highlight the deficiencies encountered with each approach.

Bromocriptine study

Bromocriptine is a dopamine receptor agonist that suppresses pituitary release of prolactin. Bromocriptine successfully blocked the acute rise in prolactin induced by a single dose of lorcaserin (100mg/kg) in female rats (**Figure 10**). Continued co-administration of both compounds resulted in severe toxicity, so this study was limited to a single dose of lorcaserin. At most, this study demonstrates that lorcaserin stimulates the pituitary to release prolactin after acute exposure. As discussed above, the acute increase induced by lorcaserin is lost after repeated dosing.

Figure 10. Plasma prolactin in female rats implanted with bromocriptine, a dopamine agonist for 10 days prior to administration of a single dose of 100 mg/kg lorcaserin.



*P<0.05, **P<0.01 versus vehicle-vehicle.

Hypophysectomy Study

Surgical removal of the pituitary should ablate lorcaserin-induced increases in prolactin and prevent any histological changes in mammary tissue. Unfortunately, the duration of dosing was limited to 10 days due to excessive body weight loss, and the dose was restricted to 30mg/kg lorcaserin because higher doses were toxic to hypophysectomized rats. Therefore, following hypophysectomy or a sham procedure, female rats were dosed daily for 10 days with 30mg/kg lorcaserin. The animals were allowed to recover, un-dosed, until day 28.

Prolactin measured at 20h post-dose on day 10 (end of dosing) and 28 (end of recovery) did not show an increase with lorcaserin in either sham or hypophysectomized animals (**Table 12**).

Table 12. Plasma prolactin in response to lorcaserin in sham or hypophysectomized female rats

Treatment		Prolactin (ng/mL)	
Surgery	PO treatment	Day 10	Day 28
Sham	Vehicle	7.2	8.5
Sham	Lorcaserin (30 mg/kg)	6.9	9.7
Hypophysectomy	Vehicle	4.2	3.8
Hypophysectomy	Lorcaserin (30 mg/kg)	4.3	3.0

Original data can be found in Arena ELN Erin Sanabria A000140-06

The sponsor contends that 30mg/kg lorcaserin increased mammary hyperplasia in sham but not hypophysectomized rats within the 10 day dosing period, and is therefore evidence for an intermediary role of prolactin in the histological change to mammary tissue (**Table 13**). Hyperplasia in this case was defined as the presence of secretory product as well as the number or size of lobules. The Agency does not agree with this conclusion, as lorcaserin did not increase prolactin in this study. Also, 18 of the 25 sham-operated animals dosed vehicle for 10 days presented with mammary hyperplasia, which is an excessively high background rate for control

animals. The further increase in hyperplasia to 24 of 25 animals with lorcaserin is considered marginal given the inexplicably high background rate of mammary hyperplasia in sham-operated animals.

Table 13: Effect of lorcaserin (30mg/kg) on the number and (percentage) of female rats with histopathological findings in mammary tissue after hypophysectomy or sham operation.

Parameter	Sham Operated		Hypophysectomy	
	Vehicle	Lorcaserin 30 mg/kg/day	Vehicle	Lorcaserin 30 mg/kg/day
n(%) of rats with:				
Hyperplasia	18 (72.0)	24 (96.0)[a]	15 (60.0)	17 (77.3)[b]
Fibrosis	24 (96.0)	25 (100)	25 (100)	25 (100)

n=25/group

Prolactin Receptor Antagonist Study

S179D is reportedly a peptidic prolactin receptor antagonist[4]. This intervention would allow lorcaserin to increase prolactin but prevent its biological effect in mammary tissue due to blockade of the prolactin receptor. Female rats were dosed with vehicle, lorcaserin, or perphenazine in the absence or presence of S179D for a 28d duration.

Lorcaserin increased plasma prolactin 2-3 fold on days 7 and 10, but not on day 25 when measured 20h post-dose.

Histological examination of mammary tissue showed that lorcaserin did not increase the mean hyperplasia score compared to control, whereas perphenazine increased the mean hyperplasia score (**Table 14**). Unfortunately, S179D did not prevent the increase in hyperplasia score induced by perphenazine, indicating that S179D did not successfully block prolactin activity.

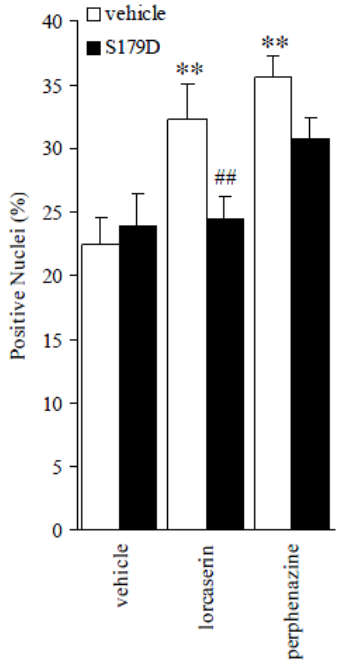
Table 14: Effect of prolactin receptor antagonist S179D on hyperplasia in rat mammary gland after 28 daily dosing of lorcaserin or perphenazine.

Treatment		Hyperplasia score (mean ± SE)
Minipump	PO treatment	
Vehicle	Vehicle	1.70 ± 0.11
Vehicle	Perphenazine (5 mg/kg)	2.59 ± 0.07[a]
Vehicle	Lorcaserin (100 mg/kg)	1.88 ± 0.07
S179D	Vehicle	1.72 ± 0.08
S179D	Perphenazine (5 mg/kg)	2.57 ± 0.10[b]
S179D	Lorcaserin (100 mg/kg)	1.83 ± 0.04

The sponsor states that lorcaserin and perphenazine increased staining for the proliferative marker PCNA which was prevented in both cases by S179D (**Figure 11**). However, the PCNA data starkly counters the histological evidence in **Table 14**, and is therefore difficult to interpret. Indeed, lorcaserin had no effect on PCNA staining in the 13week study discussed previously.

[4] Walker AM (2007) Mol Cell Endocrinol 276(1-2):1-9.

Figure 11: Effect of prolactin antagonist S179D on PCNA staining of mammary tissue in female SD rats



CRL Item #3: ***Address the unidentified mode of action and unclear safety margin for lorcaserin-emergent brain astrocytoma***

Under this item, the sponsor was tasked with providing information that would clarify or provide a better estimate of a safety margin to lorcaserin-emergent astrocytoma observed in male rats. Elucidation of a tumorigenic mode-of-action that is irrelevant to human biology would be an alternative approach to mitigating this safety concern. Conversely, demonstration of a sufficient safety margin would obviate the need for mode-of-action data.

Calculation of a safety margin is ideally based on drug concentrations in the biological compartment wherein toxicity is observed. For astrocytoma, drug levels in the CSF or brain tissue would be most appropriate. However, as discussed earlier, partitioning of lorcaserin to brain tissue in rodents and in monkeys differed by nearly 3-fold, so an accurate safety margin could not be calculated for determination of human risk. In discussions with the sponsor, it was observed that while the brain-to-plasma ratio varied by nearly 3-fold across species, the brain-to-CSF ratio was notably more constant (**Table 15**). Therefore, obtaining steady-state levels of lorcaserin in the plasma and cerebrospinal fluid of human subjects could allow the most accurate estimate of a safety margin based on the relatively consistent relationship between brain and CSF levels of lorcaserin across animal species. The Agency agrees with the Sponsor that this

approach assumes that the relatively consistent brain-to-CSF ratio observed in rodents and non-human primates translates to humans.

The sponsor conducted an open label clinical study in nine healthy overweight or obese subjects. The levels of lorcaserin in the plasma and cerebrospinal fluid were determined after 6 days dosing at 10mg bid. Partitioning of lorcaserin to the CSF in human subjects was substantially less than anticipated based on the observations in animals. Using an averaged brain-to-CSF ratio of 101 from the nonclinical species, brain levels of lorcaserin in human subjects is predicted to be 1.7 fold higher than plasma levels (**Table 15**). The predicted 1.7-fold partitioning in human subjects is substantially lower than that predicted by data in rats (25-fold) and non-human primates (10-fold).

Table 15: Lorcaserin CNS to plasma exposure ($AUC_{last, ss}$) ratios across nonclinical species (source, study MPR11007, NDA 22529)

Species	CSF/Plasma	Brain/Plasma	Brain/CSF
Mice (male, 50 mg/kg/day)	0.226	26	117
Rats (male, 10 mg/kg/day)	0.225	24	107
Rats (male, 30 mg/kg/day)	0.301	35	116
Rats (female, 10 mg/kg/day)	0.295	22	75
Monkeys (male, 10 mg/kg/day) Mean (SD)	0.112	10	90
Humans (mixed, 10 mg BID)	0.0168 (0.0027)	1.70 (0.38)[a]	101 (16)[b]

[a] $Brain AUC = \frac{Brain}{CSF} \times CSF\,AUC$ then $\frac{Brain\ estimated\ AUC12,ss}{Plasma\ AUC12,ss}$ estimated mean (SD), n=5 preclinical conditions across n=9 subject

[b] Human brain/CSF is determined by averaging the preclinical species brain/CSF ratios estimated mean (SD), n=5 preclinical conditions across n=9 subject

Based on a 1.7x brain-to-plasma ratio, the level of lorcaserin in human brain tissue at the clinical dose is estimated to be 1730 ng*h/ml AUC. When compared to the brain level calculated for rats at the highest dose not associated with a test article-related increase in astrocytoma (e.g., 10mg/kg NOAEL), the safety margin is 70-fold to the clinical dose of lorcaserin (**Table 16**).

Table 16: Reassessment of Safety Margins for Astrocytoma in Rats based on Estimated Brain Levels of Lorcaserin

	$AUC_{0\text{-}24h}$, ng*h/ml		Rat, 10 mg/kg (No astrocytoma)	Rat, 30 mg/kg (astrocytoma)
	Plasma	Brain		
Rat, 10mg/kg	4780	114720		
Rat, 30mg/kg	16900	591500		
Human, 10mg BID	**1020**	**1730**	**70x**	**360x**

In summary, the sponsor submitted clinical data indicating that partitioning of lorcaserin to the CNS in human subjects is substantially lower than predicted by nonclinical studies in rats and non-human primates. A safety margin of 70-fold for astrocytoma in rats, based on estimated brain levels of lorcaserin, presents a negligible clinical risk and obviates the need for mode-of-action data.

APPENDICES

Appendix A: Meeting Minutes from FDA Executive Carcinogenicity Assessment Committee, 10 August 2010

Executive CAC
Date of Meeting: August 10, 2010

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DHP, Alternate Member
Todd Bourcier, Ph.D., Team Leader
Fred Alavi, Ph.D., Presenting Reviewer

NDA 22-529
Drug Name: Lorcaserin HCl
Sponsor: Arena Pharmaceuticals

Executive CAC Recommendations and Conclusions:

The Committee concluded that the following tumors were drug-related:

Males
Brain: Astrocytoma at HD. Numerical, non-statistically significant increase in astrocytoma at mid-dose also considered drug-related.

Liver: Hepatocellular adenoma and carcinoma combined, at HD.

Mammary: Adenocarcinoma and fibroadenoma combined, at MD & HD.

Skin, subcutis: Fibroma at MD & HD

Skin: Squamous Carcinoma at HD. Numerical, non-statistically significant increase in squamous carcinoma at MD also considered drug-related.

Schwannoma (all sites) at HD. Numerical, non-statistically significant increase at the MD also considered drug-related.

Thyroid: Follicular cell adenoma at HD.

Females
Mammary: Adenocarcinoma + fibroadenoma at LD, MD, HD

Additional Committee Comments:

Mouse:

- The Committee agreed that the study was acceptable, as mortality was encountered at doses higher than 50mg/kg.
- The Committee concluded that the study was negative for any statistically significant drug-related tumor findings.

Rat:

- The Committee expressed some concern about the conduct and evaluation of the study. Specifically, concern was expressed about a large number of diagnostic changes of mammary tumor type in the evaluation for the mid and high dose group.

- The Committee noted that because high-dose animals died due to drug-induced tumors, the MTD was not exceeded in this study.

- The Committee was not persuaded by the sponsor's argument that mammary tumors were caused by increased prolactin levels. Specifically, the sponsor's data failed to demonstrate an increase in prolactin in repeat-dose mechanistic studies and in the 2 year carcinogenicity study.

- A mechanism for the induction of astrocytomas was not identified. Drug-induced astrocytomas were observed at exposures equal to 17x the clinical exposure, with a NOAEL that provides a 5x multiple to the clinical dose.

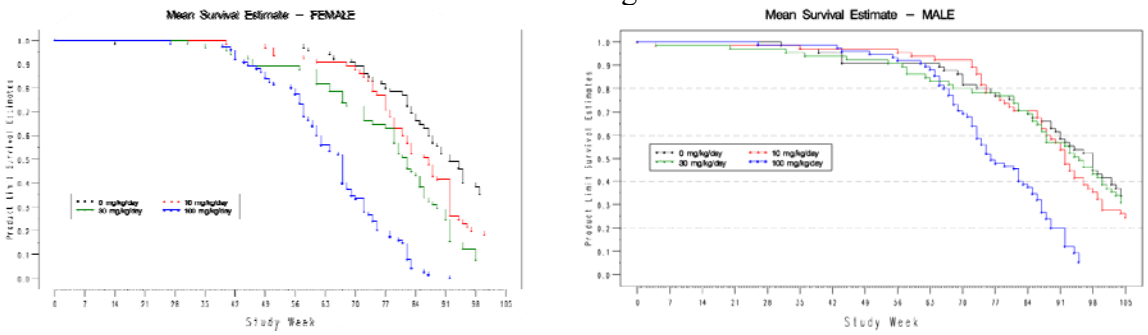
David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Agency File, DMEP
/Todd Bourcier, DMEP
/Fred Alavi, DMEP
/Pat Madara, DMEP
/ASeifried, OND IO

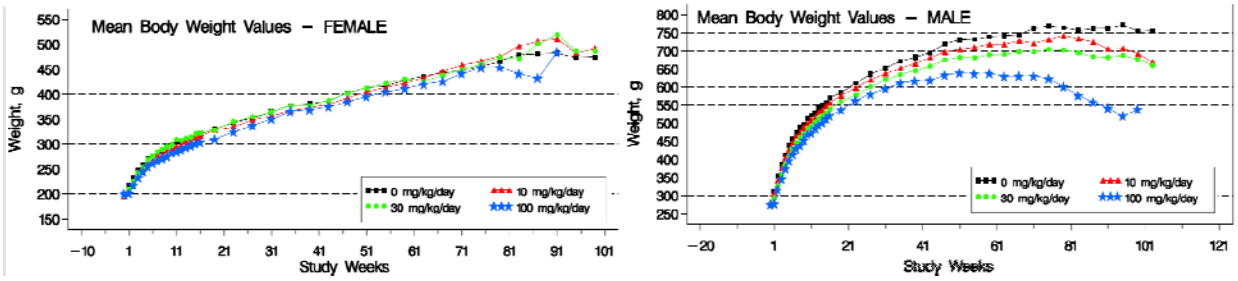
Appendix B: Survival and Body Weight Data from 2 Year Rat Study

Survival
Survival declined significantly at all doses in females due to the emergence of drug-related mammary fibroadenoma and adenocarcinoma. According to the sponsor's study report, survival also declined significantly in HD males, with the excess deaths due to the emergence of drug-related tumors in the brain, skin, mammary tissue, and peripheral nerves (schwannoma).

Excess mortality in carcinogenicity studies is considered evidence that drug exposure has exceeded the maximum tolerated dose (MTD), *but only when* the cause of mortality is related to something other than drug-induced tumors. In those cases, any tumors associated with that dose are not necessarily considered relevant to human risk. However, because the excess mortality observed with lorcaserin was due to drug-induced tumors rather than other toxicity, exposure achieved in the rats did not exceed a maximum tolerated dose, and the relevance of the tumors to human risk cannot be dismissed based on that argument.



<u>Body Weight changes</u>
Body weight declined in males, most notably at 100 mg/kg, but did not substantially change in females. Equivalent and even greater weight loss observed in carcinogenicity studies conducted with other investigational weight loss drugs is associated with improved 2 year survival and less tumor burden compared to concurrent control groups, not reduced survival and greater tumor burden as seen with lorcaserin. Therefore, weight loss observed in lorcaserin-treated males is not taken as evidence of exceeding a tolerable dose or of generalized toxicity, and is not interpreted as a reason for reduced survival or for tumor induction.



Appendix C: Skin fibroma, squamous cell carcinoma, malignant schwannoma

In addition to mammary neoplasms and astrocytoma, lorcaserin also increased the incidence of benign subcutis fibroma, squamous carcinoma of the skin, and malignant schwannoma in male rats at the mid- and high doses.

It is notable for a non-genotoxic compound to result in this array of tumor types affecting multiple tissues. Tumors of the peripheral/central nervous system and skin/subcutis are not shared by marketed centrally acting dopaminergic or serotonergic drugs or by current obesity medications. No studies or credible explanation was provided to address the spectrum of tumors induced by lorcaserin or the mechanism by which lorcaserin increased these tumors, so risk assessment must be based on the difference in exposure between rats and the clinical dose in humans. These tumors occurred at exposure 17-fold higher than the clinical dose, with a safety margin of 5x (i.e., tumors were not observed in rats at exposure 5-fold higher than the clinical dose). The acceptability of a 5x safety margin to these tumor types should be taken into consideration with the benefits that lorcaserin provides to the obese patient population.

Lorcaserin also increased the incidence of hepatocellular adenoma and carcinoma and thyroid follicular cell adenoma in male rats. Sufficient evidence suggests that lorcaserin increased liver tumors by a known mechanism in rodents involving chronic induction of liver drug-metabolizing enzymes, and early indications of hepatic hypertrophy were reported in short-term studies. With a reasonable safety margin of 17x to non-tumorigenic exposure and, more significantly, a recognized mechanism of tumorigenesis, the potential risk of hepatic and thyroid tumors to humans is considered negligible.

Appendix D: **Members of the Pathology Working Group and their affiliation**

Dr. K. A. Schafer (Vet Path Services, Inc., PWG Chairperson)
Dr. P. H. Long (Vet Path Services, Inc.)
Dr. R. E. Baumgartner (Vet Path Services, Inc.)
Dr. D. Thake (Midwest ToxPath Sciences, Inc.)
Dr. R. R. Maronpot (Maronpot Consulting, LLC)

Clinical Briefing Document
Endocrine and Metabolic Drugs Advisory Committee Meeting
May 10, 2012

New Drug Application 022529
Product: Lorcaserin hydrochloride
Sponsor: Arena Pharmaceuticals, Inc.
Clinical Reviewer: Julie Golden, M.D.

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1 Abstract

Lorcaserin is a first-in-class 5-hydroxytryptamine 2C (5HT2C) receptor agonist developed for obesity treatment. The 5HT2C receptor is concentrated in the central nervous system (CNS) where it regulates feeding behavior. The endogenous ligand is serotonin. The proposed lorcaserin dose for marketing is 10 mg twice daily (BID).

On September 16, 2010, the Endocrine and Metabolic Drugs Advisory Committee (EMDAC) was convened to discuss lorcaserin data submitted under NDA 022529 by Arena Pharmaceuticals ("the sponsor"). The original submission included two pivotal Phase 3 placebo-controlled safety and efficacy trials that evaluated more than 7000 patients with body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with at least one weight-related comorbidity (hypertension, dyslipidemia, glucose intolerance, cardiovascular disease, and/or sleep apnea):

- BLOOM: a 104-week trial that evaluated lorcaserin 10 mg BID versus placebo in a 1:1 randomization; in the second year, the lorcaserin-treated patients were re-randomized 2:1 to lorcaserin or placebo

- BLOSSOM: a one-year trial that evaluated two lorcaserin doses, 10 mg once daily (QD) and 10 mg BID versus placebo

In pooled efficacy analyses, the mean placebo-subtracted weight loss at Week 52 from baseline with lorcaserin 10 mg BID was 3.3%. Approximately 47% of patients on lorcaserin 10 mg BID and 23% of patients on placebo lost at least 5% of baseline body weight at Week 52. Modest improvements in metabolic- and cardiovascular-related secondary efficacy endpoints were seen in the lorcaserin 10 mg BID group as compared to placebo and were generally commensurate with the degree of weight loss.

The safety assessment of lorcaserin was focused on concerns related to 5HT2C receptor activation and the potential for off-target effects (i.e., activation of the 5HT2A and 5HT2B receptors), as well as theoretical concerns resulting from animal findings. The committee discussed the following safety concerns: rat carcinogenicity (notably, mammary tumors and astrocytoma), valvular heart disease, psychiatric adverse events (including psychosis, euphoria, and dissociation), and cognitive adverse events.

After weighing the risks and benefits of lorcaserin that were characterized at the time of the meeting, five members of EMDAC voted for approval and nine voted against with no abstentions. FDA subsequently issued a complete response (CR) letter, citing modest weight loss and concerns about findings in the rat carcinogenicity study.

In response to the CR letter, the sponsor submitted additional material to the NDA, including readjudication of mammary pathology from the rat carcinogenicity study, as well as three clinical studies, (1) a Phase 1 study to evaluate the exposure of lorcaserin in cerebrospinal fluid in order to address safety margins for astrocytoma, (2) a 56-day Phase 2 trial evaluating lorcaserin's effect on energy expenditure, and (3) a Phase 3 trial in 604

patients with type 2 diabetes mellitus (BLOOM-DM). Data from BLOOM-DM are most relevant to the clinical review.

Efficacy results from BLOOM-DM supported the weight loss results from the previous two larger Phase 3 trials and provide additional information regarding glycemic effect in patients with type 2 diabetes. In summary:

- At Week 52, mean placebo-subtracted weight loss from baseline for lorcaserin 10 mg BID was 3.1%

- At Week 52, 37.5% of patients on lorcaserin 10 mg BID and 16.1% of patients on placebo lost at least 5% of baseline body weight

- At Week 52, mean placebo-subtracted change in HbA1c for lorcaserin 10 mg BID was 0.49%

- At Week 52, more patients on lorcaserin 10 mg BID than placebo achieved HbA1c < 7% (50.4% vs. 26.3%), HbA1c < 6.5% (23.9% vs. 8.6%), fasting plasma glucose < 126 mg/dL (42.2% vs. 29.1%), and fasting plasma glucose < 100 mg/dL (14.1% vs. 5.7%)

- For unclear reasons, a dose-response was not seen for efficacy between the BID and QD doses, unlike in the larger BLOSSOM trial and Phase 2 dose-ranging trials

With respect to safety, results from BLOOM-DM generally supported the overall safety profile seen in the larger Phase 3 trials. A summary of safety issues in this application are as follows:

- Valvular heart disease: In the original submission, the selectivity of lorcaserin at the clinical dose for the 5HT2C receptor versus the 5HT2B receptor, which is implicated in fenfluramine-associated valvulopathy, was uncertain. Additional data have been provided with this resubmission to address the receptor selectivity and potency of lorcaserin, and as Dr. Todd Bourcier notes in his briefing document, plasma concentrations of lorcaserin at the therapeutic dose are expected to remain within the selective range for activation of 5HT2C. Nevertheless, in the pooled analysis of the Phase 3 echocardiographic data, the relative risk for FDA-defined valvular heart disease (VHD), defined as mitral regurgitation greater than mild or aortic regurgitation greater than trace was 1.16, with a 95% confidence interval (CI) of 0.81 to 1.67. This upper bound exceeds the 1.5 upper bound requested by FDA to rule out an excess risk of VHD. The point estimate and upper bound were similar in a number of sensitivity analyses conducted by the sponsor and FDA statistician. Furthermore, individual valve regurgitation was fairly consistently increased in the lorcaserin treatment group. Whether these findings can be explained by ascertainment or other bias (due to greater weight loss in the lorcaserin group) is unknown.

- Neuropsychiatric effects: Lorcaserin had poor tolerability in early phase trials in which doses of at least 40 mg were administered, particularly to lower-weight females. Hallucinatory effects were seen in a female subject treated with 40 mg at a C_{max} of 176.90 ng/mL (Phase 3 lorcaserin C_{max} range: 1-156 ng/mL). Six adverse events of euphoria were seen in the Phase 3 trials in the lorcaserin 10 mg BID group and and one in the placebo group. No euphoria was seen in BLOOM-DM. Depression adverse events overall (based on a narrow selection of adverse event terms) were not more frequent in the non-diabetes Phase 3 trials in lorcaserin versus placebo groups, although they were slightly more frequent in lorcaserin group in the BLOOM-DM trial. The BLOOM-DM trial supported the findings from the non-diabetes trials that there was a small imbalance in serious adverse events of depression, discontinuations due to adverse events of depression, and suicidality scores (based on a single questionnaire item) in the lorcaserin-treated patients as compared to placebo-treated patients. The BLOOM-DM trial also supported the finding that cognitive impairment was seen more frequently in the lorcaserin-treated patients as compared to the placebo-treated patients. Other neuropsychiatric adverse events that are dose-related and were more frequently seen in lorcaserin-treated patients include headaches, dizziness, and paresthesias.

- Prolactin increases: Prolactin was monitored in a subset of patients in BLOSSOM and in the BLOOM-DM trial due to the proposed association between prolactin increases in animals and mammary tumorigenesis. No definitive comments can be made regarding breast cancer in women from the Phase 3 trials. Lorcaserin does appear to induce a mild prolactin increase in some patients, although the proportion of patients in any treatment group with prolactin values greater than the upper limit of normal was small. At Week 52 there was a slightly increased proportion of patients treated with lorcaserin with prolactin values greater than the upper limit of normal (ULN), greater than two times (2x) ULN, and visit pre-dose > 2x baseline pre-dose values. No lorcaserin-treated patient was found to have prolactin values > 10x ULN. Similarly, adverse events related to measured increases in prolactin or that could be considered potentially related to prolactin increases (e.g., galactorrhea, gynecomastia, sexual dysfunction, or menstrual abnormalities) were infrequent.

- Cardiovascular: The lorcaserin trials were not powered or designed to rule out a prespecified degree of ischemic cardiovascular risk. In general, risk factors for cardiovascular disease, such as changes in blood pressure, lipids, and glycemia were improved with weight loss. BLOOM-DM was aberrant in that there was actually an increase in the proportion of patients treated with lorcaserin with adverse events of hypertension; this finding was not seen in the non-diabetes trials. In an unadjudicated pooled analysis, 20 (0.6%) lorcaserin 10 mg BID and 13 (0.4%) placebo patients had adverse events related to ischemic heart disease. In a separate exploratory analysis, six (0.2%) lorcaserin 10 mg BID and two (0.1%) placebo patients had adverse events of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Because of the exploratory nature of these analyses, formal statistical testing was not conducted. Of note, the sponsor contracted with physicians from the Brigham and Women's Hospital (Boston, Massachusetts) for a blinded post-hoc adjudication of

death, cardiovascular ischemic events, and cerebrovascular events from the BLOOM and BLOSSOM trials. In these two trials, the lorcaserin 10 mg BID group had five such events, lorcaserin 10 mg QD had no events, and placebo had six events. There was one event in the second year of the BLOOM trial in a patient re-randomized from lorcaserin 10 mg BID to placebo. BLOOM-DM did not have its cardiovascular events adjudicated in this post-hoc process.

- Hypoglycemia: As would be expected due to the improved glycemic control seen in patients with type 2 diabetes in the BLOOM-DM trial, adverse events of hypoglycemia were seen more frequently in lorcaserin-treated patients as compared to placebo-treated patients. Importantly, none of the adverse events was reported as serious, none led to study withdrawal or study drug discontinuation, and none required treatment by emergency personnel or with parenteral agents. No action was taken for the majority of events in all treatment groups, and all events resolved.

2 Background and Regulatory History

Lorcaserin hydrochloride is a first-in-class 5-hydroxytryptamine 2C (5HT2C) receptor agonist developed for oral administration at a dose of 10 mg twice daily for weight management. The 5HT2 receptor is a member of the G-protein-coupled family of serotonin receptors, and is the target for a variety of centrally-acting drugs, including those to treat depression, migraine, and obesity. The three sub-classes, 5HT2A, 5HT2B, and 5HT2C have widely differing tissue distributions. Differences in receptor affinity and activity may predict a 5HT2 receptor agonist's desired action as well as its toxicity. Please refer to Dr. Todd Bourcier's briefing document, which describes binding profile and functional activity of lorcaserin at the 5HT2A, 5HT2B, and 5HT2C receptors.

In brief, the 5HT2A receptor is located in the brain and peripheral tissues and mediates contractile responses of vascular, urinary, gastrointestinal, and uterine smooth muscle, and increases platelet aggregation and capillary permeability.[1] The 5HT2A receptor is thought to be the target for hallucinogens such as d-lysergic acid diethylamide (LSD).[2] The 5HT2B receptor is distributed in the brain in low concentrations, and at higher concentrations in the lung, kidney, heart, intestine, and stomach.[1] Its agonism is implicated in the valvular heart disease (VHD) associated with the metabolite of the anorexigen fenfluramine (norfenfluramine) and its racemic enantiomer, dexfenfluramine, as well as other agents, such as the ergot alkaloids.[3] The 5HT2C receptor is not known to be distributed in the periphery. Its highest density is the choroid plexus, with lower concentrations in the cerebral cortex, basal ganglia, hippocampus, and hypothalamus.[2] The 5HT2C receptor has high homology to the 5HT2A receptor, and therefore has similar

[1] Hoyer D, et al. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). Pharmacol Rev 1994 Jun; 46(2): 157-203.
[2] Roth BL, et al. 5-Hydroxytryptamine$_2$-family receptors (5-Hydroxytryptamine$_{2A}$, 5-Hydroxytryptamine$_{2B}$, 5-Hydroxytryptamine$_{2C}$): where structure meets function. Pharmacol Ther 1998; 79(3): 231-57.
[3] Rothman RB, et al. Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. Circulation 2000 Dec 5; 102(33): 2836-41.

pharmacological binding profiles.[4] The agonism of the 5HT2C receptor is thought to induce hypophagia, hyperthermia, penile erections, and anxiety, and decrease locomotor activity in rats.[5,6,7]

Fenfluramine and dexfenfluramine, nonspecific 5HT2 agonists, were FDA-approved for the treatment of obesity in 1973 and 1996, respectively. The drugs' association with primary pulmonary hypertension (PPH) had been identified prior to the U.S. approval of dexfenfluramine; however, by 1997 both drugs had been removed from the U.S. market due to the not previously described association with left-sided VHD.[8,9]

Arena Pharmaceuticals originally submitted New Drug Application (NDA) 022529 to FDA in December of 2009. Data from NDA 022529 were presented at the Endocrine and Metabolic Drugs Advisory Committee (EMDAC) on September 16, 2010. The original Phase 3 clinical program included two pivotal trials, with similar patient populations and endpoints.

- Study APD356-009 (Behavioral modification and Lorcaserin for Overweight and Obesity Management; BLOOM) was a placebo-controlled two-year trial to assess the effect of lorcaserin on weight. A total of 3182 male and female patients ages 18-65 years with a BMI 30-45 kg/m^2 with or without a co-morbid condition or 27-29.9 kg/m^2 with at least one co-morbid condition, were randomized 1:1 to lorcaserin 10 mg BID or placebo. After one year of treatment, the lorcaserin group was re-randomized 2:1 to lorcaserin 10 mg BID or placebo, stratified by 5% weight loss responder status. The placebo group remained on placebo for the second year.

- Study APD356-011 (Behavioral modification and Lorcaserin Second Study for Obesity Management; BLOSSOM) was a placebo-controlled one-year trial to assess the effect of lorcaserin on weight. A total of 4008 male and female patients ages 18-65 years with a BMI 30-45 kg/m^2 with or without a co-morbid condition or 27-29.9 kg/m^2 with at least one co-morbid condition were randomized 2:1:2 to lorcaserin 10 mg BID, lorcaserin 10 mg QD, or placebo.

2.1 Efficacy Background: Original Data

All weight loss results presented below were conducted in the modified intent-to-treat (MITT), last observation carried forward (LOCF) population.

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[4] Giorgetti M and Tecott LH. Contributions of 5HT2C receptors to multiple actions of central serotonin systems. Eur J Pharmacol 2004; 488: 1-9.

[5] Kimura Y, et al. Pharmacological profile of YM348, a novel, potent and orally active 5-HT2C receptor agonist. Eur J Pharmacol 1 Jan 2004; 483(1): 37-43.

[6] Hayashi A, et al. Thermogenic effect of YM348, a novel 5-HT$_{2C}$-receptor agonist, in rats. J Pharm Pharmacol 2004; 56(12): 1551-6.

[7] Kimura A, et al. Overexpression of 5-HT2C receptors in forebrain leads to elevated anxiety and hypoactivity. Eur J Neurosci 2009; 30: 299-306.

[8] Connolly HM, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med. 1997 Aug 28;337(9): 581-8.

[9] CDC Morbidity and Mortality Weekly Report, 14 Nov 1997; 46(45): 1061-6.

At Year 1 of the two-year BLOOM trial:

- 47.5% of patients treated with lorcaserin 10 mg BID lost ≥ 5% body weight as compared to 20.3% of patients treated with placebo ($p < 0.001$)

- Patients treated with lorcaserin 10 mg BID lost 5.9 ± 0.2 percent of baseline body weight as compared to 2.2 ± 0.1 percent in the placebo group (difference in adjusted mean change, 3.7%, $p < 0.001$)

- 22.6% of patients treated with lorcaserin 10 mg BID lost ≥ 10% weight loss from baseline to Week 52 as compared to 7.7% of patients treated with placebo ($p < 0.001$)

At Year 2 of the two-year BLOOM trial:

- 67.9% of lorcaserin-treated patients who completed Year 1 of BLOOM and were ≥ 5% weight loss "responders" maintained at least a 5% weight loss from baseline (beginning of the study) at Week 104 as compared to 50.3% of placebo-treated ≥ 5% responders ($p < 0.001$)

- All treatment groups regained body weight from Week 52 to Week 104: those lorcaserin-treated patients who were randomized to remain on lorcaserin in Year 2 regained 2.53 ± 0.19 kg, those lorcaserin-treated patients who were re-randomized to placebo regained 4.76 ± 0.31 kg, and those who were randomized to placebo for the first and second years of the trial regained 1.00 ± 0.61 kg body weight from Week 52

At Year 1 of the one-year BLOSSOM trial:

- 47.2% of patients treated with lorcaserin 10 mg BID, 40.2% of patients treated with lorcaserin 10 mg QD, and 25.0% of patients treated with placebo lost ≥ 5% of body weight ($p < 0.001$ for lorcaserin 10 mg BID vs. placebo; $p < 0.001$ for lorcaserin 10 mg QD vs. placebo)

- Patients treated with lorcaserin 10 mg BID, lorcaserin 10 mg QD, and placebo lost 5.8 ± 0.2, 4.7 ± 0.2, and 2.8 ± 0.2 percent of baseline body weight, respectively (difference in adjusted mean change 3.0%, $p < 0.001$ for lorcaserin 10 mg BID vs. placebo; 1.9%, $p < 0.001$ for lorcaserin 10 mg QD vs. placebo)

- 22.6% of patients treated with lorcaserin 10 mg BID, 17.4% of patients treated with lorcaserin 10 mg QD, and 9.7% of patients treated with placebo lost ≥ 10% of body weight after 52 weeks of treatment ($p < 0.001$ for lorcaserin 10 mg BID vs. placebo; $p < 0.001$ for lorcaserin 10 mg QD vs. placebo)

Clinical efficacy was discussed at the September 2010 EMDAC meeting. The committee felt that efficacy in these trials, although meeting one of the Agency's weight loss criteria (i.e., categorical), was modest and in fact may be overestimated in clinical trials of a relatively healthy population as compared to the typical obese patient population, which

may be at higher risk for metabolic and cardiovascular disease and less likely to achieve treatment benefits. The committee wanted a broader patient population to be studied; some members felt that the ongoing diabetes study, when completed, would provide an important contribution to the efficacy assessment. The committee acknowledged that the potential beneficial effect of lorcaserin on weight-related disease morbidity and mortality is unknown.

2.2 Safety Background: Original Data

A variety of safety issues were identified for discussion at the EMDAC meeting:

- Valvular heart disease: Lorcaserin is a 5HT2C receptor agonist. As noted above, the 5HT2C receptor is a member of the family of serotonin receptors that includes 5HT2B, agonism of which has been identified as the likely culprit for fenfluramine-, dexfenfluramine-, and ergotamine-associated valvular heart disease (VHD). Given this potential relationship, FDA required echocardiogram assessment of patients' heart valves in the Phase 3 program. FDA stressed to the sponsor that, although arbitrary, ruling out a 50% increase for the development of FDA-defined VHD (greater than mild mitral or greater than trace aortic regurgitation) would provide reassurance regarding lorcaserin's safety and therefore should be a key safety endpoint of the Phase 3 program. This non-inferiority margin requested by FDA was not achieved in the primary analysis (HR 1.07, 95% CI 0.74, 1.55).

  The advisory committee was skeptical that the risk of VHD could be definitively ruled out in preapproval trials. The committee felt that further animal studies likely would not be helpful to further characterize the risk, although some members suggested that receptor transfection studies and additional studies with use in combination with other agents might provide additional information. Echocardiography monitoring and mechanisms to facilitate reporting of valvulopathy were discussed as possible post-marketing risk management strategies.

- Rat carcinogenicity: In two-year carcinogenicity studies in rats, lorcaserin was associated with mammary gland tumors in both sexes at clinically relevant exposures, with no safety margin identified for female rats. Although the sponsor claimed that this is a prolactin-mediated phenomenon, a clear relationship between prolactin elevation and tumorigenesis was not established in the original submission. Other tumor types (astrocytoma, schwannoma, hepatocellular carcinoma and adenoma, squamous cell carcinoma and benign fibroma of skin, and benign follicular cell adenoma of the thyroid) were also seen in male rats at higher doses. Of these, astrocytoma was of particular concern – lorcaserin targets the central nervous system, and it was felt that a safety margin was not easily estimated from blood concentrations.

  Many committee members cited the findings from the rat carcinogenicity study as a major reason for their vote against a positive risk-benefit of lorcaserin. Several members asked about the utility of further animal mechanistic studies and others suggested the use of a post-marketing cancer registry.

- Psychiatric Events: Activation of the 5HT2A receptor has been associated with the psychosis, euphoria, and dissociation seen with hallucinogens. Similar events were seen with lorcaserin administration at supratherapeutic doses in normal-weight individuals in the early phase trials. In the original Phase 3 program, six patients (0.2%) treated with lorcaserin 10 mg BID developed euphoria, as compared with one patient (< 0.1%) treated with placebo.

  Although the proportion of patients in the original Phase 3 trials with adverse events specific for depression were similar between lorcaserin 10 mg BID groups and placebo, more patients on lorcaserin 10 mg BID experienced adverse events that were considered serious or led to drug discontinuation. No firm conclusions regarding depression or suicidality could be drawn from the depression inventory (BDI-II) results.

  The committee felt that baseline psychiatric history in clinical trials was limited, and given the exclusion for selective serotonin reuptake inhibitors (SSRIs), it was difficult to extrapolate the risk to the likely patient population.

- Cognitive Effects: Centrally-acting obesity drugs of a variety of mechanisms have been found to possess neuropsychiatric effects, including adverse effects on cognition. The 5HT2A receptor is thought to play a role in cognition and memory. Cognitive adverse events were primarily identified from the original Phase 3 database, in which impairments in attention and memory were seen three times as frequently in the lorcaserin 10 mg BID treated group as compared to placebo.

  Some committee members were concerned about these adverse events; particularly those characterized as 'amnesia'. Others were reassured that the events were mostly reversible and patients tended to stay on the drug. It was noted by the committee that many approved drugs have cognitive effects. In terms of post-marketing strategies, the committee stated that this was a safety issue worth monitoring because older people may be more susceptible to this adverse event.

- Primary Pulmonary Hypertension: Anorexigenic drugs that act on the serotonergic system have been associated with the development of PPH. Anorexigens associated with PPH are thought to act by increasing serotonin release via the serotonin transporter.[10] The 5HT1B, 5HT2A, and 5HT2B receptors have also been suggested as potential serotonin mediators.[11,12] It was felt that given the rarity of this condition, even upon exposure to medications with an association to PPH, it was unlikely that an

[10] Rothman RB and Baumann MH. Serotonin releasing agents. Neurochemical, therapeutic and adverse effects. Pharmacol Biochem Behav. 2002 Apr;71(4): 825-36.
[11] Dempsie Y and MacLean MR. Pulmonary hypertension: therapeutic targets within the serotonin system. Br J Pharmacol 2008; 155: 455-62.
[12] Launay J-M, et al. Function of the serotonin 5-hydroxytryptamine 2B receptor in pulmonary hypertension. Nature Med 2002 Oct; 8(10): 1129-35.

association between lorcaserin and PPH could be identified if one existed in a clinical trial setting.

2.3 Risk-Benefit Assessment and Post-Committee Update

The EMDAC was asked to vote whether the available data adequately demonstrated that the potential benefits of lorcaserin outweighed the potential risks when used long-term in a population of overweight and obese individuals. Five members voted *yes* and nine *no*, with no abstentions.

FDA considered the discussion and recommendations of the committee, and on October 2010, issued a complete response action based on the following non-clinical and clinical deficiencies:

Nonclinical

- Diagnostic uncertainty in the classification of mammary masses in female rats
- Unresolved exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma
- Unidentified mode of action and unclear safety margin for lorcaserin-emergent brain astrocytoma

Clinical

- Lack of clarity surrounding a favorable balance of benefits and risks in light of marginal weight loss and safety concerns

To address the clinical deficiency, FDA asked for the safety and efficacy results of the (at the time, ongoing) diabetes trial, BLOOM-DM (Behavioral modification and Lorcaserin for Overweight and Obesity Management-Diabetes Mellitus).

2.4 New Clinical Data

This NDA resubmission includes the following new clinical data:

- Study APD356-022 was a single-site, seven-day, open-label study of healthy overweight or obese individuals ages 18-65 years in order to evaluate the pharmacokinetic properties of lorcaserin dosed to steady state in the cerebrospinal fluid (CSF). A total of 10 subjects were planned for enrollment, 11 subjects were randomized into the study, received at least one dose of lorcaserin and were included in the safety analysis, and nine subjects completed the study and were included in the pharmacokinetic analysis.
- Study APD356-014 (TULIP) was a double-blind, randomized, placebo-controlled, parallel-group study to assess the effects of lorcaserin on energy metabolism, energy intake, and body composition during 56 days of administration to overweight and

obese male and female individuals, aged 18 to 65 years. Fifty-seven patients were randomized in a 1:1 ratio to lorcaserin 10 mg BID or placebo.

- Study APD356-010 (BLOOM-DM) was a 52-week, double-blind, randomized, placebo-controlled, parallel-group trial to assess the safety and efficacy of lorcaserin versus placebo in overweight and obese patients with type 2 diabetes mellitus managed with oral hypoglycemic agents. All patients were instructed to maintain a standardized 600 kcal deficient diet and exercise program. Approximately 750 patients were originally planned for enrollment into the study (lorcaserin 10 mg BID: lorcaserin 10 mg QD: placebo; 1:1:1) but due to slow enrollment this number was reduced to 600 in Amendment 3 (lorcaserin 10 mg BID: placebo; 1:1). Patients randomized into the lorcaserin 10 mg QD group prior to the implementation of Amendment 3 remained enrolled in the trial to complete all planned study procedures. A total of 604 patients were randomized and 603 were analyzed for safety. The efficacy analyses included three populations: Modified Intent-to-Treat (MITT, N=593), Completers (CP, N=401), and Intended Week 52 (IW52, N=417). See Appendix A for a description of the study design.

This document is organized to be similar to the original NDA briefing document. In general, the new BLOOM-DM data will be presented side-by-side with the original pooled Phase 3 data (non-diabetes population, Year 1). Because no new safety signal emerged in Year 2 of the BLOOM trial, in general, those data will not be presented again. In some cases, BLOOM-DM data will be pooled with the original Phase 3 data (echocardiography, prolactin) or discussed separately (HbA1c efficacy, hypoglycemia safety). Data from the new Phase 1 (CSF) and Phase 2 (TULIP) trials will be discussed where relevant.

3 Lorcaserin Clinical Program

3.1 Background

The lorcaserin program was designed to conform to the February 2007 FDA draft guidance for developing weight management drugs.[13] Specific study design issues addressed in the draft guidance include:

- Sample size of the Phase 3 program for safety: the draft guidance states that approximately 3,000 subjects should be randomized to active drug and no fewer than 1,500 subjects should be randomized to placebo for one year of treatment

- Primary efficacy endpoints: efficacy should be assessed by analyses of both mean and categorical changes in body weight, with a clinically significant weight loss considered to be 5%

[13] FDA Draft Guidance for Industry: Developing Products for Weight Management. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071612.pdf Accessed 9 Mar 2012.

Since the issuance of the draft weight management guidance, the division has requested that specific psychiatric screening and monitoring be incorporated in all Phase 2 and 3 trials in centrally-acting obesity therapies. This will be discussed further in section 5.5.4.2.

A key discussion during development revolved around the incorporation of cardiac echocardiography to assess whether lorcaserin increases the risk of VHD. Included in the discussion was the robustness of the database. FDA's position was that ruling out a relative risk of 1.5 for FDA-defined VHD was an arbitrary but reasonable initial endpoint (akin to the diabetes cardiovascular guidance that considers the upper bounds of the 95% confidence interval 1.8 and 1.3 as key benchmarks[14]) given the sponsor's inability to conduct a very large study with a noninferiority margin smaller than 1.5. In addition, the sponsor agreed to implement a procedure to alleviate some of the variability inherent in echocardiogram readings by utilizing a central site and two readers per (blinded) echocardiogram, and use of a third reader in case of non-agreement.

The division was alerted to cancer signals in animal carcinogenicity studies early in lorcaserin's development. This issue is addressed in depth by Dr. Fred Alavi. Because of the potential for a prolactin-mediated cause for the mammary tumors in rats and the known pharmacodynamic effect of lorcaserin on prolactin, a substudy of the second Phase 3 clinical trial BLOSSOM was undertaken to assess lorcaserin's effect on prolactin with chronic administration, the results of which were presented to the first EMDAC meeting. Prolactin was also measured in the BLOOM-DM trial. An updated analysis of the pooled prolactin data is presented in section 5.5.6.1.2.

3.2 Patient Population

With the addition of three new trials – the Phase 1 APD356-022 (cerebrospinal fluid pharmacokinetic study), Phase 2 APD356-014 (TULIP), and Phase 3 APD356-010 (BLOOM-DM) – to the lorcaserin database, a total of 5425 individuals were exposed to at least one dose of lorcaserin: 432 individuals were exposed to lorcaserin at doses ranging from 0.1 mg to 60 mg during the Phase 1 clinical development program, and 4993 obese or overweight adult patients were exposed to lorcaserin in the Phase 2 and Phase 3 trials. In the lorcaserin 10 mg BID treatment group, 2333 patients were exposed greater than 180 days and 1567 patients were exposed greater than one year. In the lorcaserin 10 mg QD treatment group, 640 patients were exposed greater than 180 days and 467 patients were exposed greater than one year. As described in the original NDA submission, 426 patients completed two years of treatment with lorcaserin.

[14] FDA Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf Accessed 6 Aug 2010.

Table 1. Summary of Patients Randomized in Lorcaserin Phase 2 and Phase 3 Trials

Protocol	Patient Population	Pbo (N)	Lorc 1 QD (N)	Lorc 5 QD (N)	Lorc 10 QD (N)	Lorc 15 QD (N)	Lorc 10 BID (N)	Treatment Duration (wks)
Phase 2								
APD356-003	Obese	86	90	89		87		4
APD356-004	Obese	118			117	118	116	12
TULIP	Overweight/obese	28					29	8
Phase 3								
BLOOM	Obese/overweight with co-morbidities	1587					1595	52
BLOSSOM	Obese/overweight with co-morbidities	1603			802		1603	52
BLOOM-DM	Type 2 diabetes overweight/obese	253			95		56	52
BLOOM re-randomized at 1 year*	Obese/overweight with co-morbidities	**Lorc / Lorc**		**Lorc / Pbo**		**Pbo / Pbo**		104
		573		283		697		
* Subgroup of original BLOOM patient population								

Source: NDA 022529 ISS, Table 4; BLOSSOM CSR, Table 14.1.1; Summary of Clinical Safety (resubmission), Tables 3 and 4

3.3 Phase 3 – Demographics and Baseline Information

The following table enumerates the demographics and baseline weight and comorbidity data for the three Phase 3 trials. The majority of the patients were female and white, although there was a somewhat larger proportion of males and minorities in the BLOOM-DM trial than in BLOOM and BLOSSOM. Patients in the BLOOM-DM trial were also slightly older than patients in the non-diabetes trials. Mean BMI was 36 kg/m^2 and mean weight was 100 kg in the BLOOM and BLOSSOM trials; baseline weight was slightly higher in the BLOOM-DM trial, likely because of a relatively higher proportion of men in the trial. The majority of diagnosed comorbidities at baseline were hypertension and dyslipidemia in the non-diabetes trials. Patients with diabetes also had increased incidences of other comorbidities. Treatment groups were generally well-matched; BLOOM-DM demographic and baseline data shown in Table 3.

Table 2. Patient Demographics and Baseline Comorbidities by Trial, Safety Population

	BLOOM N=3177	**BLOSSOM N=4004**	**BLOOM-DM N=603**
Age, years mean +/- SD	44.1 +/- 11.2	43.8 +/- 11.8	52.7 +/- 8.7
Sex, % female	83.5	79.8	54.2
Race/Ethnicity White, % Black, % Hispanic, %	 66.9 18.8 12.4	 67.0 19.6 11.0	 60.5 20.9 13.8
BMI, kg/m² mean +/- SD	36.2 (4.3)	35.9 (4.2)	36.0 (4.5)
Weight, kg mean +/- SD	100.1 (15.6)	100.2 (16.0)	103.6 (17.8)
Comorbidity Hypertension, % Dyslipidemia, % CVD/CAD*, % Diabetes mellitus, % Sleep apnea, %	 21.3 33.3 0.3 0.0 4.0	 23.6 27.7 1.1 0.0 4.3	 61.0 53.0 7.1 100.0 13.7
* reported as cardiovascular disease (CVD) in BLOOM and BLOSSOM and coronary artery disease (CAD) in BLOOM-DM			

Source: NDA 022529 BLOOM CSR, Tables 14.1.6 and 14.1.7; BLOSSOM CSR, Tables 14.1.4 and 14.1.5; BLOOM-DM CSR, Table 14.1.5; Summary of Clinical Safety (resubmission), Table 10; reviewer created from datasets

Table 3. Patient Demographics and Baseline Characteristics, BLOOM-DM (Safety Population)

	Lorc 10 BID (N=256)	**Lorc 10 QD (N=95)**	**Pbo (N=252)**
Age, yrs; mean ± sd	53.2 ± 8.26	53.1 ± 7.98	52.0 ± 9.32
Female sex; n (%)	137 (53.5)	53 (55.8)	137 (54.4)
Race; n (%)			
White	150 (58.6)	49 (51.6)	166 (65.9)
Black	55 (21.5)	26 (27.4)	45 (17.9)
Hispanic	39 (15.2)	17 (17.9)	27 (10.7)
Asian	11 (4.3)	3 (3.2)	8 (3.2)
Other	1 (0.4)	0	6 (2.4)
Height, cm; mean ± sd	169.15 ± 9.59	170.82 ± 9.93	168.78 ± 10.07
Weight, kg; mean ± sd	103.68 ± 16.95	105.96 ± 19.44	102.56 ± 18.06
BMI, kg/m^2; mean ± sd	36.15 ± 4.48	36.13 ± 4.77	35.85 ± 4.52
BMI group; n (%)			
< 30 kg/m^2	21 (8.2)	12 (12.6)	24 (9.5)
30 – < 35 kg/m^2	82 (32.0)	28 (29.5)	88 (34.9)
35 – < 40 kg/m^2	91 (35.5)	33 (34.7)	86 (34.1)
40 – < 45 kg/m^2	62 (24.2)	21 (22.1)	53 (21.0)
≥ 45 kg/m^2	0	1 (1.1)	1 (0.4)
Duration of diabetes, yrs; mean ± sd	6.3 ± 4.5	6.4 ± 4.9	6.6 ± 5.0
HbA1c, %; mean ± sd	8.06 ± 0.83	8.05 ± 0.78	8.07 ± 0.84
HbA1c, ≥ 9%; n (%)	47 (18.4)	14 (14.7)	45 (17.9)
Diabetes medication			
SFU, n (%)	129 (50.4)	47 (49.5)	127 (50.4)
Metformin, n (%)	236 (92.2)	88 (92.6)	229 (90.9)
Both, n (%)	109 (42.6)	40 (42.1)	104 (41.3)
Systolic BP, mmHg; mean ± sd	126.5 ± 12.66	126.4 ± 11.47	126.4 ± 13.42
Diastolic BP, mmHg; mean ± sd	77.9 ± 7.99	78.1 ± 9.25	78.6 ± 9.90
Baseline dyslipidemia; n (%)	140 (54.7)	46 (48.4)	149 (59.1)
Baseline hypertension; n (%)	157 (61.3)	153 (60.7)	57 (60.0)
Coronary artery disease; n (%)	18 (7.0)	7 (7.4)	17 (6.7)
Sleep apnea; n (%)	33 (12.9)	15 (15.8)	35 (13.9)
Current tobacco use, yes; n (%)	27 (10.5)	9 (9.5)	29 (11.5)

Source: NDA 022529 ISE (resubmission), Table 1; BLOOM-DM CSR, Table 14.1.5

In the BLOOM-DM trial at baseline, a similar proportion of patients in each treatment group were taking concomitant medications for hypertension (lorcaserin 10 mg BID 62.1%, placebo 61.9%) and dyslipidemia (lorcaserin 10 mg BID 61.7%, placebo 63.5%).

3.4 Phase 3 – Patient Disposition

In BLOOM, a total of 50.3% (1599/3182) of the patients initially randomized completed the first year of treatment, including 883 (55.4%) assigned to lorcaserin and 716 (45.1%) assigned to placebo. Of those re-randomized at Week 52, 72.6% (1128/1553) completed Year 2.

In BLOSSOM, a total of 55.5% (2224/4008) of the patients initially randomized completed treatment, including 917 (57.2%) assigned to lorcaserin 10 mg BID, 473 (59.0%) assigned to lorcaserin 10 mg QD, and 834 (52.0%) assigned to placebo.

In BLOOM-DM, a total of 66.4% (401/604) of the patients initially randomized completed treatment, including 169 (66.0%) assigned to lorcaserin 10 mg BID, 75 (78.9%) assigned to lorcaserin 10 mg QD, and 157 (62.1%) assigned to placebo. For unclear reasons, the proportion of completers was greater in the group of patients randomized prior to Amendment 3 than those randomized after Amendment 3, as shown in the table below.

Table 4. Patient Populations, BLOOM-DM

	Lorc 10 BID n (%)	**Lorc 10 QD n (%)**	**Pbo n (%)**
Randomized	256	95	253
Safety Population	256 (100.0)	95 (100.0)	252 (99.6)
MITT Population	251 (98.0)	94 (98.9)	248 (98.0)
Completers Population	169 (66.0)	75 (78.9)	157 (62.1)
Randomized before Amendment 3	68/96 (70.8)	75/95 (78.9)	68/95 (71.6)
Randomized after Amendment 3	101/160 (63.1)	n/a	89/158 (56.3)

Source: NDA 022529 BLOOM-DM CSR, Table 5; reviewer created from datasets

Early terminations from Phase 3 studies were attributed to one of the following categories: adverse event, patient decision (including lack of efficacy), investigator decision, sponsor decision, lost to follow-up, non-compliance, and other. The following table describes the reasons for discontinuation in the Phase 3 trials:

Table 5. Reasons for Discontinuation, Phase 3 Trials

	BLOOM		**BLOSSOM**			**BLOOM-DM**		
	Lorc 10 BID N=1595	**Pbo N=1587**	**Lorc 10 BID N=1603**	**Lorc 10 QD N=802**	**Pbo N=1603**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=253**
Discontinued (Yr 1)	712 (44.6)	871 (54.9)	686 (42.8)	329 (41.0)	769 (48.0)	87 (34.0)	20 (21.1)	96 (37.9)
Patient Decision	307 (19.2)	439 (27.7)	293 (18.3)	162 (20.2)	376 (23.5)	32 (12.5)	8 (8.4)	50 (19.8)
Lack of Efficacy	27 (1.7)	88 (5.5)	39 (2.4)	25 (3.1)	62 (3.9)	2 (0.8)	4 (4.2)	5 (2.0)
Other	280 (17.6)	351 (22.1)	254 (15.8)	137 (17.1)	314 (19.6)	30 (11.7)	4 (4.2)	45 (17.8)
Adverse Event	113 (7.1)	106 (6.7)	115 (7.2)	50 (6.2)	74 (4.6)	22 (8.6)	6 (6.3)	11 (4.3)
Lost to Follow-Up	191 (12.0)	226 (14.2)	198 (12.4)	83 (10.3)	234 (14.6)	20 (7.8)	3 (3.2)	14 (5.5)
Non-compliance	47 (2.9)	44 (2.8)	59 (3.7)	20 (2.5)	49 (3.1)	3 (1.2)	1 (1.1)	10 (4.0)
Investigator Decision	9 (0.6)	6 (0.4)	11 (0.7)	4 (0.5)	6 (0.4)	0	0	1 (0.4)
Sponsor Decision	25 (1.6)	26 (1.6)	9 (0.6)	10 (1.2)	30 (1.9)	7 (2.7)	1 (1.1)	5 (2.0)
Other	20 (1.3)	24 (1.5)	1 (0.1)	0	0	22 (8.6)	6 (6.3)	11 (4.3)

Source: NDA 022529 ISE, Table 4; BLOOM-DM CSR, Table 5; reviewer created from datasets

The relatively large proportion of patients discontinued due to "other" reasons was noted in the original NDA (discussed in the original review) and again in the BLOOM-DM trial. The largest number of "other" reasons in BLOOM-DM for study discontinuation was due to scheduling conflicts, followed by "unknown", and study site closure.

4 Efficacy

4.1 Proposed Indication

The proposed indication for lorcaserin is as follows:

- [Lorcaserin] is a selective serotonin 2C agonist indicated as an adjunct to diet and exercise for weight management, including weight loss and maintenance, in obese patients with an initial body mass index greater than or equal to 30 kg/m^2, or overweight patients with a body mass index greater than or equal to 27 kg/m^2 in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea, type 2 diabetes).

4.2 Methods

This efficacy review focuses on the BLOOM-DM trial, comparing it to the Phase 3 trials reviewed in the original NDA submission, BLOOM and BLOSSOM, where appropriate. As noted above, enrollment into the lorcaserin 10 mg QD group in the BLOOM-DM trial was halted prematurely, and therefore for the primary efficacy analyses we have not compared this group to the overall placebo or lorcaserin 10 mg BID groups.

The newly-submitted Phase 2 trial TULIP was primarily a mechanistic study; efficacy results from this trial are summarized in section 4.3.3.3.

4.3 Efficacy Results

4.3.1 Weight-Related Endpoints

4.3.1.1 5% Responder Analysis

The pooled Phase 3 population demonstrated a statistically significant difference between lorcaserin 10 mg BID and placebo for the co-primary endpoint of the proportion of patients who lost 5% of their body weight from baseline (47.2% vs. 22.6%, $p < 0.001$). Findings were similar in the individual non-diabetes trials, BLOOM and BLOSSOM.

The efficacy results in BLOOM-DM differed depending on whether the data are evaluated in combination or divided by pre- and post-Amendment 3. For unclear reasons, in the diabetes population, the lorcaserin 10 mg QD dose appeared to offer similar weight loss (as proportion of 5% responders) as the 10 mg BID dose. By contrast, a clear dose response was seen in the non-diabetes population in the larger BLOSSOM trial.

Table 6. 5% Weight Loss Responders at Week 52, BLOOM and BLOSSOM [Modified Intent to Treat (MITT) LOCF]

BLOOM		
Treatment	**N**	**n (%)**
Lorc 10 BID	1538	731 (47.5)
Pbo	1499	304 (20.3)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	27.2 (24.0, 30.5)	< 0.0001
BLOSSOM		
Treatment	**N**	**n (%)**
Lorc 10 BID	1560	737 (47.2)
Pbo	1539	385 (25.0)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	22.23 (18.94, 25.52)	< 0.0001
Pooled Non-Diabetes		
Treatment	**N**	**n (%)**
Lorc 10 mg BID	3098	1460 (47.1)
Pbo	3038	687 (22.6)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	24.52 (22.22, 26.82)	< 0.001

Source: NDA 022529 BLOOM CSR, Table 10; BLOSSOM CSR, Table 9; ISE Statistical Report, Table E1.0

Table 7. 5% Weight Loss Responders at Week 52, BLOOM-DM (MITT/LOCF)

Treatment	**N**	**n (%)**
Lorc 10 BID	251	94 (37.5)
Pbo	248	40 (16.1)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	21.3 (13.8, 28.9)	< 0.0001

Source: Dr. Janice Derr, statistical reviewer, OTS/OB/DBII

In the BLOOM-DM completers and intended Week 52 populations, a greater proportion of patients in all treatment groups achieved 5% weight loss (CP: lorcaserin 10 mg BID 44.6% vs. placebo 17.9%, $p < 0.001$; IW52: lorcaserin 10 mg BID 42.9% vs. placebo 19.4%, $p < 0.001$). The greater proportion of patients in the IW52 patient population who achieved 5% weight loss reflects the fact that this is a population of completers in addition to a self-selected group of patients (N=16) willing to return to be weighed at Week 52. (In fact, the intent of this sensitivity analysis is to bring 100%, or very close to 100%, of patients who prematurely discontinued back for follow-up weight at Week 52.[13])

To understand the differences in dose response seen in the two trials that evaluated a lorcaserin 10 mg QD dose, the weight results of the BLOSSOM trial, including the lorcaserin 10 mg QD dose are presented in contrast to the BLOOM-DM results, in those patients randomized prior to Amendment 3 (at which point randomization in the lorcaserin 10 mg QD arm ended). As noted above, whereas a dose response was seen in

the BLOSSOM trial, such a finding was not seen in the BLOOM-DM trial (Table 8 and Table 9).

In the BLOSSOM trial, the difference between the proportions of 5% weight loss responders in the lorcaserin 10 mg BID versus lorcaserin 10 mg QD groups was statistically significant (p = 0.001); in BLOOM-DM, this difference was not statistically significant (p = 0.876).

Table 8. 5% Weight Loss Responders at Week 52, BLOSSOM (MITT/LOCF)

Treatment	**N**	**n (%)**
Lorc 10 BID	1560	737 (47.2)
Lorc 10 QD	771	310 (40.2)
Pbo	1539	385 (25.0)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 QD vs. Pbo	15.19 (11.11, 19.27)	< 0.0001

Source: NDA 022529, BLOSSOM CSR, Table 9

Table 9. 5% Weight Loss Responders at Week 52, BLOOM-DM Subgroup Enrolled Prior to Amendment 3 (MITT/LOCF)

Treatment	**N**	**n (%)**
Lorc 10 BID	93	41 (44.1)
Lorc 10 QD	94	42 (44.7)
Pbo	94	20 (21.3)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 QD vs. Pbo	23.4 (10.1, 36.0)	0.0006

Source: Dr. Janice Derr, statistical reviewer, OTS/OB/DBII

The subgroup enrolled after Amendment 3 in BLOOM-DM is presented for comparison to the results of those randomized prior to Amendment 3 and in the BLOOM-DM trial overall. Fewer patients in either treatment group achieved 5% weight loss as compared to those enrolled prior to Amendment 3. As noted in section 3.4 and in Table 4, this difference between populations was also reflected in the difference in the completers enrolled prior to versus after Amendment 3.

Table 10. 5% Weight Loss Responders at Week 52, BLOOM-DM Subgroup Enrolled After Amendment 3 (MITT/LOCF)

Treatment	**N**	**n (%)**
Lorc 10 BID	158	53 (33.5)
Pbo	154	20 (13.0)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	20.6 (11.4, 29.6)	< 0.0001

Source: Dr. Janice Derr, statistical reviewer, OTS/OB/DBII

Randomization for BLOOM-DM was stratified by baseline HbA1c (≥ 9% and < 9%) and anti-hyperglycemic medication (use of sulfonylurea and metfomin). As might be

expected, patients with a higher HbA1c at baseline as well as those using sulfonylureas at baseline were less likely to achieve 5% weight loss in either the lorcaserin or placebo treatment groups.

Table 11. 5% Weight Loss Responders at Week 52, BLOOM-DM (MITT/LOCF) by Screening Diabetes Status

	Treatment	**N**	**n (%)**
HbA1c at Screening < 9%	Lorc 10 BID	205	80 (39.0)
	Pbo	204	35 (17.2)
HbA1c at Screening ≥ 9%	Lorc 10 BID	46	14 (30.4)
	Pbo	44	5 (11.4)
Use of SFU (+/- metformin) at Screening	Lorc 10 BID	126	40 (31.7)
	Pbo	125	20 (16.0)
Use of metformin only at Screening	Lorc 10 BID	128	54 (43.2)
	Pbo	123	20 (16.3)

Source: NDA 022529 BLOOM-DM CSR, Tables 40 and 41

Five percent categorical weight loss response was also examined by subgroups, including race/ethnicity, sex, and other baseline characteristics (other than diabetes status, which was shown above). The only trend noted was that there appeared to be a waning of treatment effect at higher BMI. A similar finding was noted in the non-diabetes population. This should be interpreted with caution, however, as there are fewer patients at the lowest and highest BMI groups.

Table 12. 5% Weight Loss Responders at Week 52, BLOOM-DM (MITT) by Demographic and Baseline Characteristics

	Treatment	N	n (%)
Race/Ethnicity			
White	Lorc 10 BID	148	60 (40.5)
	Pbo	165	28 (17.0)
Black	Lorc 10 BID	54	17 (31.5)
	Pbo	43	7 (16.3)
Hispanic	Lorc 10 BID	38	13 (34.2)
	Pbo	26	3 (11.5)
Asian	Lorc 10 BID	10	3 (30.0)
	Pbo	8	1 (12.5)
Other	Lorc 10 BID	1	1 (100.0)
	Pbo	6	1 (16.7)
Sex			
Male	Lorc 10 BID	116	45 (38.8)
	Pbo	113	16 (14.2)
Female	Lorc 10 BID	135	49 (36.3)
	Pbo	135	24 (17.8)
Baseline Comorbidity			
Hypertension Present	Lorc 10 BID	153	53 (34.6)
	Pbo	149	21 (14.1)
Hypertension Absent	Lorc 10 BID	98	41 (41.8)
	Pbo	99	19 (19.2)
Dyslipidemia Present	Lorc 10 BID	138	48 (34.8)
	Pbo	145	22 (15.2)
Dyslipidemia Absent	Lorc 10 BID	113	46 (40.7)
	Pbo	103	18 (17.5)
BMI Group			
< 30	Lorc 10 BID	21	11 (52.4)
	Pbo	24	5 (20.8)
30 – < 35	Lorc 10 BID	79	31 (39.2)
	Pbo	86	11 (12.8)
35 – < 40	Lorc 10 BID	91	30 (33.0)
	Pbo	86	12 (14.0)
40 – < 45	Lorc 10 BID	60	22 (36.7)
	Pbo	51	12 (23.5)
≥ 45	Lorc 10 BID	0	0
	Pbo	1	0

Source: NDA 022529 BLOOM-DM CSR, Tables 37, 38, 39, and 42

4.3.1.2 Mean Weight Change

In the pooled BLOOM and BLOSSOM intent-to-treat analysis, patients treated with lorcaserin 10 mg BID lost 5.8% of body weight compared to 2.5% lost by patients receiving placebo at Week 52; a between treatment mean difference of 3.3% (BLOOM LS mean treatment difference, 3.7%; BLOSSOM LS mean treatment difference, 3.0%). In the BLOOM-DM trial, patients treated with lorcaserin 10 mg BID lost 4.5% of body weight compared to 1.5% lost by patients receiving placebo at Week 52; a between treatment mean difference of 3.1%.

Table 13. Percent Weight Change from Baseline to Week 52, BLOOM and BLOSSOM (MITT/LOCF)

Treatment	**N**	**Baseline Mean, kg (SD)**	**Adjusted % Change from Baseline (SE)**	
Lorc 10 BID	3098	100.36 (15.67)	-5.83 (0.11)	
Pbo	3038	100.22 (15.92)	-2.50 (0.11)	
Between treatment difference			**Difference in LS means (95% CI)**	**p value**
Lorc 10 BID vs. Pbo			-3.33 (-3.63, -3.03)	<0.001

Source: NDA 022529 ISE Statistical Report, Table E4.0

Table 14. Percent Weight Change from Baseline to Week 52, BLOOM-DM (MITT/LOCF)

Treatment	**N**	**Baseline Mean, kg (SD)**	**Adjusted % Change from Baseline (SE)**	
Lorc 10 BID	251	103.5 (17.2)	-4.50 (0.35)	
Pbo	248	102.3 (18.0)	-1.45 (0.36)	
Between treatment difference			**Difference in LS means (95% CI)**	**p value**
Lorc 10 BID vs. Pbo			-3.05 (-3.90, -2.20)	< 0.001

Source: Dr. Janice Derr, statistical reviewer, OTS/OB/DBII

In the BLOOM-DM completers population at Week 52, mean weight loss from baseline was -5.5% in the lorcaserin 10 mg BID group and -1.7% in the placebo group. In the IW52 population at Week 52, mean weight loss from baseline was -5.3% in the lorcaserin 10 mg BID group and -1.8% in the placebo group. All differences from placebo were statistically significant with a p value < 0.001.

To contrast the dose-related mean percent weight change for the lorcaserin 10 mg QD dose in the non-diabetes versus the diabetes populations, Table 15 and Table 16 present the results for BLOSSOM (non-DM) and BLOOM-DM pre-Amendment 3.

Of note, in the BLOSSOM trial, the difference in mean weight loss between the lorcaserin 10 mg BID versus lorcaserin 10 mg QD groups was statistically significant (p < 0.001); in BLOOM-DM, this difference was not statistically significant (p = 0.928).

Table 15. Percent Weight Change from Baseline to Week 52, BLOSSOM (MITT/LOCF)

Treatment	**N**	**Baseline Mean, kg (SD)**	**Adjusted % Change from Baseline**	
Lorc 10 BID	1561	100.34 (15.65)	-5.84 (0.16)	
Lorc 10 QD	771	100.11 (16.74)	-4.75 (0.23)	
Pbo	1541	100.77 (16.22)	-2.84 (0.16)	
Between treatment difference			**Difference in LS means (95% CI)**	**p value**
Lorc 10 BID vs. Pbo			-3.00 (-3.44, -2.56)	< 0.0001
Lorc 10 QD vs. Pbo			-1.91 (-2.45, -1.36)	< 0.0001

Source: NDA 022529 BLOSSOM CSR, Table 11.4

Table 16. Percent Weight Change from Baseline to Week 52, BLOOM-DM Subgroup Enrolled Prior to Amendment 3 (MITT/LOCF)

Treatment	**N**	**Baseline Mean, kg (SD)**	**Adjusted % Change from Baseline**	
Lorc 10 BID	93	103.8 (15.8)	-5.44 (0.50)	
Lorc 10 QD	94	106.5 (19.5)	-5.31 (0.50)	
Pbo	94	102.8 (17.8)	-2.24 (0.50)	
Between treatment difference			**Difference in LS means (95% CI)**	**p value**
Lorc 10 BID vs. Pbo			-3.20 (-4.59, -1.82)	< 0.0001
Lorc 10 QD vs. Pbo			-3.07 (-4.08, -1.88)	< 0.0001

Source: Dr. Janice Derr, statistical reviewer, OTS/OB/DBII

In the 5% responder analysis, weight loss was evaluated by HbA1c subgroups using a 9% cut-off (which was a stratification cut-point). However, patients with an HbA1c value of 9% or greater comprised approximately 18% of the study population. Therefore, FDA conducted an analysis of weight loss as a continuous variable using a cut-off close to the mean HbA1c value: 8%. This analysis (Table 17) suggests that patients with HbA1c less than 8% had a better weight loss response to lorcaserin than those with HbA1c 8% or greater (interaction p value = 0.021).

Table 17. Percent Weight Change from Baseline to Week 52 by Screening HbA1c, BLOOM-DM (MITT/LOCF)

	Treatment	N	Baseline Mean, kg (SD)	Adjusted % Change from Baseline	
HbA1c at Screening < 8%	Lorc 10 BID	145	101.7 (17.5)	-5.55 (0.41)	
	Pbo	146	102.4 (17.6)	-1.60 (0.41)	
HbA1c at Screening ≥ 8%	Lorc 10 BID	121	104.9 (16.3)	-3.96 (0.46)	
	Pbo	116	100.7 (18.4)	-2.03 (0.46)	
Between treatment difference				**Difference in LS means (95% CI)**	**p value**
Lorc vs. Pbo, HbA1c < 8%				-3.95 (-5.09, -2.81)	<0.0001
Lorc vs. Pbo, HbA1c ≥ 8%				-1.93 (-3.20, -0.65)	0.0031

Source: Dr. Janice Derr, statistical reviewer, OTS/OB/DBII

4.3.1.3 10% Responder Analysis

The pooled Phase 3 population demonstrated a statistically significant difference between lorcaserin 10 mg BID and placebo for the co-primary endpoint of the proportion of patients who lost 10% of their body weight from baseline (22.4% vs. 8.7%, $p < 0.001$). In the BLOOM-DM trial, 16.3% of patients on lorcaserin 10 mg BID and 4.4% of patients on placebo ($p < 0.001$) lost 10% of their body weight.

Table 18. 10% Weight Loss Responders at Week 52, BLOOM and BLOSSOM (MITT/LOCF)

BLOOM		
Treatment	**N**	**n (%)**
Lorc 10 BID	1538	347 (22.6)
Pbo	1499	115 (7.7)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	14.9 (12.4, 17.4)	< 0.001
BLOSSOM		
Treatment	**N**	**n (%)**
Lorc 10 BID	1560	353 (22.6)
Pbo	1539	150 (9.7)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	12.88 (10.33, 15.43)	< 0.001
Pooled Non-Diabetes		
Treatment	**N**	**n (%)**
Lorc 10 mg BID	3098	695 (22.43)
Pbo	3038	264 (8.69)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	13.75 (11.97, 15.52)	< 0.001

Source: NDA 022529 BLOOM CSR Table 12; BLOSSOM CSR Table 12; ISE Statistical Report Table E3.0

By contrast, the proportion of patients with diabetes in the BLOOM-DM trial who achieved 10% weight loss was lower in both treatment groups than in the non-diabetes population.

Table 19. 10% Weight Loss Responders at Week 52, BLOOM-DM (MITT/LOCF)

Treatment	**N**	**n (%)**
Lorc 10 BID	251	41 (16.3)
Pbo	248	11 (4.4)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	11.90 (6.66, 17.14)	<0.001

Source: NDA 022529 BLOOM-DM CSR, Table 11

In the BLOOM-DM completers population, the proportion of patients who lost 10% of baseline body weight was 20.8% in the lorcaserin 10 mg BID group and 5.8% in the placebo group. In the IW52 population, the proportion was 20.0% in the lorcaserin 10 mg BID group and 6.7% in the placebo group. All differences from placebo were statistically significant, with a p value < 0.001.

To contrast the dose-response of 10% weight loss responders for the lorcaserin 10 mg QD dose in the non-diabetes versus the diabetes populations, the following tables present the results for BLOSSOM (non-DM) and BLOOM-DM pre-Amendment 3:

Table 20. 10% Weight Loss Responders at Week 52, BLOSSOM (MITT/LOCF)

Treatment	**N**	**n (%)**
Lorc 10 BID	1560	353 (22.6)
Lorc 10 QD	771	134 (17.4)
Pbo	1539	150 (9.7)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	12.88 (10.33, 15.43)	< 0.0001
Lorc 10 QD vs. Pbo	7.63 (4.58, 10.69)	< 0.0001

Source: NDA 022529 BLOSSOM CSR, Table 12

Table 21. 10% Weight Loss Responders at Week 52, BLOOM-DM Subgroup Enrolled Prior to Amendment 3 (MITT/LOCF)

Treatment	**N**	**n (%)**
Lorc 10 BID	93	17 (18.28)
Lorc 10 QD	94	17 (18.09)
Pbo	94	3 (3.19)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	15.09 (6.47, 23.71)	0.002
Lorc 10 QD vs. Pbo	14.89 (6.34, 23.45)	0.002

Source: NDA 022529 Summary of Clinical Efficacy (resubmission), Table CRL.E3.0

4.3.2 Glycemia-Related Endpoints

4.3.2.1 Changes in laboratory values

In the BLOOM and BLOSSOM trials – which enrolled only patients without diabetes mellitus – changes in fasting glucose, hemoglobin A1c (HbA1c), and insulin were generally favorable for lorcaserin 10 mg BID treated patients as compared to those treated with placebo.

In BLOOM-DM, lorcaserin 10 mg BID improved glycemic control in patients with type 2 diabetes mellitus, as shown by significant decreases in HbA1c (Table 22) and fasting plasma glucose (Table 23). Results were very similar in the completers population (data not shown). Fasting insulin decreased slightly from baseline in all groups, with no statistically significant difference between lorcaserin and placebo groups (Table 24). Lorcaserin 10 mg QD results were not significantly different from BID results for any of the parameters tested.

Table 22. Analysis of Change from Baseline in HbA1c (%) at Week 52, BLOOM-DM (MITT/LOCF)

Treatment	**N**	**Baseline Mean (SD)**	**Adjusted Change from Baseline (SE)**	
Lorc 10 BID	251	8.05 (0.92)	-0.93 (0.06)	
Pbo	248	8.03 (0.92)	-0.44 (0.06)	
Between treatment difference			**Difference in LS means (95% CI)**	**p value**
Lorc 10 BID vs. Pbo			-0.49 (-0.65, -0.33)	<0.001

Source: NDA 022529 BLOOM-DM CSR, Table 11.21

Table 23. Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dL) at Week 52, BLOOM-DM (MITT/LOCF)

Treatment	**N**	**Baseline Mean (SD)**	**Adjusted Change from Baseline (SE)**	
Lorc 10 BID	251	163.6 (48.3)	-27.4 (2.5)	
Pbo	248	160.0 (41.6)	-11.9 (2.5)	
Between treatment difference			**Difference in LS means (95% CI)**	**p value**
Lorc 10 BID vs. Pbo			-15.5 (-21.5, -9.5)	<0.001

Source: NDA 022529 BLOOM-DM CSR, Table 11.25

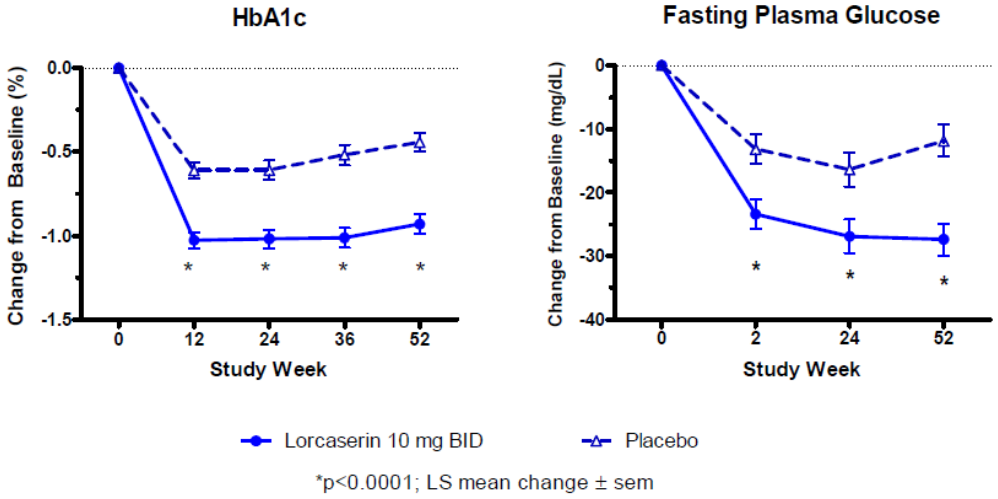
Table 24. Analysis of Change from Baseline in Fasting Insulin (μIU/mL) at Week 52, BLOOM-DM (MITT/LOCF)

Treatment	**N**	**Baseline Mean (SD)**	**Adjusted Change from Baseline (SE)**	
Lorc 10 BID	251	15.04 (10.01)	-3.02 (0.72)	
Pbo	248	16.23 (14.65)	-1.64 (0.72)	
Between treatment difference			**Difference in LS means (95% CI)**	**p value**
Lorc 10 BID vs. Pbo			-1.39 (-3.13, 0.36)	0.120

Source: NDA 022529 BLOOM-DM CSR, Table 11.22

Investigators were asked to avoid changing anti-hyperglycemic medications during the initial 12 weeks of the study to minimize confounding effects when assessing effects of study treatments on glycemic control. The following figures demonstrate that reductions in HbA1c and fasting plasma glucose were observed at all time points.

Figure 1. Change in HbA1c and Fasting Glucose by Study Visit, BLOOM-DM (MITT)



Source: NDA 022529 Summary of Clinical Efficacy (resubmission), Figure 5

Various subgroup analyses were conducted: fasting plasma glucose using a cut-off of 126 mg/dL, and HbA1c using a cut-off of 9% as assessed by the sponsor (unadjusted), and HbA1c using a cut-off of 8% as assessed by FDA (reported as LSMeans). Lorcaserin was associated with greater improvement in HbA1c and fasting glucose than placebo in each of the glycemic control subgroups. For the 9% HbA1c cut-off, the interaction p-value for the difference between treatment groups was not statistically significant (p = 0.865). When using the 8% cut-off, there is a trend toward a greater HbA1c treatment effect in the patients with higher HbA1c at baseline, interaction p-value = 0.060 (Table 26).

Table 25. Change in Glycemic Parameters from Baseline at Week 52 by Fasting Plasma Glucose and HbA1c Subgroups, BLOOM-DM (MITT/LOCF)

	Treatment	Δ HbA1c (%)		Δ FPG (mg/dL)	
		n	Mean (SE)	n	Mean (SE)
HbA1c at Screening < 9%	Lorc 10 BID	193	-0.8 (0.1)	198	-23.6 (3.1)
	Pbo	194	-0.2 (0.1)	202	-7.3 (2.9)
HbA1c at Screening ≥ 9%	Lorc 10 BID	45	-1.7 (0.2)	44	-54.3 (6.9)
	Pbo	38	-1.3 (0.2)	42	-31.0 (8.6)
Baseline FPG < 126 mg/dL	Lorc 10 BID	46	-0.5 (0.1)	47	10.4 (5.2)
	Pbo	51	-0.1 (0.1)	53	20.7 (4.6)
Baseline FPG ≥ 126 mg/dL	Lorc 10 BID	184	-1.1 (0.1)	194	-38.8 (3.1)
	Pbo	178	-0.5 (0.1)	191	-20.2 (3.1)

Source: NDA 022529 Summary of Clinical Efficacy (resubmission), Table 21

Table 26. Change in HbA1c from Baseline at Week 52 by HbA1c < 8% and ≥ 8%, BLOOM-DM (MITT/LOCF)

	Treatment	N	Baseline Mean, % (SD)	Adjusted % Change from Baseline	
HbA1c at Screening < 8%	Lorc 10 BID	130	7.33 (0.38)	-0.47 (-0.64, -0.31)	
	Pbo	129	7.33 (0.34)	-0.17 (-0.34, -0.01)	
HbA1c at Screening ≥ 8%	Lorc 10 BID	121	8.86 (0.63)	-1.37 (-1.55, -1.20)	
	Pbo	116	8.83 (0.73)	-0.75 (-0.93, -0.58)	
Between treatment difference				**Difference in LS means (95% CI)**	**p value**
Lorc vs. Pbo, HbA1c < 8%				-0.30 (-0.53, -0.06)	0.012
Lorc vs. Pbo, HbA1c ≥ 8%				-0.62 (-0.87, -0.38)	<0.001

Source: Dr. Janice Derr, statistical reviewer, OTS/OB/DBII

The entry criterion for HbA1c in the BLOOM-DM trial was 7-10%. At Week 52, more patients on lorcaserin 10 mg BID than placebo achieved HbA1c < 7% (50.4% vs. 26.3%), HbA1c < 6.5% (23.9% vs. 8.6%), fasting plasma glucose < 126 mg/dL (42.2% vs. 29.1%), and fasting plasma glucose < 100 mg/dL (14.1% vs. 5.7%). Patients on lorcaserin 10 mg QD achieved similar results to lorcaserin 10 mg BID, and the completers population achieved results consistent with the MITT population.

The original briefing document discussed that although 5% weight loss responders in the non-diabetes trials improved mean fasting glucose as compared to non-responders, lorcaserin did not appear to provide additional benefit in this group. Lorcaserin did appear to slightly mitigate the increase in fasting glucose that was seen in the non-responder group.

In the BLOOM-DM trial, patients treated with lorcaserin 10 mg BID improved HbA1c, fasting plasma glucose, and HOMA-IR at Week 52 compared with placebo-treated patients, regardless of whether they were 5% weight loss responders or not.

Table 27. Summary of Change from Baseline in Glycemic Parameters at Week 52 by Responders Groups, BLOOM-DM (MITT)

	Lorc 10 BID	Pbo
HbA1c		
Responders	n=94	n=40
Change from Baseline, mean (SE)	-1.29 (0.10)	-0.44 (0.06)
Non-Responders	n=143	n=192
Change from Baseline, mean (SE)	-0.70 (0.09)	-0.31 (0.07)
Fasting Plasma Glucose		
Responders	n=93	n=40
Change from Baseline, mean (SE)	-38.11 (4.25)	-26.00 (6.55)
Non-Responders	n=148	n=204
Change from Baseline, mean (SE)	-23.60 (3.92)	-8.48 (3.12)
Fasting Insulin		
Responders	n=93	n=40
Change from Baseline, mean (SE)	-5.71 (0.92)	-4.06 (1.17)
Non-Responders	n=150	n=204
Change from Baseline, mean (SE)	-0.80 (0.86)	-1.49 (1.02)
HOMA-IR		
Responders	n=84	n=37
Change from Baseline, mean (SE)	-0.94 (0.16)	-0.65 (0.18)
Non-Responders	n=142	n=180
Change from Baseline, mean (SE)	-0.28 (0.11)	-0.12 (0.14)

Source: NDA 022529 Summary of Clinical Efficacy (resubmission), Table 20

The homeostatic model assessment is a model used to estimate insulin resistance (HOMA-IR) and beta-cell function (HOMA-B) from fasting plasma glucose and insulin. These values correlate with the euglycemic and hyperglycemic clamp (HOMA-IR) and the intravenous glucose tolerance test and hyperglycemic clamp (HOMA-B).[15] At Week 52 in the BLOOM-DM trial, HOMA-IR decreased (between treatment difference -3.1, 95% CI: -0.57, -0.05) and HOMA-B values increased (between treatment difference +6.5, 95% CI: -1.65, 14.60) in patients treated with lorcaserin 10 mg BID at Week 52 as compared to placebo (beneficial directions of change). According to the prespecified conditional testing paradigm, formal statistical analyses were not conducted since change in insulin did not differ significantly between placebo and lorcaserin.

4.3.2.2 Diabetes medication changes

As previously noted, in the BLOOM-DM trial investigators were asked to avoid making changes in diabetes drugs during the first 12 weeks a patient was enrolled. During the remainder of the study, they were free to adjust the diabetes agents according to their clinical judgment. Table 28 demonstrates changes in diabetes drugs during the course of

[15] Matthews DR, et al. Homeostasis model assessment: insulin resistance and ß-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28:412-9.

the trial. Although the randomization scheme was different for the lorcaserin 10 mg QD arm, it is included in the table for descriptive purposes.

Across treatment groups, the majority of patients had no net change in total daily dose of diabetes medications. More patients in the lorcaserin groups decreased total daily dose, and fewer increased total daily dose as compared to placebo. Metformin doses tended to increase from baseline to Week 52 in the lorcaserin 10 mg QD and placebo groups. All other medication classes decreased among patients taking lorcaserin, whereas the placebo group had overall increases in total daily doses of sulfonylureas (SFUs) and glitazones. This could contribute to a greater observed weight treatment effect of lorcaserin (and perhaps lack of difference between lorcaserin 10 mg BID and 10 mg QD) because SFUs and glitazones tend to cause weight gain.

Table 28. Changes in Use of Drugs to Treat Type 2 Diabetes Mellitus, BLOOM-DM (MITT/LOCF)

	Lorc 10 BID N=251	**Lorc 10 QD N=94**	**Pbo N=248**
Patients with Change in Daily Dose, n (%)[a]			
Decrease	43 (17.1)	22 (23.4)	29 (11.7)
No Change	172 (68.5)	58 (61.7)	161 (64.9)
Increase	34 (13.5)	11 (11.7)	55 (22.2)
Patients who Discontinued All Diabetes Medications, n (%)	3 (1.2)	0	1 (0.4)
Mean (SD) % Daily Dose Change[b]			
Metformin	-0.8 (35.9)	3.0 (36.6)	6.6 (40.1)
SFU	-16.0 (63.0)	-24.6 (58.0)	6.5 (98.9)
Glitazone	-16.4 (40.3)	-21.3 (57.9)	3.3 (89.0)
Gliptin	-4.3 (20.9)	-16.7 (38.9)	-6.9 (34.1)
Patients who Started New Diabetes Medication by Class, n (%)[c,d]			
Metformin	3 (1.2)	1 (1.1)	3 (1.2)
SFU	9 (3.5)	3 (3.2)	10 (4.0)
Glitazone	3 (1.2)	1 (1.1)	9 (3.6)
Gliptin	10 (3.9)	3 (3.2)	13 (5.1)
Patients who Stopped Diabetes Medication by Class, n (%)[c,d]			
Metformin	10 (3.9)	2 (2.1)	0 (0.0)
SFU	21 (8.2)	13 (13.7)	8 (3.2)
Glitazone	8 (3.1)	8 (8.4)	4 (1.6)
Gliptin	1 (0.4)	2 (2.1)	3 (1.2)

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 visit
d Denominator=safety population

Source: NDA 022529 Summary of Clinical Efficacy (resubmission), Table 22; BLOOM-DM CSR, Table 14.2.214

In BLOOM and BLOSSOM (non-diabetes trials), patients who were diagnosed with diabetes mellitus were permitted to remain in the study unless an injectable agent was required. In the BLOOM trial, two patients developed type 2 diabetes while taking lorcaserin, two while taking placebo, and one while taking placebo after re-randomization from lorcaserin. One of the placebo patients was withdrawn from the trial as a result of

the diabetes diagnosis. In the BLOSSOM trial, four patients treated with lorcaserin BID, two patients treated with lorcaserin QD, and three patients treated with placebo were diagnosed with type 2 diabetes during the trial. In these trials, a similar proportion of patients treated with lorcaserin 10 mg BID and placebo required initiation or an increase in dose of anti-diabetes medication.

Table 29. Number (%) of Patients who Changed the Total Daily Dose of or Initiated Anti-Diabetes Medication from Baseline to Week 52, BLOOM and BLOSSOM (Safety Population)

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Patients with Change in Daily Dose, n (%)			
Decrease	1 (<0.1)	1 (0.1)	0
No Change	14 (0.4)	5 (0.6)	8 (0.3)
Increase	4 (0.1)	0	6 (0.2)
Patients who Initiated Diabetes Medication, n (%)	4 (0.1)	0	6 (0.2)

Source: NDA 022529 2 Apr 2010 Response to 74-Day Filing Letter Appendix 9, Tables 32.3 and 33.3

4.3.3 Additional Efficacy Endpoints

4.3.3.1 Anthropometric measures

4.3.3.1.1 Waist circumference and BMI

Consistent with the weight changes observed, waist circumference and BMI decreased to a greater extent with lorcaserin as compared with placebo. With respect to waist circumference, decreases were slightly less in both treatment groups in the BLOOM-DM trial as compared to the non-diabetes trials.

Table 30. Change from Baseline in Waist Circumference (cm) at Week 52, BLOOM and BLOSSOM (MITT/LOCF)

Treatment	N	Mean (SD)		Change from Baseline		
		Baseline	Week 52	LS Mean (SE)	95% CI	p value
Lorc 10 BID	2830	109.32 (12.13)	102.79 (12.95)	-6.55 (0.15)	(-6.83, -6.26)	<0.001
Pbo	2721	109.64 (12.17)	105.60 (12.96)	-4.01 (0.15)	(-4.30, -3.72)	<0.001
Between treatment difference				**Difference in LS means (95% CI)**		**p value**
Lorc 10 BID vs. Pbo				-2.54 (-2.95, -2.13)		<0.001

Source: NDA 022529 ISE Statistical Report, Table E14.0

Table 31. Change from Baseline in Waist Circumference (cm) at Week 52, BLOOM-DM (MITT/LOCF)

Treatment	N	Mean (SD)		Change from Baseline		
		Baseline	Week 52	LS Mean (SE)	95% CI	p value
Lorc 10 BID	251	115.8 (11.80)	110.2 (12.15)	-5.51 (0.50)	(-6.50, -4.52)	<0.001
Pbo	248	113.5 (12.62)	110.4 (12.79)	-3.34 (0.52)	(-4.35, -2.33)	<0.001
Between treatment difference				**Difference in LS means (95% CI)**		**p value**
Lorc 10 BID vs. Pbo				-2.17 (-3.40, -0.94)		<0.001

Source: NDA 022529 BLOOM-DM CSR, Table 11.13

With respect to BMI changes, results were similar between the pooled non-diabetes trials and BLOOM-DM.

Table 32. Change from Baseline in Body Mass Index (kg/m^2) at Week 52, BLOOM and BLOSSOM (MITT/LOCF)

Treatment	N	Mean (SD)		Change from Baseline		
		Baseline	Week 52	LS Mean (SE)	95% CI	p value
Lorc 10 BID	3098	36.11 (4.27)	34.03 (4.78)	-2.09 (0.04)	(-2.17, -2.01)	<0.001
Pbo	3038	36.06 (4.21)	35.16 (4.60)	-0.90 (0.04)	(-0.98, -0.82)	<0.001
Between treatment difference				**Difference in LS means (95% CI)**		**p value**
Lorc 10 BID vs. Pbo				-1.19 (-1.30, -1.08)		<0.001

Source: NDA 022529 ISE Statistical Report, Table E15.0

Table 33. Change from Baseline in Body Mass Index (kg/m^2) at Week 52, BLOOM-DM (MITT/LOCF)

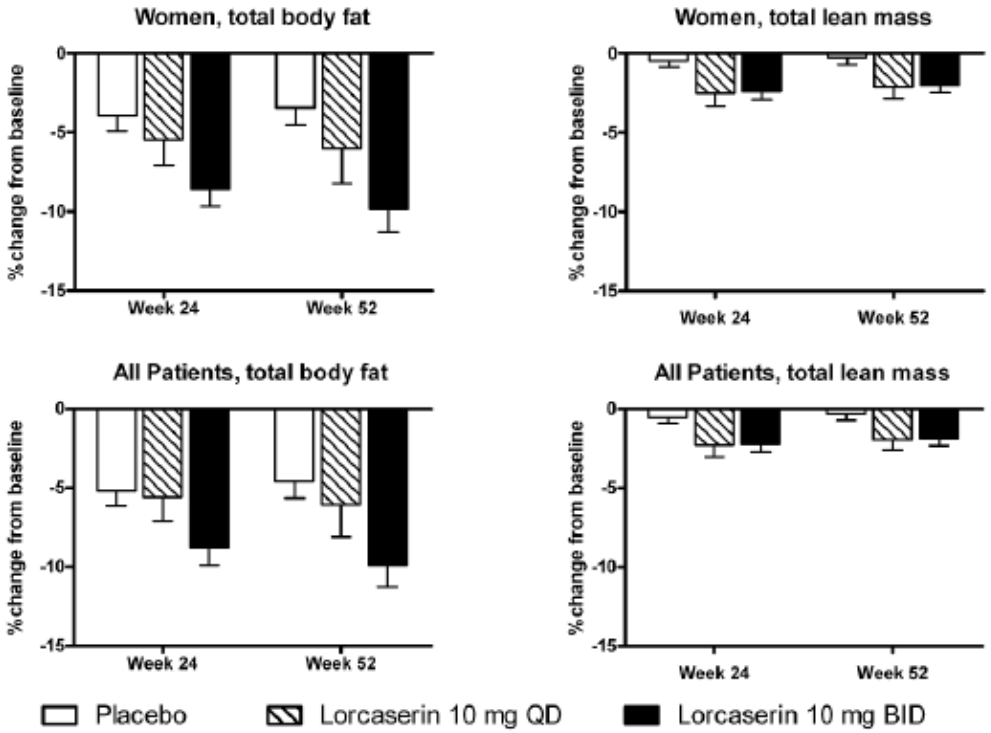
Treatment	N	Mean (SD)		Change from Baseline		
		Baseline	Week 52	LS Mean (SE)	95% CI	p value
Lorc 10 BID	251	36.09 (4.50)	34.35 (4.76)	-1.64 (0.13)	(-1.89, -1.39)	<0.001
Pbo	248	35.76 (4.54)	35.11 (4.60)	-0.57 (0.13)	(-0.82, -0.31)	<0.001
Between treatment difference				**Difference in LS means (95% CI)**		**p value**
Lorc 10 BID vs. Pbo				-1.07 (-1.39, -0.76)		<0.001

Source: NDA 022529 BLOOM-DM CSR, Table 11.5

4.3.3.1.2 DEXA

As described in the original NDA, a subset of patients in the BLOSSOM study had body composition measured by dual energy X-ray absorptiometry (DEXA) at baseline, Week 24, and Week 52. The decreases in total body fat were greater in patients randomized to receive lorcaserin 10 mg BID as compared to those receiving placebo. Patients treated with lorcaserin 10 mg BID tended to lose somewhat more lean body mass than patients treated with placebo (Week 52 lorcaserin 10 BID vs. placebo difference in mean lean body mass -0.66, p=0.024).

Figure 2. Percent Change from Baseline in Total Body Fat and Total Body Lean Mass at Week 24 and 52 by Women and Total Population in BLOSSOM, MITT



Source: NDA 022529 ISE, Figure 12

In BLOOM-DM, body composition, including total body fat mass and total body lean mass was determined with DEXA in a subset of randomized patients at selected clinical sites. DEXA scans were performed at baseline, Week 24, and Week 52/Exit. At Week 52, total body fat mass percent decreased significantly from baseline in the lorcaserin 10 mg BID group (-1.41%, p = 0.003) but not the placebo group (0.17%, p=0.930). Between-treatment difference in total body fat percent in lorcaserin 10 mg BID as compared to placebo was -1.75%, p=0.012. Lean body mass decreased from baseline to Week 52 in all study groups (lorcaserin 10 mg BID -1.78 kg, placebo -2.03 kg; between-treatment difference 0.25 kg, p=0.757).

In the Phase 2 trial TULIP, results of which were included in this resubmission, the decrease from baseline to Day 57 in fat mass measured by DEXA did not differ between the lorcaserin and placebo groups. Patients treated with lorcaserin lost significantly more lean body mass as compared to placebo ($p < 0.01$). See the TULIP summary in section 4.3.3.3, below, for more details.

4.3.3.2 Cardiovascular-related endpoints

4.3.3.2.1 Blood pressure

In the individual Phase 3 trials the mean decrease in systolic blood pressure (SBP) with lorcaserin 10 mg BID was greater than with placebo (see Table 34); the difference was

statistically significant in the BLOOM trial. By contrast, in the BLOOM-DM trial, there was no significant difference in mean SBP in the lorcaserin 10 mg BID group as compared to placebo, and although both groups had mean decreases, the placebo group had a slightly greater decrease (see Table 35). See section 5.6.2.2 in the safety review for a discussion of blood pressure outliers and adverse events.

Table 34. Change in Baseline in Systolic Blood Pressure at Week 52, BLOOM and BLOSSOM (MITT/LOCF)

Treatment	**N**	**Mean (SD)**		**Change from Baseline**		
		Baseline	**Week 52**	**LS Mean (SE)**	**95% CI**	**p value**
Lorc 10 BID	3096	121.39 (11.86)	119.66 (12.66)	-1.76 (0.20)	(-2.14, -1.38)	<0.001
Pbo	3039	121.51 (11.74)	120.46 (12.46)	-1.02 (0.20)	(-1.41, -0.64)	<0.001
Between treatment difference				**Difference in LS means (95% CI)**		**p value**
Lorc 10 BID vs. Pbo				-0.74 (-1.27, -0.20)		0.007

Source: NDA 022529 Statistical Resport for Pooled Phase 3 Efficacy Analysis, Table E11.0

Table 35. Change in Baseline in Systolic Blood Pressure at Week 52, BLOOM-DM (MITT/LOCF)

Treatment	**N**	**Mean (SD)**		**Change from Baseline**		
		Baseline	**Week 52**	**LS Mean (SE)**	**95% CI**	**p value**
Lorc 10 BID	251	126.6 (12.72)	125.8 (12.47)	-0.80 (0.84)	(-2.45, 0.85)	0.342
Pbo	248	126.5 (13.47)	125.6 (13.49)	-0.94 (0.85)	(-2.61, 0.72)	0.266
Between treatment difference				**Difference in LS means (95% CI)**		**p value**
Lorc 10 BID vs. Pbo				0.14 (-1.91, 2.20)		0.891

Source: NDA 022529 BLOOM-DM CSR, Table 11.16

For diastolic blood pressure (DBP), a statistically significant decrease was seen in the lorcaserin group as compared to the placebo group in the pooled non-diabetes trials (see Table 36), but not in the BLOOM-DM trial (see Table 37).

Table 36. Change in Baseline in Diastolic Blood Pressure at Week 52, BLOOM and BLOSSOM (MITT/LOCF)

Treatment	**N**	**Mean (SD)**		**Change from Baseline**		
		Baseline	**Week 52**	**LS Mean (SE)**	**95% CI**	**p value**
Lorc 10 BID	3096	77.44 (8.05)	75.94 (8.70)	-1.57 (0.14)	(-1.84, -1.29)	<0.001
Pbo	3039	77.71 (8.09)	76.67 (8.75)	-0.97 (0.14)	(-1.24, -0.69)	<0.001
Between treatment difference				**Difference in LS means (95% CI)**		**p value**
Lorc 10 BID vs. Pbo				-0.60 (-0.99, -0.21)		0.003

Source: NDA 022529 Statistical Resport for Pooled Phase 3 Efficacy Analysis, Table E12.0

Table 37. Change in Baseline in Diastolic Blood Pressure at Week 52, BLOOM-DM (MITT/LOCF)

Treatment	N	Mean (SD)		Change from Baseline		
		Baseline	Week 52	LS Mean (SE)	95% CI	p value
Lorc 10 BID	251	77.9 (8.02)	76.8 (8.88)	-1.06 (0.56)	(-2.17, 0.04)	0.059
Pbo	248	78.7 (7.92)	77.5 (8.17)	-0.66 (0.57)	(-1.78, 0.46)	0.248
Between treatment difference				**Difference in LS means (95% CI)**		**p value**
Lorc 10 BID vs. Pbo				-0.41 (-1.78, 0.97)		0.563

Source: NDA 022529 BLOOM-DM CSR, Table 11.17

In the non-diabetes trials, weight loss responders (defined as patients who lost ≥ 5% body weight from baseline at Week 52) had a greater decrease in blood pressure parameters than non-responders. The pooled placebo and lorcaserin 10 mg BID groups by responder status appeared to have similar – or perhaps in some cases, less favorable – mean changes from baseline. A similar analysis was not conducted for BLOOM-DM.

Table 38. Change in Blood Pressure at Week 52 by Responder Groups, BLOOM and BLOSSOM (MITT/LOCF)

	Responders		Non-Responders	
	Lorc 10 BID N=1460	Pbo N=687	Lorc 10 BID N=1636	Pbo N=2352
SBP, mmHg				
Baseline Mean (SD)	122.00 (11.74)	123.23 (12.00)	120.85 (11.94)	121.01 (11.62)
Mean Change (SE)	-3.33 (0.32)	-3.84 (0.44)	-0.30 (0.30)	-0.24 (0.24)
DBP, mmHg				
Baseline Mean (SD)	77.70 (7.85)	78.09 (7.96)	77.21 (8.22)	77.60 (8.12)
Mean Change (SE)	-2.68 (0.23)	-2.94 (0.33)	-0.44 (0.22)	-0.48 (0.18)

Source: NDA 022529, ISE Statistical Report Tables E69.0 and E70.0

The following table from the original briefing document suggests that slightly fewer patients treated with lorcaserin 10 mg BID than placebo or lorcaserin 10 mg QD required initiation or an increase in dose of antihypertensive medication in the pooled non-diabetes trials. This could account for any unfavorable blood pressure differences noted between treatment groups.

Table 39. Number (%) of Patients who Changed the Total Daily Dose of or Initiated Antihypertensive Medications from Baseline to Week 52, BLOOM and BLOSSOM (Safety Population)

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
Decrease	70 (2.2)	17 (2.1)	54 (1.7)
No Change	594 (18.6)	133 (16.6)	595 (18.7)
Increase	70 (2.2)	25 (3.1)	95 (3.0)
Initiated Antihypertensive	35 (1.1)	12 (1.5)	44 (1.4)

Source: NDA 022529 2 Apr 2010 Response to 74-Day Filing Letter Appendix 9, Tables 32.3 and 33.3

In the BLOOM-DM trial, antihypertensive agents were evaluated by specific drug type and whether or not a patient was on a particular agent at any time during the trial. Treatment groups were fairly well-matched throughout.

Table 40. Number (%) of Patients Receiving Antihypertensive Concomitant Medications at Any Time in the Trial, BLOOM-DM (Safety Population)

	Lorc 10 BID N=256	**Lorc 10 QD N=95**	**Pbo N=252**
Patients receiving any antihypertensive agent	191 (74.6)	70 (73.7)	174 (69.0)
Renin-angiotensin system agents	163 (63.7)	62 (65.3)	156 (61.9)
Miscellaneous antihypertensives	9 (3.5)	3 (3.2)	3 (1.2)
Beta-blocking agents	48 (18.8)	18 (18.9)	44 (17.5)
Calcium channel blocking agents	21 (8.2)	9 (9.5)	25 (9.9)
Diuretic agents	51 (19.9)	21 (22.1)	41 (16.3)
Peripheral vasodilators	0	0	2 (0.8)

Source: NDA 022529 CR Appendix 2: Safety Tables and Figures, Table CLR.01.1

4.3.3.2.2 Lipids

In the non-diabetes Phase 3 trials, treatment with lorcaserin was associated with decreases in triglycerides (TG). HDL cholesterol initially decreased from baseline in lorcaserin and placebo treatment groups before returning to baseline values and increasing in the lorcaserin group. These changes are consistent with HDL-C changes that occur with active weight loss and weight maintenance.[16,17] The lowest mean LDL cholesterol and total cholesterol values were observed after four weeks of treatment with lorcaserin 10 mg BID, and values increased from baseline during the remaining study period in both the lorcaserin- and placebo-treated groups. For all lipid parameters, the responders had more favorable changes than non-responders. As compared to placebo, the beneficial effect of lorcaserin on TG was seen in the responder group, but not in the non-responder group. Conversely, HDL-C appeared to increase to a greater extent in the placebo responders as compared to the lorcaserin responders. Fewer patients treated with

[16] Dattilo AM and Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr 1992; 56:320-8.
[17] Thompson PD, et al. Unexpected decrease in plasma high density lipoprotein cholesterol with weight loss. Am J Clin Nutr 1979; 32: 2016-21.

lorcaserin 10 mg BID than placebo required initiation or an increase in dose of lipid-altering medications.

In the BLOOM-DM trial, the lipid analysis was performed according to the prespecified testing procedure such that after the primary study endpoint was met, the lipid family endpoints were tested in the following order: triglycerides, HDL cholesterol, LDL cholesterol, and total cholesterol. The percent change from baseline in triglycerides was not significant for either of the lorcaserin dosing groups. Therefore, no further testing was done for HDL-C, LDL-C, or total cholesterol. No analyses were conducted assessing changes in lipid-altering medications. A summary of changes in lipids in lorcaserin 10 mg BID and placebo from the BLOOM-DM trial is provided below.

Table 41. Percent Change in Lipids at Week 52, BLOOM-DM (MITT/LOCF)

	Lorc 10 BID	**Pbo**	**Between Treatment Difference (95% CI)**
% (SE) change Total C, mg/dL	-0.65 (1.31)	-0.13 (1.16)	-0.52 (-3.29, 2.26)
% (SE) change LDL-C, mg/dL	4.20 (2.57)	5.01 (2.63)	-0.81 (-7.11, 5.50)
% (SE) change HDL-C, mg/dL	5.22 (1.03)	1.58 (1.05)	3.64 (1.12, 6.15)
% (SE) change TG, mg/dL	-10.74 (2.45)	-4.84 (2.50)	-5.90 (-11.91, 0.11)

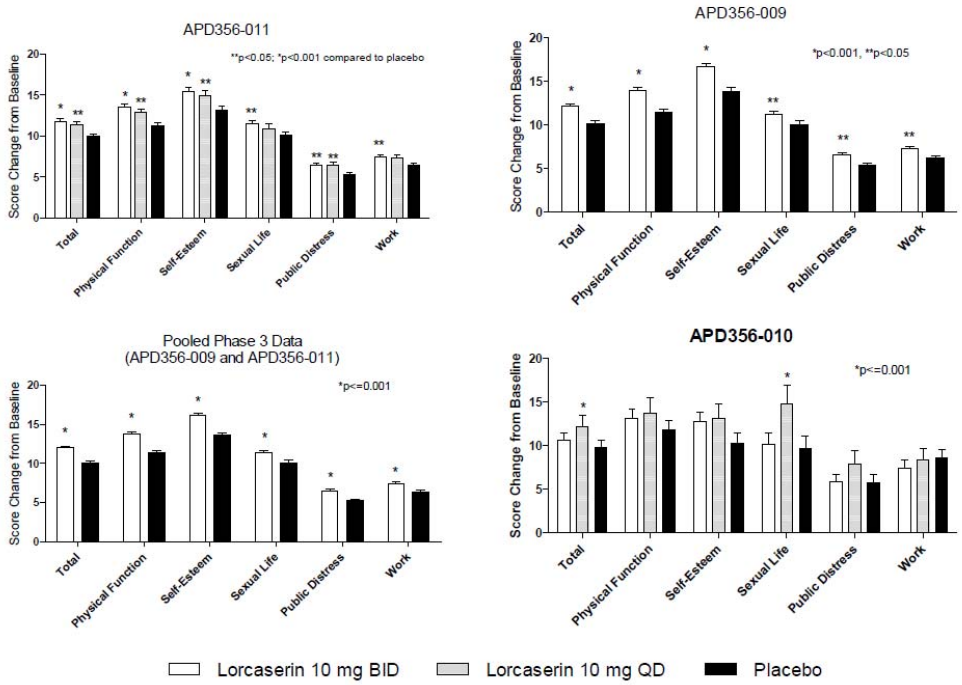
Source: NDA 022529 BLOOM-DM CSR, Tables 11.6, 11.7, 11.8, and 11.10

4.3.3.2.3 Quality of life

Quality of life was evaluated using the Impact of Weight on Quality of Life (IWQOL) - Lite questionnaire, a 31-item self-report measure of obesity-specific quality of life. The IWQOL-Lite provides an overall total score as well as scores on five domains: (1) physical function, (2) self esteem, (3) sexual life, (4) public distress, and (5) work. Scores range from 0 to 100, with 100 representing the best and 0 the most impaired quality of life.[18] The assessments were given at baseline, Week 24, and Week 52. In all Phase 3 studies, mean increase (improvement) in IWQOL-Lite score was numerically greater in lorcaserin groups than in the placebo group. Figure 3 describes the results; lorcaserin groups as compared to placebo in BLOOM-DM generally did not reach statistical significance, which may have been due to smaller sample size than the non-diabetes trials. The clinical significance of the degree of changes observed is unknown.

[18] Duval K, et al. An overview of obesity-specific quality of life questionnaires. Obesity Reviews. 2006; 7:347-60.

Figure 3. Summary of Mean Change from Baseline in Quality of Life Questionnaire Score at Week 52 in Phase 3 Trials (MITT)†



† APD356-009 = BLOOM, APD356-010 = BLOOM-DM, APD356-011 = BLOSSOM
Source: NDA 022529 Integrated Summary of Efficacy (resubmission), Figure 11

4.3.3.3 TULIP

The TULIP trial was a Phase 2b, double-blind, randomized, placebo-controlled parallel-group study to assess the effects of lorcaserin on energy expenditure during 56 days of administration to overweight and obese male and female patients, aged 18-65 years. A total of 57 patients were randomized in a 1:1 ratio to lorcaserin 10 mg BID (N = 29) or placebo (N = 28). The number (percent) of patients who completed the trial were: 28 (96.6%) lorcaserin 10 mg BID and 25 (89.3%) placebo.

Beginning on Day 8, a standardized lifestyle modification program was instituted for all patients, consisting of a 600 kcal deficit diet and the encouragement of 30 minutes of moderate exercise per day.

Each subject underwent screening procedures within 28 days of dosing on Day 1. This was followed by an initial inpatient period of four days, a three-day outpatient period, a second four-day inpatient period, a second outpatient period over 45 days which included seven visits, and a final three-day inpatient period.

The primary efficacy analysis was change in 24-hr energy expenditure (EE) (kcal/day) from baseline to the Day 56 visit, as measured in a metabolic chamber. A tendency for reduced 24-hr EE was seen in patients treated with lorcaserin versus placebo (-162 ± 20 kcal/24 hr vs. -103 ± 21 kcal/24 hr, p = 0.05). Similarly, mean resting metabolic rate (RMR) as measured by a hood calorimeter decreased more in the lorcaserin as compared

to the placebo group on Day 56 (-84 ± 21 kcal/24 hr vs. -0.71 ± 22 kcal/24 hr, $p = 0.008$). The between-treatment results were not significantly different after adjusting for body composition, implying no prevention of metabolic adaptation with lorcaserin. In summary, lorcaserin neither increased EE nor prevented the metabolic adaptation (i.e., the typical decrease of EE) associated with weight loss.

There was no effect of lorcaserin on respiratory quotient (RQ) measured by hood calorimeter after first dose, after seven days, or after 56 days of treatment. There was no effect of lorcaserin on 24-hr fat oxidation, 24-hr carbohydrate oxidation, or 24-hr protein oxidation.

Energy intake, measured as kcal consumed at lunch and dinner, was significantly reduced in patients treated with lorcaserin but not placebo after seven days of treatment, though the change did not differ between groups ($p = 0.27$). After 56 days, patients treated with lorcaserin experienced a greater reduction in energy intake than patients treated with placebo (-470 ± 87 kcal vs. -205 ± 91 kcal, $p < 0.05$).

Armband accelerometers were used to estimate physical activity. Metabolic equivalences of task (METs) were not significantly different between the lorcaserin (0.14 ± 0.05) and placebo (0.03 ± 0.05) groups after seven days, $p = 0.13$, or after 56 days (0.16 ± 0.05 vs. 0.23 ± 0.06, $p = 0.39$).

Lorcaserin treatment resulted in a greater reduction in body weight as compared to placebo (-3.84 ± 0.45 kg vs. -2.11 ± 0.47 kg; $p < 0.01$). Body composition was measured by dual-energy X-ray absorptiometry (DEXA). The decrease from baseline to Day 57 in fat mass did not differ between the lorcaserin and placebo groups. Patients treated with lorcaserin lost significantly more lean body mass as compared to placebo ($p < 0.01$).

Table 42. Change from Baseline at End of Study in Body Composition Derived from DEXA Scan, TULIP Trial

	Lorc 10 BID	Pbo
Total Body Lean Mass, kg		
Baseline	N=29	N=28
Mean (SE)	57.22 (2.51)	60.53 (2.57)
Day 57	N=28	N=25
Mean (SE)	56.14 (2.61)	61.98 (2.71)
LS Mean Δ (SE)	-1.27 (0.27)	-0.19 (0.29)
Diff from placebo (95% CI)	-1.08 (-1.88, -0.28)	-
p-value vs. placebo	0.009	-
Total Body Fat, %		
Baseline	N=29	N=28
Mean (SE)	41.10 (1.28)	40.46 (1.22)
Day 57	N=28	N=25
Mean (SE)	40.22 (1.31)	38.46 (1.23)
LS Mean Δ (SE)	-0.88 (0.22)	-1.15 (0.23)
Diff from placebo (95% CI)	0.28 (-0.36, 0.92)	-
p-value vs. placebo	0.39	-

Source: NDA 022529 TULIP CSR, Table 14.2.3.2

5 Safety

This review primarily focuses on the Phase 3 trials and will update what was previously reviewed for the original advisory committee meeting with data from BLOOM-DM.

5.1 Deaths

Two deaths occurred in the entire development program, both in patients randomized to placebo; one patient from the BLOOM trial (motor vehicle accident) and one patient from the BLOSSOM trial (asthma exacerbation). There were no deaths in the BLOOM-DM or in the newly-submitted Phase 1 CSF pharmacokinetic trial or in the TULIP trial.

5.2 Other Serious Adverse Events

5.2.1 Phase 1 and Phase 2

There were no serious adverse events in the newly-submitted Phase 1 trial or the TULIP trial.

5.2.2 Phase 3

In the BLOOM and BLOSSOM trials, the incidence of serious adverse events from Year 1 of the pooled dataset was 2.7% in the lorcaserin 10 mg BID group, 3.4% in the lorcaserin 10 mg QD group, and 2.3% in the placebo group (Table 43).

In the BLOOM-DM trial, 41 (6.8%) patients experienced 50 serious adverse events. Of these, 16 (6.3%) were in the lorcaserin 10 mg BID treatment group, eight (8.4%) were in the lorcaserin 10 mg QD treatment group, and 17 (6.7%) were in the placebo treatment

group. A higher proportion of patients randomized prior to Amendment 3 experienced serious adverse events as compared to those randomized after, perhaps because there were more completers in those randomized prior to Amendment 3.

Table 43. Serious Adverse Events by SOC, Phase 3 Trials, Year 1

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**
Total	87 (2.7)	27 (3.4)	73 (2.3)	16 (6.3)	8 (8.4)	17 (6.7)
Before Amendment 3 – BLOOM-DM				7/96 (7.3)	8/95 (8.4)	8/95 (8.4)
After Amendment 3 – BLOOM-DM				9/160 (5.6)	n/a	9/157 (5.7)
Infections and Infestations	11 (0.3)	1 (0.1)	6 (0.2)	3 (1.2)	1 (1.1)	3 (1.2)
Musculoskeletal and Connect Tissue Disorders	11 (0.3)	5 (0.6)	13 (0.4)	3 (1.2)	0	1 (0.4)
Neoplasms Benign,Malignant and Unspecified	11 (0.3)	4 (0.5)	12 (0.4)	2 (0.8)	1 (1.1)	3 (1.2)
Injury, Poisoning and Procedural Complications	9 (0.3)	5 (0.6)	10 (0.3)	0	0	0
Hepatobiliary Disorders	9 (0.3)	2 (0.2)	5 (0.2)	1 (0.4)	0	0
Cardiac Disorders	9 (0.3)	1 (0.1)	3 (0.1)	1 (0.4)	2 (2.1)	3 (1.2)
Reproductive System and Breast Disorders	8 (0.3)	2 (0.2)	7 (0.2)	0	0	0
Gastrointestinal Disorders	7 (0.2)	5 (0.6)	7 (0.2)	0	0	3 (1.2)
Nervous System Disorders	7 (0.2)	2 (0.2)	10 (0.3)	0	2 (2.1)	1 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	6 (0.2)	1 (0.1)	4 (0.1)	0	0	1 (0.4)
Psychiatric Disorders	6 (0.2)	0	0	1 (0.4)	1 (1.1)	0
General Disorders and Administr Site Conditions	4 (0.1)	1 (0.1)	2 (0.1)	3 (1.2)	0	3 (1.2)
Metabolism and Nutrition Disorders	1 (<0.1)	0	0	1 (0.4)	0	0
Vascular Disorders	1 (<0.1)	0	0	1 (0.4)	0	1 (0.4)
Blood and Lymphatic System Disorders	0	1 (0.1)	0	0	1 (1.1)	0
Ear and Labyrinth Disorders	0	1 (0.1)	0	0	0	0
Investigations	0	1 (0.1)	0	0	0	0
Eye Disorders	0	0	2 (0.1)	0	0	0
Immune System Disorders	0	0	2 (0.1)	1 (0.4)	0	1 (0.4)
Congenital, Familial and Genetic Disorders	0	0	1 (<0.1)	0	0	0
Pregnancy, Puerperium and Perinatal Conditions	0	0	1 (<0.1)	0	0	0

Source: NDA 022529 ISS, Table A4; BLOOM-DM CSR, Table 50; reviewer created from datasets

In the original NDA submission, the imbalance in psychiatric serious adverse events was noted. The psychiatric serious adverse events are listed here with the two additional serious adverse events from the BLOOM-DM trial added. Psychiatric adverse events will be discussed further in section 5.5.4. Other notable serious adverse events from the BLOOM-DM trial will be discussed in relevant sections of this document.

Table 44. Psychiatric Serious Adverse Events, Phase 3 Trials Year 1

Study	ID	Treatment	Age/Sex/Race	Verbatim Term	Preferred Term	Severity	Hospitalized?	Drug Discontinued/ Study Withdrawal
BLOOM	180-S141	Lorc 10 BID	36/F/W	Suicide attempt	Suicide attempt	Severe	Yes	Yes
BLOSSOM	2139-S030	Lorc 10 BID	57/M/W	Alcohol induced psychotic disorder	Alcoholic psychosis	Severe	Yes	Yes
BLOSSOM	2174-S061	Lorc 10 BID	53/F/W	Nervous breakdown	Mental disorder	Moderate	Yes	No
BLOSSOM	2182-S037	Lorc 10 BID	39/F/W	Suicidal thoughts	Suicidal ideation	Severe	Yes	Yes
BLOSSOM	2255-S030	Lorc 10 BID	30/F/Hisp	Moderate depression	Depression	Moderate	No	Yes
BLOSSOM	2255-S039	Lorc 10 BID	58/M/W	Psychiatric crisis	Acute psychosis	Severe	Yes	Yes
BLOOM-DM	1174-S040	Lorc 10 QD	56/F/Asian	Depression	Depression	Moderate	Yes	Yes
BLOOM-DM	1187-S021	Lorc 10 BID	37/M/Asian	Psychogenic non-epileptic seizures	Conversion disorder	Moderate	Yes	Yes

Source: Reviewer created from datasets

Serious adverse events from Year 2 of BLOOM were discussed in the original briefing document, including one additional attempted suicide (coded under the 'Injury, Poisoning, and Procedural Complications' SOC as 'intentional overdose'). This event occurred in a patient treated with placebo (re-randomized from lorcaserin 10 mg BID after the first year).

5.3 Adverse Events Associated with Discontinuation

5.3.1 Phase 1 and Phase 2

There were no adverse events leading to discontinuation in the newly-submitted Phase 1 trial or in the TULIP trial.

5.3.2 Phase 3

Adverse events resulting in discontinuation of study drug OR withdrawal from study were combined, given that there was not a clear distinction between these two options in the protocols.

Adverse events leading to withdrawal/study drug discontinuation were similar between lorcaserin and placebo in the original NDA (see Table 45). In the BLOOM-DM trial, lorcaserin treatment was associated with higher discontinuation incidence due to adverse events than placebo treatment.

Table 45. Discontinuations Due to Adverse Events by SOC, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**
Total	274 (8.6)	60 (7.5)	217 (6.8)	22 (8.6)	7 (7.4)	14 (5.6)
Before Amendment 3				7/96 (7.3)	7/95 (7.4)	6/95 (6.3)
After Amendment 3				15/160 (9.4)	n/a	8/157 (5.1)
Nervous System Disorders	84 (2.6)	15 (1.9)	49 (1.5)	5 (2.0)	4 (4.2)	2 (0.8)
Psychiatric Disorders	71 (2.2)	13 (1.6)	36 (1.1)	4 (1.6)	1 (1.1)	3 (1.2)
General Disorders and Administr Site Cond	38 (1.2)	4 (0.5)	19 (0.6)	3 (1.2)	0	0
Gastrointestinal Disorders	37 (1.2)	10 (1.2)	37 (1.2)	1 (0.4)	1 (1.1)	3 (1.2)
Musculoskeletal and Connect Tiss Disorders	19 (0.6)	5 (0.6)	9 (0.3)	4 (1.6)	0	0
Cardiac Disorders	15 (0.5)	3 (0.4)	13 (0.4)	0	0	0
Neoplasms Benign, Malignant And Unspec	14 (0.4)	4 (0.5)	11 (0.3)	1 (0.4)	1 (1.1)	2 (0.8)
Respiratory, Thoracic and Mediast Disorders	12 (0.4)	1 (0.1)	7 (0.2)	0	0	1 (0.4)
Vascular Disorders	11 (0.3)	1 (0.1)	8 (0.3)	1 (0.4)	1 (1.1)	2 (0.8)
Reproductive System and Breast Disorders	9 (0.3)	0	8 (0.3)	0	0	0
Hepatobiliary Disorders	4 (0.1)	0	2 (0.1)	2 (0.8)	0	0
Metabolism and Nutrition Disorders	3 (0.1)	4 (0.5)	3 (0.1)	2 (0.8)	0	0
Skin and Subcutaneous Disorders	13 (0.4)	4 (0.5)	18 (0.6)	2 (0.8)	0	1 (0.4)
Renal and Urinary Disorders	2 (0.1)	1 (0.1)	2 (0.1)	1 (0.4)	0	0

Source: NDA 022529 ISS, Table 40; Response to Information Request 7 February 2012, Table CRL.20

In the original NDA, neurological and psychiatric adverse events led to greater discontinuations (Table 46). In the BLOOM-DM trial, preferred terms of 'dizziness', 'cerebrovascular accident', and 'depression' led to more than one patient treated with lorcaserin to discontinue from study drug.

Table 46. Discontinuations due to Nervous System and Psychiatric Disorders Adverse Events, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**
Nervous System Disorders	84 (2.6)	15 (1.9)	49 (1.5)	5 (2.0)	4 (4.2)	2 (0.8)
Headache	41 (1.3)	10 (1.2)	24 (0.8)	1 (0.4)	0	0
Dizziness	23 (0.7)	2 (0.2)	6 (0.2)	1 (0.4)	2 (2.1)	0
Migraine	5 (0.2)	1 (0.1)	1 (<0.1)	1 (0.4)	0	0
Disturbance in attention	4 (0.1)	1 (0.1)	1 (<0.1)	1 (0.4)	0	0
Facial palsy	0	0	0	1 (0.4)	0	0
Facial spasm	0	0	0	1 (0.4)	0	0
Cerebrovascular accident	0	0	0	0	2 (2.1)	0
Convulsion	1 (<0.1)	0	0	0	0	1 (0.4)
Somnolence	2 (0.1)	0	2 (0.1)	0	0	1 (0.4)
Psychiatric Disorders	71 (2.2)	13 (1.6)	36 (1.1)	4 (1.6)	1 (1.1)	3 (1.2)
Depression	29 (0.9)	1 (0.1)	16 (0.5)	2 (0.8)	1 (1.1)	0
Anxiety	12 (0.4)	3 (0.4)	8 (0.3)	0	0	2 (0.8)
Suicidal ideation	7 (0.2)	0	2 (0.1)	0	0	0
Depressed mood	6 (0.2)	1 (0.1)	2 (0.1)	0	0	0
Insomnia	5 (0.2)	2 (0.2)	6 (0.2)	0	0	0
Irritability	4 (0.1)	2 (0.2)	2 (0.1)	0	0	0
Confusional state	0	0	0	1 (0.4)	0	0
Conversion disorder	0	0	0	1 (0.4)	0	0
Major depression	0	0	0	1 (0.4)	0	0
Nervousness	0	0	0	0	0	1 (0.4)

Source: NDA 022529 ISS, Table S06.3; Response to Information Request 7 February 2012, Table CRL.20

5.4 Common Adverse Events

Adverse events that were common in all trials with lorcaserin included headache, dizziness, nausea, and fatigue. Headache and dizziness are discussed in section 5.5.5. Nausea was dose- and exposure-related, seen primarily in patients with the lowest baseline body weight, and seen early after dosing (typically within the first four hours). As would be expected, hypoglycemia was not frequently seen in the trials of patients without diabetes, but as the preferred term 'hypoglycaemia' was the most common adverse event in the BLOOM-DM trial, it is included in Table 47. Hypoglycemia is discussed further in section 5.5.3.

Table 47. Preferred Terms Reported by ≥ 5% of Lorcaserin-treated Patients and More Commonly than with Placebo in the Pooled Non-Diabetes Phase 3 Trials and BLOOM-DM

	BLOOM + BLOSSOM		**BLOOM-DM**	
	Lorc 10 BID N = 3195	**Placebo N = 3185**	**Lorc 10 BID N = 256**	**Placebo N = 252**
Hypoglycaemia	2 (0.1)	1 (<0.1)	75 (29.3)	53 (21.0)
Headache	537 (16.8)	321 (10.1)	37 (14.5)	18 (7.1)
Nasopharyngitis	414 (13.0)	381 (12.0)	29 (11.3)	25 (9.9)
Dizziness	270 (8.5)	122 (3.8)	18 (7.0)	16 (6.3)
Nausea	264 (8.3)	170 (5.3)	24 (9.4)	20 (7.9)
Fatigue	229 (7.2)	114 (3.6)	19 (7.4)	10 (4.0)
Urinary tract infection	207 (6.5)	171 (5.4)	23 (9.0)	15 (6.0)
Back pain	201 (6.3)	178 (5.6)	30 (11.7)	20 (7.9)

Source: Reviewer created from datasets

5.5 Targeted Safety Issues

5.5.1 Heart Valve Assessment

As noted in the original review for the EMDAC meeting in September 2010, drugs that release serotonin or target 5HT receptors are under scrutiny due to the observation that certain of these drugs have been associated with an unusual cardiac valvular disease, characterized by fibrotic, regurgitant valves.[8,19,20] In the years since fenfluramine and dexfenfluramine have been removed from the U.S. market, researchers have identified activation of the 5HT2B receptor as the likely mechanism of this adverse event.[3,21] Despite its relative 5HT2C specificity as compared to 5HT2B, lorcaserin is a novel 5HT2 agonist, and therefore a comprehensive program of echocardiographic screening and monitoring was undertaken in the development program.

[19] Redfield MM, et al. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. Ann Intern Med July 1992; 117(1): 50-52.
[20] Steiger M, et al. Risk of valvular heart disease associated with the use of dopamine agonists in Parkinson's disease: a systematic review. J Neural Transm 2009; 116: 179-91.
[21] Setola V, et al. Molecular determinants for the interaction of the valvulopathic anorexigen neorfenfluramine with the 5-HT2B receptor. Mol Pharmacol 2005; 68(1): 20-33.

The original series of VHD associated with fenfluramine and dexfenfluramine use was characterized by valvular lesions on both sides of the heart, with a left-sided (mitral or aortic) valve affected in all cases.[9] Mild or less mitral regurgitation (MR), and trace or less aortic regurgitation (AR), are relatively common conditions in the general population; therefore the definition employed for clinically significant VHD due to anorexigen use was defined as mild or greater AR and/or moderate or greater MR (termed FDA-defined VHD), for use in observational studies.[9] The original reports suggested as many as one in three exposed patients were affected with this degree of VHD.[9] More recently, two published meta-analyses evaluated the literature on fenfluramine- and dexfenfluramine-associated VHD and have provided refined (and considerably lower) estimates:

- Sachdev, et al. [22] evaluated nine articles, with a total of 3769 patients exposed to fenfluramine or dexfenfluramine and 5009 patients unexposed. These authors found a pooled prevalence of FDA-defined VHD among patients treated for greater than 90 days of 12.0% compared with 5.9% for the unexposed group (prevalence odds ratio 2.2, 95% CI 1.7-2.7). This increase was primarily the result of mild or greater aortic regurgitation (exposed 9.6%, unexposed 4.5%, prevalence odds ratio 2.5, 95% CI 1.9-3.3). The combined analyses also identified a small but statistically significant increase in MR (exposed 3.5%, unexposed 1.8%, prevalence odds ratio 1.6, 95% CI 1.05-2.3). Among patients exposed for less than or equal to 90 days, a trend toward more regurgitation was not statistically significant by either FDA criteria (exposed 6.8%, unexposed 5.8%, prevalence odds ratio 1.4, 95% CI 0.8-2.4) or by individual valve.

- Loke, et al.[23] found that of the 1279 patients evaluated in seven uncontrolled cohort studies, 236 (18%) and 60 (5%) were found to have AR and MR, respectively. Pooled data from six controlled cohort studies (exposed N=3035, unexposed N = 1781) yielded for AR a relative risk ratio of 2.32 (95% CI 1.79 to 3.01). Pooled data from six controlled cohort studies (exposed = 3273, unexposed = 2017) yielded for MR a relative risk ratio of 1.55 (95% CI 1.06 to 2.25). These authors also noted that only one case of VHD was detected in 57 randomized controlled trials of appetite suppressants; notably these randomized controlled trials did not employ echocardiographic monitoring.

In assessing the valvular safety of lorcaserin, the Phase 3 VHD results have been updated based on echocardiography measurements with the results from the BLOOM-DM trial. Echocardiogram procedures for BLOOM, BLOSSOM, and BLOOM-DM are provided in Appendix B; the procedures for BLOOM-DM were identical to those of BLOSSOM. In all three trials, echocardiograms were conducted at baseline and at each six-month time point (Weeks 24 and 52 for the one-year cohort; patients in the two-year BLOOM trial also had echocardigrams conducted at Weeks 76 and 104).

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[22] Sachdev M, et al. Effect of fenfluramine-dericvative diet pills on cardiac valves: A meta-analysis of observational studies. Am Heart J 2002; 144:1065-73.

[23] Loke YK, et al. Appetite suppressants and valvular heart disease – a systematic review. BMC Clin Pharmacol 2002 Aug 23;2:6.

5.5.1.1 FDA-Defined Valvular Heart Disease

5.5.1.1.1 Primary Endpoint

In the original NDA submission, the primary pre-specified echocardiographic endpoint was the proportion of patients who developed new FDA-defined VHD from baseline to Week 52 in the pooled Phase 3 echocardiographic safety population. These analyses excluded patients who had FDA-defined VHD at baseline. For patients with at least one post-baseline echocardiogram measurement, the last non-baseline observation carried forward method was used to impute missing data. Patients who discontinued from the trials prior to Week 52 but returned for a Week 52 echo were included in the pooled safety analyses. Given the relatively large proportion of drop-outs in the Phase 3 trials, there are limitations to the LOCF approach; therefore, these analyses have addressed this issue with a variety of sensitivity analyses as well. The majority of analyses are limited to a comparison of lorcaserin 10 mg BID and placebo.

Table 48. Incidence of FDA-Defined VHD at Week 52 by Treatment Group, Patients with Baseline VHD Excluded (Safety Population, LOCF)

	BLOOM		**BLOSSOM**		**BLOOM-DM**	
	Lorc 10 BID N=1278	**Pbo N=1191**	**Lorc 10 BID N=1208**	**Pbo N=1153**	**Lorc 10 BID N=210**	**Pbo N=209**
FDA-VHD, n (%)	34 (2.66)	28 (2.35)	24 (1.99)	23 (1.99)	6 (2.86)	1 (0.48)
Relative Risk (95% CI)	1.13 (0.69, 1.85)		1.00 (0.57, 1.75)		5.97 (0.73, 49.17)	
Pooled RR (95% CI)	**1.16 (0.81, 1.67)**					

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

5.5.1.1.2 Individual Valves Comprising Primary Endpoint

The primary safety endpoint of Week 52 FDA-defined VHD in the Phase 3 population was further categorized by valve. As noted above in the Sachdev and Loke metaanalyses, fenfluramine-associated VHD was driven by increases in aortic regurgitation.[22,23] Interestingly, the association between lower BMI and VHD cited by the sponsor as a potential source of ascertainment or other bias is primarily driven by mitral (or tricuspid) regurgitation; this particular relationship was not noted with aortic regurgitation.[24] FDA's analyses demonstrate that the imbalance in FDA-defined VHD appears to be driven by an increase in MR (Table 49 and Table 50). See section 5.5.1.1.5 for a discussion of FDA-defined VHD and weight loss.

[24] Singh JP, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol. 1999 Mar 15; 83(6): 897-902.

Table 49. Incidence of Mild or Greater Aortic Regurgitation at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

		Total Patients*	Number of Events	Incidence	RR (95% CI)	Pooled RR** (95% CI)
BLOOM	**Lorc 10 BID**	1278	18	1.41%	0.96 (0.69, 1.34)	0.89 (0.56, 1.42)
	Pbo	1191	18	1.51%		
BLOOM-DM	**Lorc 10 BID**	210	4	1.90%	2.51 (0.43, 14.54)	
	Pbo	209	1	0.48%		
BLOSSOM	**Lorc 10 BID**	1208	13	1.08%	0.84 (0.62, 1.13)	
	Pbo	1153	18	1.56%		
Total		5249	72	1.37%		

* Number without missing, excluding baseline valvulopathy
** Stratified Mantel-Haenszel approach

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 50. Incidence of Moderate or Greater Mitral Regurgitation at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

		Total Patients*	Number of Events	Incidence	RR (95% CI)	Pooled RR** (95% CI)
BLOOM	**Lorc 10 BID**	1278	17	1.33%	1.31 (0.80, 2.14)	1.95 (1.05, 3.59)
	Pbo	1191	10	0.84%		
BLOOM-DM	**Lorc 10 BID**	210	2	0.95%	-	
	Pbo	209	0	0%		
BLOSSOM	**Lorc 10 BID**	1208	12	0.99%	1.67 (0.80, 3.48)	
	Pbo	1153	5	0.43%		
Total		5249	46	0.88%		

* Number without missing, excluding baseline valvulopathy
** Stratified Mantel-Haenszel approach

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

There were no cases of moderate or severe aortic regurgitation (AR) or severe mitral regurgitation (MR) that comprised the primary endpoint. The valvular changes during BLOOM-DM for the six patients treated with lorcaserin 10 mg BID and one patient treated with placebo (in addition to the two patients treated with lorcaserin 10 mg QD, 2.5%) who had VHD at the 52-week time point are presented in the following table to demonstrate the degree of valvular regurgitation change throughout this trial.

Table 51. Listing of Patients with Week 52 (LOCF) FDA-Defined VHD and Regurgitation Scores, BLOOM-DM

	Patient ID	Age/Race/Sex	Screening	Week 24	Week 52
Lorc 10 BID	1146-S007	64/black/M	Trace AR	Trace AR	**Mild AR**
	1146-S018	48/white/M	Mild MR	**Moderate MR**	**Moderate MR**
	1161-S061	60/white/M	Trace MR	Trace MR	**Moderate MR**
	1174-S111	59/white/M	Trace AR	**Mild MR**	**Mild MR**
	1217-S020	47/black/M	Trace AR	**Mild AR**	**Mild AR**
	1226-S012	57/white/F	Trace AR	Absent AR	**Mild AR**
Lorc 10 QD	1161-S052*	60/black/M	Trace AR	**Mild AR**	-
	1174-S027	59/black/M	Absent AR	Absent AR	**Mild AR**
Placebo	1119-S004*	57/white/F	Trace AR	**Mild AR†**	**-**

Bold indicates FDA-defined VHD
***** Patient discontinued prematurely from trial; last available echo data were carried forward for Week 52 analysis of primary echocardiographic endpoint
† Unscheduled echo

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 54

5.5.1.1.3 FDA-Defined VHD at Additional Time Points

If patients with FDA-defined VHD at Week 24 withdrew from the study at a higher incidence than those without, this could artificially diminish any lorcaserin effect at Week 52. In BLOOM, five patients in the lorcaserin BID group and eight patients in the placebo group whose Week 24 echocardiogram met FDA-defined VHD criteria withdrew prior to Week 52. One patient in each treatment group stated that the echocardiogram change was the reason for withdrawal. In BLOSSOM, four patients assigned to lorcaserin BID, three assigned to lorcaserin QD, and two assigned to placebo had FDA-defined VHD at Week 24 and discontinued prior to Week 52. One of the patients assigned to lorcaserin QD was withdrawn because of the Week 24 echocardiogram result. In BLOOM-DM, one patient with FDA-defined VHD at Week 24 on lorcaserin 10 mg QD and one patient on placebo prematurely withdrew prior to Week 52.

In the pooled non-diabetes trials, 27 lorcaserin 10 mg BID and 21 placebo patients who were diagnosed with FDA-defined VHD at Week 24 subsequently "reverted" back to no VHD at Week 52. Eleven percent of the lorcaserin-treated reverters and 29% of the placebo-treated reverters had discontinued drug prior to the Week 52 visit. In BLOOM-DM, two lorcaserin 10 mg BID patients and three placebo patients with Week 24 VHD reverted to no VHD at Week 52. None of these patients prematurely discontinued prior to the Week 52 visit.

If the lorcaserin "reverters" from Week 24 to Week 52 improved VHD scores because they prematurely discontinued the trial and then improved off of drug, the Week 52 LOCF analysis could underestimate a drug effect. However, as shown in the Table 52, the pooled Week 24 analysis of FDA-defined VHD was very similar to the Week 52 analysis. In addition, a greater relative risk (point estimate) for FDA-defined VHD was seen in the ITT population than in the completers population (Table 53).

Table 52. Incidence of FDA-Defined VHD at Week 24 by Treatment Group, Patients with Baseline VHD Excluded (Safety Population, LOCF)

	BLOOM		BLOSSOM		BLOOM-DM	
	Lorc 10 BID N=1213	**Pbo N=1089**	**Lorc 10 BID N=1170**	**Pbo N=1103**	**Lorc 10 BID N=203**	**Pbo N=206**
FDA-VHD, n (%)	25 (2.06)	21 (1.93)	27 (2.31)	20 (1.81)	5 (2.46)	4 (1.94)
Relative Risk (95% CI)	1.07 (0.60, 1.90)		1.27 (0.72, 2.26)		1.27 (0.35, 4.66)	
Pooled RR (95% CI)	**1.18 (0.80, 1.73)**					

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 53. Incidence of FDA-Defined VHD at Week 52 by Treatment Group, Patients with Baseline VHD Excluded (Completers Population)

	BLOOM		BLOSSOM		BLOOM-DM	
	Lorc 10 BID N=857	**Pbo N=698**	**Lorc 10 BID N=853**	**Pbo N=790**	**Lorc 10 BID N=157**	**Pbo N=147**
FDA-VHD, n (%)	29 (3.38)	21 (3.01)	13 (1.52)	19 (2.41)	6 (3.82)	0
Relative Risk (95% CI)	1.12 (0.65, 1.95)		0.63 (0.32, 1.27)		--	
Pooled RR (95% CI)	**1.03 (0.68, 1.57)**					

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Another way to evaluate the risk of developing FDA-defined VHD from baseline to Week 52 is to compare the incidence of FDA-defined VHD at either Week 24 or Week 52. In this sensitivity analysis, patients who had VHD at either Week 24 or Week 52 were considered as VHD cases at Week 52. The point estimate and upper bound of the 95% CI of the pooled relative risk are similar to those in the primary analysis.

Table 54. Incidence of FDA-Defined VHD at Either Week 24 or Week 52 by Treatment Group, Patients with Baseline VHD Excluded (Safety Population)

	BLOOM		BLOSSOM		BLOOM-DM	
	Lorc 10 BID N=1278	**Pbo N=1191**	**Lorc 10 BID N=1208**	**Pbo N=1153**	**Lorc 10 BID N=210**	**Pbo N=209**
FDA-VHD, n (%)	45 (3.52)	38 (3.19)	40 (3.31)	34 (2.95)	8 (3.81)	4 (1.91)
Relative Risk (95% CI)	1.10 (0.72, 1.69)		1.12 (0.72, 1.76)		1.99 (0.61, 6.51)	
Pooled RR (95% CI)	**1.16 (0.86, 1.56)**					

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Finally, FDA-defined VHD in Year 2 of BLOOM is presented below:

Table 55. Proportion of Patients Who Developed FDA-Defined VHD from Screening at Weeks 76 and 104, BLOOM Year 2

Treatment	N	n (%)
Week 76		
Lorc/Lorc	486	14 (2.9)
Lorc/Pbo	250	9 (3.6)
Pbo/Pbo	609	19 (3.1)
Week 104		
Lorc/Lorc	500	13 (2.6)
Lorc/Pbo	258	5 (1.9)
Pbo/Pbo	627	17 (2.7)

Source: NDA 22529, BLOOM CSR Table 72

5.5.1.1.4 FDA-Defined VHD by Subgroup

The following subgroups of the pooled safety population were explored for development of FDA-defined VHD at Week 52: sex, race/ethnicity, age, baseline weight quartile, and weight loss responders (Table 56, Table 57, Table 58, Table 59, and Table 60, respectively).

Table 56. FDA-Defined VHD by Subgroup, Sex

			N	n	%	Relative Risk (95% CI)	Pooled Relative Risk (95% CI)
Females	**BLOOM**	Lorc 10 BID	1043	27	2.59%	1.11 (0.64, 1.93)	1.17 (0.78, 1.77)
		Pbo	990	23	2.32%		
	BLOSSOM	Lorc 10 BID	963	22	2.28%	1.26 (0.67, 2.39)	
		Pbo	884	16	1.81%		
	BLOOM-DM	Lorc 10 BID	112	1	0.89%	1.04 (0.07, 16.50)	
		Pbo	117	1	0.85%		
Males	**BLOOM**	Lorc 10 BID	235	7	2.98%	1.20 (0.39, 3.71)	1.11 (0.51, 2.42)
		Pbo	201	5	2.49%		
	BLOSSOM	Lorc 10 BID	245	2	0.82%	0.31 (0.07, 1.50)	
		Pbo	269	7	2.60%		
	BLOOM-DM	Lorc 10 BID	98	5	5.10%	--	
		Pbo	92	0	0%		

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 57. FDA-Defined VHD by Subgroup, Race/Ethnicity

			N	n	%	Relative Risk (95% CI)	Pooled Relative Risk (95% CI)
White	**BLOOM**	Lorc 10 BID	918	26	2.83%	1.03 (0.59, 1.79)	1.09 (0.72, 1.64)
		Pbo	835	23	2.75%		
	BLOSSOM	Lorc 10 BID	849	18	2.12%	0.99 (0.51, 1.91)	
		Pbo	794	17	2.14%		
	BLOOM-DM	Lorc 10 BID	128	4	3.13%	4.31 (0.49, 38.08)	
		Pbo	138	1	0.72%		
Black	**BLOOM**	Lorc 10 BID	218	6	2.75%	1.39 (0.40, 4.85)	1.65 (0.65, 4.17)
		Pbo	202	4	1.98%		
	BLOSSOM	Lorc 10 BID	211	4	1.90%	1.38 (0.31, 6.11)	
		Pbo	219	3	1.37%		
	BLOOM-DM	Lorc 10 BID	44	2	4.55%	--	
		Pbo	38	0	0%		
Hispanic	**BLOOM**	Lorc 10 BID	118	1	0.85%	--	0.35 (0.04, 3.06)
		Pbo	136	0	0%		
	BLOSSOM	Lorc 10 BID	117	0	0%	--	
		Pbo	113	3	2.65%		
	BLOOM-DM	Lorc 10 BID	31	0	0%	--	
		Pbo	22	0	0%		

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 58. FDA-Defined VHD by Subgroup, Age

			N	n	%	Relative Risk (95% CI)	Pooled Relative Risk (95% CI)
Age ≤ 50	**BLOOM**	Lorc 10 BID	821	17	2.07%	1.40 (0.66, 2.97)	1.47 (0.81, 2.69)
		Pbo	744	11	1.48%		
	BLOSSOM	Lorc 10 BID	782	8	2.28%	1.27 (0.44, 3.64)	
		Pbo	745	6	1.81%		
	BLOOM-DM	Lorc 10 BID	73	2	2.74%	--	
		Pbo	79	0	0%		
Age > 50	**BLOOM**	Lorc 10 BID	457	17	3.72%	0.98 (0.51, 1.89)	1.02 (0.65, 1.61)
		Pbo	447	17	3.80%		
	BLOSSOM	Lorc 10 BID	426	16	3.76%	0.90 (0.46, 1.76)	
		Pbo	408	17	4.17%		
	BLOOM-DM	Lorc 10 BID	130	4	2.92%	3.80 (0.43, 33.51)	
		Pbo	137	1	0.77%		

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 59. FDA-Defined VHD by Subgroup, Phase 3 Trials Pooled, Baseline Weight Quartile

	Lorc 10 BID	Pbo	Relative Risk (95% CI)
Q1 (≤ 88.3 kg)	21/577 (3.6%)	16/545 (2.9%)	1.24 (0.66, 2.35)
Q2 (> 88.3 - 98.7 kg)	12/576 (2.1%)	9/545 (1.7%)	1.25 (0.54, 2.93)
Q3 (> 98.7 - 110.5 kg)	13/569 (2.3%)	14/521 (2.7%)	0.85 (0.41, 1.80)
Q4 (> 110.5 kg)	11/569 (1.9%)	8/497 (1.6%)	1.17 (0.47, 2.95)

Source: NDA 022529 CR Appendix 2, Tables Pool3 E25.3.a, E25.3.b, E25.3.c, and E25.3.d

Table 60. FDA-Defined VHD by Subgroup, Phase 3 Trials Pooled, 5% Weight-Loss Responder Status

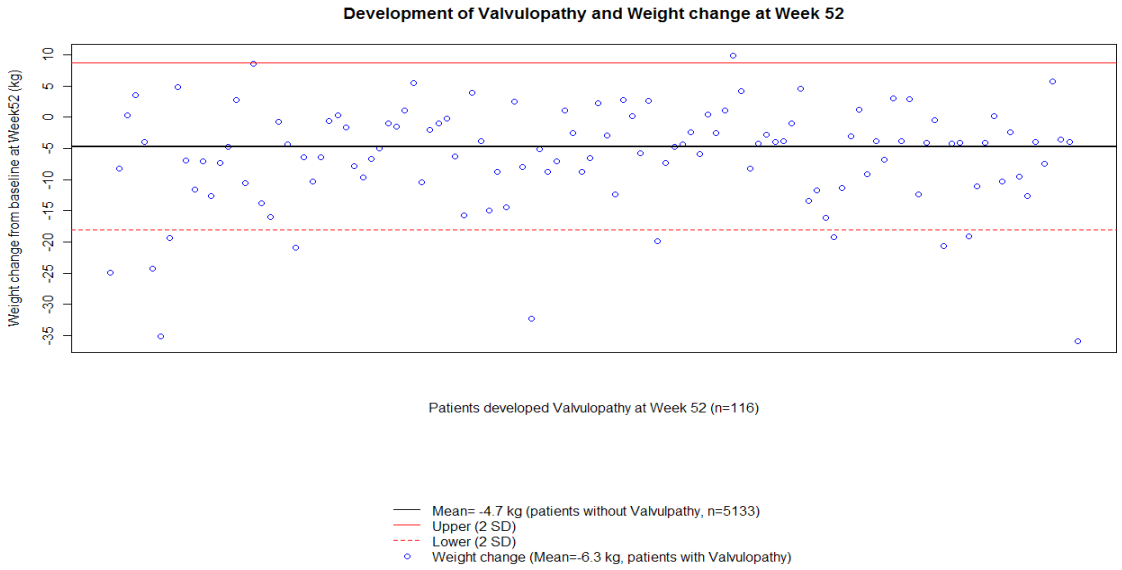
	Lorc 10 BID	Pbo	Relative Risk (95% CI)
Responders	35/1288 (2.7)	18/392 (3.0)	0.86 (0.49, 1.50)
Non-Responders	22/1003 (2.2)	29/1516 (1.9)	1.15 (0.66, 1.99)

Source: NDA 022529 CR Appendix 2, Tables Pool3 E25.4.a and E25.4.b

5.5.1.1.5 FDA-Defined VHD and Weight Loss

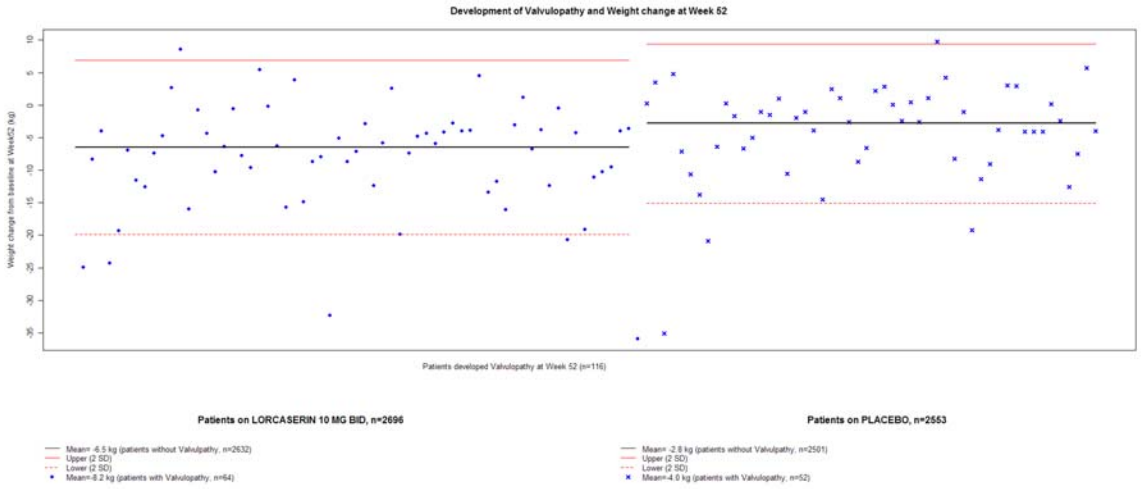
To explore how weight loss is related to a Week 52 VHD diagnosis, plots were generated illustrating the weight loss of patients with FDA-defined VHD overlaying a representation of the mean weight loss +/- two standard deviations (2 SD) of those without VHD. Figure 4 and Figure 5 represent the weight loss of individual patients with VHD, depicted as individual circles, superimposed on the mean and 2 SD of the population without VHD, represented by the lines. As seen in Figure 4, mean weight loss in patients without FDA-defined VHD was 4.7 kg, mean weight loss in patients with FDA-defined VHD at Week 52 was 6.3 kg. However, when three FDA-defined VHD outliers are removed, the mean change – and difference between groups – is attenuated (mean weight loss in patients with FDA-defined VHD is 5.2 kg). This may suggest that weight loss per se does not fully explain the difference in VHD between groups.

Figure 4. Development of FDA-Defined VHD and Weight Change at Week 52



Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Figure 5. Development of FDA-Defined VHD and Weight Change by Treatment Group at Week 52



Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

5.5.1.1.6 Inter- and Intra-variability Assessment

Each trial had a pool of centrally trained and located cardiologists who read the echocardiograms in a blinded fashion. Each echocardiogram was read by two cardiologists, 'Reader A' and 'Reader B'. Whenever possible, all echocardiograms for a single patient were read by the same primary reader (either Reader 'A' or Reader 'B') throughout the study to minimize variability. The secondary reader was assigned randomly for each patient throughout the study. When the two readings matched according to prespecified criteria, the results from the primary reader were entered into the database. In the event of discrepant reads, a third reader determined which of the two reads was entered into the database.

Variability with echocardiography reading was assessed in two ways in each Phase 3 trial: (1) inter-reader variability was assessed from an analysis of concordance in reading screening echocardiograms in BLOOM and baseline echocardiograms in BLOSSOM, and (2) inter- and intra-reader variability was assessed with a standard set of echocardiograms.

Methods and results of this assessment were presented in the original NDA and were discussed at the last EMDAC meeting. A speaker for the sponsor cited about 25 to 30 percent test-retest variability in the obese patient population.[25] Overall, the inter- and intra-reader variability observed using the standard echocardiograms was consistent with variability data reported by other investigators.[26] By contrast, inter-reader variability of the pool of cardiologists chosen to read the echocardiograms as assessed using the baseline echocardiograms was greater than that of the standard echocardiogram assessment.

We evaluated the impact of inter-reader variability by conducting a sensitivity analysis of the primary endpoint (incidence of FDA-defined VHD) for Reader A only and Reader B only (i.e., unadjudicated, raw echocardiogram reads). For both Reader A and Reader B, the relative risk and upper bound of the 95% CI was consistent with that of the adjudicated reads in the pooled primary analysis.

[25] Weisman N, EMDAC 16 September 2010

[26] Gottdiener JS, et al. Testing the test: the reliability of echocardiography in the sequential assessment of valvular regurgitation. Am Heart J 2002; 144(1): 115-121.

Table 61. Relative Risk of FDA-Defined VHD by Reader, Patients with Baseline VHD Excluded (Safety Population, LOCF)

	BLOOM		BLOSSOM		BLOOM-DM	
	Lorc 10 BID	Pbo	Lorc 10 BID	Pbo	Lorc 10 BID	Pbo
Reader A						
VHD, n (%)	35 (2.74)	24 (2.02)	38 (3.16)	29 (2.52)	4 (1.90)	5 (2.38)
Relative Risk (95% CI)	1.36 (0.81, 2.27)		1.25 (0.78, 2.02)		0.80 (0.22, 2.94)	
Pooled RR (95% CI)	**1.26 (0.90, 1.76)**					
Reader B						
VHD, n (%)	28 (2.21)	28 (2.38)	27 (2.24)	19 (1.66)	9 (4.37)	4 (1.93)
Relative Risk (95% CI)	0.93 (0.55, 1.56)		1.35 (0.76, 2.42)		2.26 (0.71, 7.23)	
Pooled RR (95% CI)	**1.19 (0.83, 1.71)**					
Adjudicated Reads (Primary Analysis)						
VHD, n (%)	34 (2.7%)	28 (2.4%)	24 (2.0%)	23 (2.0%)	6 (2.9%)	1 (0.5%)
Relative Risk (95% CI)	1.13 (0.69, 1.85)		1.00 (0.57, 1.75)		5.97 (0.73, 49.17)	
Pooled RR (95% CI)	**1.16 (0.81, 1.67)**					

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

5.5.1.2 Secondary Endpoints

The proportion of patients who experienced any increase in individual valve regurgitation from baseline at Weeks 24 and 52 was analyzed; the first set of tables include increases from absent to trace, and the second set excludes those increases, as they may not be clinically meaningful changes.

Table 62. Proportion of Patients Who Experienced Any Increase from Baseline in Valvular Regurgitation at Week 52 LOCF, Pooled Phase 3 Trials

	Lorc 10 BID	Pbo	Relative Risk (95% CI)	P value
Aortic	8.30%	7.04%	1.18 (0.98, 1.42)	0.08
Mitral	21.11%	19.21%	1.10 (0.99, 1.22)	0.09
Pulmonic	17.00%	15.51%	1.10 (0.97, 1.24)	0.14
Tricuspid	17.89%	16.13%	1.11 (0.98, 1.25)	0.09
Any Valve	**46.88%**	**42.02%**	**1.11 (1.05, 1.18)**	**<0.001**

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 63. Proportion of Patients Who Experienced Any Increase from Baseline in Valvular Regurgitation at Week 24, Pooled Phase 3 Trials

	Lorc 10 BID	Pbo	Relative Risk (95% CI)	P value
Aortic	8.72%	7.62%	1.15 (0.95, 1.38)	0.15
Mitral	20.60%	17.64%	1.17 (1.02, 1.31)	0.007
Pulmonic	16.72%	15.60%	1.07 (0.94, 1.22)	0.30
Tricuspid	18.24%	15.41%	1.18 (1.05, 1.34)	0.008
Any Valve	**45.38%**	**41.06%**	**1.11 (1.04, 1.18)**	**0.002**

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 64. Proportion of Patients Who Experienced Any Increase from Baseline in Valvular Regurgitation at Week 52 LOCF (excluding Absent to Trace), Pooled Phase 3 Trials

	Lorc 10 BID	Pbo	Relative Risk (95% CI)	P value
Aortic	1.34%	1.45%	0.92 (0.59, 1.44)	0.71
Mitral	9.92%	8.19%	1.21 (1.02, 1.43)	0.03
Pulmonic	17.00%	15.51%	1.10 (0.97, 1.24)	0.14
Tricuspid	12.18%	9.88%	1.23 (1.06, 1.44)	0.008
Any Valve	**32.37%**	**28.24%**	**1.15 (1.06, 1.24)**	**0.001**

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 65. Proportion of Patients Who Experienced Any Increase from Baseline in Valvular Regurgitation at Week 24 (excluding Absent to Trace), Pooled Phase 3 Trials

	Lorc 10 BID	Pbo	Relative Risk (95% CI)	P value
Aortic	1.43%	1.43%	1.01 (0.64, 1.59)	0.98
Mitral	10.23%	7.86%	1.30 (1.09, 1.55)	0.003
Pulmonic	16.72%	15.60%	1.07 (0.94, 1.22)	0.30
Tricuspid	12.77%	9.45%	1.35 (1.15, 1.58)	<0.001
Any Valve	**31.28%**	**27.82%**	**1.12 (1.03, 1.22)**	**0.007**

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

The majority of the increases from baseline in mitral valvular regurgitation score were by one; in either treatment group at Week 52, the maximum increase was two. Only one patient in the Phase 3 program developed severe MR, a patient randomized to placebo.

Table 66. Number (%) of Patients with a Given Change from Baseline in Mitral Regurgitation, Patients Without FDA-VHD at Baseline (LOCF/Safety Population)

	BLOOM + BLOSSOM		BLOOM-DM	
	Lorc 10 BID	**Pbo**	**Lorc 10 BID**	**Pbo**
Week 24				
N	2383	2192	203	206
Increased by 1, n (%)	457 (19.2)	364 (16.6)	48 (23.7)	36 (17.5)
Increased by 2, n (%)	30 (1.3)	21 (1.0)	2 (1.0)	0
Increased by 3, n (%)	1 (<0.1)	0	0	0
Week 52				
N	2486	2344	210	209
Increased by 1, n (%)	508 (20.4)	434 (18.5)	38 (18.1)	30 (14.4)
Increased by 2, n (%)	30 (1.2)	23 (1.0)	2 (1.0)	2 (1.0)

Source: NDA 022529 ISS Statistical Report, Tables E40.1 and E40.5; CR Appendix 2, Tables CRL18.2.3 and CRL18.2.4

The majority of the increases from baseline in aortic valvular regurgitation score were by one; in either treatment group at Weeks 24 and 52, the maximum increase was two. No patients in the Phase 3 program developed severe AR.

Table 67. Number (%) of Patients with a Given Change from Baseline in Aortic Regurgitation, Patients Without FDA-VHD at Baseline (LOCF/Safety Population)

	BLOOM + BLOSSOM		BLOOM-DM	
	Lorc 10 BID	**Pbo**	**Lorc 10 BID**	**Pbo**
Week 24				
N	2383	2192	203	206
Increased by 1, n (%)	189 (7.9)	154 (7.0)	31 (15.3)	21 (10.2)
Increased by 2, n (%)	10 (0.4)	8 (0.4)	0	1 (0.5)
Week 52				
N	2486	2344	210	209
Increased by 1, n (%)	183 (7.4)	150 (6.4)	33 (15.7)	15 (7.2)
Increased by 2, n (%)	12 (0.5)	15 (0.6)	0	0

Source: NDA 022529 ISS Statistical Report, Tables E40.0 and E40.4; CR Appendix 2, Tables CRL18.2.1 and CRL18.2.2

In the BLOSSOM and BLOOM-DM trials, patients who had FDA-defined VHD at baseline were permitted to enroll into the trial. Lorcaserin-treated patients did not appear to develop worsening of their valvular disease over the 52-week course of the trials as compared to placebo-treated patients.

Table 68. Number (%) of Patients with FDA-Defined VHD at Baseline who Experienced an Increase in Mitral or Aortic Valvular Regurgitation at Week 52

	Lorc 10 BID	**Pbo**
Worsening of MR	7/75 (9.3)	13/60 (21.7)
Worsening of AR	2/75 (2.7)	4/59 (6.8)

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 55

As Table 62 to Table 65 above demonstrate, some suggestion of increased tricuspid and pulmonic valve regurgitation with lorcaserin treatment was seen. Although the FDA definition of anorexigen-related VHD includes the left-sided valves only, the original reports of these cases noted that pathology could affect any valve.[8,9] Carcinoid- and ergot-related VHD have also been described as involving the tricuspid valve.[27,28] Specific grade increases of tricuspid valves regurgitation were further assessed. The majority of the increases from baseline in tricuspid valvular regurgitation score were by one.

Table 69. Number (%) of Patients with a Given Change from Baseline in Tricuspid Regurgitation, Patients Without FDA-VHD at Baseline (LOCF/Safety Population)

	BLOOM + BLOSSOM		**BLOOM-DM**	
	Lorc 10 BID	**Pbo**	**Lorc 10 BID**	**Pbo**
Week 24				
N	2354	2170	203	206
Increased by 1, n (%)	397 (16.9)	327 (15.1)	36 (17.7)	27 (13.1)
Increased by 2, n (%)	31 (1.3)	11 (0.5)	0	0
Increased by 3, n (%)	1 (<0.1)	0	0	0
Week 52				
N	2460	2319	210	209
Increased by 1, n (%)	416 (16.9)	356 (15.4)	34 (16.2)	31 (14.8)
Increased by 2, n (%)	26 (1.1)	20 (0.9)	0	0
Increased by 3, n (%)	0	0	0	0

Source: NDA 22529, ISS Statistical Report Tables E40.3 and E40.7

Nine patients developed severe tricuspid regurgitation during the trials [four patients treated with lorcaserin 10 mg BID (0.1%), four patients treated with lorcaserin 10 mg QD (0.5%), and one patient treated with placebo (<0.1%)]; none were from the BLOOM-DM trial. None of these patients had a pulmonary artery systolic pressure (PASP) greater than 35 mmHg.

[27] Robiolio PA, et al. Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. Circulation. 1995 Aug 15; 92(4): 790-5.

[28] Redfield MM, et al. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. Ann Intern Med July 1992; 117(1): 50-52.

Table 70. Patients with Severe Tricuspid Regurgitation, Phase 3 Trials

ID	Treatment	Study Day	Baseline value	Exam value
143-S060	Lorc 10 BID	571	Mild	Severe
159-S009	Lorc 10 BID	582	Moderate	Severe
		740	Moderate	Severe
175-S002	Lorc 10 BID	545	Moderate	Severe
2118-S153	Lorc 10 BID	27	Moderate	Severe
2142-S080	Lorc 10 QD	365	Mild	Severe
2169-S002	Lorc 10 QD	174	Mild	Severe
2213-S003*	Lorc 10 QD	170	Mild	Severe
2250-S043	Lorc 10 QD	100	Trace	Severe
137-S033	Pbo	351	Moderate	Severe
*This patient also developed FDA-defined VHD (moderate MR) at Week 24; discontinued due to "sponsor decision"				

Source: Reviewer created from datasets

Alternative definitions of drug-related VHD have been used, notably in the investigations into dopamine agonist-associated VHD;[29] therefore, in the original review of the non-diabetes Phase 3 trials, an exploratory analysis of the proportion of patients who developed moderate or severe mitral, aortic, and/or tricuspid regurgitation at Week 52 (LOCF) was assessed. Excluding patients with this degree of regurgitation at baseline, 52/2554 (2.0%) of patients on lorcaserin 10 mg BID and 40/2398 (1.7%) of patients on placebo developed moderate or severe valvular regurgitation at Week 52. In an evaluation of the BLOOM-DM trial, excluding patients with moderate regurgitation at baseline, 4/210 (1.9%) patients on lorcaserin 10 mg BID and 2/209 (1.0%) patients on placebo developed moderate regurgitation at Week 52 (LOCF). No patients in BLOOM-DM developed severe regurgitation at any valve.

5.5.1.3 Adverse Events, Echocardiogram Alerts, and Physical Examination Findings Related to Heart Valves

No patient in any of the Phase 3 trials treated with lorcaserin required heart valve surgery or replacement. From the data available, no patient treated with lorcaserin reported symptoms from valvular regurgitation.

The sponsor conducted an analysis of cardiac valve adverse events utilizing a grouping of preferred terms related to cardiac valves. Because the majority of adverse events were generated from echocardiogram data and investigators reported echocardiographic findings of valvular regurgitation inconsistently, these data should be interpreted cautiously. Nevertheless, it is worth evaluating this analysis, given that there may be aspects of a particular case that would lead an investigator to report a finding as an adverse event.

The following is the sponsor's custom query for cardiac valve disorder preferred terms; terms actually identified in the Phase 3 database are bolded:

[29] Steiger M, et al. Risk of valvular heart disease associated with the use of dopamine agonists in Parkinson's disease: a systematic review. J Neural Transm 2009; 116: 179-91.

Table 71. Cardiac Valve Insufficiency-Related Preferred Terms (PTs)

Cardiac Valve Insufficiency PTs
Aortic valve disease
Aortic valve incompetence
Aortic valve prolapse
Aortic valvular disorders
Carcinoid heart disease
Cardiac valve disease
Cardiac valve disorders NEC
Cardiac valve rupture
Echocardiogram
Echocardiogram abnormal
Heart valve incompetence
Heart valve insufficiency
Mitral valve disease
Mitral valve incompetence
Mitral valve prolapse
Mitral valvular disorders
Pulmonary valve disease
Pulmonary valve incompetence
Pulmonary valvular disorders
Tricuspid valve disease
Tricuspid valve incompetence
Tricuspid valve prolapse
Tricuspid valvular disorders

NEC=not elsewhere classified

Source: NDA 22529, ISS Table 55

Table 72. Cardiac-Valve Related Adverse Events, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**
Total, Cardiac Valve-Related AEs	12 (0.4)	2 (0.2)	6 (0.2)	0	0	0
Pulmonary valve incompetence	5 (0.2)	1 (0.1)	1 (<0.1)	0	0	0
Mitral valve incompetence	4 (0.1)	0	4 (0.1)	0	0	0
Tricuspid valve incompetence	2 (0.1)	1 (0.1)	0	0	0	0
Cardiac valve disease	1 (<0.1)	0	0	0	0	0
Aortic valve incompetence	0	0	2 (0.1)	0	0	0

Source: Reviewer created from datasets

For certain echocardiographic findings that were likely to have clinical significance, a notification was provided to the study site and additional follow-up was requested. The notification criteria were as follows:

- Recommend referral to a cardiologist for the following findings:
  - Mitral regurgitation (MR) increased at least two categories from baseline *and* rated moderate or greater
  - Aortic regurgitation (AR) rated moderate or greater

    - Pulmonary artery pressure greater than 50 mm Hg with at least 10 mm Hg increase from baseline
    - LVEF ≤ 35

- Withdrawal of study medication and referral to a cardiologist for the following findings:
    - Severe MR
    - Severe AR
    - Pulmonary artery pressure ≥ 60 mmHg

In the BLOOM-DM trial, three patients had echocardiogram alerts involving heart valves.

- Patient 1206-S010 was a 60-year-old female randomized to lorcaserin 10 mg BID, with mild AR at baseline, moderate AR at Week 24 (leading to the alert), and mild AR again at Week 52. The patient had no signs or symptoms referable to AR. She was referred to her primary care physician who did not refer her to a cardiologist.

- Patient 1161-S061 was a 61-year-old male randomized to lorcaserin 10 mg BID, who had an alert of moderate MR plus an increase of two categories from baseline. He was found to have trace MR at baseline, trace MR at Week 24, and moderate MR at Week 52. No signs or symptoms referable to MR were reported. According to the investigator, the patient was doing very well, running six miles daily. The patient was not referred to cardiology, as the investigator believed the change in echocardiogram did not have clinical significance.

- Patient 1274-S004 was a 60-year-old male randomized to lorcaserin 10 mg BID, with mild AR at baseline, trace AR at Week 24, and moderate MR at Week 52 (cause of the alert). No signs or symptoms referable to AR were reported. The patient's cardiologist noted the increase in aortic valve disease in his notes and and planned to repeat the echocardiogram in the next six months. The patient returned two weeks later for a pharmacologic stress test, which showed no ischemia but moderate to severe inferoapical defects suggestive of a previous infarct versus a diaphragmatic attenuation artifact.

In the pooled (non-diabetes) Phase 3 trials, 10 (0.3%) patients on lorcaserin 10 mg BID, one (0.1%) patient on lorcaserin 10 mg QD, and four (0.1%) patients on placebo were reported to have a cardiac murmur. In the BLOOM-DM trial, two (0.8%) patients on lorcaserin 10 mg BID were reported to have a murmur and none in the other groups; of note, there were no increases in regurgitation scores for any valve in those two patients.

In those patients who were enrolled in the BLOSSOM and BLOOM-DM trials with baseline FDA-defined VHD, adverse events were evaluated for potential congestive heart failure (CHF)-related terms in the event that even a small increase in regurgitation could lead to CHF decompensation. Among CHF-related search terms only the adverse event of peripheral edema was reported: one patient in the lorcaserin 10 mg BID group and one

in the lorcaserin 10 mg QD group in the BLOSSOM trial, and one patient in the placebo group in the BLOOM-DM trial.

5.5.2 Pulmonary Hypertension

Primary pulmonary hypertension (PPH) is a rare disease characterized by restricted flow through the pulmonary arterial circulation, which leads to pulmonary vascular resistance and ultimately, right heart failure.[30] The anorexigen, aminorex fumarate, was associated in the 1960s with an "epidemic" of PPH in Europe, and in 1996, a case-control epidemiological study calculated that the use of anorexigens – mainly fenfluramine and its derivatives – was associated with an increased risk of PPH (23-fold increase when used for more than 3 months).[31] It has been estimated that one in 1000 or fewer patients who are exposed to such agents ultimately develop PPH.[32]

Although cardiac catheterization is required for definitive PPH diagnosis, echocardiography is used as a screening tool to estimate pulmonary artery systolic pressure (PASP) and evaluate right heart hemodynamics. Echocardiographically-derived PASP is limited by precision (more so underestimation than overestimation) as compared to true PASP measured by right heart catheterization.[33]

PASP positively correlates with age and BMI and is higher in men than women.[34] Higher PASP may in fact be physiological in very obese patients.[33] There are no universally agreed-upon echocardiographic variables used to diagnose PPH, although the European Task Force suggest (in their words, arbitrary) cutoffs of PASP > 50 mmHg as "likely" and PASP 37-50 mmHg as "possible".[35] Importantly, echocardiogram evaluation of the pulmonary artery was not a prespecified endpoint in these trials, and therefore these results are only descriptive.

PASP was estimated from the tricuspid regurgitant (TR) jet velocity. In many cases, PASP was not measurable due to inadequate or immeasurable TR jet velocity. In patients with no or limited tricuspid valve regurgitation, an accurate TR jet could not be measured.

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[30] McLaughlin VV, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. Circulation. 2009 Apr 28;119(16): 2250-94.

[31] Abenhaim L, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med. 1996 Aug 29; 335(9): 609-16.

[32] Rich S. EMDAC (NDA 20344, Dexfenfluramine hydrochloride), 28 September 1995. Transcript accessed 5 April 2012: http://www.fda.gov/ohrms/dockets/ac/95/3107t1b.pdf

[33] Milan A, et al. Echocardiographic indexes for the non-invasive evaluation of pulmonary hemodynamics. J Am Soc Echocardiogr 2010; 23: 225-39.

[34] McQuillan BM, et al. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. Circulation. 2001 Dec 4;104(23): 2797-802.

[35] Galie N, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. The task force for the diagnosis and treatment of pulmonary hypertension of the European Society for Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009; 30 (20): 2493-2537.

The least squared mean between treatment difference in PASP in the lorcaserin 10 mg BID versus the placebo group was 0.16 mmHg (95% CI -0.20, 0.52, p=0.38) in the pooled non-diabetes trials and -0.47 mmHg (95% CI -2.64, 1.70, p=0.67) in BLOOM-DM. The following table pools the three trials for mean change in PASP by treatment group:

Table 73. Change from Baseline in PASP (mmHg) at Week 52, Pooled BLOOM, BLOSSOM, and BLOOM-DM (LOCF)

	Lorc 10 BID	**Lorc 10 QD**	**Pbo**
N	1278	349	1195
Baseline PASP, Mean (SD)	25.7 (5.2)	25.1 (5.0)	25.3 (5.0)
PASP Change from Baseline, Mean	0.19 (0.17)	0.13 (0.28)	0.05 (0.17)

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 59

The proportion of patients who experienced changes of ≥ 15 mmHg, ≥ 20 mmHg, or ≥ 25 mmHg from baseline to Week 24 or Week 52 is summarized in the table below. One patient treated with lorcaserin 10 mg QD in the BLOOM-DM trial had change in baseline PASP ≥ 15 mmHg (not shown in the table below). The narrative for this patient is presented below.

Table 74. Patients with Increases in PASP from Baseline, Phase 3 Trials

	BLOOM + BLOSSOM		**BLOOM-DM**	
	Lorc 10 BID	**Pbo**	**Lorc 10 BID**	**Pbo**
Week 24	n=1045	n=936	n=60	n=59
≥ 15 mmHg	10 (1.0)	8 (0.9)	0	0
≥ 20 mmHg	2 (0.2)	2 (0.2)	0	0
≥ 25 mmHg	0	0	0	0
Week 52	n=1210	n=1130	n=65	n=68
≥ 15 mmHg	13 (1.1)	7 (0.6)	0	0
≥ 20 mmHg	4 (0.3)	1 (0.1)	0	0
≥ 25 mmHg	1 (0.1)	0	0	0

Source: NDA 022529, ISS Table 191; BLOOM-DM CSR Table 14.3.72

Two patients treated with lorcaserin 10 mg BID in the pooled non-diabetes trials had PASP values ≥ 50 mmHg. One patient treated with lorcaserin 10 mg QD in the BLOOM-DM trial had PASP values ≥ 60 mmHg (not shown in the table below). This is the same patient with PASP change ≥ 15 mmHg and whose narrative is presented below.

Table 75. Patients with Selected PASP Values, Pooled Phase 3 Trials

	BLOOM + BLOSSOM		BLOOM-DM	
	Lorc 10 BID	**Pbo**	**Lorc 10 BID**	**Pbo**
Week 24	n=1495	n=1281	n=106	n=89
≥ 40 mmHg	3 (0.2)	4 (0.3)	1 (0.9)	1 (1.1)
≥ 50 mmHg	0	0	0	0
≥ 60 mmHg	0	0	0	0
Week 52	n=1838	n=1632	n=84	n=79
≥ 40 mmHg	5 (0.3)	3 (0.2)	0	0
≥ 50 mmHg	2 (0.1)	0	0	0
≥ 60 mmHg	0	0	0	0

Source: NDA 22529, ISS Table 192; BLOOM-DM CSR, Table 14.3.71; reviewer created from datasets

- Patient 1158-S019 (lorcaserin 10 mg QD) was a 66-year-old black female whose PASP in BLOOM-DM was noted to have increased from 25.1 mmHg at baseline to 61.7 mmHg at Week 24 and 76.2 mmHg at Week 52. She had a medical history of diabetes, diabetic neuropathy, hypertension, hyperlipidemia, shortness of breath, breast cancer status post radiation, stable angina, COPD (according to the medical records but apparently not recorded in the study database), chronic gastritis, myocardial infarction (not confirmed by the cardiologist who evaluated her), and endoscopic colonic polyp removal with GI bleed and anemia. Her social history was notable for an approximately 1.5 cigarette pack per day smoking history of unknown duration, and that she stopped working in 2007 due to weakness and fatigue. Concomitant medications included metformin, pioglitazone, glimepiride, aspirin, metoprolol, enalapril, hydrochlorothiazide, atorvastatin, ranitidine, albuterol, calcium, iron, capsaicin cream, naproxen, and nitroglycerin, which was added during study (details are not available). During the trial, the patient experienced adverse events of vertigo (day 76) and anemia related to GI bleed (SAE; day 90). During the hospitalization for the bleed, the patient had a chest X-ray, which demonstrated cardiomegaly and "probable chronic interstitial disease" in part acute due to "pneumonitis versus interstitial edema of the pulmonary artery hypertension". She completed BLOOM-DM. She was referred to a cardiologist after the Week 24 and 52 echocardiogram result was received; these evaluations confirmed the elevated PASP. The consulting cardiologist offered no specific diagnosis or etiology for the elevated PASP and did not recommend any changes to management (other than presumably adding NTG). Of note, after the patient completed the study, she underwent cardiac stress testing, which was positive. Subsequent cardiac catheterization demonstrated coronary artery disease and a pulmonary artery pressure of 60 mmHg. Several months later, the patient underwent coronary artery bypass surgery. She was found in bed deceased a short time thereafter.

5.5.3 Hypoglycemia

Weight loss is associated with improved glycemic control in patients with diabetes mellitus, and drug-related weight loss can contribute to hypoglycemia in patients on medical treatment for diabetes.[36]

[36] Xenical (orlistat) Prescribing Information

Monitoring for hypoglycemia included (1) routine adverse event reporting, (2) glucose self-monitoring using instruments that allowed study personnel to download results, and (3) an interactive voice response system (IVRS) that collected information from patients who suspected that they were experiencing hypoglycemia. The adverse event records include events that were identified using the glucose monitors and events reported through IVRS; however, not all events reported through IVRS were reported as adverse events.

The protocol provided guidance that was intended to standardize adverse event reporting. Events reported through the IVRS system were classified by the study site as adverse events of hypoglycemia if one or more of the following criteria were met:

- self-monitored glucose during the event is ≤ 65 mg/dL; or

- no glucose value is available or self-monitored glucose > 65 mg/dL, AND assistance of another person was required to administer treatment (food, beverage, glucose, glucagon) that leads to resolution of symptoms; or

- any event for which intravenous glucose or parenteral glucagon was administered.

For purposes of adverse event reporting and possible adjustments to anti-hyperglycemic medication doses, the following definitions of hypoglycemic intensity were used:

- Mild/moderate hypoglycemia: capillary glucose < 65 mg/dL that the patient is able to treat himself/herself; or, if glucose is not measured, symptoms of hypoglycemia that resolve within 15 minutes with administration of oral carbohydrates

- Severe hypoglycemia: capillary glucose < 50 mg/dL associated with confusion, loss of consciousness, or seizures; or, in the absence of a glucose determination, confusion, loss of consciousness, or seizures that resolve with the administration of oral carbohydrate, glucagon, or intravenous glucose by another person

- Catastrophic hypoglycemia: severe hypoglycemia that resulted in life-threatening injury to the patient or another person, hospitalization, and/or death; reported as a serious adverse event

During the trial, 113 patients made 537 calls to the IVRS system. One (0.2%) patient treated with lorcaserin 10 mg BID reported the use of an injectable agent to treat the episode (could not be confirmed by the study site). No patient called 911 or reported to a medical facility for treatment of suspected hypoglycemia. Six patients (three lorcaserin BID, two lorcaserin QD, and one placebo) reported that they required the assistance of another person during a suspected hypoglycemic episode; of these, two (one lorcaserin BID, one placebo) reported that they could not have helped themselves. The following table enumerates the severity of hypoglycemia in the IVRS calls.

Table 76. Summary of Patients with IVRS-Reported Suspected Hypoglycemic Events by Protocol-Defined Severity Category

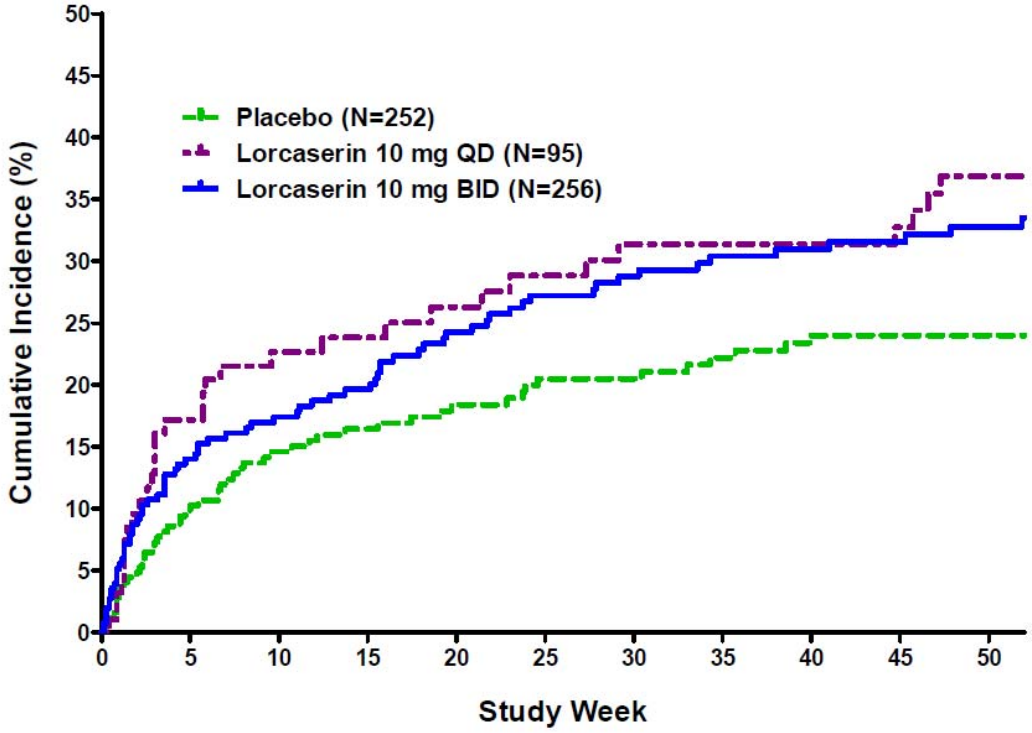
	Lorc 10 BID N=256	**Lorc 10 QD N=95**	**Pbo N=252**
n (%) Patients[a,b]	54 (21.1)	27 (28.4)	32 (12.7)
Severe	3 (5.6)	2 (7.4)	1 (3.1)
Mild/Moderate	36 (66.7)	21 (77.8)	25 (78.1)
Neither severity category[c]	15 (27.8)	4 (14.8)	6 (18.8)
Documented symptomatic	40 (74.1)	23 (85.2)	26 (81.3)
Probable symptomatic	13 (24.1)	4 (14.8)	8 (25.0)
Relative	12 (22.2)	10 (37.0)	11 (34.4)
Subgroup analysis by baseline anti-diabetic agent			
Metformin	14/125 (11.2%)	8/48 (16.7%)	5/123 (4.1%)
SFU (+/- metformin)	40/126 (31.7%)	19/46 (41.3%)	27/125 (21.6%)

a Patients reporting one or more events are counted once in the maximum category across all such events.
b patients reporting one or more events are counted once for each category, and may therefore be counted in multiple categories. As a result, the number of patients in each category may sum to more than the number of patients reporting events.
c Patients in "neither" had reported blood glucose > 65 mg/dL.

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 34

With respect to adverse events of hypoglycemia, the figure below demonstrates the time course of first hypoglycemia events. Hypoglycemia was reported with greater frequency by patients in both lorcaserin groups as compared to the placebo group. The time to event analysis showed a significant difference between placebo and lorcaserin 10 mg BID (p=0.041).

Figure 6. Time to First Event of Hypoglycemia, BLOOM-DM



Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52
Placebo	252	152	94
Lorcaserin 10 mg QD	95	55	35
Lorcaserin 10 mg BID	256	147	88

Source: NDA 022529 Summary of Clinical Safety (resubmission), Figure 3

None of the MedDRA preferred term 'hypoglycaemia' events was reported as a serious adverse event, none led to study withdrawal or study drug discontinuation, and none required treatment by emergency personnel or with parenteral agents. No action was taken for the majority of events in all treatment groups, and all events resolved.

Table 77. Summary of All Adverse Event Terms of 'Hypoglycaemia' and 'Blood Glucose Decreased'

	Lorc 10 BID N=256	**Lorc 10 QD N=95**	**Pbo N=252**
No. (%) patients with PT 'hypoglycaemia'[a]	75 (29.3)	32 (33.7)	53 (21.0)
No. of events with PT 'hypoglycaemia'	523	254	323
Action taken[b]			
None	464 (88.7)	193 (76.0)	233 (72.1)
Took food or beverage	52 (9.9)	60 (23.6)	88 (27.2)
Took concomitant medications	4 (0.8)	0 (0.0)	1 (0.3)
Decreased or stopped diabetic medications	3 (0.6)	1 (0.4)	1 (0.3)
Outcome[b]			
Resolved	523 (100.0)	254 (100.0)	323 (100.0)
Total patients with PT 'blood glucose decreased'[a]	1 (0.4)	3 (3.2)	2 (0.8)
Total events with PT 'blood glucose decreased'	2	59	2
Severity[a,c]			
Mild	59 (23.0)	23 (24.2)	42 (16.7)
Moderate	11 (4.3)	6 (6.3)	10 (4.0)
Severe	4 (1.6)	2 (2.1)	1 (0.4)

a denominator = total number of patients
b denominator = total number of events
c patients reporting one or more adverse events are counted once at the maximum intensity of all adverse events

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 32

In the table above, the 59 events in the lorcaserin 10 mg QD group with 'blood glucose decreased' was noted to come from three patients, all from the same study site (1132). Notably, only three patients in the rest of BLOOM-DM had a total of four such events. The sponsor explained this discrepancy as follows:

> *Site 1132 reported incidents in which the patient reported measured blood glucose of < 70 mg/dL as "low blood glucose," which coded to the preferred term "blood glucose decreased," if the patient reported no associated symptoms of hypoglycemia. If a patient reported blood glucose < 70 mg/dL and concurrent symptoms consistent with hypoglycemia, the site reported a verbatim term of "symptomatic hypoglycemia low blood sugar of <value>," which coded to the preferred term "hypoglycaemia" ... This approach to reporting is the paradigm specified in the protocol, and was designed to distinguish asymptomatic blood glucose values from symptomatic hypoglycemia. Most sites did not follow this paradigm, as illustrated by the presence of asymptomatic events … and the lack of terms coded to "blood glucose decreased."*

Finally, laboratory data were explored for patients who achieved low values during the BLOOM-DM trial. These data are limited because they are only blood glucose values captured during protocol-specified blood draws.

Table 78. Incidence of Low Fasting Plasma Glucose Values During 52 Weeks of Study, BLOOM-DM (Safety Population)

	Lorc 10 BID N=244	Lorc 10 QD N=93	Pbo N=242
< LLN – 55 mg/dL	6 (2.5)	4 (4.3)	4 (1.6)
< 55 – 40 mg/dL	4 (1.7)	1 (1.1)	0
< 40 – 30 mg/dL	0	0	1 (0.4)
< 30 mg/dL	0	0	0

Source: NDA 022529 BLOOM-DM CSR, Table 14.3.145

5.5.4 Psychiatric Safety Issues

5.5.4.1 Perceptual or Dissociative Adverse Events

Lorcaserin is known to possess activity at the 5HT2A receptor. An adverse event profile consistent with 5HT2A activity could include hallucinations, euphoria, and other perceptual or dissociative symptoms.[37] Such adverse events were seen predominantly in the studies in healthy (lower weight) individuals at supratherapeutic doses and were discussed at the original EMDAC meeting.

In contrast to the studies in healthy populations and with therapeutic doses, trials in obese patients demonstrated lorcaserin-associated dissociative adverse events infrequently. The BLOOM-DM trial had a similar overall imbalance between groups as the non-diabetes trials, although some of the imbalance was due to non-specific lorcaserin-associated adverse events, such as paraesthesia and dizziness (Table 79).

In the non-diabetes Phase 3 trials, six patients assigned to lorcaserin 10 mg BID and three assigned to lorcaserin QD reported 'euphoric mood', as compared to one patient assigned to placebo. Euphoric mood tended to occur on Day 1 of dosing, with symptoms generally lasting from one day to one month. In the BLOOM-DM trial, there were no patients with an adverse event of 'euphoric mood'.

In the non-diabetes trials, two patients on lorcaserin reported serious adverse events that were coded as a psychotic episode ('alcoholic psychosis', not included in the table below, and 'acute psychosis'). Adverse events of 'abnormal dreams' occurred at slightly excess frequency in the lorcaserin 10 mg BID group (0.5% of patients) as compared to placebo (0.2%). 'Dissociation' was reported in two patients on lorcaserin 10 mg BID. An adverse event of 'hallucination' in the non-diabetes trials occurred in a patient taking placebo.

In BLOOM-DM, no patients had an adverse event related to psychosis. There was one patient on lorcaserin 10 mg BID and one patient on placebo with an adverse event of 'abnormal dreams'. There were no adverse events of 'dissociation' or 'hallucination'. One patient on placebo had an adverse event of 'paranoia'. There was one serious

[37] Nichols DE. Hallucinogens. Pharmacol Ther 2004 Feb; 101(2): 131-81.

adverse event of ‘conversion disorder’ in the lorcaserin 10 mg BID group. The patient’s narrative is as follows:

- Patient 1187-S021 (lorcaserin 10 mg BID) was a 38-year-old Asian male with a history of diabetes, hyperlipidemia, asthma, and sleep apnea. On Study Day 255, the patient presented to the emergency department complaining of tongue numbness and difficulty chewing. He was noted to have a left side facial paresis, was diagnosed with Bell’s palsy, and prescribed methylprednisolone. The following day the patient was transported to the emergency department for abnormal sensations and rapid tonic-clonic type movements in his upper extremities, in addition to his eyes rolling back in his head and developing an inability to speak. This lasted for approximately 15-20 minutes; there was no loss of consciousness or awareness. The patient was hospitalized for further evaluation. The patient had multiple similar episodes during the hospitalization, with no loss of consciousness, no loss of bowel or bladder function, and no associated neurological dysfunction. Electroencephalogram (EEG) recordings during episodes did not reveal epileptic activity, and medications had no effect on the behavior. Additionally, no acute disease process was identified on CT scan, MRI, or MRA. The patient was diagnosed with psychogenic non-epileptic seizure (MedDRA PT: ‘conversion disorder’). Treatment during hospitalization consisted of diazepam, methylprednisolone, venlafaxine, lorazepam, and desvenlafaxine. The event resolved and study drug was permanently discontinued.

Table 79. Incidence of Potential Perceptual or Dissociative Adverse Events, Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM		BLOOM-DM	
	Lorc 10 BID N=3195	Pbo N=3185	Lorc 10 BID N=256	Pbo N=252
Total Perceptual or Dissociative-Related AEs	659 (20.6)	370 (11.6)	59 (23.0)	39 (15.5)
Total, euphoria-related AEs	283 (8.9)	127 (4.0)	18 (7.0)	16 (6.3)
Dizziness	270 (8.5)	122 (3.8)	18 (7.0)	16 (6.3)
Feeling abnormal	7 (0.2)	3 (0.1)	0	0
Euphoric mood	6 (0.2)	1 (<0.1)	0	0
Dizziness postural	4 (0.1)	1 (<0.1)	1 (0.4)	0
Feeling drunk	2 (0.1)	0	0	0
Feeling of relaxation	0	1 (<0.1)	0	0
Total, perceptual disturbances and psychotomimetic-related effects AEs	99 (3.1)	52 (1.6)	13 (5.1)	6 (2.4)
Paraesthesia	37 (1.2)	15 (0.5)	4 (1.6)	2 (0.8)
Abnormal dreams	16 (0.5)	6 (0.2)	1 (0.4)	1 (0.4)
Hypoaesthesia	13 (0.4)	19 (0.6)	4 (1.6)	2 (0.8)
Confusional state	6 (0.2)	1 (<0.1)	1 (0.4)	0
Disorientation	4 (0.1)	4 (0.1)	0	0
Anger	4 (0.1)	2 (0.1)	0	0
Nightmare	4 (0.1)	1 (<0.1)	0	0
Hypoaesthesia facial	3 (0.1)	1 (<0.1)	0	0
Dysaesthesia	3 (0.1)	0	0	0
Dysarthria	3 (0.1)	0	1 (0.4)	0
Sensory disturbance	2 (0.1)	2 (0.1)	1 (0.4)	0
Paraesthesia oral	2 (0.1)	0	0	0
Hyperaesthesia	2 (0.1)	1 (<0.1)	1 (0.4)	0
Dissociation	2 (0.1)	0	0	0
Aggression	1 (<0.1)	1 (<0.1)	0	0
Speech disorder	1 (<0.1)	1 (<0.1)	0	0
Acute psychosis	1 (<0.1)	0	0	0
Hypoaesthesia eye	1 (<0.1)	0	0	0
Tachyphrenia	1 (<0.1)	0	0	0
Paranoia	0	0	0	1 (0.4)
Hallucination	0	1 (<0.1)	0	0

Source: NDA 022529 ISS Statistical Report, Table S10.1; Summary of Clinical Safety (resubmission), Table 23; reviewer created from datasets

5.5.4.2 Depression and suicidality

5.5.4.2.1 Depression

Major depression, anxiety, or other psychiatric disease requiring treatment with prescription medication (e.g., SSRIs, SNRIs, tricyclics, antipsychotics, lithium) within the past two years in the BLOOM trial and within the past one year in the BLOSSOM and BLOOM-DM trials were exclusion criteria for the lorcaserin program. In the BLOOM-DM trial, 5.8% of patients reported a history of depression or situational depression. This compares to 8.6% of patients in BLOOM and 7.4% of patients in BLOSSOM.

In the non-diabetes trials, 0.8% of patients treated with lorcaserin 10 mg BID group compared with 1.1% of patients treated with placebo initiated antidepressants, and 0.1% of patients treated with lorcaserin 10 mg BID versus < 0.1% of patients treated with placebo increased their doses of anti-depressants during 52 weeks of treatment. In BLOOM-DM, 2.0% of patients treated with lorcaserin 10 mg BID and 2.4% of patients treated with placebo were on antidepressant medications at any time during the trial, despite the protocol requirement that the use of bupropion, SSRIs, SNRIs, tricyclics, and MAOIs were not permitted by study participants.

Beck Depression Inventory-II

Depression in the Phase 3 program was evaluated with standard adverse event reporting, and prospectively with the Beck Depression Inventory-II (BDI-II).[38] The BDI-II is a widely used self-report instrument for determining the severity of depression. Numerous published studies have shown that weight loss in obese patients is associated with mean improvements in the BDI total score, in patients treated with diet and exercise,[39] pharmacotherapy,[39] and bariatric surgery.[40]

The 21 items evaluated by this instrument are as follows:

1. Sadness
2. Pessimism
3. Past failure
4. Loss of pleasure
5. Guilty feelings
6. Punishment feelings
7. Self-dislike
8. Self-criticalness
9. Suicidal thoughts or wishes
10. Crying
11. Agitation
12. Loss of interest
13. Indecisiveness
14. Worthlessness
15. Loss of energy
16. Changes in sleeping pattern
17. Irritability
18. Changes in appetite
19. Concentration difficulty

[38] Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory (BDI-II). 2nd ed. San Antonio, TX: The Psychological Association; 1996.
[39] Faulconbridge LF, et al. Changes in symptoms of depression with weight loss: results of a randomized trial. Obesity 2009 May; 17(5): 1009-16.
[40] Hayden MJ, et al. Characterization of the improvement in depressive symptoms following bariatric surgery. Obes Surg. 2010 Jun 18. [Epub ahead of print]

20. Tiredness or fatigue
21. Loss of interest in sex

Each item is ranked 0, 1, 2, or 3 to indicate the degree of severity, with 3 being the most severe. A total score of 0-13 is considered normal or minimal depression, 14-19 corresponds to mild depression, 20-28 corresponds to moderate depression, and 29-63 corresponds to severe depression.[38] Special attention was paid to question 9 (Suicidal Thoughts or Wishes), and the results of this analysis are presented separately.

Patients with a total score on the BDI-II ≥ 20 or a score > 0 on question 9 at baseline were excluded from all three trials.

The BDI-II was administered at screening and Weeks 4, 12, 24, 36, and 52/exit in the BLOOM trial and at screening and Weeks 4, 24, and 52/exit in the BLOSSOM and BLOOM-DM trials.

BDI-II total score results were evaluated by mean and categorical changes.

As Table 80 shows, BDI-II mean total score decreased in both treatment groups and with no statistically significant difference between lorcaserin and placebo. Baseline BDI-II scores were lower than what has been previously described in obesity trials.[39,40]

Table 80. Mean Change in BDI-II Score, Week 52 LOCF, Phase 3 Trials

	Treatment	N	Baseline Mean (SD)	Week 52 Mean (SD)	Change from Baseline LS Mean (95% CI)	Difference in LS Means (95% CI)	p-value
BLOOM + BLOSSOM	Lorc 10 BID	2981	4.1 (4.13)	3.2 (4.47)	-0.92 (-1.07, -0.78)	-0.08 (-0.29, 0.13)	0.453
	Pbo	2905	4.1 (4.06)	3.2 (4.45)	-0.84 (-0.99, -0.69)		
BLOOM-DM	Lorc 10 BID	250	4.4 (4.27)	4.2 (5.30)	-0.09 (-0.71, 0.53)	0.17 (-0.61, 0.95)	0.669
	Pbo	242	4.0 (3.57)	3.8 (4.15)	-0.26 (-0.90, 0.37)		

Source: NDA 022529 ISS Statistical Report, Table S18.3; BLOOM-DM CSR, Table 14.3.24

Categorical assessments of the BDI-II total score were also undertaken, using the definitions for depression severity as described above. The categorical results were evaluated at Week 52, and found a small increase in the proportion of patients with "severe" depression at Week 52 in the lorcaserin 10 mg BID group vs. placebo. A similar trend for mild and moderate depression was noted only in the BLOOM-DM trial. The majority of patients scored in the lowest depression category (0-13).

Table 81. Summary of Categorical BDI-II Total Score at Week 52 (LOCF), Phase 3 Trials

	BLOOM		BLOSSOM		BLOOM-DM	
	Lorc 10 BID	**Pbo**	**Lorc 10 BID**	**Pbo**	**Lorc 10 BID**	**Pbo**
Severe Depression (score: 29 – 63)	4 (0.3%)	2 (0.1%)	6 (0.4%)	2 (0.1%)	2 (0.8%)	0
Moderate Depression (score: 20 – 28)	15 (0.9%)	19 (1.2%)	9 (0.6%)	15 (0.9%)	4 (1.6%)	1 (0.4%)
Mild Depression (score: 14 – 19)	35 (2.2%)	35 (2.2%)	40 (2.5%)	36 (2.3%)	8 (3.2%)	5 (2.0%)
None to Minimal Depression (score: 0 – 13)	1423 (89.3%)	1372 (86.6%)	1455 (90.8%)	1433 (89.5%)	236 (94.4%)	238 (97.5%)
Unknown	116 (7.3%)	156 (9.9%)	92 (5.7%)	115 (7.2%)	-	-

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7 (BLOOM + BLOSSOM); reviewer created from datasets (BLOOM-DM)

Because the appetite item subscore on the BDI-II may be related to the mechanism of action of lorcaserin, this item was explored separately. As expected, lorcaserin was associated with greater decreases in appetite. Conversely, reports of greater appetite/food cravings, which can also be an indicator of depression, were generally not seen more frequently in the lorcaserin group as compared to the placebo group, although there were a few more patients in the lorcaserin group than placebo who reported much greater appetite/food cravings in the BLOOM-DM trial.

Table 82. Summary of Categorical BDI-II, Item 18 (Highest Score after Baseline), Phase 3 Trials

	BLOOM		BLOSSOM		BLOOM-DM	
	Lorc 10 BID	**Pbo**	**Lorc 10 BID**	**Pbo**	**Lorc 10 BID**	**Pbo**
No appetite at all (score=3A)	3 (0.2%)	5 (0.3%)	6 (0.4%)	2 (0.1%)	0	0
Appetite is much less (score=2A)	268 (16.8%)	126 (8.0%)	274 (17.1%)	138 (8.6%)	38 (15.2%)	21 (8.6%)
Appetite is somewhat less (score=1A)	857 (53.8%)	685 (43.2%)	818 (51.1%)	760 (47.5%)	129 (51.6%)	122 (50.0%)
No Appetite change (score=0)	336 (21.1%)	580 (36.6%)	395 (24.7%)	540 (33.7%)	60 (24.0%)	71 (29.1%)
Appetite is somewhat greater (score=1B)	13 (0.1%)	27 (1.7%)	16 (1.0%)	42 (2.6%)	15 (6.0%)	25 (10.2%)
Appetite is much greater (score=2B)	1 (0.1%)	2 (0.1%)	1 (0.1%)	1 (0.1%)	6 (2.4%)	4 (1.6%)
Crave food all the time (score=3B)	0 (0%)	4 (0.3%)	1 (0.1%)	3 (0.2%)	2 (0.8%)	1 (0.4%)
Unknown	115 (7.2%)	155 (9.8%)	91 (5.7%)	115 (7.2%)	-	-

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7 (BLOOM + BLOSSOM); reviewer created from datasets (BLOOM-DM)

Adverse Events

As an additional assessment of the potential for lorcaserin to cause depression, the sponsor evaluated the adverse event database for depression-related adverse events by using the standardized MedDRA query (SMQ) for depression.[41] The following preferred terms were used in the search; the bolded items were those found in the lorcaserin database:

[41] Medical Dictionary for Regulatory Activities (MedDRA), version 13.0

Table 83. Standardized MedDRA Queries (Narrow and Broad) for Depression

Narrow PTs	Broad PTs
Activation syndrome	**Affect lability**
Adjustment disorder with depressed mood	Alcohol abuse
Adjustment disorder with mixed anxiety and depressed mood	Alcohol problem
Agitated depression	Alcohol rehabilitation
Anhedonia	Alcoholism
Antidepressant therapy	**Apathy**
Childhood depression	Blunted affect
Decreased interest	Constricted affect
Depressed mood	**Crying**
Depression	**Disturbance in attention**
Depression postoperative	Drug abuse
Depressive symptom	Drug abuser
Dysphoria	Drug dependence
Dysthymic disorder	Drug dependence, antepartum
Electroconvulsive therapy	Drug dependence, postpartum
Feeling guilty	**Dyssomnia**
Feeling of despair	Emotional distress
Feelings of worthlessness	**Hypersomnia**
Major depression	Hyposomnia
Menopausal depression	Impaired self-care
Postpartum depression	**Initial insomnia**
	Intentional drug misuse
	Listless
	Maternal use of illicit drugs
	Memory impairment
	Middle insomnia
	Mood altered
	Mood swings
	Morose
	Negative thoughts
	Neglect of personal appearance
	Polysubstance dependence
	Poor quality sleep
	Psychomotor hyperactivity
	Psychomotor retardation
	Psychosocial support
	Psychotherapy
	Self esteem decreased
	Substance abuse
	Substance abuser
	Tearfulness
	Terminal insomnia

Source: MedDRA 13.0 Browser version 3.0.1

As seen in Table 84, there was a slightly higher percentage of narrow depression terms in the lorcaserin groups versus placebo in BLOOM-DM trial as compared to the non-diabetes population, in which the incidence of narrow depression was similar between groups. The broadened terms that could be related to depression, such as sleep disturbance and psychomotor changes, led to an imbalance in the lorcaserin 10 mg BID group as compared to placebo in all Phase 3 trials. There were fewer of these events overall in BLOOM-DM.

Table 84. Incidence of Depression, Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**
Depression, Narrow SMQ	81 (2.5)	17 (2.1)	78 (2.4)	9 (3.5)	5 (5.3)	6 (2.4)
Depression	59 (1.8)	9 (1.1)	53 (1.7)	6 (2.3)	5 (5.3)	5 (2.0)
Depressed mood	20 (0.6)	7 (0.9)	23 (0.7)	2 (0.8)	0	0
Depressive symptom	2 (0.1)	0	1 (<0.1)	0	0	0
Decreased interest	1 (<0.1)	0	0	0	0	1 (0.4)
Dysthymic disorder	0	1 (0.1)	0	0	0	0
Feeling of despair	0	0	1 (<0.1)	0	0	0
Major depression	0	0	1 (<0.1)	1 (0.4)	0	0
Depression, Broad SMQ	86 (2.7)	15 (1.9)	44 (1.4)	3 (1.2)	1 (1.1)	1 (0.4)
Memory impairment	22 (0.7)	0	5 (0.2)	2 (0.8)	0	0
Disturbance in attention	20 (0.6)	2 (0.2)	9 (0.3)	1 (0.4)	0	0
Initial insomnia	13 (0.4)	2 (0.2)	4 (0.1)	0	0	0
Hypersomnia	7 (0.2)	0	3 (0.1)	0	0	0
Crying	6 (0.2)	0	4 (0.1)	0	0	0
Mood swings	5 (0.2)	2 (0.2)	5 (0.2)	0	0	0
Mood altered	5 (0.2)	1 (0.1)	0	0	0	0
Affect lability	4 (0.1)	1 (0.1)	1 (<0.1)	0	0	0
Psychomotor hyperactivity	3 (0.1)	2 (0.2)	0	0	0	0
Poor quality sleep	3 (0.1)	1 (0.1)	4 (0.1)	0	0	0
Apathy	2 (0.1)	1 (0.1)	3 (0.1)	0	0	0
Psychomotor retardation	2 (0.1)	0	0	0	0	0
Terminal insomnia	1 (<0.1)	2 (0.2)	3 (0.1)	0	0	0
Middle insomnia	1 (<0.1)	0	5 (0.2)	0	1 (1.1)	0
Substance abuse	0	1 (0.1)	0	0	0	0
Dyssomnia	0	0	1 (<0.1)	0	0	0
Tearfulness	0	0	0	0	0	1 (0.4)
Total Narrow + Broad	155 (4.9)	25 (3.1)	115 (3.6)	12 (4.7)	6 (6.3)	7 (2.8)

Source: NDA 022529 ISS Statistical Report, Table S09.1; Response to FDA Questions from 16 July 2010 email, Table 2; Summary of Clinical Safety (resubmission), Table 24

There was one serious adverse event of depression in BLOOM-DM, in a patient treated with lorcaserin 10 mg QD:

- Patient 1147-S040 (lorcaserin 10 mg QD) was a 57-year-old Asian female with a history of diabetes, headaches, short term memory loss, and depression. On Study Day 132, the patient was admitted to the hospital with complaints of a near-syncopal event. During the hospitalization, the evaluation focused on the long-standing memory loss and depression that appeared to underlie the patient's other complaints. On Study Day 134, the event of depression resolved and the patient was discharged from the hospital with the diagnosis of pseudodementia secondary to severe depression. According to the MedWatch form: "The primary investigator felt the syncopal episode was due to the depression which caused an autonomic imbalance making the patient prone to vasovagal attacks…. The neurologist felt the memory loss was secondary to depression … He did not feel there was any significant

underlying dementia." The patient was prescribed venlafaxine for depression and withdrew from the study due to the event of depression.

Patients treated with lorcaserin 10 mg BID were more likely to discontinue drug due to depression-related adverse events. In the pooled non-diabetes trials, 1.3% of patients discontinued drug due to depression-related adverse events in the lorcaserin 10 mg BID group as compared to 0.8% of patients in the placebo group. In BLOOM-DM, 1.2% of patients in the lorcaserin 10 mg BID group and no patients in the placebo group discontinued drug due to depression-related adverse events.

Depression in Subgroups

Some studies have suggested that patients with obesity are at a higher risk for depression,[42] with a particularly consistent relationship in women.[43,44] (This is supported by the baseline incidence of depression in the Phase 3 database: 8.6% of women and 4.7% of men in the pooled Phase 3 trials, and 7.3% of women and 4.0% of men in BLOOM-DM, reported a past medical history of depression.) When evaluating the results from the pooled non-diabetes trials and BLOOM-DM together, there is a suggestion of an excess in depression-related adverse events with lorcaserin treatment in females only. The opposite was seen for males (Table 85).

The lorcaserin database did not suggest that higher weight individuals within this patient population were at higher risk overall for developing depression over the course of the study (Table 85). The results do suggest that that the incidence of depression in the lorcaserin 10 mg BID group may be greater than placebo at the lowest body weight, possibly reflecting greater drug exposure.

Table 85. Depression, Narrow SMQ by Weight Quartile and Sex, Pooled Phase 3 Trials and BLOOM-DM (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID	**Lorc 10 QD**	**Pbo**	**Lorc 10 BID**	**Lorc 10 QD**	**Pbo**
Female	73 (2.8)	16 (2.4)	62 (2.4)	6 (4.4)	4 (7.5)	2 (1.5)
Male	8 (1.4)	1 (0.7)	16 (2.6)	3 (2.5)	1 (2.4)	4 (3.5)
Q1 (lowest)	27 (3.4)	2 (0.9)	18 (2.3)	2 (3.3)	2 (9.1)	0
Q2	18 (2.3)	6 (2.8)	24 (3.0)	1 (1.5)	1 (6.3)	1 (1.5)
Q3	20 (2.5)	3 (1.7)	17 (2.1)	4 (5.6)	1 (3.7)	4 (7.4)
Q4 (highest)	16 (2.0)	6 (3.0)	19 (2.5)	2 (3.5)	1 (3.3)	1 (1.6)

Source: NDA 022529 ISS, Table 215; ISS Statistical Report, Tables S20.1 and S20.2; Summary of Clinical Safety (resubmission), Tables 44 and 48

[42] Simon GE, Von Korff M, Saunders K, et al. Association between obesity and psychiatric disorders in the US adult population. Arch Gen Psychiatry. 2006; 63(7): 824–30.
[43] Carpenter KM, Hasin DS, Allison DB, et al. Relationships between obesity and DSM-IV major depressive disorder, suicide ideation, and suicide attempts: results from a general population study. Am J Public Health. 2000; 90(2): 251–7.
[44] Heo M, Pietrobelli A, Fontaine KR, et al. Depressive mood and obesity in US adults: comparison and moderation by sex, age, and race. Int J Obes (Lond). 2006; 30(3): 513–9.

5.5.4.2.2 Suicidality

Centrally-acting drugs used to treat obesity may be associated with an increased risk for suicidality.[45,46] In recent years, FDA has worked with companies to ensure assessment of suicidality in clinical trials, preferably using the prospective instrument, the Columbia-Suicide Severity Rating Scale (C-SSRS).[47] A retrospective scale by the same research group, the Columbia-Classification Algorithm for Suicide Assessment (C-CASA), was initially designed to evaluate the risk of suicidality in children and adolescents taking anti-depressants,[48] and is recommended by FDA for those obesity development programs that have not implemented C-SSRS.

The development program for lorcaserin was already underway when the C-SSRS recommendation became standard in obesity programs, and therefore, the C-SSRS was not implemented. Suicidality was evaluated in the lorcaserin trials prospectively using the suicide question in the BDI-II (question 9), as well as retrospectively by reviewing the adverse event database. The sponsor used a modified application of C-CASA to retrospectively assess their adverse event database for suicidal events.

Question 9 on the BDI-II specifically asked patients to rate their degree of suicidal thoughts or wishes on the following scale:

0 I don't have any thoughts of killing myself
1 I have thoughts of killing myself, but I would not carry them out
2 I would like to kill myself
3 I would kill myself if I had the chance

The following rating scale for adverse events related to suicidality was modified from the original C-CASA scale:

1 Completed suicide
2 Suicide Attempt: Self- injurious behavior associated with some intent to die. Intent can be stated or inferred by rater. No injury needed.
3 Preparatory Acts Towards Imminent Suicidal Behavior: Person takes steps to injure self but is stopped by self or other. Intent to die is either stated or inferred.
4 Self-Injurious Behavior: Self- injurious behavior where associated intent to die is unknown and cannot be inferred.
5 Suicidal Ideation: Passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior.
6 Not Enough Information

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[45] FDA EMDAC Briefing Document, NDA 21888 (rimonabant for obesity), 2007. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-backgrounder.pdf Accessed 12 Aug 2010.

[46] FDA EMDAC Briefing Document, NDA 22580 (Qnexa for obesity), 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM218824.pdf Accessed 12 Aug 2010.

[47] Developed by K. Posner, et al.

[48] Posner K, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007; 164(7): 1035-43.

In BLOOM, the majority of suicidality ratings were based on the BDI-II question 9 results and the adverse events that were reported for these BDI-II results. Two events of suicidal behavior, 'suicide attempt' (lorcaserin group) and 'intentional overdose' (lorcaserin/placebo group in the second year, while on placebo) were reported as adverse events independent of BDI-II administration. With the exception of two patients, all positive responses on question 9 in the BLOOM trial were = "1" (I have thoughts of killing myself, but I would not carry them out). Patient 145-S044 (lorcaserin/placebo; serious adverse event of 'intentional overdose') responded "2" (I would like to kill myself) at the early termination visit, and patient 188-S039 (lorcaserin/placebo) responded "3" (I would kill myself if I had the chance) at the Year 2 termination visit. Patient 188-S039 had no adverse events, and declined to discuss her response of "3" other than to state that she did not intend to harm herself. All modified C-CASA suicidality scores related to BDI-II responses were "5" (Suicidal Ideation: Passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior) with the exception of the two patients who engaged in self-injurious behavior [both with scores of "2" (Suicide Attempt: Self-injurious behavior associated with some intent to die)]. These events were reported as serious adverse events.

In BLOSSOM and BLOOM-DM, all patients with adverse events of suicidal ideation had a positive BDI-II question 9 score. All positive BDI-II scores were = "1" (thoughts of killing self) and all modified C-CASA ratings were coded by the investigators as "5" (passive ideation).

The following table is a summary of patients in the Phase 3 program with positive scores to question 9 as well as those with suicidal behaviors:

Table 86. Summary of Suicidal Scores (BDI-II) and Adverse Events, Phase 3 Trials

	BLOOM + BLOSSOM			**BLOOM-DM**			**All Phase 3 Trials**	
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**	**Lorc 10 BID N=3451**	**Pbo N=3437**
Post-baseline BDI-II Q9 ≥ 1	34 (1.1)	6 (0.7)	28 (0.9)	3 (1.2)	2 (2.1)	1 (0.4)	37 (1.1)	29 (0.8)
Post-baseline BDI-II Q9 ≥ 1, excl. pts with BL Q9 ≥ 1	30/3188 (0.9)	6/801 (0.7)	27/3184 (0.8)	3/256 (1.2)	2/95 (2.1)	1/252 (0.4)	33/3444 (1.0)	28/3436 (0.8)
AEs of suicidal behavior	1 (<0.1)	0	1 (<0.1)*	0	0	0	1 (<0.1)	1 (<0.1)*
* One patient in the BLOOM trial attempted suicide while on placebo in Year 2; she had been assigned to lorcaserin during Year 1								

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 27; Response to FDA Questions from 23 March 2010 email

5.5.5 Neurological Safety Issues

5.5.5.1 Cognitive effects

Centrally-acting obesity drugs of a variety of mechanisms have been found to possess neuropsychiatric effects, including adverse effects on cognition.[49] The 5HT2A receptor is thought to play a role in cognition and memory, and alterations in 5HT2A receptor signaling are implicated in the cognitive dysfunction seen in disorders such as schizophrenia and depression.[37,50] Cognitive tests conducted in the early phase trials were generally unrevealing. In a 14-day study with doses of lorcaserin up to 20 mg, some evidence for impairment to Numeric Working Memory – Speed was seen with the 20 mg dose. However, there was not a clear dose effect, nor was there supportive evidence for effects on Numeric Working Memory – Sensitivity Index, Spatial Working Memory, or other reaction time measures. The clinical relevance of this finding is unclear, although impairment in working memory is consistent with 5HT2A activation.[50]

An exploratory analysis of cognitive impairment in the Phase 3 trials using the MedDRA Dementia SMQ was conducted. Because this SMQ contains a broader list of preferred terms than might be appropriate for this relatively young patient population, it was modified to include the following terms (e.g., PTs related to the behavioral sequelae of dementia were removed); those PTs found in the lorcaserin Phase 3 database are bolded:

[49] Nathan PJ, et al. Neuropsychiatric adverse effects of centrally acting obesity drugs. CNS Neurosci Ther 2011 Oct; 17(5): 490-505.

[50] Williams GV, et al. The physiological role of 5-HT_{2A} receptors in working memory. J Neurosci 1 Apr 2002; 22: 2843-2854.

Table 87. MedDRA Preferred Terms of Interest Related to Cognitive Function

Modified Dementia SMQ	Additional Cognitive Preferred Terms of Interest
Activities of daily living impaired	**Disturbance in attention**
Agnosia	**Dysphasia**
Amnesia	**Psychomotor retardation**
Amnestic disorder	
Anterograde amnesia	
Aphasia	
Apraxia	
Borderline mental impairment	
Change in sustained attention	
Cognitive disorder	
Confusional state	
Dementia	
Disorientation	
Executive dysfunction	
Intelligence test abnormal	
Judgement impaired	
Learning disability	
Learning disorder	
Memory impairment	
Mental disorder	
Mental impairment	
Mental status changes	
Mini mental examination abnormal	
Neuropsychological test abnormal	
Speech disorder	
Symbolic dysfunction	
Thinking abnormal	

Source: Reviewer generated from MedDRA 13.0 Browser version 3.0.1

Table 88 demonstrates that patients in the lorcaserin 10 mg BID treatment group reported these cognitive adverse events more frequently than those in the lorcaserin 10 mg QD or placebo groups; this table has been updated with the new data from BLOOM-DM, which, although having fewer events, is consistent with the original NDA's finding.

Table 88. Cognitive-Related Adverse Events, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Total Cognitive-Related AEs	76 (2.4)	7 (0.9)	24 (0.8)	5 (2.0)	0	1 (0.4)
Memory impairment	22 (0.7)	0	5 (0.2)	2 (0.8)	0	0
Disturbance in attention	20 (0.6)	2 (0.2)	9 (0.3)	1 (0.4)	0	0
Amnesia	16 (0.5)	2 (0.2)	3 (0.1)	1 (0.4)	0	1 (0.4)
Confusional state	6 (0.2)	2 (0.2)	1 (<0.1)	1 (0.4)	0	0
Disorientation	4 (0.1)	1 (0.1)	4 (0.1)	0	0	0
Mental impairment	4 (0.1)	0	0	0	0	0
Aphasia	2 (0.1)	0	2 (0.1)	0	0	0
Cognitive disorder	2 (0.1)	0	0	0	0	0
Psychomotor retardation	2 (0.1)	0	0	0	0	0
Speech disorder	1 (<0.1)	0	1 (<0.1)	0	0	0
Apraxia	1 (<0.1)	0	0	0	0	0
Dysphasia	1 (<0.1)	0	0	0	0	0
Mental disorder	1 (<0.1)	0	0	0	0	0

Source: Reviewer created from datasets

In the BLOOM-DM trial, the adverse events of 'disturbance in attention' and 'confusional state' led to drug discontinuation. None of these adverse events were considered serious.

The preferred term 'amnesia' was discussed at the original EMDAC meeting. There were two adverse events of 'amnesia' in BLOOM-DM, one in a patient treated with lorcaserin 10 mg BID (verbatim term: 'increased memory loss') and one in a patient treated with placebo (verbatim term: 'short term memory loss'). Neither patient discontinued due to this adverse event.

5.5.5.2 Paraesthesia

In the original submission, paraesthesia was seen more frequently in lorcaserin-treated groups than in those treated with placebo, particularly in early-phase supratherapeutic doses. In the first year of the pooled Phase 3 trials (non-diabetes), 1.2% of patients treated with lorcaserin 10 mg BID and 0.5% of patients treated with placebo had adverse events of parasthesia ('paraesthesia' and 'paraesthesia oral'). In BLOOM-DM, 1.6% of patients treated with lorcaserin 10 mg BID and 0.8% of patients treated with placebo had adverse events of paresthesia.

5.5.5.3 Dizziness

Dizziness was frequently reported with lorcaserin use, and included such verbatim terms in the Phase 3 dataset as 'dizziness', 'lightheadedness', and 'wooziness'. Dizziness was dose-related, with a large proportion of the events occurring on the first day of dosing. In the single-dose studies, the peak incidence occurred 1 to 4 hours after dosing.

In the first year of the pooled Phase 3 trials (non-diabetes), 8.5% of patients treated with lorcaserin 10 mg BID and 3.9% of patients treated with placebo had adverse events of dizziness. Conversely, in the BLOOM-DM trial, 7.0% of patients treated with lorcaserin 10 mg BID versus 6.3% of patients treated with placebo had an adverse event of dizziness (PT: 'dizziness', 'dizziness postural', or 'dizziness exertional').

Original NDA data suggested that lower weight patients and women are more susceptible to lorcaserin-related dizziness, although this trend was not noted in the BLOOM-DM trial.

5.5.5.4 Headache

Headache was frequently reported with lorcaserin use, and was dose-related. In the single-dose studies, the peak incidence occurred 4 to 12 hours after dosing.

The incidence of headache in the BLOOM-DM trial (14.5% lorcaserin 10 mg BID vs. 7.1% placebo) was consistent with that seen in the pooled non-diabetes trials (16.8% lorcaserin 10 mg BID vs. 10.1% placebo).

Discontinuations due to headache in the Phase 3 trials were seen slightly more frequently in the lorcaserin 10 mg BID (1.3%) group than the placebo (0.8%) group. There was only one discontinuation due to headache in BLOOM-DM, in a patient randomized to lorcaserin 10 mg BID.

5.5.6 Carcinogenicity

In the original submission, concern arose over the results of two-year carcinogenicity studies in rats, in which lorcaserin was associated with mammary gland tumors in both sexes at clinically relevant exposures. Other tumor types (astrocytoma, schwannoma, hepatocellular carcinoma and adenoma, squamous cell carcinoma and benign fibroma of skin, and benign follicular cell adenoma of the thyroid) were also seen in male rats at higher doses. As part of the activities for the complete response, all mammary and lung tissues from the female rat carcinogenicity study were re-adjudicated by a panel of five veterinary pathologists, who read the tissues in a blinded fashion. Please see Dr. Fred Alavi's review for details of the animal findings. It is noted that the re-adjudicated data showed a numerically lower incidence of mammary adenocarcinoma in low- and mid-dose female rats than had been shown previously; a significant increase in mammary adenocarcinoma was seen only at the high dose of 100 mg/kg/day, providing a 24-fold exposure margin for the dose at which no increase in mammary adenocarcinoma was observed (30 mg/kg/day). However, benign mammary fibroadenoma was increased by lorcaserin at all doses tested, and the sponsor believes that these findings are secondary to increased prolactin stimulation of the mammary tissue.

Overall, malignancies were seen infrequently in the Phase 3 program; see Table 89 for an updated table including the BLOOM-DM data (reviewer pooled with BLOOM and BLOSSOM); the second year data from the BLOOM trial is reproduced from the original briefing document. No formal cancer screening was conducted.

Table 89. Neoplasms (MedDRA Malignant or unspecified tumours SMQ), BLOOM, BLOSSOM, and BLOOM-DM

	Lorc 10 BID N=3451	Lorc 10 QD N=896	Pbo N=3437
Total	24 (0.8)	6 (0.7)	35 (1.0)
Basal cell carcinoma	4 (0.1)	2 (0.2)	7 (0.2)
Breast cancer	4 (0.1)	0	4 (0.1)
Thyroid neoplasm	3 (0.1)	1 (0.1)	5 (0.1)
Prostate cancer	2 (0.1)	2 (0.2)	3 (0.1)
Lung adenocarcinoma	2 (0.1)	0	0
Multiple myeloma	2 (0.1)	0	0
Breast cancer in situ	1 (<0.1)	1 (0.1)	0
Squamous cell carcinoma	1 (<0.1)	1 (0.1)	2 (0.1)
Lung neoplasm	1 (<0.1)	0	1 (<0.1)
Malignant melanoma	1 (<0.1)	0	1 (<0.1)
Carcinoid tumour	1 (<0.1)	0	0
Nasopharyngeal cancer	1 (<0.1)	0	0
Neuroendocrine carcinoma	1 (<0.1)	0	0
Rectal neoplasm	1 (<0.1)	0	0
Skin cancer	1 (<0.1)	0	1 (<0.1)
Bladder cancer	0	0	3 (0.1)
Bladder transitional cell carcinoma stage I	0	0	1 (<0.1)
Dysplastic naevus syndrome	0	0	1 (<0.1)
Metastatic squamous cell carcinoma	0	0	1 (<0.1)
Ocular neoplasm	0	0	1 (<0.1)
Parathyroid tumour	0	0	1 (<0.1)
Transitional cell carcinoma	0	0	1 (<0.1)
Endometrial cancer	0	0	1 (<0.1)
Oesophageal cancer	0	0	1 (<0.1)
Urethral cancer	0	0	1 (<0.1)

Source: Reviewer created from datasets

Table 90. Neoplasms (MedDRA Malignant or unspecified tumours SMQ), BLOOM Year 2

	Lorc/Lorc N=573	Lorc/Pbo N=283	Pbo/Pbo N=697
Total	4 (0.7)	4 (1.4)	7 (1.0)
Basal cell carcinoma	2 (0.3)	3 (1.1)	5 (0.7)
Thyroid neoplasm	2 (0.3)	0	1 (0.1)
Breast cancer	0	1 (0.4)	0
Colon cancer	0	1 (0.4)	0
Prostate cancer	0	1 (0.4)	0
Skin cancer	0	1 (0.4)	0
Malignant melanoma	0	0	1 (0.1)
Papillary thyroid cancer	0	0	1 (0.1)
Squamous cell carcinoma	0	0	1 (0.1)

Source: Reviewer created from datasets

5.5.6.1 Breast Cancer and Prolactin

The sponsor suggests that the mammary neoplasm findings in rats can be attributed to lorcaserin-stimulated prolactin release. Prolactin has been shown to cause mammary gland tumors in rodents and promote growth of normal and malignant breast cells *in vitro*.[51] Dr. Alavi's review will address the sponsor's support for attributing lorcaserin-induced increases in mammary tumors to prolactin. The relationship of prolactin to human breast carcinogenesis is unknown. Because it was noted that lorcaserin increased prolactin concentrations after single doses in a Phase 1 trial, the sponsor was asked to conduct an evaluation of chronic prolactin release in the Phase 3 program.

In the lorcaserin Phase 3 trials the potential relevance of the rat findings of mammary tumors was evaluated by adverse event reporting of breast neoplasia and prolactin measurement in the BLOSSOM and BLOOM-DM trials.

5.5.6.1.1 Breast neoplasms

Over the two years of the Phase 3 trials (BLOOM and BLOSSOM), seven women randomized to lorcaserin 10 mg BID, one woman randomized to lorcaserin 10 mg QD, and five women randomized to placebo were diagnosed with a breast neoplasm, as shown in Table 91. No patient in the BLOOM-DM trial had a diagnosis of breast cancer.

[51] Reviewed in: Hankinson SE, et al. Plasma prolactin levels and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Instit 1999 Apr; 91(7): 629-34.

Table 91. Breast Neoplasms, Phase 3 Trials, Years 1 and 2

Treatment	Study	ID	Age (yr)	Race	Study Day	AE Term	SAE?	Relevant Medical History
Lorc 10 BID	BLOOM	117-S033	52	White	287	Ductal carcinoma in situ	No	
		122-S109	44	Hispanic	294	Atypical ductal hyperplasia	Yes	
		146-S015	59	White	89	Left breast cancer	No	Fibroglandular pattern of the corpora of both breasts
		170-S005	60	White	401	Tubular cancer, left breast	No	Fibrocystic breast disease
		196-S018	40	White	84	Breast cancer	No	Thyroid cancer
	BLOSSOM	2105-S070	61	White	161	Breast cancer	Yes	Left breast cyst
		2270-S040	36	White	116	Breast cancer	Yes	
Mean			**50.3 yrs**		**204.6 days**			
Lorc 10 QD	BLOSSOM	2141-S039	49	White	361	Ductal carcinoma in situ	No	
Placebo	BLOOM	113-S228	53	White	33	Breast cancer	Yes	
		119-S064	55	Hispanic	336	Invasive ductal carcinoma with mucinous differentiation	Yes	Breast cancer of right breast; lymphedema of right arm; breast lumps
		139-S043	45	Black	10	Left breast cancer	Yes	
		161-S087	52	White	1	Breast cancer	No	
	BLOSSOM	2203-S032	55	Black	247	Intraductal papilloma of breast	No	Right breast microcalcifications
Mean			**52.0 yrs**		**125.4 days**			

Source: NDA 22529, ISS Table 60

The sponsor also presented the breast tumor data from the Phase 3 trials combined as time-to-event using Kaplan-Meier curves, and as incidence per patient-year, summarized by treatment arm as well as by 'any lorcaserin dose' vs. placebo.

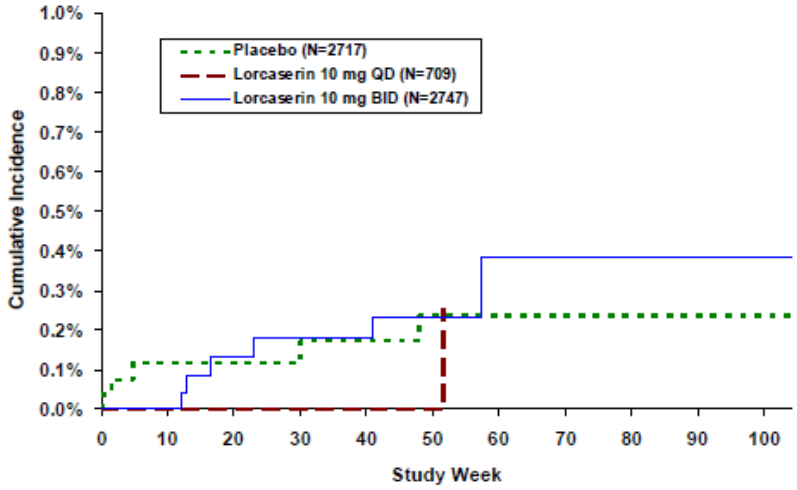
The sponsor conducted two searches: the first was based on the MedDRA SMQ, 'breast neoplasm', which is a list of preferred terms that fit into categories of malignant tumors of the breast (e.g., 'breast cancer', 'breast sarcoma', 'inflammatory carcinoma of the breast', 'mastectomy', etc.) and breast tumors of unspecified malignancy (e.g., 'breast lump removal', 'breast neoplasm', 'nipple neoplasm', etc.). The adverse event term in Table 91 above, 'atypical ductal hyperplasia', mapped to 'breast mass', so it was not included in this search. Table 92 and Figure 7 below demonstrate these findings.

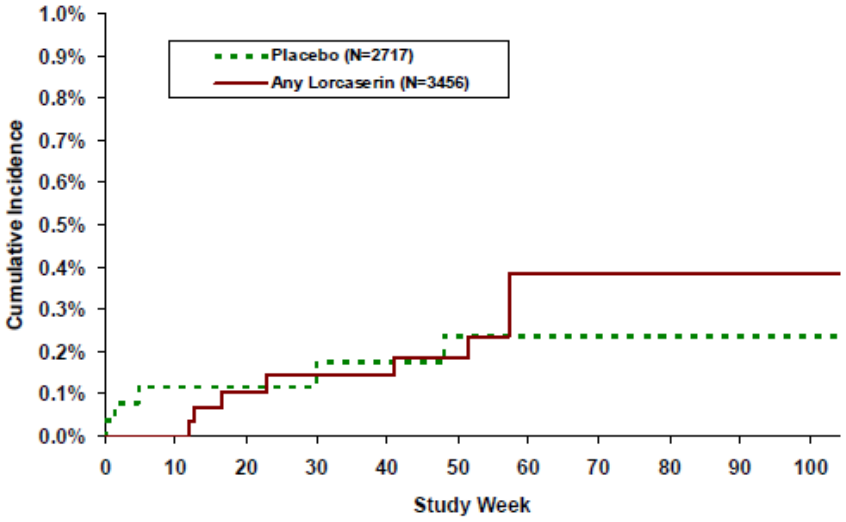
Table 92. Analysis of Time to First Event of SMQ 'Breast Neoplasms' in All Women Enrolled in Phase 3 Trials

	Pooled Lorcaserin 10 mg BID N=2747	**Pooled Lorcaserin 10 mg QD N=709**	**Any Lorcaserin Dose N=3456**	**Pooled Placebo N=2717**
Total Patient-years	564	2698	3261	2418
No. (%) of patients with event	6 (0.2)	1 (0.1)	7 (0.2)	5 (0.2)
Incidence per 100 patient-years (95% CI)	0.2 (0.1, 0.5)	0.2 (0.0, 1.0)	0.2 (0.1, 0.4)	0.2 (0.1, 0.5)
Hazard ratio (95% CI) relative to placebo	1.10 (0.34, 3.61)	1.27 (0.12, 13.41)	1.18 (0.28, 5.09)	--

Source: NDA 022529 Breast Cancer Report Amendment 2, Table 5

Figure 7. Kaplan-Meier Plot: Time to First Event of SMQ 'Breast Neoplasm' during Entire Study, All Women in Phase 3 Trials





Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52	Week 76	Week 104
Pooled Placebo	2717	1870	1298	467	218
Pooled Lorcaserin 10 mg QD	709	550	349	--	--
Pooled Lorcaserin 10 mg BID	2747	2062	1492	584	259
Any Locaserin Dose	3456	2613	1842	584	259

Source: NDA 022529 Breast Cancer Report Amendment 2, Figure 1

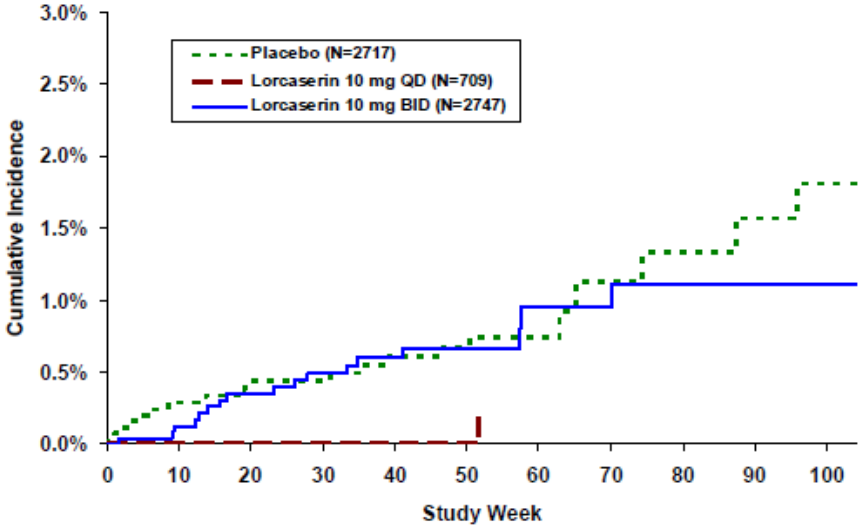
The sponsor also conducted a custom search in which they added the preferred term 'breast mass' to the original SMQ search. These results are presented in Table 93 and Figure 8, below.

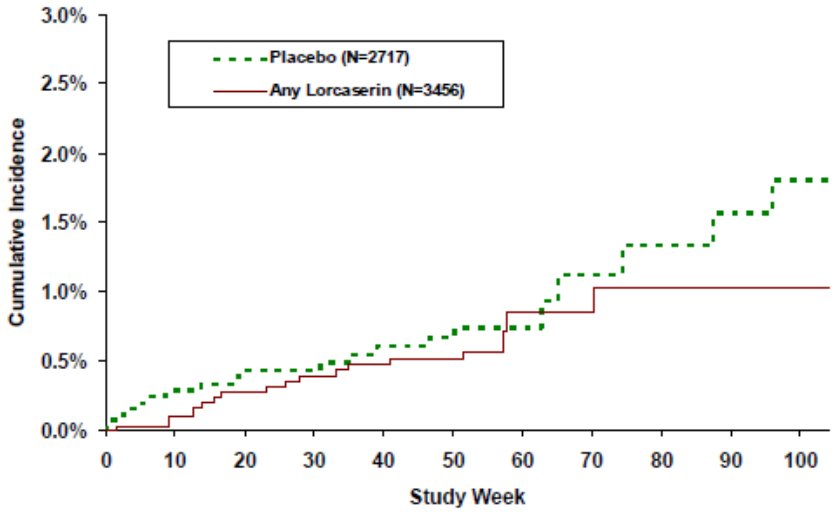
Table 93. Analysis of Time to First Event of SMQ 'Breast Neoplasms' + Arena Custom Search 'Breast Mass' in All Women Enrolled in Phase 3 Trials

	Pooled Lorcaserin 10 mg BID N=2747	**Pooled Lorcaserin 10 mg QD N=709**	**Any Lorcaserin Dose N=3456**	**Pooled Placebo N=2717**
Total Patient-years	2689	564	3252	2408
No. (%) of patients with event	17 (0.6)	1 (0.1)	18 (0.5)	20 (0.7)
Incidence per 100 patient-years (95% CI)	0.6 (0.4, 1.0)	0.2 (0.0, 1.0)	0.6 (0.3, 0.9)	0.8 (0.5, 1.3)
Hazard ratio (95% CI) relative to placebo	0.76 (0.40, 1.46)	0.26 (0.03, 2.02)	0.44 (0.15, 1.36)	--

Source: NDA 022529 Breast Cancer Report Amendment 2, Table 5

Figure 8. Kaplan-Meier Plot: Time to First Breast Cancer or Mass Identified by Arena Custom Search during Entire Study, All Women in Phase 3 Studies





Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52	Week 76	Week 104
Pooled Placebo	2717	1863	1288	463	215
Pooled Lorcaserin 10 mg QD	709	550	349	--	--
Pooled Lorcaserin 10 mg BID	2747	2057	1484	580	256
Any Locaserin Dose	3456	2608	1834	580	256

Source: NDA 022529 Breast Cancer Report Amendment 2, Figure 2

5.5.6.1.2 Prolactin

Prolactin is a polypeptide hormone secreted from the anterior pituitary gland and is negatively regulated by dopamine release from the hypothalamus. Serotonin has been

shown to increase prolactin via a number of receptors, including 5HT2C.[52] A key effect of prolactin is lactogenesis, which is regulated by activation of prolactin receptors on breast tissue. During pregnancy, serum prolactin increases by 10-20 times the non-pregnant value.[53]

A recent comprehensive review of this topic suggests that epidemiological data support a modest association between prolactin concentrations in women and the risk of breast cancer.[54] A number of medications are known to increase prolactin concentrations, including antipsychotics, oral contraceptives, reserpine, methyldopa, cimetidine, and tricyclic and selective serotonin reuptake inhibitor antidepressants. During antipsychotic treatment, prolactin concentrations can increase 10-fold or more above pretreatment values.[53] With the exception of oral contraceptives, a relationship between these medications and breast cancer has not been definitely demonstrated to date.[54] However, studies have generally been limited by short duration and low risk populations. As stated in some antipsychotic drug labels, tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, which could be of importance in a patient with previously detected breast cancer.[55]

Transient increases in plasma prolactin were observed after single-dose lorcaserin administration. Prolactin C_{max} increased approximately 1.5-fold over placebo after 10 mg and 2-fold after 20 and 40 mg doses. Prolactin AUC_{0-6} increased approximately 1.2-, 1.6-, and 1.4-fold over placebo after lorcaserin 10, 20, and 40 mg dose administration, respectively.

Prolactin results from the BLOSSOM trial were presented in the original NDA submission and summarized for the 2010 advisory committee meeting. The following is an update of these data, incorporating the prolactin results from the BLOOM-DM trial.

In BLOSSOM, blood samples for prolactin measurement were collected from all patients at selected sites (n=20 sites, 1504 patients), constituting approximately 38% of randomized patients. In BLOOM-DM, blood samples for prolactin measurements were collected at all study sites that participated in the trial.

Samples were obtained in the morning prior to administration of study medication and 2 ± 0.5 hours after study drug administration at baseline and at Weeks 4 (BLOSSOM only), and 12, 24 and 52/exit (BLOSSOM + BLOOM-DM). Reproductive status and the start date of last menstrual period were documented at each of these visits in female patients. Baseline pre-dose prolactin data were divided into quartiles by subgroup (sex, menopausal status) and treatment group. The baseline characteristics were well-matched and reflected those of the lorcaserin Phase 3 program overall.

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[52] Freeman ME, et al. Prolactin: structure, function, and regulation of secretion. Physiol Rev 2000; 80: 1523-631.
[53] Haddad PM and Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. Drugs 2004; 64(20): 2291-314.
[54] Tworoger SS and Hankinson SE. Prolactin and breast cancer etiology: an epidemiologic perspective. J Mammary Gland Biol Neoplasia 2008 Mar; 13(1): 41-53.
[55] Risperdal (NDA 020272) package insert

The reported normal values for the prolactin assay was 1.9-25.0 ng/mL in females and 2.5-17.0 ng/mL in males.

Table 94. Baseline Prolactin Concentrations (Mean and Range), BLOSSOM Substudy + BLOOM-DM

	Lorc 10 BID N=875	**Lorc 10 QD N=373**	**Pbo N=840**
Mean (SD), ng/mL	8.8 (7.09)	8.7 (6.41)	9.0 (9.68)
Range, ng/mL	1.4-87.6	0.3-68.6	1.9-141.0

Source: NDA 022529 Prolactin Study Report, Table 1

At baseline, prolactin concentrations in quartiles were as follows:

Table 95. Baseline Prolactin Concentrations (Quartiles, ng/mL), BLOSSOM Substudy + BLOOM-DM

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
Pre/perimenopausal Pbo	≤ 6.00	> 6.00-8.15	> 8.15-11.80	> 11.80
Pre/perimenopausal Lorc 10 QD	≤ 6.30	> 6.30-8.40	> 8.40-11.70	> 11.70
Pre/perimenopausal Lorc 10 BID	≤ 5.80	> 5.80-7.90	> 7.90-11.50	> 11.50
Postmenopausal Pbo	≤ 4.60	> 4.60-6.00	> 6.00-8.10	> 8.10
Postmenopausal Lorc 10 QD	≤ 4.00	> 4.00-5.75	> 5.75-8.30	> 8.30
Postmenopausal Lorc 10 BID	≤ 4.40	> 4.40-5.60	> 5.60-7.70	> 7.70
Men Pbo	≤ 5.20	> 5.20-7.30	> 7.30-10.70	> 10.70
Men Lorc 10 QD	≤ 5.60	> 5.60-7.70	> 7.70-11.40	> 11.40
Men Lorc 10 BID	≤ 5.10	> 5.10-7.30	> 7.30-10.70	> 10.70
Total Pbo	≤ 5.10	> 5.10-7.00	> 7.00-9.80	> 9.80
Total Lorc 10 QD	≤ 5.20	> 5.20-7.00	> 7.00-10.20	> 10.20
Total Lorc 10 BID	≤ 5.10	> 5.10-7.00	> 7.00-9.80	> 9.80

Source: NDA 022529 Prolactin Study Report, Table 34

By contrast, the Nurses' Health Study demonstrated higher quartile cutoffs of prolactin concentrations, with the 4th quartile in particular associated with an increase in risk of breast cancer (Table 96; RR top vs. bottom quartile in an analysis of pooled pre- and postmenopausal women = 1.3, 95% CI 1.1-1.6[54]). It is unclear if the lower baseline prolactin concentrations in the BLOSSOM and BLOOM-DM trials reflect a true prolactin difference in the obese population, a lower baseline breast cancer risk than the general population, or an assay-related difference. Based on a National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool (BCRT) survey[56] analysis conducted by the sponsor, the population studied in the lorcaserin Phase 3 trials appears to be representative of the general population for background risk.

[56] http://www.cancer.gov/bcrisktool Accessed 10 July 2010.

Table 96. Quartile Information for Prolactin (ng/mL), Nurses' Health Study (NHS)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
NHS, premenopausal / unknown menopause	≤ 9.8	> 9.8 – 13.0	> 13.0 – 17.6	> 17.6
NHS, postmenopausal	≤ 7.4	> 7.4 – 9.4	> 9.4 – 12.3	> 12.3

Source: References 57 and 58

Lorcaserin was associated with small mean increases in prolactin from pre-dose to post-dose at all time points (Table 97) and the proportion of patients who increased in prolactin quartile from pre- to post-dose increased at all time points (Table 99).

Table 97. Serum Prolactin Baseline Values and Change from Pre- to Post-Dose in Pooled Trials BLOSSOM and BLOOM-DM

Visit	Treatment Group	N	Pre-Dose Mean (SD)	Mean (SD) Δ (post- minus pre-dose)	Min, Max
Day 1	Lorc 10 mg BID	796	8.57 (7.15)	0.24 (3.82)	-57.60, 22.00
	Lorc 10 mg QD	340	8.58 (6.25)	0.16 (3.35)	-15.00, 42.10
	Pbo	760	8.95 (10.03)	-1.17 (4.45)	-86.20, 21.70
Week 12	Lorc 10 mg BID	537	8.76 (6.50)	-0.38 (3.09)	-16.60, 21.00
	Lorc 10 mg QD	225	9.03 (6.63)	-0.53 (4.24)	-27.90, 24.50
	Pbo	494	8.28 (5.98)	-1.21 (3.09)	-30.00, 17.10
Week 24	Lorc 10 mg BID	482	8.49 (6.67)	-0.34 (3.50)	-20.70, 23.60
	Lorc 10 mg QD	214	9.29 (8.71)	-0.43 (3.91)	-34.00, 15.30
	Pbo	441	8.10 (5.94)	-1.15 (3.96)	-55.00, 23.00
Week 52	Lorc 10 mg BID	408	8.87 (7.51)	-0.47 (3.46)	-30.40, 17.10
	Lorc 10 mg QD	181	8.99 (6.77)	-0.67 (3.81)	-28.50, 9.60
	Pbo	357	8.08 (6.74)	-1.16 (4.19)	-62.90, 13.60

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 62

Lorcaserin was also associated with small increases in mean pre-dose prolactin from baseline to post-baseline visits (Table 98). However, lorcaserin was not associated with an increase in the proportion of patients with an increase in prolactin quartile baseline to post-baseline (Table 99).

[57] Tworoger SS, et al. A prospective study of plasma prolactin concentrations and risk of premenopausal and postmenopausal breast cancer. J Clin Oncol 2007 April; 25(12): 1482-8.
[58] Tworoger SS, et al. Plasma prolactin concentrations and risk of postmenopausal breast cancer. Cancer Res 2004 Sept; 64: 6814.

Table 98. Change from Baseline in the Pre-Dose Prolactin Measurements (ng/mL) by Visit, BLOSSOM Substudy and BLOOM-DM

Visit	Treatment	N	BL Pre-Dose Mean (SD)	Visit Pre-Dose Mean (SD)	Change from BL in Pre-Dose		
					Mean (SD)	Median	Min, Max
Week 12	Lorc 10 BID	599	8.33 (6.50)	8.97 (6.40)	0.64 (4.02)	0.50	-26.50, 19.50
	Lorc 10 QD	250	8.29 (6.43)	8.89 (6.43)	0.60 (4.07)	0.40	-20.80, 19.40
	Pbo	555	8.30 (7.56)	8.32 (5.76)	0.02 (6.97)	0.10	-112.70, 33.90
Week 24	Lorc 10 BID	503	8.10 (6.39)	8.59 (6.62)	0.49 (4.43)	0.20	-25.20, 24.20
	Lorc 10 QD	217	8.48 (6.82)	9.13 (8.62)	0.65 (4.70)	0.30	-27.50, 33.40
	Pbo	450	8.43 (8.64)	8.29 (6.72)	-0.15 (7.85)	0.00	-109.10, 62.80
Week 52	Lorc 10 BID	413	7.95 (6.27)	8.85 (7.37)	0.90 (5.29)	0.50	-26.30, 51.40
	Lorc 10 QD	181	8.11 (5.27)	9.03 (6.82)	0.91 (4.90)	0.30	-26.10, 23.20
	Pbo	377	8.30 (8.60)	8.10 (6.69)	-0.19 (8.75)	0.00	-112.80, 62.60

Source: NDA 022529 Prolactin Study Report, Table 16

Table 99. Percent of Patients with Increase in Prolactin Quartile, BLOSSOM Substudy + BLOOM-DM

		Pre- to Post-Dose			Baseline to Post-Baseline		
		Lorc 10 BID	Lorc 10 QD	Pbo	Lorc 10 BID	Lorc 10 QD	Pbo
Baseline	Pre/perimenopausal	27.6	27.3	7.5	-	-	-
	Postmenopausal	27.0	25.6	9.0	-	-	-
	Men	22.8	25.0	11.7	-	-	-
	Total	21.6	19.4	8.0	-	-	-
Week 12	Pre/perimenopausal	34.0	30.4	14.3	24.0	26.1	21.2
	Postmenopausal	24.1	21.7	14.8	26.0	18.1	26.2
	Men	22.7	46.4	24.7	23.9	31.1	25.3
	Total	27.8	28.0	17.8	29.4	26.4	26.5
Week 24	Pre/perimenopausal	33.9	33.9	25.7	25.0	23.4	25.9
	Postmenopausal	26.6	18.3	14.5	27.6	16.4	22.7
	Men	19.9	35.3	18.8	24.5	35.8	27.5
	Total	25.2	23.7	17.8	29.8	20.7	30.2
Week 52	Pre/perimenopausal	30.4	33.3	19.2	32.7	24.1	25.0
	Postmenopausal	32.6	22.6	14.6	33.6	17.5	22.9
	Men	24.1	30.4	12.3	29.4	27.7	27.3
	Total	30.7	25.0	16.3	33.7	28.7	30.5

Source: NDA 022529, Prolactin Study Report, Tables 5 and 6

Finally, an outlier analysis was conducted to determine if there was an imbalance of the number of patients with especially high values of prolactin that could be considered clinically meaningful. As Table 100 demonstrates, the proportion of patients in any treatment group with prolactin values greater than the upper limit of normal was small.

At Week 52 there was a slightly increased proportion of patents treated with lorcaserin with prolactin values > ULN, > 2x ULN, and visit pre-dose > 2x baseline pre-dose values. No lorcaserin-treated patient was found to have prolactin values > 10x ULN.

Table 100. Proportion of patients with Prolactin Outlier Values by Visit in Pooled Trials, BLOSSOM and BLOOM-DM

Visit	Prolactin Change Criterion	Lorc 10 mg BID	Lorc 10 mg QD	Pbo
Day 1 (Baseline)	Pre-dose > ULN	3.3%	2.4%	2.9%
	Pre-dose > 2x ULN	0.8%	0.5%	1.0%
	Pre-dose > 5x ULN	0.1%	0	0.1%
	Pre-dose > 10x ULN	0	0	0
	Pre- to post-dose Δ > 2x pre-dose	0.5%	0.3%	0.1%
	Pre- to post-dose Δ > 5x pre-dose	0	0.3%	0
	Pre- to post-dose Δ > 10x pre-dose	0	0	0
Week 12	Pre-dose > ULN	3.0%	3.9%	1.9%
	Pre-dose > 2x ULN	0.8%	0.4%	0.2%
	Pre-dose > 5x ULN	0	0	0
	Pre- to post-dose Δ > 2x pre-dose	0.4%	0.9%	0.2%
	Pre- to post-dose Δ > 5x pre-dose	0.2%	0	0
	Pre- to post-dose Δ > 10x pre-dose	0	0	0
	Pre-dose > 2x baseline pre-dose	0.7%	0.8%	1.1%
	Pre-dose > 5x baseline pre-dose	0.2%	0	0.2%
	Pre-dose > 10x baseline pre-dose	0	0	0
Week 24	Pre-dose > ULN	2.8%	3.4%	3.1%
	Pre-dose > 2x ULN	0.8%	0.4%	0.6%
	Pre-dose > 5x ULN	0	0	0
	Pre- to post-dose Δ > 2x pre-dose	1.2%	0.5%	0.5%
	Pre- to post-dose Δ > 5x pre-dose	0	0	0
	Pre-dose > 2x baseline pre-dose	1.4%	0.5%	1.3%
	Pre-dose > 5x baseline pre-dose	0.2%	0	0.2%
	Pre-dose > 10x baseline pre-dose	0	0	0.2%
Week 52	Pre-dose > ULN	3.7%	2.9%	1.9%
	Pre-dose > 2x ULN	1.3%	0	0.5%
	Pre-dose > 5x ULN	0	0	0
	Pre- to post-dose Δ > 2x pre-dose	0.5%	0	0.3%
	Pre- to post-dose Δ > 5x pre-dose	0	0	0.3%
	Pre- to post-dose Δ > 10x pre-dose	0	0	0.3%
	Pre-dose > 2x baseline pre-dose	2.4%	2.2%	0.5%
	Pre-dose > 5x baseline pre-dose	0	0	0

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 64

Adverse events that could potentially be associated with hyperprolactinemia are presented in the table below.

Table 101. Adverse Events that Could be Related to Hyperprolactinemia, Phase 3 Trials

	BLOOM		BLOSSOM		BLOOM-DM	
	Lorc 10 BID N=1593	Pbo N=1584	Lorc 10 BID N=1602	Pbo N=1601	Lorc 10 BID N=256	Pbo N=252
Galactorrhea	1 (0.1)	0	0	0	0	0
Gynecomastia	0	0	0	1 (0.1)	0	0
Amenorrhea	4 (0.3)	4 (0.3)	1 (0.1)	1 (0.1)	0	0
Oligomenorrhea	0	0	0	1 (0.1)	0	0
Hypomenorrhea	0	0	1 (0.1)	1 (0.1)	0	0
Erectile dysfunction	3 (0.2)	1 (0.1)	3 (0.2)	1 (0.1)	1 (0.4)	0
Infertility	0	0	0	0	0	0
Libido decreased	7 (0.4)	6 (0.4)	5 (0.3)	3 (0.2)	1 (0.4)	0
Libio disorder	0	0	0	0	0	0
Male sexual dysfunction	0	0	1 (0.1)	0	0	0
Female sexual dysfunction	0	0	0	0	0	0
Hypogonadism	0	0	0	0	0	0
Hyperprolactinemia	0	0	0	0	0	0
Prolactin increased	0	0	4 (0.2)	3 (0.2)	1 (0.4)	0
Other related terms						
Ejaculation delayed	0	0	0	0	0	0
Ejaculation failure	0	0	1 (0.1)	0	0	0
Anorgasmia (female)	0	0	1 (0.1)	0	0	0
Orgasm abnormal	0	1 (0.1)	0	0	0	
Disturbance in sexual arousal	1 (0.1)	0	0	0	0	0

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 30

The one patient (181-S001, lorcaserin 10 mg BID, BLOOM trial) who had an adverse event of 'galactorrhea' also had a prolactinoma diagnosed during the trial.

In the BLOOM-DM trial, there were two prolactin-adverse adverse events in the lorcaserin 10 mg QD arm that was not included in the table above: one patient with an adverse event of 'hypogonadism' and one patient with an adverse event of 'libido decreased'.

There was one adverse event of increased prolactin in the BLOOM-DM trial. Patient 1160-S012 was a 47-year-old black female with an adverse event of 'blood prolactin increased' treated with lorcaserin 10 mg BID. The event was asymptomatic and resolved spontaneously. No action was reported in response to this adverse event. Her laboratory values were as follows:

Table 102. Serum Prolactin Concentrations in Patient 1160-S012 with Adverse Event of 'Blood Prolactin Increased'

	Baseline	Week 12*	Unscheduled	Week 24	Week 52
Pre-dose prolactin (ng/mL)	24	35.6	13.5	8.6	19.5
Post-dose prolactin (ng/mL)	32.7	40.3	-	9.2	20.1
* Adverse event reported					

Source: NDA 022529 Response to FDA Request of 31 January 2012, Table 2

Relevant prolactin data were not acquired at the time of diagnosis for any of the patients diagnosed with breast cancer during the study (Table 91). Two of these patients had prolactin concentrations collected at other times during the BLOSSOM substudy (2203-S032 and 2141-S039); all values were within normal limits.

5.5.6.2 Cerebrospinal Fluid Concentrations and Safety Margin Calculations

In a carcinogenicity study in rats, astrocytoma was noted. As lorcaserin targets the central nervous system and brain concentrations in humans are unknown, it was of obvious concern that safety margins for this finding might be lower than what might be apparent from plasma concentrations.

Because a more consistent relationship was seen between cerebrospinal fluid (CSF) and brain concentrations of lorcaserin across species (rats and monkeys) versus the variable plasma:brain ratio in these species, it was thought that a more reliable estimation of brain drug concentrations in humans could be made based on measured CSF concentrations of lorcaserin.

Study APD356-022 was an open-label Phase 1 study to assess the pharmacokinetic properties of lorcaserin at steady state in the CSF of healthy volunteers. This study was a single-site, open-label study of healthy overweight or obese adult male or female subjects ages 18-65 years with a BMI 27-35 kg/m^2.

A total of 10 subjects were planned for enrollment. Eleven subjects were randomized into the study, received at least one dose of lorcaserin and were included in the safety analysis, and nine subjects completed the study and were included in the pharmacokinetic analysis.

Lorcaserin was administered at a dose of 10 mg BID for six days, and then once in the morning on the seventh day to reach steady state.

The following conclusions are based on the results of pharmacokinetic analyses:

- Plasma steady-state was achieved by Day 4. All subjects were at steady-state on Day 7, when CSF was sampled.

- The plasma $C_{max,ss}$ geometric mean was 61.7 ng/mL at 2 h.

- The CSF $C_{max,ss}$ geometric mean was 0.87 ng/mL at 6 h.

- At steady state, the geometric mean ratio of CSF to plasma exposure was (GMR [90% CI)]):
    - AUC_{0-t}: 0.017 (0.015, 0.018)
    - $C_{max,ss}$: 0.014 (0.012, 0.016)
    - $C_{min,ss}$: 0.016 (0.013, 0.018)

Non-clinical brain:CSF ratios were used to project human brain exposure, and brain exposure ratios were calculated. At the 10 mg/kg/day (no astrocytoma seen) and 30 mg/kg/day (astrocytoma seen) doses used in the two-year male rat carcinogenicity study, brain exposure margins relative to human brain at the maximum recommended dose were greater than or equal to 70 and 360, respectively. In the female rat, where astrocytoma was not increased even at the 100 mg/kg/day dose, the exposure margin was calculated to be > 1000.

5.5.7 Serotonin Syndrome and other Serotonin-Related Events

Serotonin toxicity is a constellation of neuromuscular, psychiatric, and autonomic nervous system symptoms and signs that result from an excess of serotonin.[59,60] Recent work in this area suggests that agonism at the 5HT2A receptor contributes to serotonin syndrome.[59,61]

There were no adverse events of serotonin syndrome in the BLOOM-DM trial. There were two cases within the lorcaserin development program (first submission, presented the the original briefing document) that the investigators considered to fall within the spectrum of serotonin toxicity:

- Patient 25/007 from Phase 2 study APD356-004 (lorcaserin 10 mg BID) was a 44-year-old white female who discontinued the trial after experiencing a constellation of symptoms that included tremor, palpitations, headache, and vomiting on Study Days 1 and 5. The sponsor considered it possible that these symptoms could have represented a mild form of serotonin toxicity.

- There was one adverse event with a preferred term of 'serotonin syndrome' in the BLOSSOM trial. Patient 2109-S025 (lorcaserin 10 mg BID) was a 29-year-old white female with a history of asthma and celiac sprue. On Study Day 57, she developed symptoms of an upper respiratory syndrome and started a course of clarithromycin the next day (Study Day 53). Four days later, she took her morning dose of the study drug and then took over-the-counter guaifenisen with dextromethorphan. Approximately 30 minutes later, she developed vertigo, nausea, vomiting, diarrhea with some minor blood spots in stools, and a blood pressure increase to 135/105 per patient's home reading (in clinic, her BP was 100-122/75-80 on previous visits). The symptoms resolved after approximately five hours, but re-appeared with her evening dose of study drug and again taking guaifenisen with dextromethorphan. The next morning, the symptoms were resolved. She did not take the study drug that morning. She took her last dose of clarithromycin three days later, and started amoxicillin two days after cessation of clarithromycin (Study Day 62).

[59] Boyer EW and Shannon M. The serotonin syndrome. N Engl J Med 2005; 352 (11): 1112-20.
[60] Wappler F, et al. Pathological role of serotonin system in malignant hyperthermia. Br J Anaesth 2001; 87: 794-8.
[61] Isbister GK and Whyte IM. Serotonin toxicity and malignant hyperthermia: role of 5HT2 receptors. Br J Anaesth 2002; 88(4): 603.

At the Week 8 clinic visit (Study Day 62), her BP was 110/80 and she was asymptomatic. The investigator diagnosed serotonin syndrome of moderate severity, probably related to study drug's interaction with dextromethorphan. She was directed by the investigator to withhold study drug, discontinue dextromethorphan, and restart study drug approximately one week after the initial symptoms. The rechallenge was uneventful, with no reappearance of symptoms.

The sponsor conducted a search of preferred terms that might be suggestive of serotonin toxicity (Arena search terms, Table 103, below). In the original NDA, nonspecific preferred terms of chills, tremor, and confusional state drove the imbalance between lorcaserin and placebo. These preferred terms were infrequent in the BLOOM-DM trial. Additional MedDRA SMQs were searched as shown below; a clear imbalance between treatment groups was not evident.

Table 103. Serotonin Toxicity Terms, Pooled Phase 3 Trials and BLOOM-DM (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Arena Search Terms	56 (1.8)	13 (1.6)	18 (0.6)	4 (1.6)	1 (1.1)	4 (1.6)
Chills	32 (1.0)	6 (0.7)	6 (0.2)	1 (0.4)	1 (1.1)	0
Tremor	10 (0.3)	3 (0.4)	3 (0.1)	1 (0.4)	0	3 (1.2)
Confusional state	6 (0.2)	2 (0.2)	1 (<0.1)	1 (0.4)	0	0
Disorientation	4 (0.1)	1 (0.1)	4 (0.1)	1 (0.4)	0	0
Hyperhidrosis	2 (0.1)	1 (0.1)	6 (0.2)	1 (0.4)	0	1 (0.4)
Intention tremor	1 (<0.1)	0	0	0	0	0
Serotonin syndrome	1 (<0.1)	0	0	0	0	0
Neuroleptic Malignant Syndrome, Narrow SMQ	1 (<0.1)	0	0	0	0	0
Neuroleptic Malignant Syndrome, Broad SMQ	194 (6.1)	47 (5.9)	174 (5.5)	26 (10.2)	10 (10.5)	23 (9.1)
Dystonia, Narrow SMQ	1 (<0.1)	0	0	0	0	0
Dystonia, Broad SMQ	67 (2.1)	16 (2.0)	70 (2.2)	12 (4.7)	3 (3.2)	11 (4.4)

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 22

5.6 Other Adverse Events and Related Laboratory Findings

5.6.1 Hepatobiliary Events and Related Laboratory Data

5.6.1.1 Hepatic events

Hepatic events were infrequent in the lorcaserin development program. As discussed in the briefing document for the first EMDAC meeting:

- Patient 111-S002 (lorcaserin 10 mg BID; BLOOM trial) experienced adverse events of 'hepatomegaly' and 'elevated liver function tests' and discontinued drug prior to the Week 8 visit due to these adverse events. This patient had an elevated alanine

aminotransferase (ALT) at randomization with a value of 140 U/L. The ALT value of 236 was recorded at a follow-up visit on Study Day 15. Both ALT and aspartate aminotransferase (AST) declined on subsequent visits. Total bilirubin was not elevated at any time point.

- Two other liver-related adverse events from the hepatobiliary SOC occurred in two patients randomized to placebo in the Year 1 pooled dataset: 'hepatic cyst' and 'hepatomegaly'.

- Two adverse events of 'hepatic steatosis' occurred in the second year of BLOOM: one patient was treated with lorcaserin 10 mg BID in the first year and re-randomized to placebo in the second year (adverse event occurred on Study Day 602) and one patient was treated with placebo throughout the two-year trial (adverse event occurred on Study Day 496).

Adverse events in BLOOM-DM that are liver- or liver laboratory test-related were infrequent (see Table 104). Two adverse events leading to discontinuation in the lorcaserin 10 mg BID group are discussed below.

Table 104. Liver-Related Adverse Events, Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**
Total, liver-related adverse events	25 (0.8)	15 (1.9)	30 (0.9)	4 (1.6)	1 (1.1)	1 (0.4)
Aspartate aminotransferase increased	11 (0.3)	9 (1.1)	14 (0.4)	1 (0.4)	0	1 (0.4)
Alanine aminotransferase increased	11 (0.3)	8 (1.0)	12 (0.4)	2 (0.8)	0	0
Liver function test abnormal	6 (0.2)	3 (0.4)	5 (0.2)	0	0	0
Hepatic enzyme increased	4 (0.1)	1 (0.1)	4 (0.1)	1 (0.4)	1 (1.1)	0
Blood alkaline phosphatase increased	3 (0.1)	0	1 (<0.1)	0	0	0
Blood bilirubin increased	2 (0.1)	0	3 (0.1)	0	0	0
Hepatomegaly	1 (<0.1)	0	1 (<0.1)	0	0	0
Hepatic enzyme abnormal	0	0	1 (<0.1)	0	0	0
Hepatitis	0	0	0	1 (0.4)	0	0

Source: Reviewer created from datasets

In BLOOM-DM, there was one adverse event of 'hepatitis' (led to discontinuation):

- Patient 1195-S013 (lorcaserin 10 mg BID) was a 55-year-old Hispanic female with a history of diabetes, cholelithiasis status post cholecystectomy, chronic diarrhea, urinary incontinence status post bladder suspension, hypercholesterolemia, hypertension, hyperthyroidism status post partial thyroidectomy, sleep apnea, and seasonal allergies. Concomitant medications at study start were metformin, sitagliptin, olmesartan, l-thyroxine, Caudet, montelukast, aspirin, multivitamin, calcium, and ibuprofen. The patient was also taking a variety of herbal agents and supplements, including cinnamon, Nopal Ultra, aloe vera, cranberry, and Mega Greens. Social history is relevant for absence of drug abuse and for infrequent alcohol use (2-3 glasses of wine per year). Transfusion, sexual, and travel histories

were unavailable. The diagnosis of hepatitis was made on the basis of elevated liver function tests (see below). At screening, HBsAg and HCV screens were negative, as was the HIV screen. No follow-up virology screen was documented. The patient was withdrawn from the trial as a result of the adverse event. It was reported as mild intensity, possibly related, and reported as ongoing at study exit.

Table 105. Liver-Related Laboratories, Patient 1195-S013

	Screening	Day 1	Week 4	Week 12	Week 24	Unscheduled	Exit
Study Day	**-28**	**1**	**27**	**82**	**168**	**179**	**217**
ALT (U/L)	89	110	117	109	223	217†	143
AST (U/L)	54	77	63	68	156	155	77
Total bilirubin (mg/dL)	0.3	0.2	0.3	0.2	0.2	0.3	0.3
Alkaline phosphatase (U/L)	156	148	162	149	169	156†	136
† Denoted "clinically significant" by investigator Normal ranges: Alkaline phosphatase 40-135 U/L, ALT 0-47 U/L, AST 0-37 U/L, Total bilirubin 0.2-1.3 mg/dL							

Source: NDA 022529 Response to Information Request 7 February 2012, Table 1

There was also one patient who withdrew from the trial due to an adverse event of 'hepatic enzyme increased':

- Patient 1121-S024 (lorcaserin 10 mg BID) was a 52-year-old Hispanic female with a history of diabetes, hypertension and hyperlipidemia. Concomitant medications at study start were metformin, estradiol patch, losartan, simvastatin, citalopram, and sitagliptin. She had no reported history of alcohol use or substance abuse. The patient was discontinued early at Week 24 due to an adverse event of 'hepatic enzyme increased'. See table below for the patient's laboratory values; transaminases decreased after discontinuing medication, then increased again approximately two weeks later.

Table 106. Liver-Related Laboratories, Patient 1121-S024

	Screening	Day 1	Week 4	Week 12	Week 24	Unscheduled	Week 52
Study Day	**-30**	**1**	**26**	**83**	**169**	**211**	**223**
ALT (U/L)	69	94	74	133	196	130	219
AST (U/L)	48	63	51	80	107	89	152
Total bilirubin (mg/dL)	0.2	0.5	0.4	0.4	0.3	0.4	0.4
Alkaline phosphatase (U/L)	80	95	78	88	94	85	85
† Denoted "clinically significant" by investigator Normal ranges: Alkaline phosphatase 40-135 U/L, ALT 0-47 U/L, AST 0-37 U/L, Total bilirubin 0.2-1.3 mg/dL							

Source: Reviewer created from datasets

The FDA Guidance for evaluating premarketing drug-induced liver injury[62] considers the best predictor for severe hepatotoxicity as aminotransferase (AT) elevation accompanied by increased serum total bilirubin, not explained by any other cause and without evidence

[62] FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf Accessed 28 July 2010.

of cholestasis (i.e., "Hy's law"), together with an increased incidence of AT elevations in the overall trial population compared to control. No Hy's law cases were identified in any clinical study in the lorcaserin development program.

In the Phase 3 trials, the predefined limits of change for evaluation of ALT were: greater than the upper limit of normal (ULN), > 3x ULN, > 5x ULN, and > 20x ULN. In Year 1, there were five (0.2%) lorcaserin 10 mg BID, one (0.1%) lorcaserin 10 mg QD, and four (0.1%) placebo patients meeting the > 5x ULN category in the pooled Phase 3 (non-diabetes) trials; none in the BLOOM-DM trial met this criterion (Table 107). No patients in the lorcaserin treatment groups and one patient in the placebo group in any of the trials met the > 20x ULN criterion.

In Year 2 of BLOOM, three patients experienced ALT elevations > 3x ULN; two assigned to lorcaserin/lorcaserin and one assigned to lorcaserin/placebo. One patient (109-S025, lorcaserin/lorcaserin) had a value > 5x ULN. On Week 64, she had an adverse event reported of 'hepatic enzyme elevated'; study drug was stopped and restarted.

Table 107. Number (%) Patients with ALT Values Exceeding Selected Cutoffs, Pooled Phase 3 Trials (Non-Diabetes, Year 1) and BLOOM-DM

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=2991	Lorc 10 QD N=754	Pbo N=2918	Lorc 10 BID N=250	Lorc 10 QD N=93	Pbo N=244
ALT						
> ULN	317 (10.6)	95 (12.6)	375 (12.9)	45 (18.0)	21 (22.6)	58 (23.8)
> 3x ULN	11 (0.4)	4 (0.5)	13 (0.4)	2 (0.8)	1 (1.1)	0
> 5x ULN	5 (0.2)	1 (0.1)	4 (0.1)	0	0	0
> 20x ULN	0	0	1 (<0.1)	0	0	0
AST						
> ULN	231 (7.7)	74 (9.8)	284 (9.7)	40 (16.0)	18 (19.4)	46 (18.9)
> 3x ULN	13 (0.4)	3 (0.4)	12 (0.4)	2 (0.8)	1 (1.1)	1 (0.4)
> 5x ULN	2 (<0.1)	1 (0.1)	5 (0.2)	0	1 (1.1)	1 (0.4)
> 20x ULN	0	0	1 (<0.1)	0	0	0
Alk Phos						
> ULN	68 (2.3)	14 (1.9)	71 (2.4)	8 (3.2)	1 (1.1)	4 (1.6)
> 1.5x ULN	3 (0.1)	1 (0.1)	6 (0.2)	0	0	0
> 2.5x ULN	2 (<0.1)	0	2 (<0.1)	0	0	0
> 5x ULN	0	0	0	0	0	0
T. bili						
> ULN	86 (2.9)	27 (3.6)	111 (3.8)	6 (2.4)	4 (4.3)	9 (3.7)
> 1.5x ULN	16 (0.5)	4 (0.5)	27 (0.9)	2 (0.8)	0	0
> 2x ULN	2 (<0.1)	0	7 (0.2)	0	0	0
> 3x ULN	0	0	0	0	0	0
ALT/AST + T. bili						
ALT > 3x ULN + T. bili > 1.5x ULN	0	0	0	0	0	0
AST > 3x ULN + T. bili > 1.5x ULN	0	0	0	0	0	0

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 65; ISS CR Appendix 2, Table S14.1.1; BLOOM-DM CSR, Table 14.3.145

5.6.1.2 Gallbladder events

In the Phase 3 program, the remainder of adverse events in the hepatobiliary SOC consisted of cholelithiasis, biliary dyskinesia, and cholecystitis events. Obesity and rapid weight loss are associated with an increased risk for gallstone formation.[63]

In the non-diabetes trials, patients randomized to lorcaserin had more serious adverse events of cholelithiasis and cholecystitis than those randomized to placebo. Overall, gallbladder-related adverse events were infrequent and only slightly more commonly seen in patients treated with lorcaserin. A similar pattern was seen in Year 2 of BLOOM (data not shown).

In BLOOM-DM, one patient randomized to lorcaserin 10 mg BID had a serious adverse event of cholecystitis and was withdrawn from the trial.

Table 108. Gallbladder-Related Adverse Events, Pooled Phase 3 Trials (Non-Diabetes, Year 1) and BLOOM-DM (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Total Gallbladder-Related AEs	26 (0.8)	5 (0.6)	16 (0.5)	2 (0.8)	0	1 (0.4)
Cholelithiasis	11 (0.3)	2 (0.2)	10 (0.3)	1 (0.4)	0	0
Cholecystitis	8 (0.3)	2 (0.2)	5 (0.2)	1 (0.4)	0	1 (0.4)
Biliary dyskinesia	3 (0.1)	0	1 (<0.1)	0	0	0
Gallbladder disorder	2 (0.1)	1 (0.1)	1 (<0.1)	0	0	0
Cholecystitis acute	2 (0.1)	0	2 (0.1)	0	0	0
Cholecystitis chronic	2 (0.1)	0	0	0	0	0
Biliary colic	1 (<0.1)	0	0	0	0	0
Gallbladder non-functioning	1 (<0.1)	0	0	0	0	0
Gallbladder pain	1 (<0.1)	0	0	0	0	0

Source: NDA 022529 ISS, Table 76; reviewer created from datasets

5.6.2 Cardiovascular Events and Electrocardiograms

5.6.2.1 Electrocardiograms and related adverse events and vital signs

Study APD356-007 (original NDA submission) was designed to evaluate the potential for lorcaserin to prolong QTc in healthy individuals at the proposed therapeutic dose of 15 mg and a supra-pharmacological dose (40 mg) compared to placebo. The study was a single-site, double-blind, randomized, placebo- and positive-controlled, parallel-designed, steady-state/multiple-dose trial. As discussed in the original EMDAC briefing document, the study was reviewed by the FDA Interdisciplinary Review Team for QT studies (IRT). Findings included:

[63] Stinton LM, et al. Epidemiology of gallstones. Gastroenterol Clin North Am 2010 Jun; 39(2): 157-69, vii.

- No significant QT prolongation effect of lorcaserin at either dose. The largest upper bounds of the 2-sided 90% CI for the mean difference between lorcaserin and placebo were below 10 ms.

- A small dose-related increase in PR interval and decrease in heart rate (HR) due to lorcaserin.

The PR interval increases and HR decreases seen in study APD356-007 were explored in the Phase 2 and 3 trials. In the Phase 2 trials APD356-003 and APD356-004, there was a dose-related increase in incidence of patients with PR interval changes > 15 msec. In the pooled non-diabetes Phase 3 trials, there was a greater mean decrease in HR and slightly greater mean increase in PR interval in the lorcaserin 10 mg BID group as compared to the placebo group.

Table 109. Selected ECG Findings, Phase 3 Trials

	BLOOM + BLOSSOM			**BLOOM-DM**		
	Lorc 10 BID	**Lorc 10 QD**	**Pbo**	**Lorc 10 BID**	**Lorc 10 QD**	**Pbo**
Mean (SE) Δ in HR from BL at Week 52*	-1.9 (0.2)	-0.3 (0.4)	-0.3 (0.2)	-2.1 (0.8)	-3.3 (1.1)	0.1 (0.8)
Mean (SE) Δ in RR from BL at Week 52	29.9 (2.8)	6.4 (5.1)	4.1 (2.9)	31.2 (8.8)	26.3 (12.6)	6.8 (8.1)
Mean (SE) Δ in PR from BL at Week 52	2.9 (0.3)	1.9 (0.5)	2.1 (0.3)	2.5 (0.9)	4.0 (1.7)	1.3 (0.9)
% of patients with PR > 200 msec and PR Δ > 40 msec	0.2%	0	0.4%	0.5%	1.2%	0.5%
* Heart rate results for BLOOM-DM taken from vital signs; HR from ECG not reported						

Source: NDA 022529, ISS Tables 138, 139, 141, and 142; BLOOM-DM CSR, Tables 67, 14.3.48, 14.3.49, and 14.3.104

A search of the lorcaserin Phase 3 databases was conducted to determine whether these ECG changes were reported as adverse events and whether such changes might translate to adverse events of bradyarrhythmia such as bradycardia or heart block. As Table 110 shows, in the Phase 3 trials, events related to bradyarrhythmia were infrequent, but more than twice as common in lorcaserin 10 mg BID treated patients.

Table 110. Bradyarrhythmia Adverse Events, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID	Lorc 10 QD	Pbo	Lorc 10 BID	Lorc 10 QD	Pbo
Total, Bradyarrhythmia AEs	14 (0.4)	2 (0.2)	6 (0.2)	1 (0.4)	0	0
Sinus bradycardia	5 (0.2)	0	2 (0.1)	0	0	0
Bradycardia	4 (0.1)	1 (0.1)	1 (<0.1)	1 (0.4)	0	0
Atrioventricular block first degree	3 (0.1)	0	1 (<0.1)	0	0	0
Electrocardiogram PR prolongation	1 (<0.1)	0	2 (0.1)	0	0	0
Heart rate decreased	1 (<0.1)	0	0	0	0	0
Sick sinus syndrome	0	1 (0.1)	0	0	0	0

Source: Reviewer created from datasets

Analyses of HR in the non-diabetes pooled Phase 3 trials found that 1.2% lorcaserin 10 mg BID versus 0.8% placebo-treated patients had a HR less than 45 BPM during 52 weeks of treatment. By contrast, in the BLOOM-DM trial, 0.8% lorcaserin 10 mg BID versus 1.2% placebo-treated patients had a HR less than 45 BPM during 52 weeks of treatment. Of note, although infrequent, there were also more patients in the lorcaserin groups with tachycardia (HR > 100 BPM) than placebo in the BLOOM-DM trial. The converse was seen in the pooled non-diabetes trials.

Table 111. Assessment of Categorical Heart Rate (BPM) Values at Any Time During the Trial, Pooled Phase 3 and BLOOM-DM (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3095	Lorc 10 QD N=771	Pbo N=3038	Lorc 10 BID N=251	Lorc 10 QD N=94	Pbo N=248
Heart Rate - Low						
50-54	574 (18.5)	126 (16.3)	421 (13.9)	26 (10.4)	12 (12.8)	17 (6.9)
45-49	176 (5.7)	35 (4.5)	101 (3.3)	8 (3.2)	3 (3.2)	4 (1.6)
<45	37 (1.2)	4 (0.5)	23 (0.8)	2 (0.8)	1 (1.1)	3 (1.2)
Heart Rate - High						
101-115	30 (1.0)	9 (1.2)	47 (1.5)	6 (2.4)	6 (6.4)	1 (0.4)
116-130	0	0	5 (0.2)	0	0	2 (0.8)
>130	0	0	0	0	0	0

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 75

5.6.2.2 Blood pressure and related adverse events

In the pooled non-diabetes trials, 23% of patients in the lorcaserin 10 mg BID and 23% of patients in the placebo-treated group had a history of hypertension. In the BLOOM-DM trial, 61% of lorcaserin 10 mg BID patients and 61% of placebo-treated patients had a history of hypertension.

Increases in blood pressure may portend adverse cardiovascular outcomes with weight loss medications[64] and therefore, despite the generally favorable effects of lorcaserin on

[64] James WP, et al. Effect of sibutramine of cardiovascular outcomes in overweight and obese subjects. N Engl J Med. 2010 Sep 2; 363 (10):905-17.

mean blood pressure (see section 4.3.3.2.1), outlier blood pressure analyses and related adverse events were explored to ensure there was no concerning signal.

Table 112. Categorical Blood Pressure Values at Any Time During Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3095	**Lorc 10 QD N=771**	**Pbo N=3038**	**Lorc 10 BID N=251**	**Lorc 10 QD N=94**	**Pbo N=248**
Systolic BP - High						
120-139	2517 (81.3)	660 (85.6)	2540 (83.6)	235 (93.6)	90 (95.7)	225 (90.7)
140-159	650 (21.0)	215 (27.9)	701 (23.1)	120 (47.8)	44 (46.8)	122 (49.2)
≥ 160	53 (1.7)	16 (2.1)	74 (2.4)	20 (8.0)	7 (7.4)	20 (8.1)
Systolic BP - Low						
85-89	56 (1.8)	12 (1.6)	42 (1.4)	1 (0.4)	1 (1.1)	2 (0.8)
80-84	17 (0.5)	4 (0.5)	15 (0.5)	1 (0.4)	0	0
< 80	14 (0.5)	5 (0.6)	9 (0.3)	0	0	0
Diastolic BP - High						
80-89	2211 (71.4)	601 (78.0)	2284 (75.2)	204 (81.3)	79 (84.0)	207 (83.5)
90-99	624 (20.2)	205 (26.6)	708 (23.3)	74 (29.5)	30 (31.9)	79 (31.9)
≥ 100	69 (2.2)	26 (3.4)	68 (2.2)	8 (3.2)	4 (4.3)	8 (3.2)
Diastolic BP - Low						
< 60	393 (12.7)	78 (10.1)	292 (9.6)	30 (12.0)	11 (11.7)	24 (9.7)

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 75

The hypertension SMQ includes preferred terms such as 'hypertension' and 'blood pressure increased'. The following is an analysis of the pooled (non-diabetes) and BLOOM-DM databases using a modified hypertension SMQ (i.e., removing the preferred term 'metabolic syndrome'). In the review of BLOOM-DM, it was noted that there was an excess of lorcaserin-treated patients with a hypertension-related adverse event. The significance of this finding is unknown as such a finding was not seen in the pooled non-diabetes trials and no significant increase in blood pressure in any trial with lorcaserin.

Table 113. Incidence of Hypertension, Phase 3 Trials Year 1 (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**
Total, Hypertension SMQ	111 (3.5)	27 (3.4)	117 (3.7)	15 (5.9)	7 (7.4)	9 (3.6)
Hypertension	70 (2.2)	19 (2.4)	78 (2.4)	13 (5.1)	6 (6.3)	8 (3.2)
Blood pressure increased	38 (1.2)	8 (1.0)	35 (1.1)	0	1 (1.1)	0
Blood pressure systolic increased	2 (0.1)	0	5 (0.2)	1 (0.4)	0	1 (0.4)
Blood pressure diastolic increased	1 (<0.1)	0	1 (<0.1)	1 (0.4)	0	0
Diastolic hypertension	1 (<0.1)	0	0	0	0	0
Orthostatic hypertension	1 (<0.1)	0	0	0	0	0

Source: Reviewer created from datasets

Hypotension adverse events were also explored. There is a slight imbalance with lorcaserin greater than placebo, although the overall incidence is low.

Table 114. Incidence of Hypotension, Phase 3 Trials Year 1 (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Total, Hypotension-related AEs	20 (0.6)	4 (0.5)	10 (0.3)	2 (0.8)	0	0
Blood pressure decreased	9 (0.3)	3 (0.4)	5 (0.2)	0	0	0
Hypotension	7 (0.2)	1 (0.1)	4 (0.1)	2 (0.8)	0	0
Orthostatic hypotension	4 (0.1)	0	1 (<0.1)	0	0	0

Source: Reviewer created from datasets

5.6.2.3 Ischemic cardiac adverse events

As described above, lorcaserin does not appear to share the sympathetic nervous system activation that has been described with sibutramine: mean heart rate and blood pressure were generally shown to be decreased or unchanged with lorcaserin treatment. Nevertheless, activation of the 5HT2A receptor is involved in vasoconstriction and platelet aggregation and 5HT2A antagonists have been evaluated for treatment of vascular disease.[65] Any potential relevance of these 5HT2A cardiovascular effects to lorcaserin is unknown.

As discussed in section 3.3, the background history of cardiovascular disease in the non-diabetes Phase 3 program was very low at 0.3-1.1%; by contrast, coronary artery disease history in the BLOOM-DM trial was reported to be 7.1%.

An exploratory analysis of ischemic cardiac adverse events was conducted. Preferred terms within the MedDRA Ischemic heart disease SMQ were searched; this SMQ includes the Myocardial infarction SMQ and Other ischemic heart disease SMQ. Preferred terms are presented in the table below. Terms seen in the lorcaserin database are bolded.

[65] Adams JW, et al. APD791, 3-methoxy-n-(3-(1-methyl-1h-pyrazol-5-yl)-4-(2-morpholinoethoxy)phenyl)benzamide, a novel 5-hydroxytryptamine 2A receptor antagonist: pharmacological profile, pharmacokinetics, platelet activity and vascular biology. J Pharmacol Exp Ther. 2009 Oct; 331(1): 96-103.

Table 115. Ischemic Heart Disease-Related Preferred Terms

Myocardial infarction SMQ	Other ischemic heart disease SMQ
Acute coronary syndrome	**Angina pectoris**
Acute myocardial infarction	**Angina unstable**
Blood creatine phosphokinase MB abnormal	Arteriosclerosis coronary artery
Blood creatine phosphokinase MB increased	Arteriospasm coronary
Coronary artery embolism	Coronary angioplasm
Coronary artery occlusion	Coronary arterial stent insertion
Coronary artery reocclusion	Coronary artery bypass
Coronary bypass thrombosis	**Coronary artery disease**
Kounis syndrome	Coronary artery dissection
Myocardial infarction	Coronary artery insufficiency
Myocardial reperfusion injury	Coronary artery restenosis
Papillary muscle infarction	Coronary artery stenosis
Post procedural myocardial infarction	Coronary endarterectomy
Postinfarction angina	Coronary no-flow phenomenon
Silent myocardial infarction	Coronary ostial stenosis
Postinfarction angina	Coronary revascularization
Silent myocardial infarction	Dissecting coronary artery aneurysm
Troponin I increased	ECG signs of myocardial ischaemia
Troponin increased	External counterpulsation
Troponin T increased	Haemorrhage coronary artery
Blood creatine phosphokinase abnormal	In-stent coronary artery restenosis
Blood creatine phosphokinase increased	Ischaemic cardiomyopathy
Cardiac enzymes increased	Microvascular angina
Coronary artery restenosis	**Myocardial ischaemia**
Electrocardiogram Q wave abnormal	Percutaneous coronary intervention
Electrocardiogram ST segment abnormal	Prinzmetal angina
Electrocardiogram ST segment elevation	Stress cardiomyopathy
Electrocardiogram ST-T segment elevation	Subclavian coronary steal syndrome
Infarction	Subendocardial ischaemia
In-stent coronary artery restenosis	Arteriogram coronary abnormal
Scan myocardial perfusion abnormal	**Cardiac stress test abnormal**
Vascular graft occlusion	Computerised tomogram coronary artery abnormal
	Electrocardiogram ST segment depression
	Electrocardiogram ST-T change*
	Electrocardiogram ST-T segment abnormal
	Electrocardiogram ST-T segment depression
	Electrocardiogram T wave abnormal
	Electrocardiogram T wave inversion
	Exercise electrocardiogram abnormal
	Exercise test abnormal
	* PT not found in MedDRA 13.0

Source: MedDRA 13.0 Browser version 3.0.1

An imbalance in ischemic adverse events was seen in Year 1 of the pooled non-diabetes Phase 3 trials. The placebo incidence was primarily driven by the relatively nonspecific preferred term 'blood creatine phosphokinase increased'. By contrast, events occurred more frequently in the placebo and lorcaserin 10 mg QD arms in the BLOOM-DM trial than the lorcaserin 10 mg BID arm.

It should be noted that events such as 'myocardial infarction' and 'acute coronary syndrome' were not formally adjudicated, nor were they prospectively defined and the

results should therefore be interpreted with caution. Combining adverse events from BLOOM, BLOSSOM, and BLOOM-DM demonstrates that 20 (0.6%) lorcaserin 10 mg BID, 4 (0.4%) lorcaserin 10 mg QD, and 13 (0.4%) placebo patients had unadjudicated adverse events related to ischemic heart disease.

Table 116. Ischemic Heart Disease Adverse Events, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**
Total, MedDRA Ischaemic heart disease SMQ	15 (0.5)	1 (0.1)	6 (0.2)	5 (2.0)	3 (3.2)	7 (2.8)
Myocardial infarction	4 (0.1)	0	0	0	0	2 (0.8)
Angina pectoris	2 (0.1)	1 (0.1)	0	0	1 (1.1)	1 (0.4)
Electrocardiogram T wave abnormal	2 (0.1)	0	0	0	0	0
Coronary artery disease	1 (<0.1)	0	2 (0.1)	0	1 (1.1)	0
Angina unstable	1 (<0.1)	0	1 (<0.1)	1 (0.4)	0	0
Troponin increased	1 (<0.1)	0	1 (<0.1)	0	0	0
Acute coronary syndrome	1 (<0.1)	0	0	0	0	0
Acute myocardial infarction	1 (<0.1)	0	0	0	0	0
Cardiac stress test abnormal	1 (<0.1)	0	0	0	0	0
Electrocardiogram ST segment abnormal	1 (<0.1)	0	0	0	0	0
Electrocardiogram ST-T change	1 (<0.1)	0	0	0	0	0
Myocardial ischaemia	1 (<0.1)	0	0	0	0	0
Blood creatine phosphokinase increased	0	0	3 (0.1)	4 (1.6)	1 (1.1)	4 (1.6)
Coronary artery occlusion	0	0	0	1 (0.4)	0	0

Source: Reviewer created from datasets

The Year 1 Phase 3 dataset was also explored for the typical components of Major Adverse Cardiovascular Events (MACE): cardiovascular death, myocardial infarction, and stroke, and the following preferred terms were found (Table 117). In the pooled non-diabetes Phase 3 trials, all events occurred in patients treated with lorcaserin 10 mg BID. There was one death due to cardiorespiratory arrest in a placebo patient, but this was attributed to an asthma exacerbation, and so not included in Table 117.

In the BLOOM-DM trial, events of 'cerebrovascular accident' occurred in two patients on lorcaserin 10 mg QD and events of 'myocardial infarction' occurred in two patients on placebo. Narratives of the cardiovascular serious adverse events from the BLOOM-DM trial are included in Appendix C.

In total, six (0.2%) lorcaserin 10 mg BID, two (0.2%) lorcaserin 10 mg QD, and two (0.1%) placebo patients had unadjudicated adverse events of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

Table 117. MACE (Exploratory/Unadjudicated), Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**
Total, "MACE"	6 (0.2)	0	0	0	2 (2.1)	2 (0.8)
Myocardial infarction	4 (0.1)	0	0	0	0	2 (0.8)
Acute myocardial infarction	1 (<0.1)	0	0	0	0	0
Cerebrovascular accident	1 (<0.1)	0	0	0	2 (2.1)	0

Source: Reviewer created from datasets

Cardiac ischemic events were not reported in the lorcaserin-treated group in BLOOM Year 2, although there were cardiac ischemic events in two patients treated with placebo re-randomized from lorcaserin and two patients treated with placebo since the start of the trial. There were no events of stroke or cardiovascular death in Year 2.

Prior to the first advisory committee for lorcaserin, the sponsor had cardiovascular events from the BLOOM and BLOSSOM trials independently adjudicated in a post-hoc fashion. These results were not previously reviewed by FDA; results were included in the lorcaserin complete response resubmission and are presented below.

The adjudication process was conducted by an independent committee (the Cardiovascular Clinical Events Committee (CCEC)) consisting of physicians from the Brigham and Women's Hospital (Boston, Massachusetts). Of note, adverse events from BLOOM-DM were not adjudicated, either in a prespecified or a post-hoc fashion.

The goal of the CCEC was to define and adjudicate the following potential endpoints from BLOOM and BLOSSOM in a consistent and unbiased manner:

- Cardiovascular Death
- Cardiovascular Ischemic Events including myocardial infarction and hospitalization for unstable angina
- Cerebrovascular Events including stroke and transient ischemic attack

The sponsor was responsible for identifying potential events from BLOOM and BLOSSOM for review. Potential events were triggered by either (1) death of a subject, (2) report of a serious adverse event (SAE) with a preferred term of chest pain or chest discomfort, or (3) a SAE meeting any of the specific terms in the Ischaemic heart disease SMQ (including the Myocardial infarction SMQ, Other ischaemic heart disease SMQ, Ischaemic cerebrovascular conditions SMQ, and Conditions associated with central nervous system haemmorhages and cerebrovascular accidents SMQ).

The two physician reviewers were to independently review the cases assigned to them, document and provide supporting information for each event's adjudication directly on the endpoint form, and were responsible for bringing their assigned cases with them to a

scheduled review session. At this session, the two physicians that were assigned to each case reviewed the event together and compare adjudications. If the two adjudications agreed on all data fields, the event was considered complete and a single form was signed by both reviewers. If there was initial disagreement and if after discussion, consensus between the two reviewers was reached on a final adjudication, a single form was signed by both reviewers and represented the final adjudication. If after discussion, no consensus was reached, the case would be presented to a third reviewer for final adjudication and a single form would be submitted with all three signatures indicating a final adjudication.

The CCEC received a total of 25 cases blind to treatment assignment for adjudication including 19 potential ischemic events, four potential cerebrovascular events, and two deaths. The two physician reviewers reportedly found the documents provided adequate to adjudicate all cases and reached consensus on all cases.

Overall, 19 potential ischemic event cases yielded five myocardial infarctions, four hospitalizations for unstable angina, and 10 events that did not formally meet either of these criteria. Of the four potential cerebrovascular events, the reviewers coded one stroke, two transient ischemic attacks, and one event that did not formally meet either of these definitions. Both deaths were felt to be non-cardiovascular in nature, with one coded as pulmonary cause, and the other as accident/trauma.

The sponsor unblinded the adjudications, with the results as follows: five lorcaserin 10 mg BID, zero lorcaserin 10 mg QD, six placebo, and one lorc/pbo (Year 2):

Table 118. Cardiovascular Clinical Endpoints Committee Results Summary (Post-Hoc Adjudication), BLOOM and BLOSSOM

Subject ID	Verbatim Term	Preferred Term	Result	Treatment Assignment (Added by Arena)
119084	UNSTABLE ANGINA	Angina unstable	Hosp for UA	Lorc 10 BID
2128-S010	ACUTE MI	Acute myocardial infarction	MI-Spontaneous	Lorc 10 BID
2203-S058	NON Q WAVE MYOCARDIAL INFARCTION	Myocardial infarction	MI-Spontaneous	Lorc 10 BID
2236-S032	MYOCARDIAL INFARCTION	Myocardial infarction	MI-Spontaneous	Lorc 10 BID
2250-S008	MYOCARDIAL INFARCTION	Myocardial infarction	MI-Spontaneous	Lorc 10 BID
192006	ATYPICAL CHEST PAIN	Chest pain	No MI/UA	Lorc 10 BID
2102-S039	CHEST PAIN-MUSCULOSKELETAL	Musculoskeletal chest pain	No MI/UA	Lorc 10 BID
2137-S050	CHEST PAIN OF UNKNOWN ETIOLOGY	Chest pain	No MI/UA	Lorc 10 BID
2137-S083	ANGINA	Angina pectoris	No MI/UA	Lorc 10 BID

Subject ID	Verbatim Term	Preferred Term	Result	Treatment Assignment (Added by Arena)
2196-S002	PROBABLY ACUTE CORONARY SYNDROME	Acute coronary syndrome	No MI/UA	Lorc 10 BID
2213-S076	NON CARDIAC CHEST PAIN	Non-cardiac chest pain	No MI/UA	Lorc 10 BID
2255-S073	CHEST PRESSURE	Chest discomfort	No MI/UA	Lorc 10 BID
2202-S062	CHEST PAIN NON-CARDIAC	Non-cardiac chest pain	No MI/UA	Lorc 10 QD
2267-S007	TRANSIENT ISCHEMIC ATTACK	Transient iscaemic attack	No Stroke/TIA	Lorc 10 QD
180080	CORONARY ARTERY DISEASE	Coronary artery occlusion	Hosp for UA	Lorc / Pbo
188048	CORONARY ARTERY 95% BLOCK	Coronary artery occlusion	Hosp for UA	Pbo
2146-S090	CORONARY ARTERY DISEASE	Coronary artery disease	Hosp for UA	Pbo
156006	REMOTE LATERAL MYOCARDIAL INFARCTION	Myocardial infarction	MI-Silent	Pbo
146067	CHEST PAIN	Chest pain	No MI/UA	Pbo
2125-S001	CHEST PAIN	Chest pain	No MI/UA	Pbo
2223-S009	CEREBRAL GLOBAL ANOXIA	Cerebral ischaemia	Non CV Death – Pulmonary Stroke Ischaemic	Pbo
132023		Road traffic accident	Non CV Death – Accident/Trauma	Pbo
177074	TRANSIENT ISCHEMIC ATTACK	Transient ischaemic attack	TIA	Pbo
2180-S078	TRNSIENT ISCHEMIC ATTACK	Transient ischaemic attack	TIA	Pbo

Source: NDA 022529 CV Study Report, pg 25 of 54

5.6.3 Renal Events and Related Laboratory Data

In the 52-week study in monkeys, histopathological findings in the kidneys were identified, consisting of focal tubular epithelial cell degeneration (high dose), regeneration (all doses), and cellular casts (mid and high doses).

Preferred terms within the acute renal failure SMQ, narrow and broad, were searched (Table 119). Bolded terms were those found in the lorcaserin Phase 3 program.

Within the pooled (non-diabetes) Phase 3 trials, one (< 0.1%) patient assigned to lorcaserin 10 mg BID and no patients assigned to placebo had adverse events within the acute renal failure narrow SMQ. When the broad SMQ was applied to the non-diabetes population, 17 (0.5%) lorcaserin 10 mg BID patients and 12 (0.4%) placebo patients experienced adverse events. As discussed in the original review, no patients treated with

lorcaserin in the second year of BLOOM had an adverse event in the narrow or broad acute renal failure SMQ.

Patients with diabetes may be prone to kidney injury. Reassuringly, the BLOOM-DM trial did not reveal any increase in acute renal failure adverse events in the lorcaserin-treated patients.

Table 119. Acute Renal Failure SMQ Preferred Terms

Narrow PTs	Broad PTs
Acute prerenal failure	Albuminuria
Anuria	Blood creatinine abnormal
Azotaemia	**Blood creatinine increased**
Continuous hemodiafiltration	Blood urea abnormal
Dialysis	**Blood urea increased**
Haemodialysis	Blood urea nitrogen/creatinine ratio increased
Neonatal anuria	Creatinine renal clearance abnormal
Nephropathy toxic	Creatinine renal clearance decreased
Oliguria	Glomerular filtration rate abnormal
Peritoneal dialysis	Glomerular filtration rate decreased
Renal failure	Hypercreatininaemia
Renal failure acute	Nephritis
Renal failure neonatal	Oedema due to renal disease
Renal impairment	**Protein urine present**
Renal impairment neonatal	**Proteinuria**
	Renal function test abnormal
	Renal transplant
	Renal tubular disorder
	Renal tubular necrosis
	Tubulonterstitial nephritis
	Urea renal clearance decreased
	Urine output decreased

Source: NDA 022529 2 Apr 2010 Response to 74-day filing letter requests, Table 7

Table 120. Renal Failure SMQ, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Total, MedDRA Renal Failure Narrow SMQ	**1 (<0.1)**	**1 (0.1)**	**0**	**1 (0.4)**	**0**	**2 (0.8)**
Renal failure	0	1 (0.1)	0	0	0	1 (0.4)
Renal failure acute	1 (<0.1)	0	0	0	0	0
Renal impairment	1	0	0	1 (0.4)	0	0
Acute prerenal failure	0	0	0	0	0	1 (0.4)
Total, MedDRA Renal Failure Broad SMQ	**17 (0.5)**	**5 (0.6)**	**12 (0.4)**	**2 (0.8)**	**0**	**2 (0.8)**
Protein urine present	7 (0.2)	3 (0.4)	1 (<0.1)	0	0	0
Proteinuria	8 (0.3)	2 (0.2)	9 (0.3)	1 (0.4)	0	2 (0.8)
Blood creatinine increased	2 (0.1)	0	1 (<0.1)	0	0	0
Blood urea increased	2 (0.1)	0	1 (<0.1)	0	0	0
Urine output decreased	0	0	1 (<0.1)	1 (0.4)	0	0

Source: NDA 022529 2 Apr 2010 Response to 74-day filing letter requests, Table S09.1.0; reviewer created from datasets

Evaluations of categorical laboratory data for creatinine, calculated creatinine clearance, and blood urea nitrogen (BUN) do not suggest a significant drug effect.

Table 121. Categorical Laboratory Data, Kidney Parameters, Phase 3 Trials (Safety Populaton)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID	**Lorc 10 QD**	**Pbo**	**Lorc 10 BID**	**Lorc 10 QD**	**Pbo**
Creatinine						
> Baseline or > ULN	53.1%	57.2%	53.9%	60.0%	62.4%	61.5%
> 1.5x Baseline or > 1.5x ULN	0.5%	0.7%	0.5%	1.2%	0	1.6%
> 3x Baseline or > 3x ULN	<0.1%	0	<0.1%	0	0	0
> 6x ULN	0	0	<0.1%	0	0	0
Creatinine Clearance						
< 60-30 mL/min	0.6%	0.4%	0.3%	2.0%	0	1.7%
< 30-15 mL/min	0	0	<0.1%	0	0	0
< 15 mL/min	0	0	<0.1%	0	0	0
Creatinine Clearance (IBW)						
< 60-30 mL/min	15.6%	15.3%	16.0%	18.4%	12.9%	17.2%
< 30-15 mL/min	0.1%	0	0	0.4%	0	1.2%
< 15 mL/min	0	0	0.1%	0	0	0
BUN						
23-26 mg/dL	4.5%	4.4%	5.5%	15.2%	17.2%	12.7%
27-31 mg/dL	1.1%	1.3%	1.3%	5.6%	6.5%	4.9%
> 31 mg/dL	0.2%	0.3%	0.3%	1.2%	4.3%	1.6%

Source: NDA 022529 2 Apr 2010 Response to 74-day filing letter requests, Table S14.1.1; BLOOM-DM CSR, Table 14.3.145

5.6.4 Priapism

Serotonin activation at the 5HT2C receptor has been implicated in priapism seen in animals.[66] In the nonclinical studies of lorcaserin, penile extension was seen in rats at single doses of ≥ 100 mg/kg and in monkeys at all doses in a 28-day multiple dose toxicity study. This effect in animals decreased significantly with continued dosing of lorcaserin.

The Phase 3 database was searched for the following terms related to priapism. There was no active surveillance for priapism-related adverse events. Table 123 shows that priapism was not reported in the lorcaserin 10 mg BID group in Year 1. In Year 2 of BLOOM, no events were reported in the lorcaserin/lorcaserin-treated group.

Although no adverse events of priapism were reported, a definitive conclusion regarding lorcaserin and priapism is limited given that the investigators did not actively question patients about this event.

[66] Millan MJ, et al. 5-HT2C receptors mediate penile erections in rats: actions of novel and selective agonists and antagonists. Eur J Pharmacol 1997; 325: 9–12.

Table 122. MedDRA Search Terms for Priapism

LLT	PT	HLT	SOC
Priapism	Priapism	Erection and ejaculation disorders	Reproductive system and breast disorders
Priapism aggravated			
Clitoral engorgement	Clitoral engorgement	Vulvovaginal signs and symptoms	
Clitorimegaly	Enlarged clitoris	Female gonadal function disorders	Endocrine disorders
Clitoris engorgement			
Clitoris enlarged			
Hypertrophy of clitoris			
Vulvodynia	Vulvovaginal pain		
Erection increased	Erection increased	Sexual arousal disorders	Psychiatric disorders
Penile edema	Penile oedema	Penile disorders NEC	
Penile vascular disorder	Penile vascular disorder		
Penile pain	Penile pain		
Spontaneous penile erection	Spontaneous penile erection		
LLT=lower level term			

Source: NDA 022529 7 Mar 2010 Response to 74-day filing letter requests, Table 8

Table 123. Priapism Adverse Events, Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Priapism	0	1 (0.1)	2 (0.1)	0	0	0
Spontaneous penile erection	0	1 (0.1)	1 (<0.1)	0	0	0
Erection increased	0	0	1 (<0.1)	0	0	0

Source: NDA 022529 2 Apr 2010 Response to 74-day filing letter requests, Table S09.1.0; Summary of Clinical Safety (resubmission), Table 43

5.6.5 Hematology Events and Related Laboratory Data

In the mouse, at exposure multiples of 25 and 27 times (males and females) clinical exposure, decreases in red blood cell (RBC) mass were seen. In the non-diabetes Phase 3 trials, 0.9% of patients treated with lorcaserin 10 mg BID as compared to 0.7% of patients treated with placebo had hemoglobin values less than 10 g/dL. In the BLOOM-DM trial, the proportion was 2.0% for lorcaserin 10 mg BID and 3.3% for placebo. In the non-diabetes trials, slightly more patients in the lorcaserin 10 mg BID treated group had adverse events related to anemia or related red blood cell count decreases in the Phase 3 trials; this trend was reversed in the BLOOM-DM trial.

Table 124. Low RBC-Related Adverse Events, Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**
Total, Low RBC-Related AEs	31 (1.0)	6 (0.7)	22 (0.7)	2 (0.8)	2 (2.1)	7 (2.8)
Anaemia	22 (0.7)	5 (0.6)	17 (0.5)	2 (0.8)	1 (1.1)	3 (1.2)
Haemoglobin decreased	9 (0.3)	1 (0.1)	5 (0.2)	0	1 (1.1)	2 (0.8)
Haematocrit decreased	6 (0.2)	1 (0.1)	2 (0.1)	0	0	3 (1.2)
Red blood cell count decreased	2 (0.1)	0	0	0	0	0

Source: Reviewer created from datasets

Dose-related decreases in white blood cells (WBC), neutrophils, and lymphocytes were noted (Table 125). Adverse events related to decreases in WBCs were infrequent, but greater in lorcaserin-treated patients than those who were placebo-treated (Table 126).

Table 125. Percent of Patients with Neutrophil Counts below Pre-Defined Cut-Offs, Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID	**Lorc 10 QD**	**Pbo**	**Lorc 10 BID**	**Lorc 10 QD**	**Pbo**
< Lower limit of normal (LLN)	5.8%	5.7%	4.5%	2.8%	4.3%	1.2%
$< 1.5 \times 10^9$/L	2.8%	2.7%	2.2%	0.8%	2.2%	0
$< 1 \times 10^9$/L	0.6%	0.4%	0.3%	0.4%	0	0
$< 0.5 \times 10^9$/L	<0.1%	0.1%	0	0	0	0

Source: NDA 022529 2 Apr 2010 Response to 74-day filing letter requests, Table S14.2.1; BLOOM-DM CSR, Table 14.3.145

Table 126. Low WBC-Related Adverse Events, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**	**Lorc 10 BID N=256**	**Lorc 10 QD N=95**	**Pbo N=252**
Total, Low WBC-Related AEs	10 (0.3)	5 (0.6)	3 (0.1)	1 (0.4)	0	0
White blood cell count decreased	6 (0.2)	1 (0.1)	2 (0.1)	0	0	0
Neutrophil count decreased	3 (0.1)	2 (0.2)	0	0	0	0
Neutropenia	2 (0.1)	3 (0.4)	2 (0.1)	1 (0.4)	0	0
Leukopenia	2 (0.1)	1 (0.1)	0	0	0	0
Lymphocyte count decreased	1 (<0.1)	0	0	0	0	0
Lymphopenia	1 (<0.1)	0	0	0	0	0

Source: Reviewer created from datasets

All adverse events of neutropenia were considered mild and non-serious. No patient discontinued due to a neutropenia adverse event.

In the Phase 3 trials, a mean decrease in platelets was only seen in the lorcaserin 10 mg BID group, although a similar proportion of patients in the treatment groups had platelet counts less than LLN and 75×10^9/L. One patient in the non-diabetes trials and one patient in BLOOM-DM had adverse events of 'thrombocytopenia' (mild), both in the

lorcaserin 10 mg BID group, and two patients in the non-diabetes trials had adverse events of ‘platelet count decreased’ (one mild, one moderate), both in the lorcaserin 10 mg BID group. No patient discontinued the trial due to these adverse events.

6 APPENDICES

6.1 Appendix A. BLOOM-DM Study Design

6.1.1 Objectives

6.1.1.1 Primary

- To assess the weight loss effect of lorcaserin during one year of treatment

6.1.1.2 Secondary

- To assess the ongoing safety of lorcaserin
- To assess changes in glycemic control during one year of lorcaserin treatment
- To assess changes in body composition between Baseline and Week 52
- To assess changes in cardiovascular risk factors associated with obesity (i.e., dyslipidemia, hypertension) between Baseline and Week 52
- To assess echocardiographically-determined heart valve regurgitant scores and pulmonary artery pressure changes during one year of lorcaserin treatment
- To assess changes in Quality of Life measures during one year of lorcaserin treatment
- To assess population pharmacokinetics of lorcaserin

6.1.2 Design

This was a randomized, double-blind, placebo-controlled clinical trial of one year duration. Approximately 750 patients were originally planned for enrollment into the study, randomized in a 1:1:1 ratio to placebo, lorcaserin 10 mg QD or lorcaserin 10 mg BID. Due to slow enrollment, the total enrollment target was reduced to 600 by discontinuing randomization to the low dose group. After the implementation of protocol Amendment 3, patients were randomized in a 1:1 ratio to placebo or lorcaserin 10 mg BID. Patients randomized into the lorcaserin 10 mg QD group prior to the implementation of Amendment 3 remained enrolled in the trial to complete all planned study procedures.

Each patient completed screening procedures within six weeks of dosing on Day 1. Eligible patients were randomized to receive study medication for 52 weeks, with periodic follow-up visits to assess efficacy and safety parameters.

Randomization was stratified by:

- HbA1c: $< 9\%$ and $\geq 9\%$
- Medication used to treat diabetes: patients taking a sulfonylurea (alone or in combination) or patients taking metformin (alone or in combination). Patients taking both metformin and a sulfonylurea were included in the sulfonylurea group.

Patients were required to participate in the Arena Healthy Lifestyle Program® diet and exercise program. The prescribed diet consisted of approximately 600 calories less per day than the patient's calculated Estimated Energy Requirement (EER). The EER was

calculated using WHO criteria with a fixed activity factor of 1.3 for most patients; however, for patients who engage in ≥ 1 hour /day aerobic exercise, an activity factor of 1.4 was used.

With respect to adjustment of medications for the treatment of diabetes:

- The increase or addition of anti-hyperglycemic medications was not recommended prior to the Week 12 visit because weight loss could obviate the need for increased medication.

- It was recommended that anti-hyperglycemic medication dose be reduced in the event of one documented and otherwise unexplained hypoglycemic event [blood glucose (BG) < 65 mg/dL] or two undocumented and otherwise unexplained suspected hypoglycemic events between two scheduled visits. For patients on more than one anti-hyperglycemic medication, the recommended order in which to reduce medication dose was:
    1. Decrease/discontinue sulfonylurea
    2. Decrease/discontinue anti-hyperglycemic medications other than metformin (e.g., TZD, DPP-IV inhibitor, metiglinide)
    3. Decrease/discontinue metformin

- If the majority of fasting plasma glucose (FPG) self-monitoring readings for a patient were ≥ 10 mg/dL at the 12-week or subsequent study visit, or several self-monitored fasting BG measurements between scheduled visits at 12 weeks or later were > 240 mg/dL, increasing the anti-hyperglycemic medication dose was considered, in the following order:
    1. If on a single agent, increase the dose of that agent
    2. If on more than one agent:
        - Increase metformin to maximum tolerated or recommended dose
        - Increase or add another agent (TZD, DPP-IV inhibitor, etc.)

- Any patient with (1) HbA1c increase of ≥ 1.5% from baseline at any scheduled measurement, or (2) HbA1c ≥ 11% at any scheduled measurement, or (3) FPG > 270 mg/dL on two consecutive study visits was withdrawn from the study and referred to his/her primary care physician for management of uncontrolled diabetes.

- To avoid confounding effects on weight:
    - Patients must not have initiated use of insulin in any form during the study
    - Patients must not have initiated use of exenatide or pramlintide during the study

Other concomitant medication guidelines/restrictions included the following:

- Medications for the treatment of hypertension may have been started, discontinued or adjusted during the study if, in the judgment of the PI or the patient's physician, such a change was medically indicated

- Medications for the treatment of dyslipidemia may have been started, discontinued or adjusted during the study if, in the judgment of the PI or the patient's physician, such a change was medically indicated

- Patients must not have initiated use of prescription weight loss drugs (e.g., phentermine, sibutramine, orlistat) or OTC medication (including herbal supplements) for the treatment of obesity for the duration of the study

- Patients must not have initiated the use of topiramate at any time during the study

- Patients must not have initiated use of agents that have documented correlation with increased incidence of valvulopathy and/or pulmonary hypertension (e.g., cyproheptadine, trazodone, nefazodone, amoxapine, tricyclic antidepressants, mirtazapine, pergolide, ergotamine, methysergide) during the study

- Patients must not have initiated use of prescribed medication for the treatment of depression, anxiety, or other psychiatric disease (e.g., buproprion, SSRIs, SNRIs, tricyclics, MAOIs) during the study

- Patients must not have initiated the use of prescribed SSRIs, SNRIs or buproprion for treatment of other indications (e.g., migraine, weight loss, smoking cessation) during the study

- Patients must not have initiated use of St. John's Wort during the study

Investigational product dispensed was recorded on the Drug Accountability Form. Patients were instructed to bring their study drug (blister cards) with them to each visit. Compliance was assessed by the number of remaining tablets. Patients were instructed not take more than the prescribed amount of one tablet in the morning and one tablet in the evening. If a dose was missed, this was recorded in the CRF as part of the compliance assessment. Continued noncompliance (< 80%) was a valid reason for removal from the study.

Table 127. Schedule of Events

Evaluation	Screening[a]	Randomization	Dosing Period (Study Week)														F/U
	-42 to -1	Day 1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/Exit[b]	56
Informed Consent	X																
Medical History	X	X[c]															
Physical Exam	X	X[c]		X					X							X	
BDI-II	X			X					X							X	
Binge Eating Scale	X																
Echocardiogram	X[d]								X							X	
12-Lead ECG	X															X	
Clinical Labs	X	X		X		X			X			X				X	
Drugs of Abuse Screen	X																
Thyroid Function Tests (T4, TSH)	X															X	
Hemoglobin A1c	X	X				X			X			X				X	
Fasting Insulin, CRP		X	X						X							X	
Prolactin[e]		X				X			X							X	
Pregnancy Test[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Virology Screen (HIV, Hep C, and HBsAg)	X																
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Waist and Hip Circumference[h]		X							X							X	
DEXA[i]		X							X							X	
PK Blood Collection						X			X							X	
Quality of Life Assessment		X							X							X	
Diet and Exercise Counseling		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Compliance Check			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication Assessments		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IVRS Call[j]		X				X			X			X			X	X	

Evaluation	Screening[a]	Randomization	Dosing Period (Study Week)													F/U
	-42 to -1	Day 1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/Exit[b]	56
Drug Administration[k]		◄	———	———	———	———	———	———	———	———	———	———	———	———	———	►	
Adverse Event Monitoring		◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►

a All screening activities are to be completed within 42 days, or sooner, prior to dosing on Day 1.
b At the completion of the study or upon early termination from the study, all procedures should be performed as indicated. For patients who prematurely discontinue, an exit visit will be performed upon exit from the study and a follow-up phone call will be performed approximately 30 days after the exit visit. Discontinued patients will be asked to return at the intended Week 52 visit, even if interim visits have been missed, for a follow-up body weight and echocardiogram.
c Partial examination and medical history to update findings from that performed at screening.
d Baseline echocardiogram must be acquired before randomization; randomization may occur as soon as echo core lab determines that the echo is technically adequate; interpretation need not be completed prior to randomization.
e Blood samples for prolactin measurement will be collected prior to administration of study medication and 2 ± 0.5 hours after study drug administration.
f Serum hCG pregnancy test required at Screening and Week 52/Exit. Urine pregnancy test will be dose at other study visits as indicated.
g Vital sign measurement s(blood pressure heart rate,a nd body temperature taken in supine position after 5-minute rest); Day 1 measurements will be taken before first dose and approximately 2 hours after the first dose. Height will be measured at screening only.
h Hip and waist circumference to be measured in triplicate. Final result will be the average of the 3 measurements.
i DEXA scan to be performed Day 1/Randomization (+ 2 weeks), Week 24 (± 2 weeks), and Week 52/Exit (± 2 weeks) at designated sites.
j Sites will call the IVRS at Day 1 and Weeks 12, 24, 36, and 48. The IVRS will be used to track each patient's progress through the study to ensure that adequate drug supply is at the site. In addition, sites will call the IVRS at Screening and study completion or early termination.
k Randomized patients will be instructed to administer one dose in the morning (about 60 minutes prior to breakfast) and one dose in the evening (about 60 minutes prior to dinner).

Source: NDA 022529 BLOOM-DM CSR, Table 4

6.1.3 Patient Population

6.1.3.1 Inclusion Criteria

The following are selected inclusion criteria:

- Male or female, 18 - 65 years
- Ambulatory and able to perform exercise program
- Non-pregnant, non-lactating, non childbearing potential or used an accepted method of birth control (females)
- Surgically sterile or used an accepted method of birth control (males)
- BMI 27 - 45 kg/m^2
- Type 2 diabetes mellitus
  - Treated with metformin, sulfonylurea, or either agent in combination with other oral medications (e.g., TZDs, DPP-IV inhibitors, metiglinides, or acarbose) at a stable dose (TZD had to be stable for at least 6 months, for all other medications, 3 months)
  - HbA1c 7 - 10%
  - Fasting glucose ≤ 240 mg/dL
  - No history of ketoacidosis or hypoglycemic unawareness
- Considered to be in stable health in the opinion of the Investigator

6.1.3.2 Exclusion Criteria

The following are selected exclusion criteria:

- Prior participation in any study of lorcaserin
- Clinically significant new illness in past month
- Not suitable to participate in the study in the opinion of the Investigator
- Recent history (within one year before entering the study) of major depression, anxiety, or other psychiatric disease requiring treatment with prescription medication
- Beck Depression Inventory-II (BDI-II) total score ≥ 20 or > 0 on Question 9 (pertaining to suicidal thoughts)
- History of a binge eating disorder (score >17 on the Binge Eating Scale)
- History of seizure disorder
- Surgical treatment of obesity
- Uncontrolled hypertension (≥ 150/95 on two different days)
- History of any of the following cardiovascular conditions:
  - Valve replacement surgery
  - Myocardial infarction (MI), cerebrovascular accident (CVA), transient ischemic attack (TIA), or reversible ischemic neurological deficit (RIND) within six months of screening; cardiac arrhythmia requiring medical or surgical treatment within six months of screening
  - Unstable angina
  - History of congestive heart failure caused by insufficiency, damage, or stenosis of any heart valve
  - History of pulmonary artery hypertension
- History of organ transplantation

- TSH > 1.5x ULN
- Hyperthyroidism, T4 > ULN, TSH < LLN, taking methimazole or PTU and/or beta-blockers for hyperthyroidism
- AST or ALT > 2.5x ULN or total bilirubin > 1.5x ULN
- Serum creatinine > 1.5x ULN
- Fasting triglycerides > 499 mg/dL on two days
- LDL-cholesterol ≥ 160 mg/dL
- Positive HIV, hepatitis B, or hepatitis C screens
- Malignancy within five years of the screening visit (except basal cell or squamous cell carcinoma with clean surgical margins)
- Use of insulin within three months
- Use of exenatide (Byetta) or pramlintide (Symlin) within three months
- Use of one or more of the following:
  - fenfluramine or related derivatives (i.e., dexfenfluramine, norfenfluramine)
  - agents that have documented correlation with increased incidence of valvulopathy and/or primary pulmonary hypertension (e.g., cyproheptadine, trazodone, nefazodone, amoxapine, mirtazapine, pergolide, ergotamine, methysergide)
- Recent over-the-counter weight loss products, appetite suppressants, or prescription anti-obesity drugs
- Recent history of alcohol or drug abuse
- Significant change in smoking habits
- Change in weight of > 5 kg within three months of screening
- Use of very-low calorie liquid weight loss diet within six months
- Recent major surgical procedure

6.1.4 Treatment Groups

Prior to the implementation of Amendment 3, treatment groups were as follows:

- lorcaserin 10 mg QD: lorcaserin 10 mg BID: placebo; 1:1:1

After implementation of Amendment 3, randomization changed to:

- lorcaserin 10 mg BID: placebo; 1:1

6.1.5 Endpoints

6.1.5.1 Efficacy Measurements

6.1.5.1.1 Body Weight

Each patient was weighed throughout the study at designated times to assess changes in body weight. All efforts were made to schedule study visits prior to 10:00 AM to capture the fasting body weight and to reduce the variability in body weight normally observed throughout the day. All weights were measured in kilograms (kg). Patients were weighed at each study visit using a digital scale provided by Arena, or by a similar scale already at the site as approved by Arena. All scales met NTEP standards, had a precision to the nearest 100 g, and were approved for providing certifiable weights.

6.1.5.1.2 Waist and Hip Measurements

For a given patient, all attempts were made to have the same site personnel measure the waist and hips throughout the study to avoid variability in the method of measurement. Waist measurements were done according to the NHLBI Guideline in the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (September 1998). Hip measurements were performed using a tape measure to comfortably measure the distance around the largest extension of the buttocks. All measurements were reported in centimeters (cm). Each measurement was made and recorded 3 times at baseline, Week 24, and Week 52; the average of the 3 values at each time point was reported.

6.1.5.1.3 Changes in Use of Oral Hypoglycemic Medications

Changes in the use of hypoglycemic medications at each visit were recorded as follows:

- Start new hypoglycemic medication
- Increase dose of existing hypoglycemic medication
- No change
- Decrease dose of existing hypoglycemic medication
- Discontinue hypoglycemic medication

6.1.5.1.4 Body Composition

Body composition, including total body fat mass and total body lean mass was determined using Dual Energy X-ray Absorptiometry (DEXA) in a subset of randomized patients at selected Radiant Research, Inc. sites. BioClinica, Inc. (formerly Bio-Imaging Technologies, Inc.) of Newtown, PA provided all administration and project management services for DEXA scanning. This included site and image data management services, as well as site training and certification.

DEXA scans were performed on baseline (+ 2 weeks), Week 24 (± 2 weeks), and Week 52/Exit (± 2 weeks).

6.1.5.1.5 Quality of Life Assessment

The Impact of Weight on Quality of Life-Lite© (IWQOL-Lite) is a 31-item self-report measure of obesity-specific quality of life. The IWQOL-Lite provides an overall total score as well as scores on five domains: 1) physical function, 2) self esteem, 3) sexual life, 4) public distress, and 5) work.

The assessments were given at Day 1, Week 24, and Week 52 visits.

6.1.5.1.6 Metabolic Parameters and Markers of Cardiovascular Risk

Plasma lipids (total cholesterol, LDL-C, HDL-C, triglycerides, apolipoprotein B, apolipoprotein A1), hemoglobin A1c, and change in blood pressure (systolic and diastolic) were measured periodically during the study.

6.1.5.2 Pharmacokinetic Parameters

Blood samples were collected at Week 12, Week 24 and Week 52 for assessment of lorcaserin concentrations for use in the population pharmacokinetic analysis. Blood

samples were collected at three time points during each of the three visits: 15 minutes prior to study drug administration, 1.5-2.5 hours post-dose, and 3.5-6 hours post-dose.

6.1.5.3 Safety Measurements

- Vital signs: blood pressure, heart rate, oral temperature

- Clinical laboratory tests: serum chemistry, hematology, urinalysis, virology screens, drugs of abuse screens, urine pregnancy testing

- Physical and neurological examination

- 12-lead electrocardiograms (ECGs) were performed at Screening and Week 52/Exit and sent to a central reading laboratory for evaluation

- Adverse events

- Glycemic monitoring: Patients were asked to perform glucose self-monitoring at least twice daily and in the event of a suspected hypoglycemic event. Patients were asked to call the IVRS system to answer a series of questions at each suspected hypoglycemic event. The call was to be made after treatment for the event was completed. The patient was asked to provide the date and time of the event, self-monitored glucose value, action(s) taken, whether the assistance of another person was required, and whether hospitalization was required.

- Blood samples for prolactin measurement were collected in the morning prior to administration of study medication, and 2 ± 0.5 hours after study drug administration on Day 1 and on the same days that PK samples were collected (Week 12, 24 and 52/exit).

- Depression assessment: Symptoms of depression were assessed at screening and at Weeks 4, 12, 24, 36, and 52 (or early termination) by the Beck Depression Inventory Second Edition (BDI-II), in part to proactively provide evaluation or intervention if indicated. BDI-II is a 21-item self-report instrument intended 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).

- Echocardiography was performed at screening, Week 24, and Week 52/Exit

6.1.6 Protocol Amendments and Changes to the Planned Analyses

Table 128. Changes to the Conduct of BLOOM-DM

Amendment	Date	Changes
1	12 Nov 2007	• Removed screening echocardiogram requirement and added baseline echocardiogram requirement in relevant sections • Changed window for DEXA scan from "± 4 weeks" to "+ 2 weeks "(Day 1/Randomization) and "± 2 weeks" (Week 24) • Changed method of assigning patients to treatment groups to delete "7" from "HbAlc: 7-9%" and replace with "< 9%" • Added "Binge Eating Scale" to list of screening/enrollment procedures • Added clarifications to Exit Procedures/Early Termination and Exit echocardiogram procedures.
2	27 Nov 2007	• Revised prolactin and pharmacokinetic schedule as follows: "For females, reproductive status and the start date of last menstrual period will be documented at each visit for prolactin measurement" • Deleted text in Echocardiography Procedures as follows: "In these cases, a patient will qualify on the basis that the pulmonary valve flow acceleration time will be ≥ 120 msec, indicating the pulmonary artery pressure is not elevated"
3	01 Aug 2008	• Revised text in relevant sections to indicate discontinuation of patient randomization into lorcaserin 10 mg QD dose group • Adjusted sample size to accommodate discontinuation of lorcaserin 10 mg QD dose group • Revised hypothesis, efficacy assessments, and data analysis sections to accommodate inclusion of 10% weight reduction group in overall analyses • Added exclusion of topiramate to avoid confounding effects on weight

6.2 Appendix B. Echocardiogram Procedures in the Phase 3 Program

Valvular regurgitation was rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; for the pulmonic valve the rating was absent or present.

All echocardiograms were over-read by two blinded central readers (primary and secondary). In the BLOOM study, a panel of 19 cardiologists, in the BLOSSOM study, a panel of 23 cardiologists, and in the BLOOM-DM study a panel of 14 cardiologists trained on the protocol by Biomedical Systems (BMS) served as blinded central readers for this study. Out of the 14 readers in BLOOM-DM, 12 were readers in BLOOM and 12 were readers in BLOSSOM.

Whenever possible, all echocardiograms for a single patient were read by the same primary reader throughout the study to minimize variability in the over-read process. The secondary reader was assigned randomly for each patient throughout the study. Any discrepant readings between the primary and secondary readers were adjudicated by a third reader at BMS. When the two readings "matched" according to the following criteria, the results from the primary reader was entered into the database; in the event of discrepant reads, the third reader determined which read was entered into the database.

"Match" criteria for primary and secondary echocardiogram reads were defined as follows:

- Aortic and mitral valve regurgitation scores were identical (BLOOM) or if both were identical or less than or equal to "trace" ("trace" versus "absent" reads were not adjudicated; the primary read was used) (BLOSSOM and BLOOM-DM)

- LVEF: absolute value from secondary reader was within ±10% of primary reader (example: primary read = 50%; secondary read must have been 40-60 to "match")

- Pulmonary artery systolic pressure: value from secondary reader was within 10 mmHg of primary reader (example: primary read = 20 mmHg; secondary read must have been 10-30 mm Hg to "match")

An independent Echocardiographic Data Safety Monitoring Board (EDSMB) reviewed unblinded echocardiographic data at Week 24 and Week 52 to determine whether pre-defined study-stopping criteria had been met.

In the BLOOM study, echocardiograms were acquired at screening and at Weeks 24, 52, 76, and 104/Exit.

If a patient discontinued during Year 1, the following guidance applied for the Exit echocardiogram:

- If the patient discontinued from the study prior to Week 24 Visit, then an Exit echocardiogram was performed at the time of exit and the patient was scheduled for an additional post-study echocardiogram at the intended Week 52 visit.

- If the patient discontinued from the study after the Week 24 echocardiogram, but prior to the Week 36 visit, then the Week 24 echocardiogram served as the Exit echocardiogram and the patient was scheduled for an additional post-study echocardiogram to occur at least 3 months after the Week 24 echocardiogram (i.e., no sooner than the intended Week 36 Visit, but no later than the intended Week 52 Visit).

- If the patient discontinued at or after the Week 36 Visit, but prior to the Week 52 echocardiogram, then an exit echocardiogram was done at the time of exit and no additional echocardiogram was performed.

For patients who discontinued from the trial prior to Week 52, but who returned for the intended Week 52 echocardiogram and had FDA-defined VHD on the intended Week 52 echocardiogram, the patient was asked to return for an additional echocardiogram at the time of the intended Week 76 echocardiogram.

Patients who completed the initial 52 weeks of treatment were eligible to participate in the Year 2 dosing period.

If a patient discontinued during Year 2, the following guidance applied for the Exit echocardiogram:

- If the patient discontinued from the study prior to Week 76 echocardiogram, an Exit echocardiogram was performed at the time of exit and no additional echocardiograms were performed, except as follows:
    - If a patient had FDA-defined VHD on the echocardiogram obtained at Week 52, and the patient discontinued from the study between Week 52 and Week 76, the following additional paradigm was followed to assure that an appropriate subsequent echocardiogram was obtained:
        - If the Exit echocardiogram was obtained prior to Week 64, the patient was asked to return for another echocardiogram at the time (±4 weeks) of the intended Week 76 echocardiogram. This echocardiogram was analyzed as the Week 76 echocardiogram.
        - If the Exit echocardiogram was obtained after Week 64, the Exit echocardiogram was analyzed as the Week 76 echocardiogram.

- If the patient discontinued from the study after the Week 76 echocardiogram, but prior to the Week 88 Visit, then the Week 76 echocardiogram served as the exit echocardiogram and no additional echocardiograms were performed.

- If the patient discontinued from the study after the Week 88 Visit, but prior to the Week 104 echocardiogram, an exit echocardiogram was performed at the time of exit and no additional echocardiograms were performed.

In BLOSSOM and BLOOM-DM, echocardiography was performed at screening, Week 24, and Week 52/Exit. Although the image acquisition was performed during the screening period, a patient could be randomized as soon as the site received confirmation from the echocardiogram core lab that a technically adequate study was performed. The echocardiogram did not need to be interpreted by the cardiologist prior to randomization of the patient. Patients who required referral or treatment for cardiac valve abnormalities were to be followed until the condition stabilized or until 30 days after their scheduled Week 52 visit. All patients, even those who discontinued from the study, were asked to return for the scheduled Week 52 echocardiogram.

In BLOOM, BLOSSOM, and BLOOM-DM, if the following findings were found, the sponsor recommended referral to a cardiologist:

- Mitral regurgitation increased at least 2 categories from baseline *and* rated moderate or greater

- Aortic regurgitation rated ≥ moderate

- Pulmonary artery pressure > 50 mm Hg with at least 10 mm Hg increase from baseline

- LVEF ≤ 35

In BLOSSOM and BLOOM-DM, a careful medical history and physical examination was additionally recommended in the event of the above findings. Patients who were asymptomatic and had no clinical signs were to have remained enrolled in the study on study medication until the evaluation was performed and an AE was only to be recorded if clinical signs or symptoms were present.

In BLOOM, BLOSSOM, and BLOOM-DM, if the following findings were found, the sponsor recommended withdrawal of study medication and referral to a cardiologist:

- Severe mitral regurgitation
- Severe aortic regurgitation
- Pulmonary artery pressure ≥ 60 mm Hg

The BLOSSOM and BLOOM-DM protocols specifically stated that an AE should only be recorded if this was a change from baseline or if cardiovascular symptoms worsened or developed since baseline.

6.3 Appendix C. Ischemic Cardiovascular SAEs – BLOOM-DM

6.3.1 Lorcaserin 10 mg BID

6.3.1.1 Coronary artery occlusion

- Patient 1146-S018 was a 49-year-old male with a medical history of diabetes, hypertension, carpal tunnel, gout, hyperlipidemia, heart disease status post angioplasty and four stents, gastroesophageal reflux disease, ankle/foot edema, and splenomegaly. Concomitant medications included metformin, furosemide, atenolol, rosuvastatin, amlodipine, valsartan, aspirin, naproxen, isosorbide nitrate, and potassium chloride. Approximately 10 months into the trial, the patient presented to his cardiologist with complaints of exertional chest pain for a period of two weeks. ECG demonstrated sinus bradycardia and nonspecific intraventricular block. He was admitted to the hospital one week later and underwent a cardiac catheterization that demonstrated a 90% stenosis of the proximal left anterior descending artery and a 75% stenosis of the distal right coronary artery; drug-eluting stents were placed. There was also a 40% stenosis of the proximal right coronary artery. The ejection fraction was 55% with mild inferior hypokinesia of the inferior wall. Treatment medications included clopidogrel, carvedilol, simvastatin, morphine, ondansetron, oxycodone/acetaminophen, and temazepam. The drug was temporarily stopped due to this event.

6.3.2 Lorcaserin 10 mg QD

6.3.2.1 Coronary artery disease

- Patient 1131-S002 was a 67-year-old male history of diabetes, obesity, hypertension, migraine, and hyperlipidemia. On Study Day 372, approximately 10 days after the

final dose of study drug, the patient was evaluated for right arm and chest pain. An ECG showed no acute abnormalities, and two sets of cardiac enzymes were negative. The patient was hospitalized with a diagnosis of atypical chest pain and discharged the next day. The patient was re-hospitalized on Study Day 382 with substernal chest discomfort and mild shortness of breath. A cardiac catheterization revealed significant coronary artery disease for which percutaneous coronary intervention was performed on Study Day 399.

6.3.2.2 Angina pectoris

- Patient 1174-S029 was a 61-year-old male with a history of diabetes, coronary artery disease, dyslipidemia, and hypertension. On Study Day 264 the patient was admitted to the hospital for chest pain. A coronary angiogram revealed mild plaque of the left main and large dominant right coronary artery. A myocardial infarction was ruled out (troponin not reported). The patient was treated with aspirin and atorvastatin in addition to the concomitant medications, which included carvedilol and losartan. The drug was not discontinued.

6.3.2.3 Cerebrovascular accident

- Patient 1227-S002 was a 55-year-old female with a history of diabetes, hypertension, obesity, hyperlipidemia, and left carotid artery occlusion. The left carotid artery occlusion was unknown to the investigator at the time of randomization. Family history included cerebrovascular accident. On Study Day 61, the patient began to experience confusion and difficulty concentrating with additional blurred vision on Study Day 66. The patient informed the study site of her symptoms on Study Day 73 and was advised to discontinue study drug. At her study visit on Study Day 78, she was found to have elevated blood pressure (162/90 mmHg) and blurred vision. The patient was advised to go to an emergency department. She was admitted to the hospital on Study Day 78 and was diagnosed with a hypertensive cerebrovascular event. The patient was discharged the following day with advice to exercise regularly and control her diabetes through better dietary control. The drug was discontinued as a result of this event.

- Patient 1275-S005 was a 48-year-old male with a history of diabetes, hypertension, hyperlipidemia, and chronic heart failure with systolic dysfunction. On Study Day 24, the patient presented to the hospital with a three-day history of nausea, vomiting, loss of appetite, dizziness, vertigo, blurred vision, and the feeling of being off-balance. On the day of admission he also reported left leg numbness, mild left side weakness, and some numbness and tingling in his hands and feet. The patient was diagnosed with a posterior cerebellar stroke and admitted to the hospital. Study drug was permanently discontinued on Study Day 23. Six days later the patient was transferred to a rehabilitation center. He was discharged 14 days later.

6.3.3 Placebo

6.3.3.1 Myocardial infarction

- Patient 1130-S050 was a 55-year-old male with a history of diabetes, hypertension, and erectile dysfunction. On Study Day 363, the patient was determined to have a lateral myocardial infarction based on the results of scheduled study procedures (ECG and echocardiogram). The narrative states that the event may have occurred three months prior to diagnosis. Study drug was not discontinued due to this event.

- Patient 1243-S011 was a 64-year-old male with a history of diabetes and hypertension. On Study Day 283, the patient presented with the emergency department with chest pain and diagnosed with an anteroseptal myocardial infarction. Peak troponin was 4.04 ng/mL. Treatment included cardiac stent placement, acetylsalicylic acid, heparin, clopidogrel, simvastatin, diphenhydramine, and famotodine. The patient was discharged three days later. Drug was interrupted but not permanently withdrawn due to this event.

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

BRIEFING DOCUMENT

ADVISORY COMMITTEE, MAY 10, 2012

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 briefing document: April 13, 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2
Statistical Reviewer:	Janice Derr, Ph.D.
Concurring Reviewer:	J. Todd Sahlroot, Team Leader and Deputy Division Director
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Julie Golden, M.D., Medical Reviewer
	Eric Colman, M.D., Medical Team Leader and Deputy Division Director
	Mary H. Parks, M.D., Division Director
Project Manager:	Patricia Madara

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 $p=0.0430$).

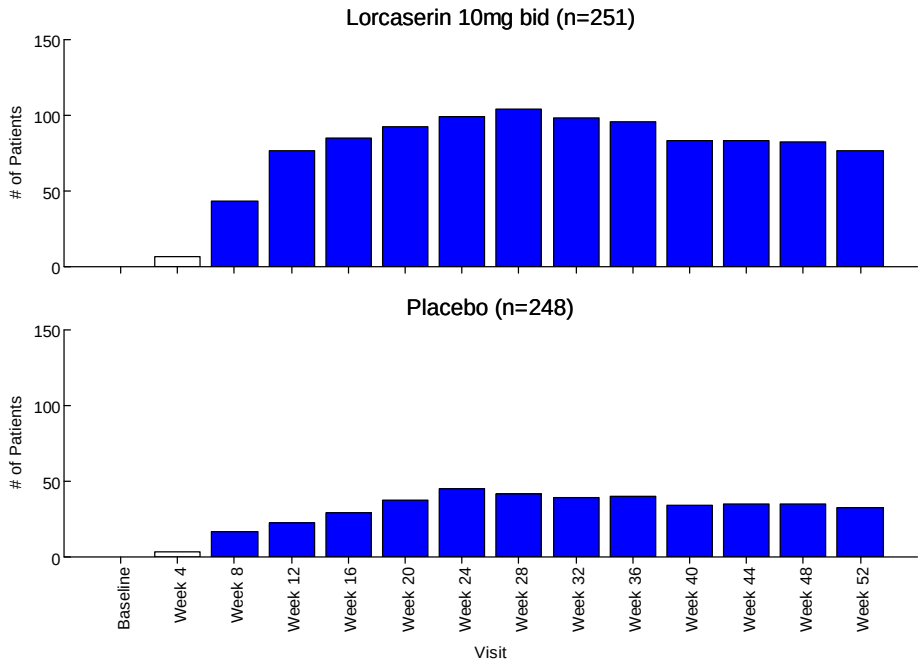
TABLE 1 Weight as a percent change from baseline at week 52 in Study 009, Study 011 and Study 010

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 model[1]					
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. This approach may be 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 kg/m^2), or overweight with at least one weight related co-morbid condition (BMI 27-30 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 kg/m^2), or overweight subjects (BMI $\geq$ 27-30 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]

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

[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.

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. 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)

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

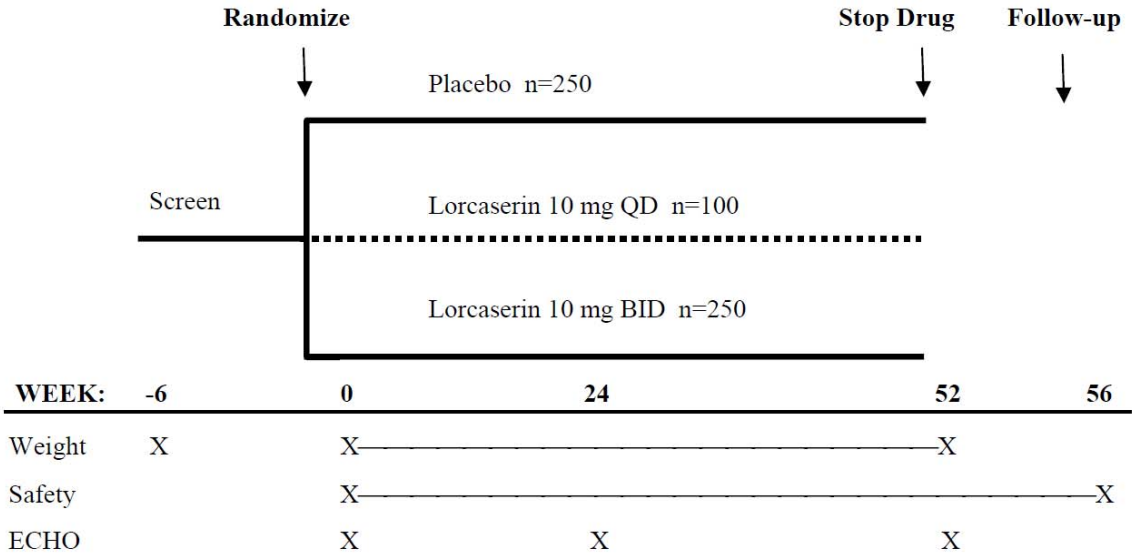
Design: Study 010 was designed to evaluate the effects of lorcaserin on overweight or obese subjects with type 2 diabetes during 52 weeks of treatment. The study was designed as a randomized, double-blind, placebo-controlled clinical trial. All subjects received dietary and exercise counseling at each 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/m^2, 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 $\geq$ 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 ≥ 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 group[3]. 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.

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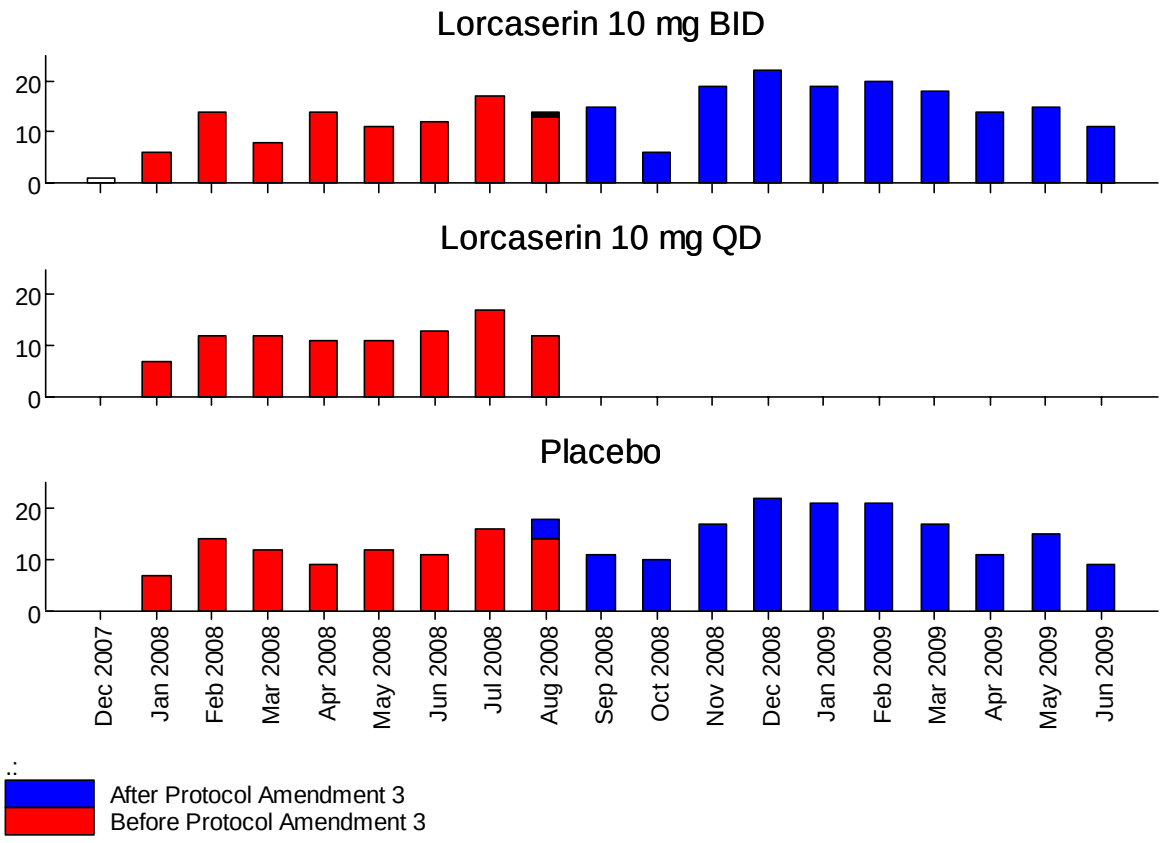
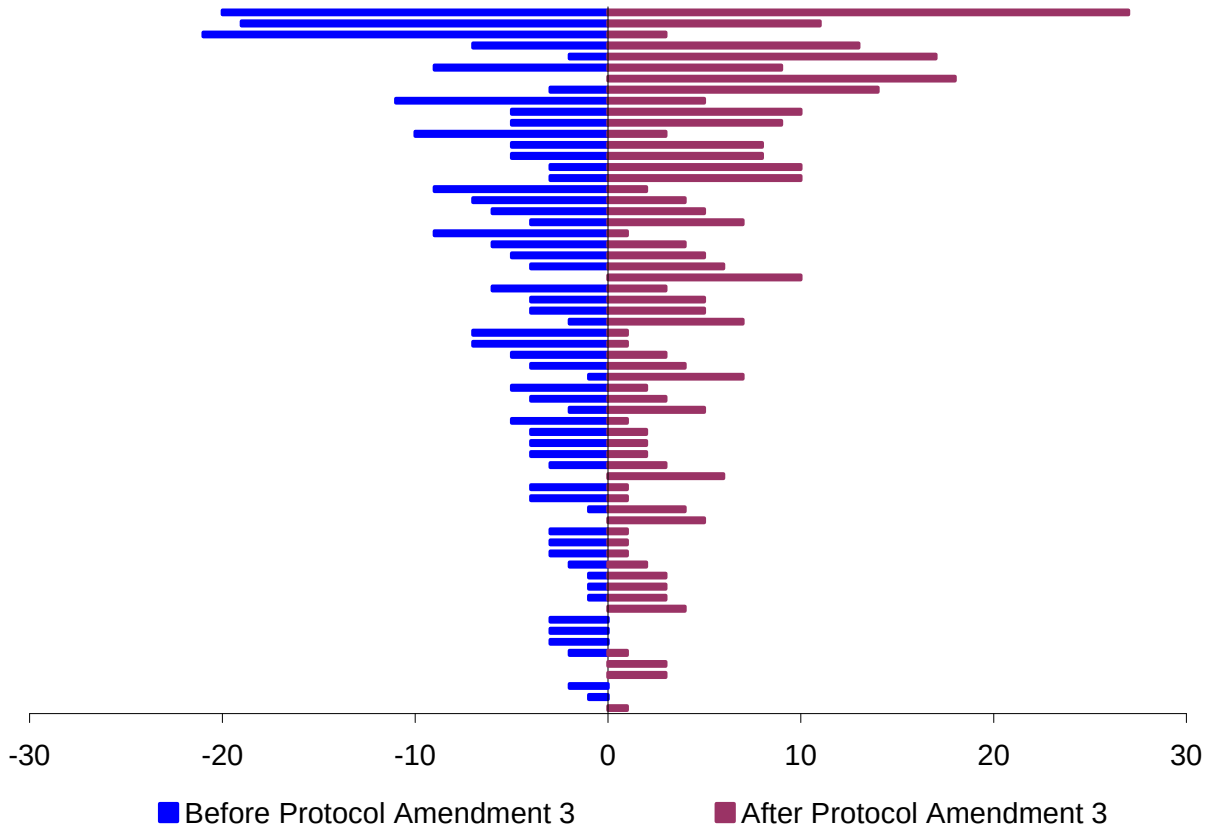


Source: Analysis by this reviewer

[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 ≥ 1.5% from baseline at any scheduled measurement or (2) HbA1c ≥ 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/m^2, 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/m^2 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).

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. However, this relationship did not appear to have changed with the implementation of Protocol Amendment 3 (FIGURE 10).

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.

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/m^2. 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. Disposition[1]			
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

Notes

[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"

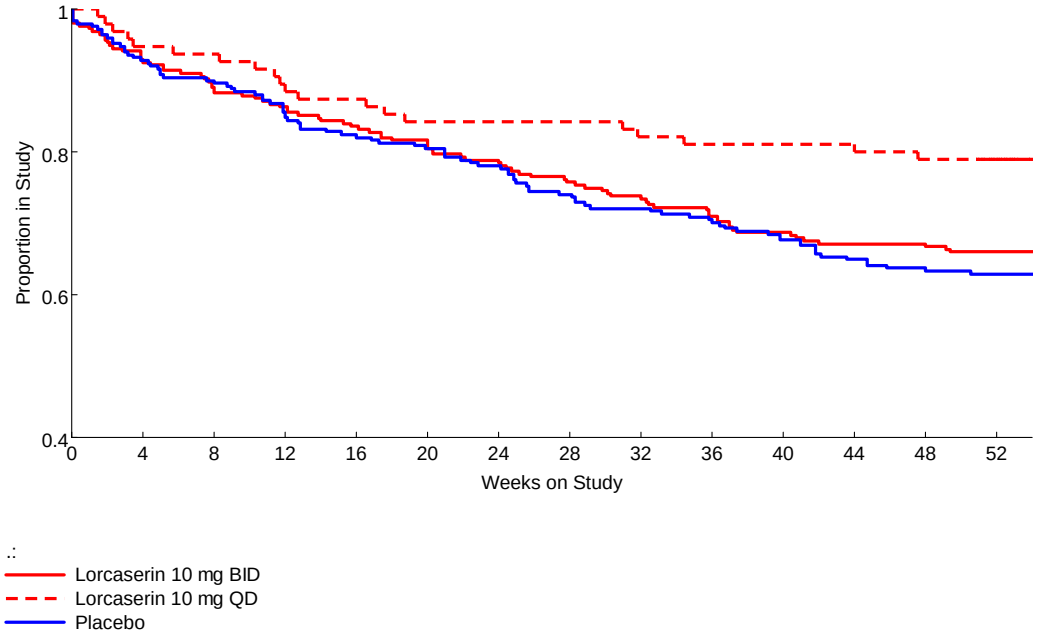
[3] Placebo arm, withdrawal of consent for diabetes-related reasons: Subject 1216-0548 "stated her blood sugars were going too high due to study meds"; Subject 1250-0227 "was put on insulin per DR in ER, insulin not allowed per protocol, subject withdrew consent"

[4] Lorcaserin 10 mg qd arm, PI decision; Subject 1236-0263 "A1c increase > 1.5% from baseline at week 36"

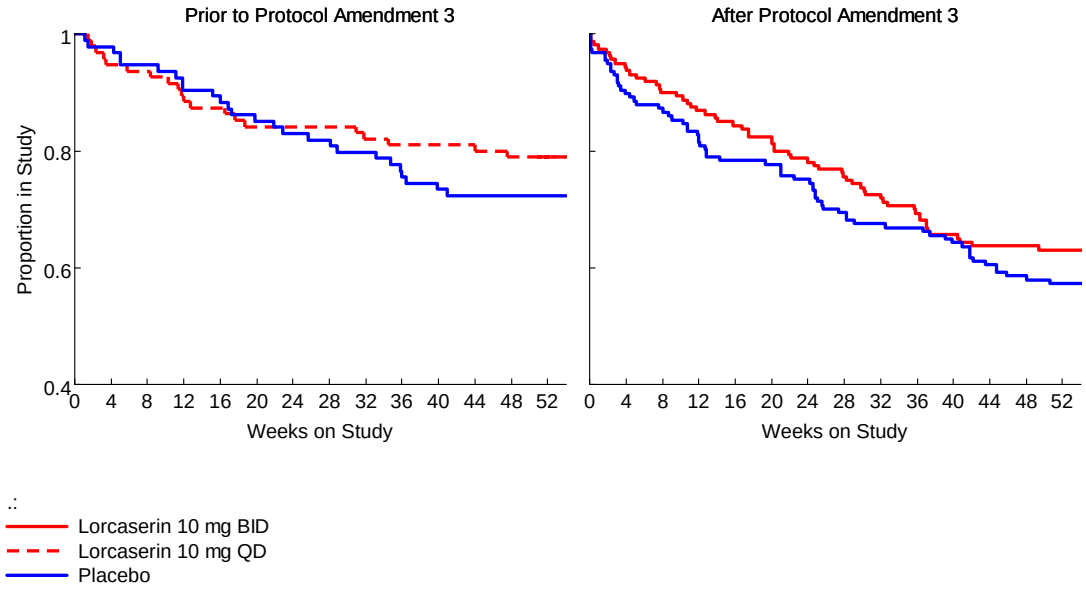
Sources: Study 010 clinical report, Figure 2, Table 5, and additional analysis by this reviewer

FIGURE 5 Disposition of subjects in Study 010 by week 52

A. Disposition for all randomized subjects

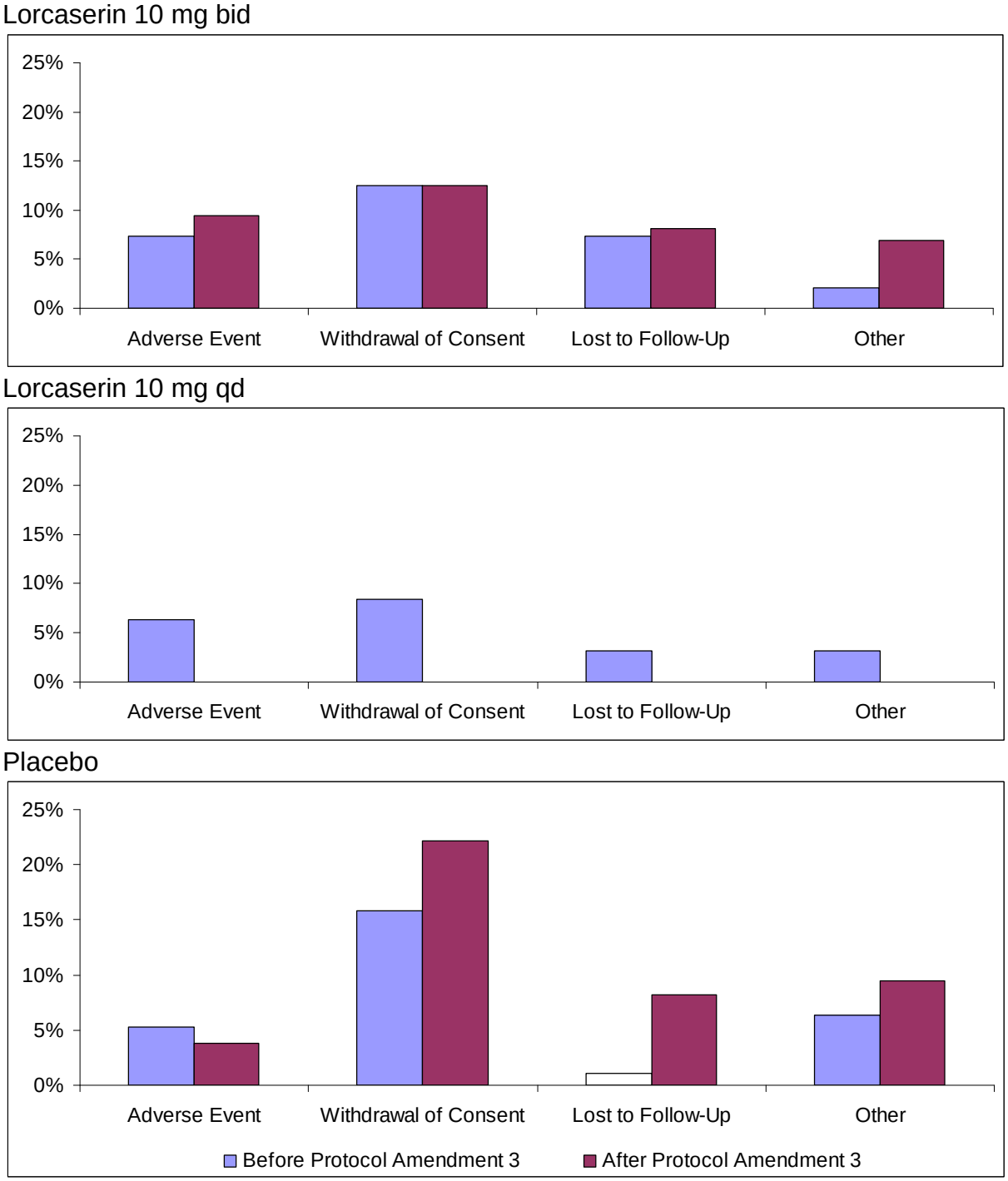


B. Disposition subdivided by the implementation of Protocol Amendment 3



Source: Analysis by this reviewer

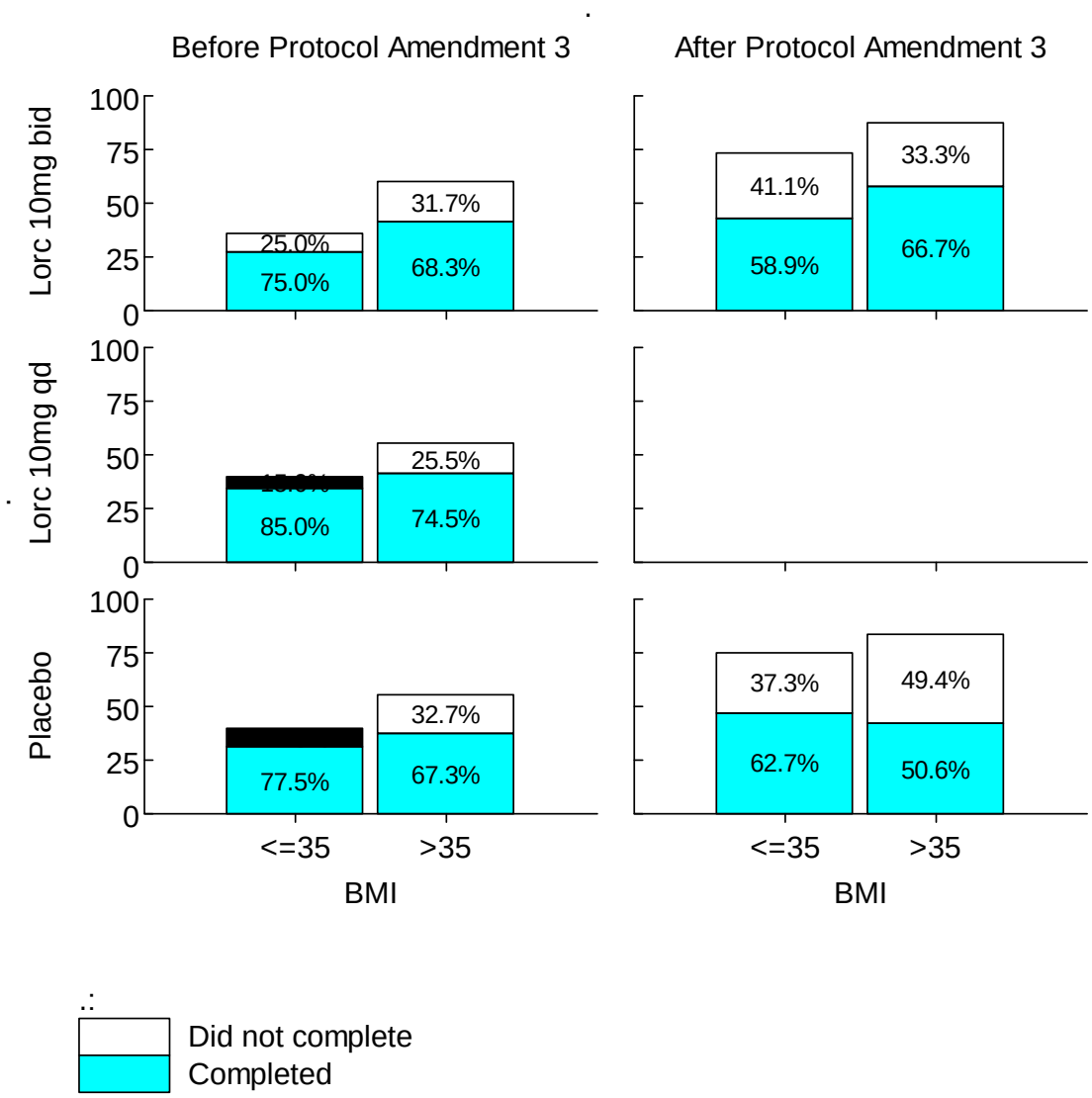
FIGURE 6 Study 010; Reason for early discontinuation by study arm and enrollment subgroup defined by the implementation of Protocol Amendment 3



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

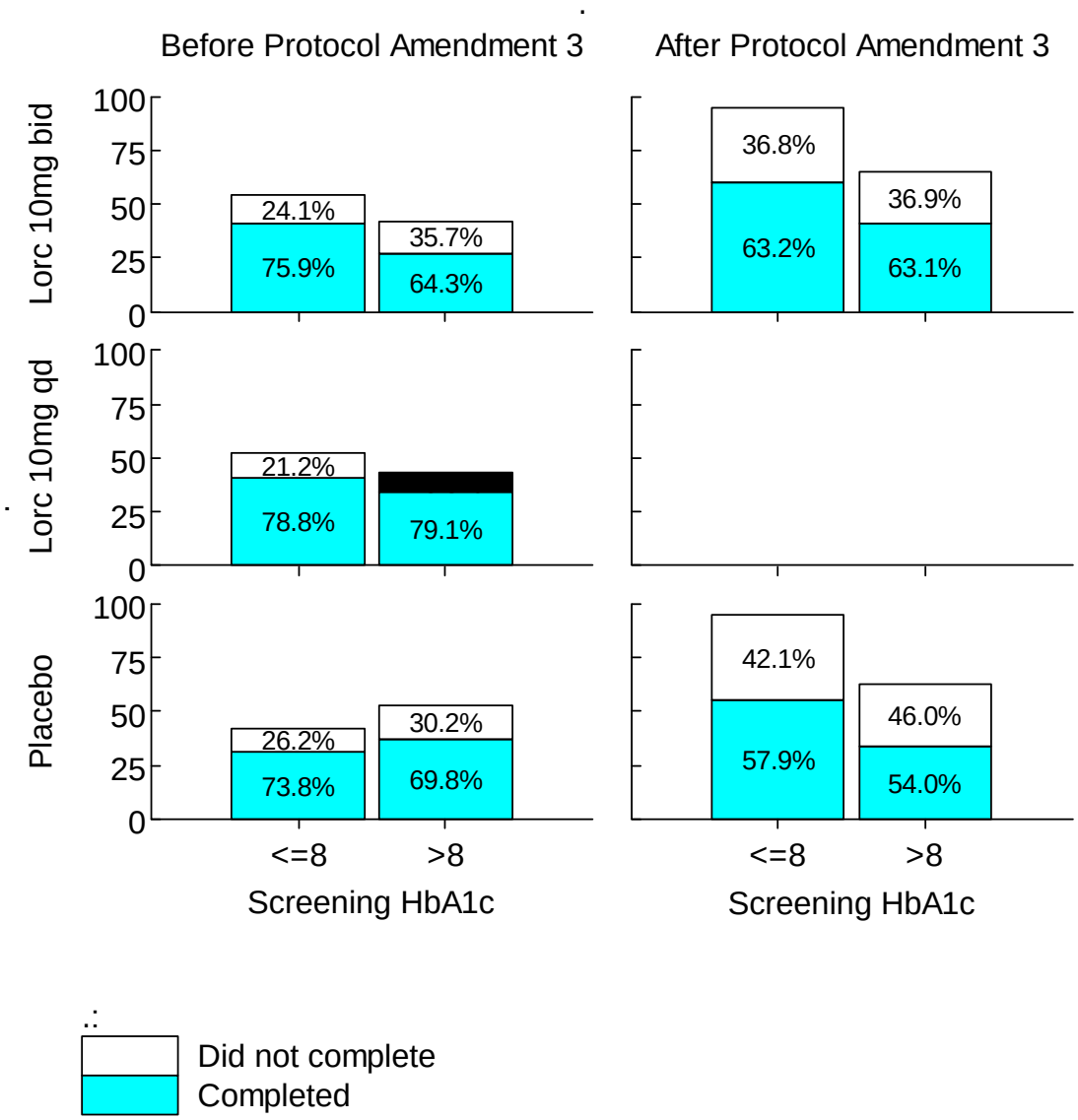
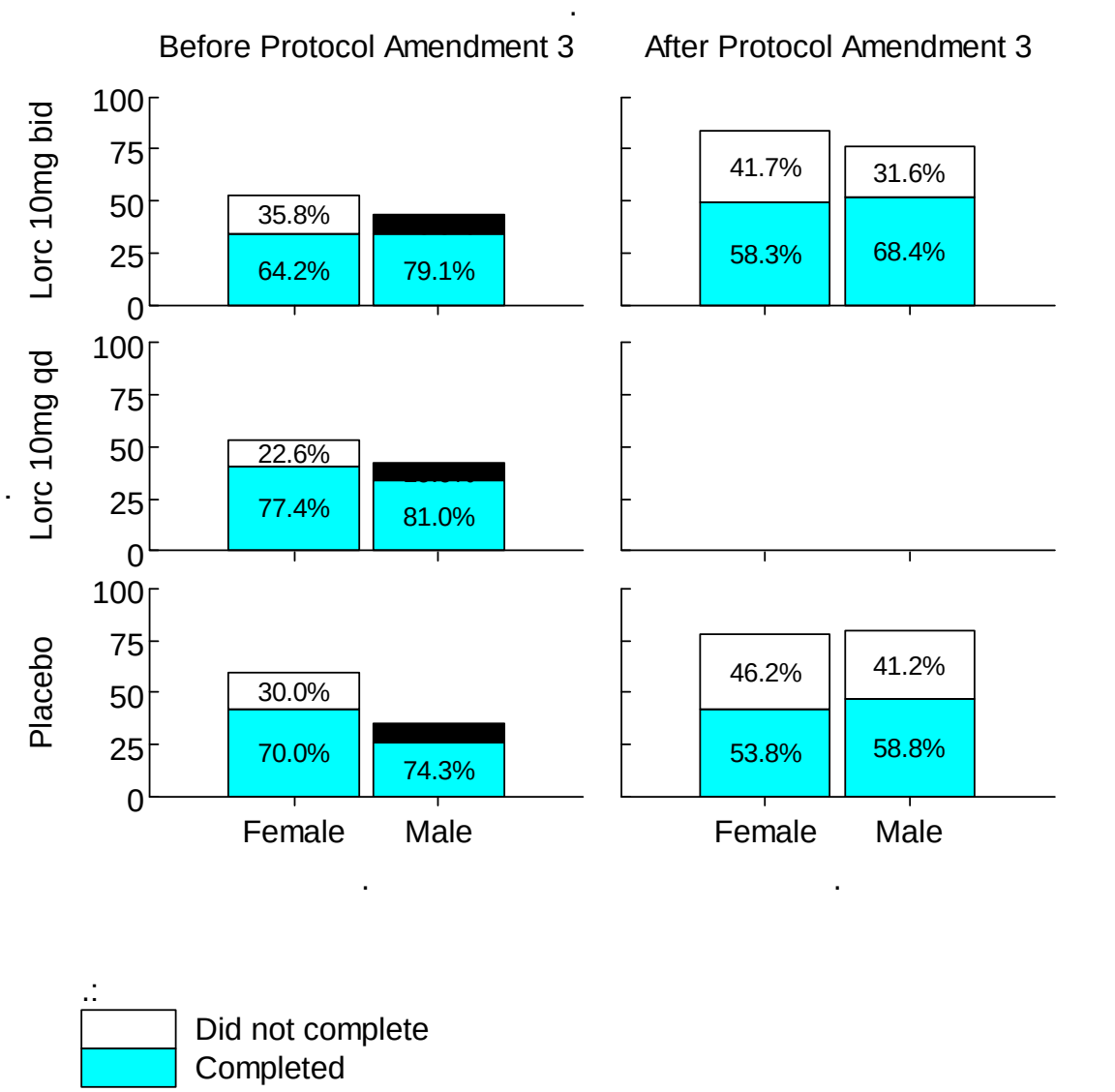


FIGURE 9 Percentage of early withdrawals (before week 52) in Study 010, and the relationship to sex



Source: Analysis by this reviewer

FIGURE 10 Percentage of early withdrawals (before week 52) in Study 010, and the relationship to being a 5% responder at week 52 (with LOCF imputation)

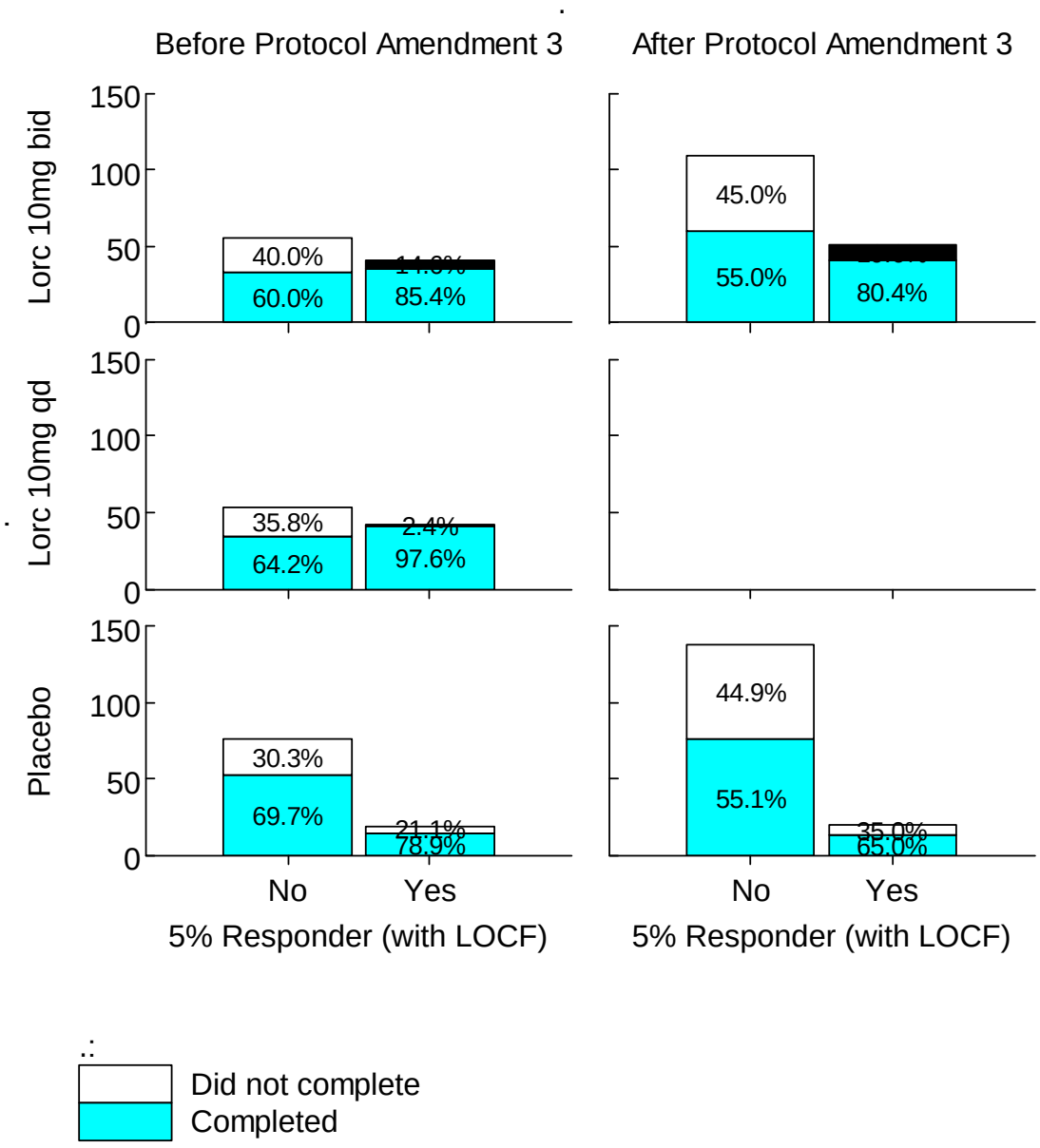


TABLE 5 Study 010; Changes in use of drugs to treat Type 2 diabetes during the 52-week double-blind period

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

Number of randomized subjects	Lorcaserin 10mg bid n=256	Lorcaserin 10mg qd n=95	Placebo n=252
Age (years)			
Mean ± SD	53.2 ± 8.3	53.1 ± 8.0	52.0 ± 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 ± SD	103.7 ± 17.0	106.0 ± 19.4	102.6 ± 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 ± SD	36.2 ± 4.5	36.1 ± 4.8	35.9 ± 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 ± SD	8.1 ± 0.8	8.1 ± 0.8	8.1 ± 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 ≥ 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%)

Note: [1] The stratification variable combined the two categories of SU with and without metformin.

Source: 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 lorcaserin, 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		

Sources: 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 model[1]					
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		

Notes:

[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%)			

Notes:

[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.

Sources:

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%)			

Notes:

[1] The difference in proportions and 95% CI were calculated using normal approximation.

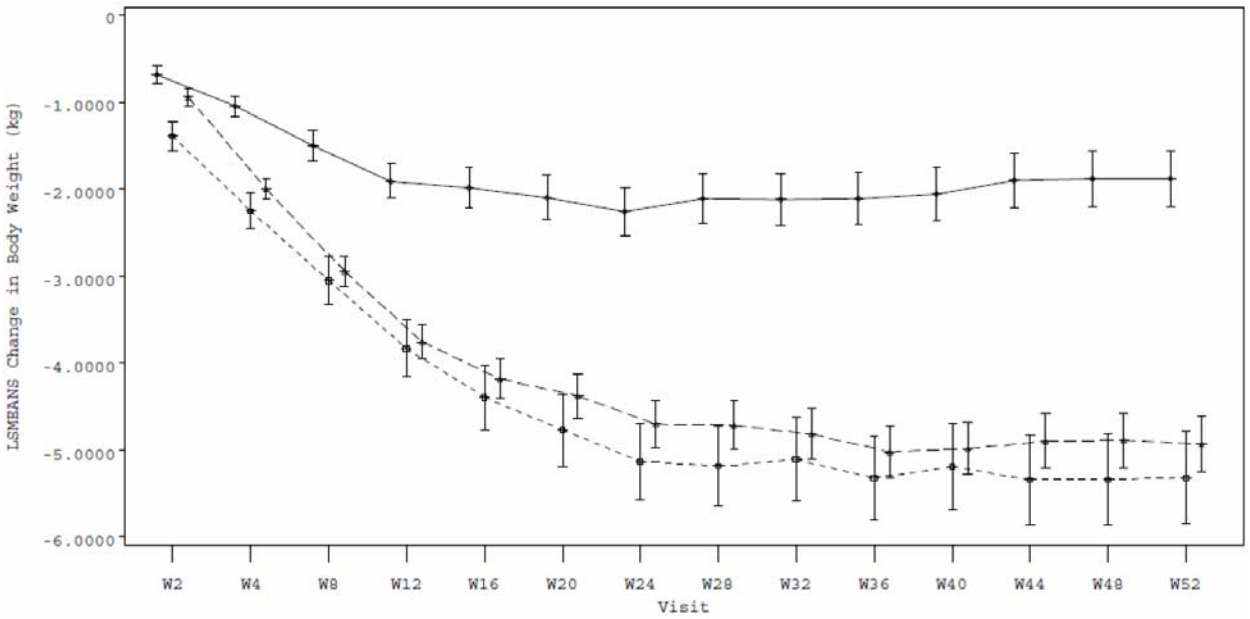
[2] The odds ratios and p-values were calculated by using the logistic regression model specified for the primary analysis, with effects for treatment, gender and baseline body weight.

[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

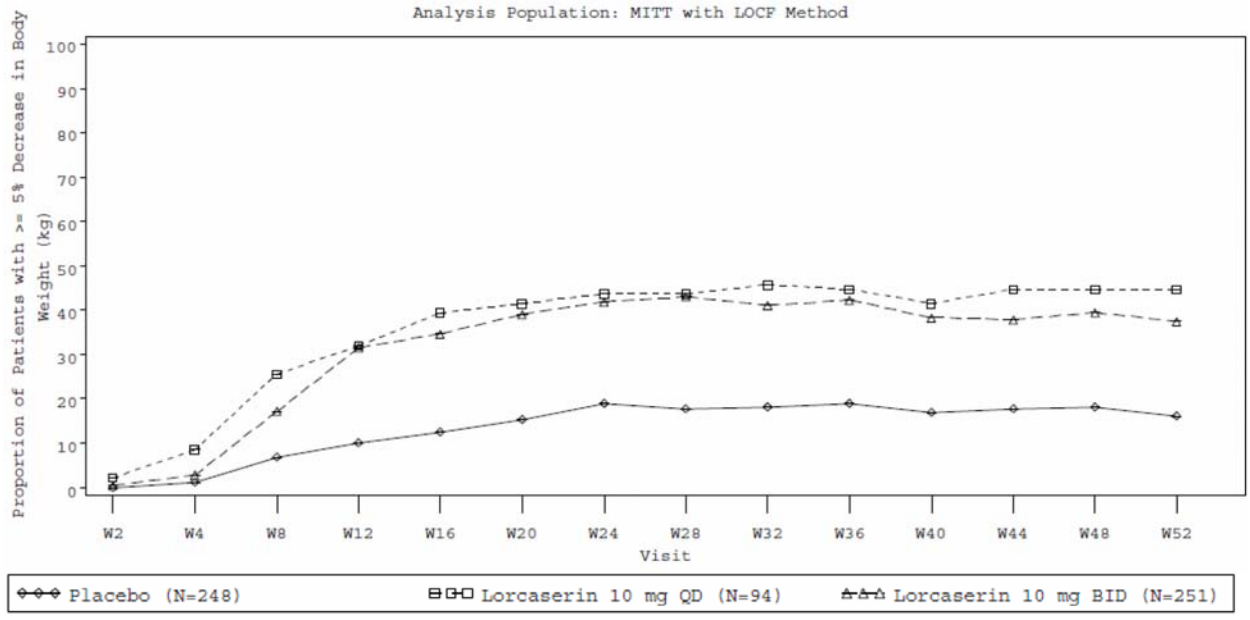
Sources: Study 10 clinical report, Table 8, and additional analysis by this reviewer

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

A. Mean change from baseline in body weight (kg)

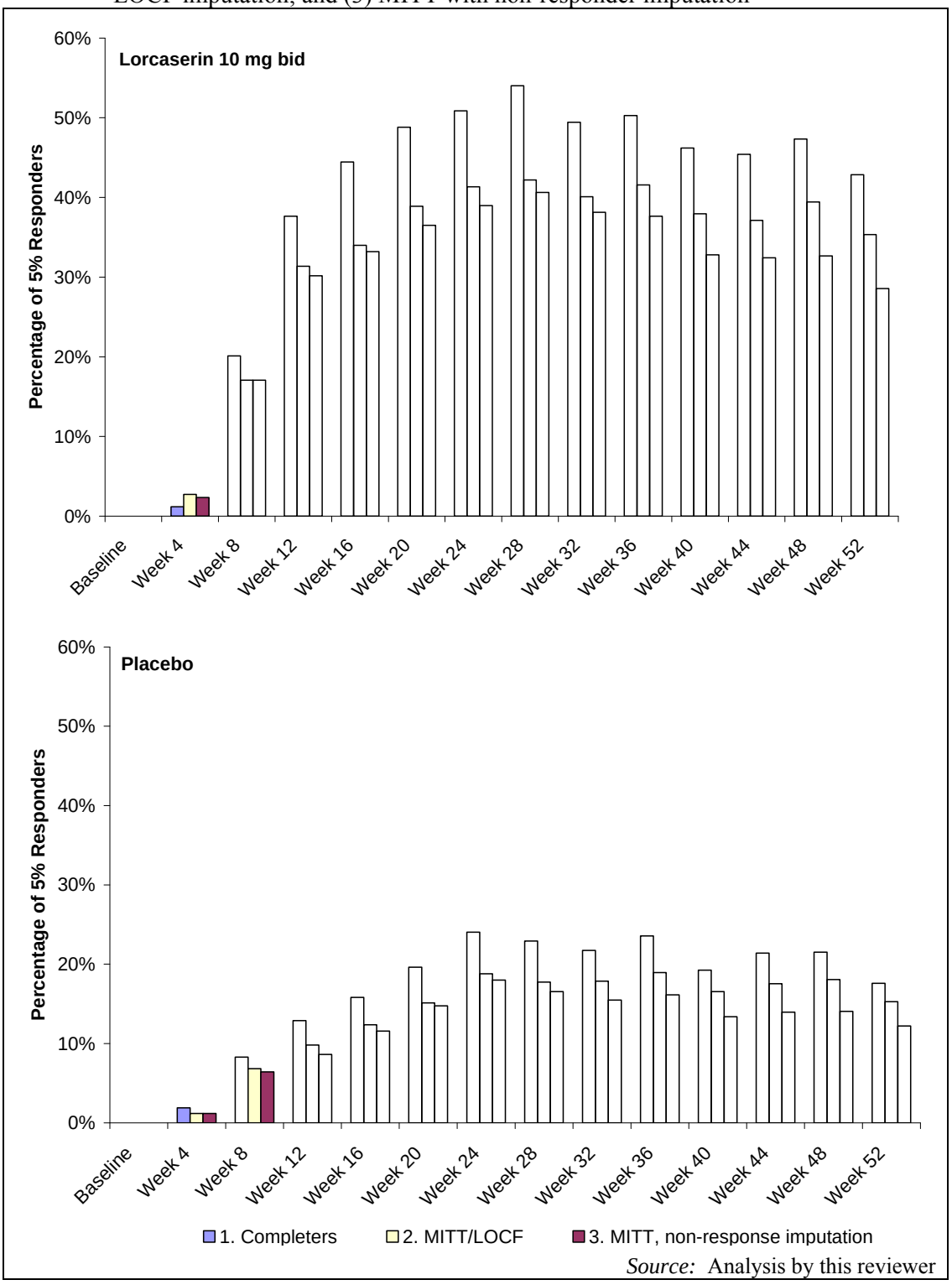


B. Proportion of patients achieving ≥ 5% reduction in body weight



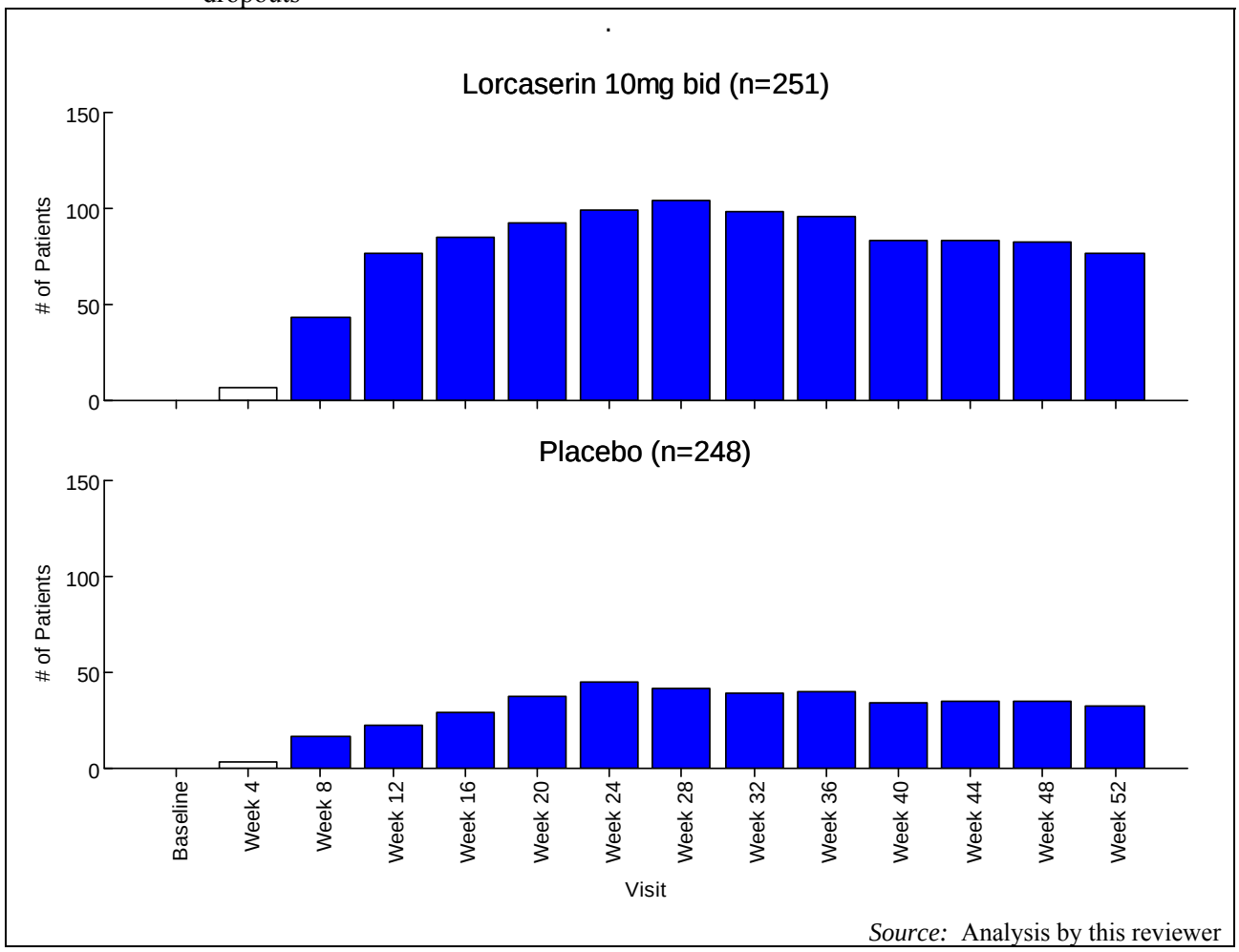
Source: Study 010 clinical report, Figure 3 and Figure 4

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



Source: Analysis by this reviewer

FIGURE 13 Study 010; 5% non-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		
Notes: [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. [2] Endpoints are listed in the pre-specified order for testing within this group.				*Sources:* From the Study 010 clinical report: 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. [4] Endpoints are listed in the pre-specified order for testing within this group.				*Sources:* From the Study 010 clinical report: 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 ± 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 ± 0.8	0.1 (-1.9, 2.2)	0.8905
Placebo	248	126.5 (13.5)	-0.9 ± 0.9		
2. Diastolic Blood Pressure (mmHg)					
Lorcaserin 10 mg bid	251	77.9 (8.0)	-1.1 ± 0.6	-0.4 (-1.8, 1.0)	0.5633
Placebo	248	78.7 (7.9)	-0.7 ± 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.				*Sources:* 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 ± 0.6	-1.8 (-3.1, -0.4)	0.0116
Placebo	248	43.2 (6.5)	0.0 ± 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.				*Source:* 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 ± 0.7	1.1 (-0.7, 2.8)	0.2206
Placebo	248	74.0 (17.6)	10.2 ± 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. [8] A change in the overall converted score in the positive direction represents an improvement in the overall quality of life.				*Source:* From the Study 010 clinical report, Table 36	

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 $\geq$ 30 kg/m^2), or overweight with at least one weight related co-morbid condition (BMI 27-30 kg/m^2). 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

	Study 009 "Bloom"		**Study 011 "Blossom"**			**Study 010 "Bloom-DM"**		
Number of randomized subjects (n)	**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: Lorcaserin

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 model[1]					
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		

Notes:

[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.

Sources:

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%)			

Notes:

[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.

Sources:

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/m^2 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 ≥ 8.0 (treatment arm by baseline HbA1c subgroup interaction p = 0.0209; FIGURE 19).

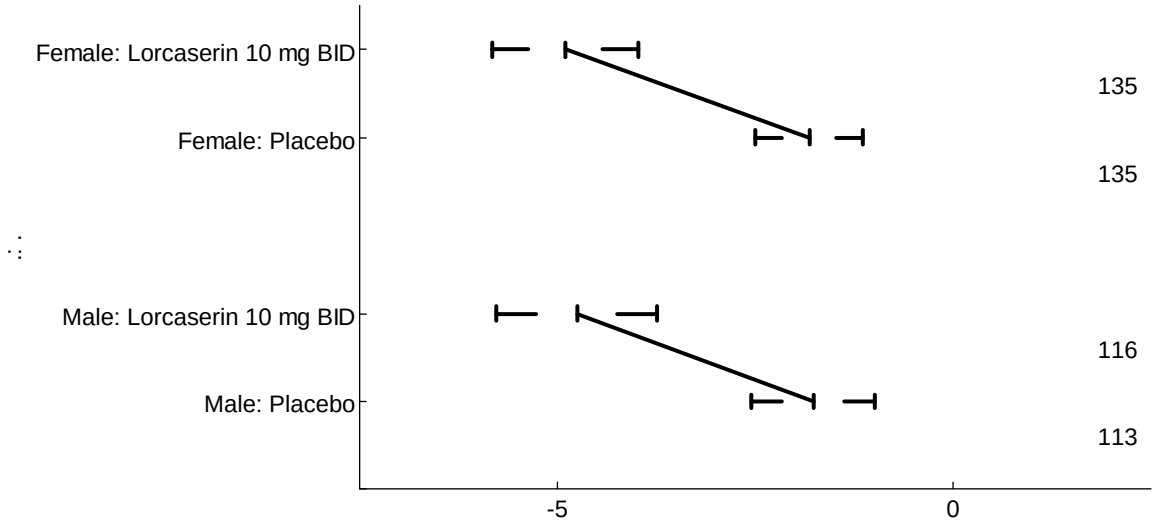
Subgroup analysis for the HbA1c change from baseline at week 52:

Subjects with baseline HbA1c ≥ 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

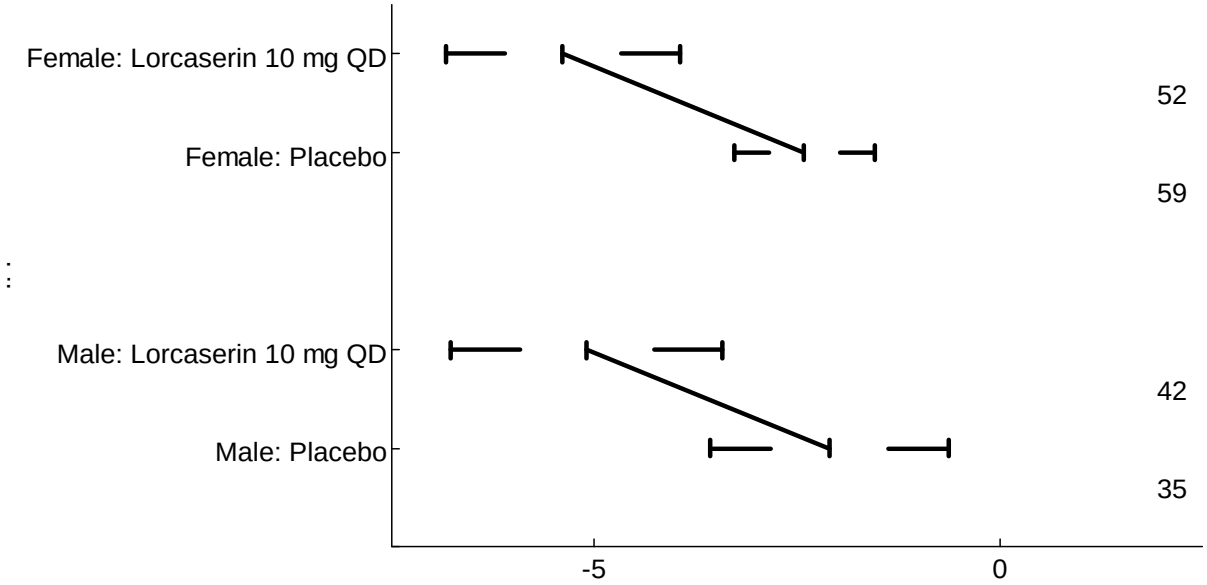
Mean weight at week 52 as % change from baseline by sex (MITT/LOCF)

A. Full Enrollment Set: Lorcaserin 10 mg BID vs Placebo



sex x treatment: p=0.8676

B. Enrollment Prior to Protocol Amendment 3: Lorcaserin 10 mg QD vs Placebo



sex x treatment: p=0.9575

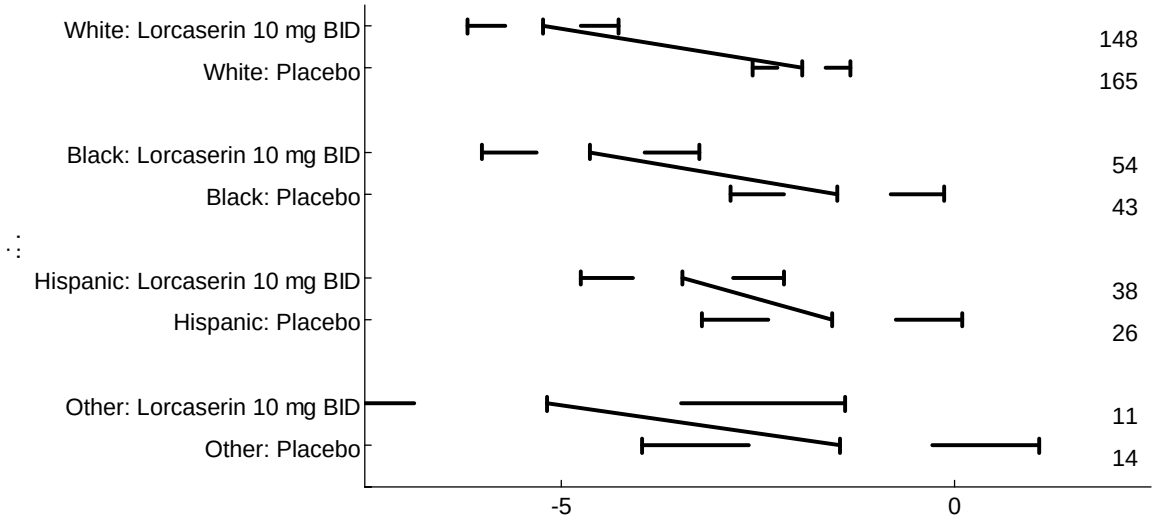
Note: The means and 95% confidence intervals are depicted for each subgroup and treatment arm. The p-values are from the analysis of covariance model based on the primary analysis model, with the following general form: baseline weight, HbA1c stratification factor, diabetes medication stratification factor, treatment arm, sex and sex by treatment arm interaction.

Source: Analysis by this reviewer

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

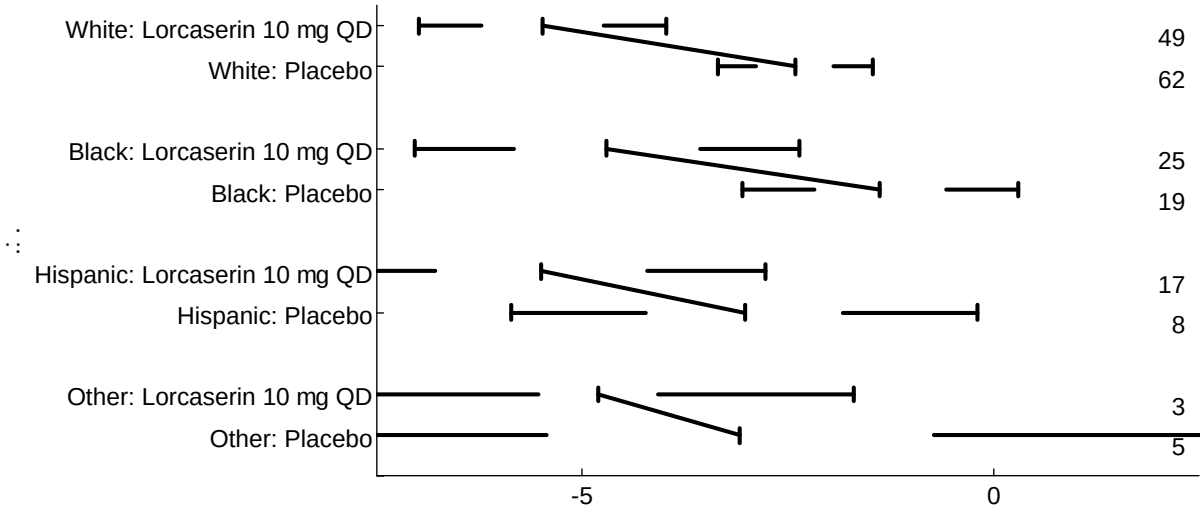
Mean weight at week 52 as % change from baseline by race (MITT/LOCF)

A. Full Enrollment Set: Lorcaserin 10 mg BID vs Placebo



race x treatment: p=0.7376

B. Enrollment Prior to Protocol Amendment 3: Lorcaserin 10 mg QD vs Placebo



race x treatment: p=0.9151

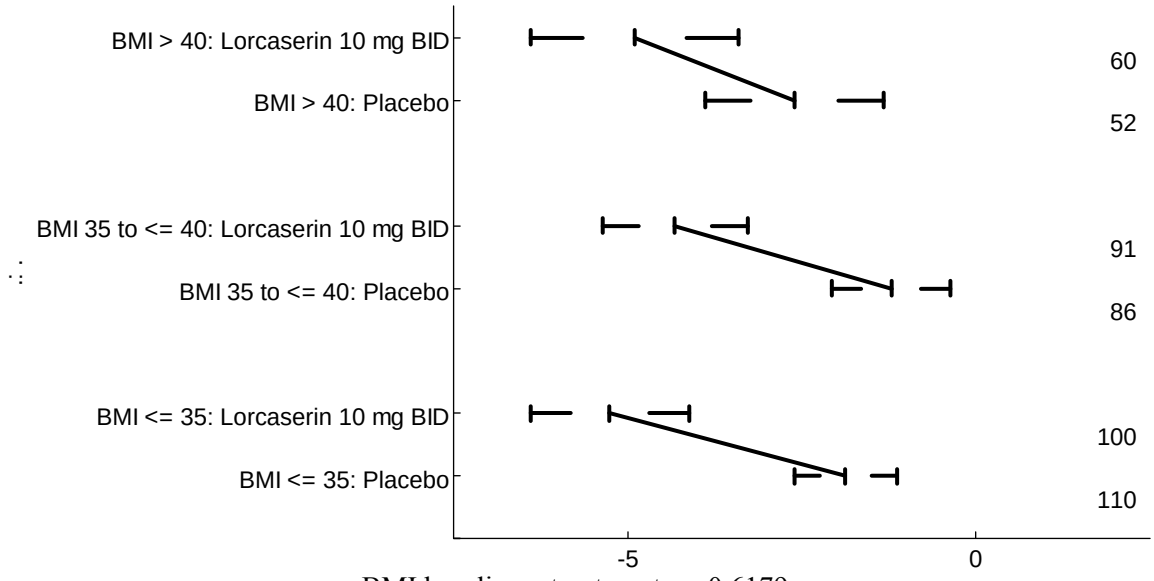
Note: The means and 95% confidence intervals are depicted for each subgroup and treatment arm. The p-values are from the analysis of covariance model based on the primary analysis model, with the following general form: baseline weight, HbA1c stratification factor, diabetes medication stratification factor, treatment arm, race and race by treatment arm interaction.

Source: Analysis by this reviewer

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

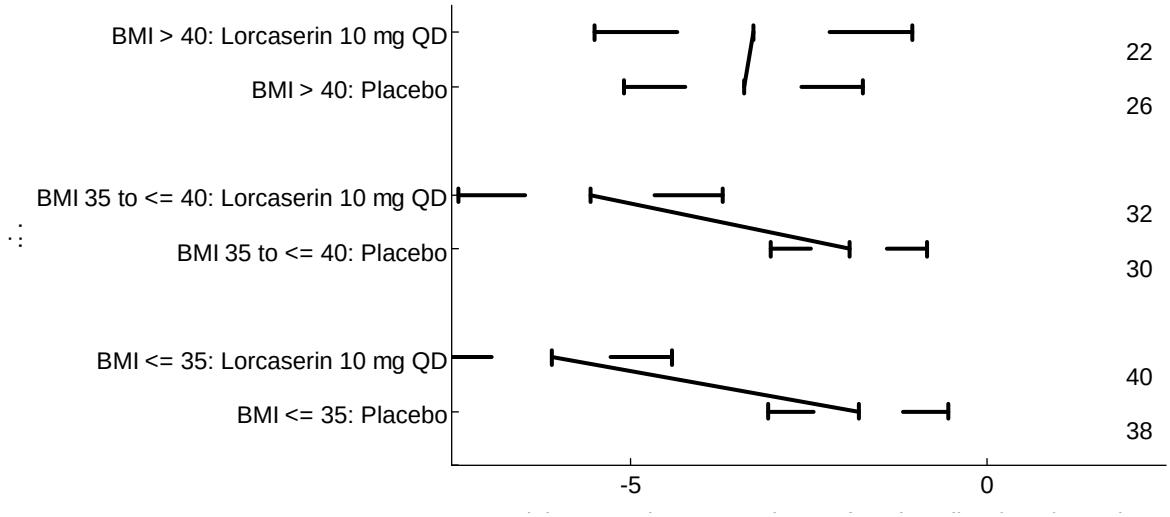
Mean weight at week 52 as % change from baseline by BMI at baseline (MITT/LOCF)

A. Full Enrollment Set: Lorcaserin 10 mg BID vs Placebo



BMI baseline x treatment: p=0.6179

B. Enrollment Prior to Protocol Amendment 3: Lorcaserin 10 mg QD vs Placebo



BMI baseline x treatment: p=0.0271

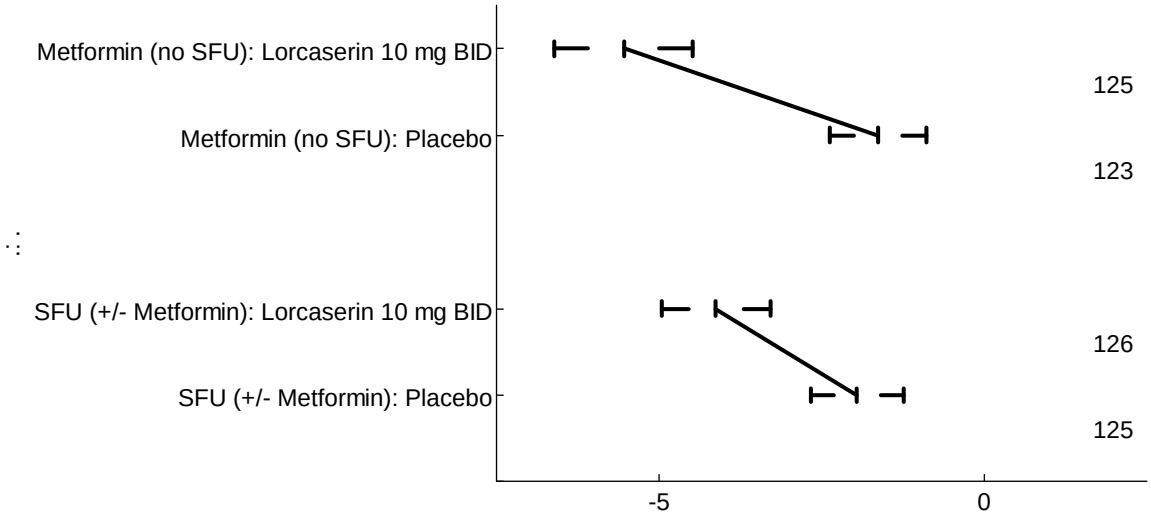
Note: The means and 95% confidence intervals are depicted for each subgroup and treatment arm. The p-values are from the analysis of covariance model based on the primary analysis model, with the following general form: baseline weight, HbA1c stratification factor, diabetes medication stratification factor, treatment arm, BMI and BMI by treatment arm interaction.

Source: Analysis by this reviewer

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

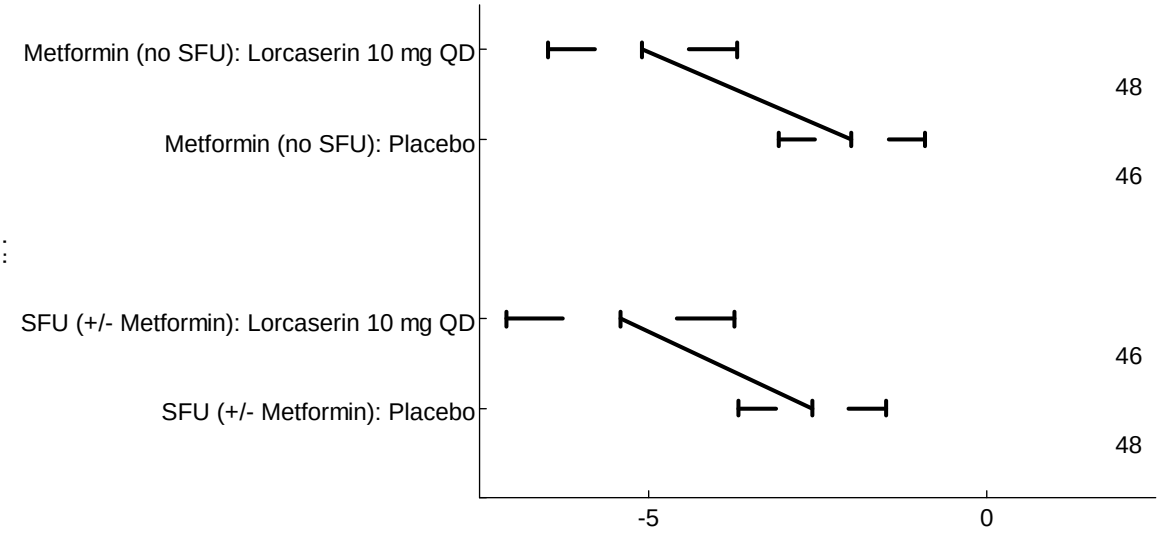
Mean weight at week 52 as % change from baseline by HbA1c at baseline (MITT/LOCF)

A. Full Enrollment Set: Lorcaserin 10 mg BID vs Placebo



diabetes medication x treatment: p=0.0430

B. Enrollment Prior to Protocol Amendment 3: Lorcaserin 10 mg QD vs Placebo



diabetes medication x treatment: p=0.7781

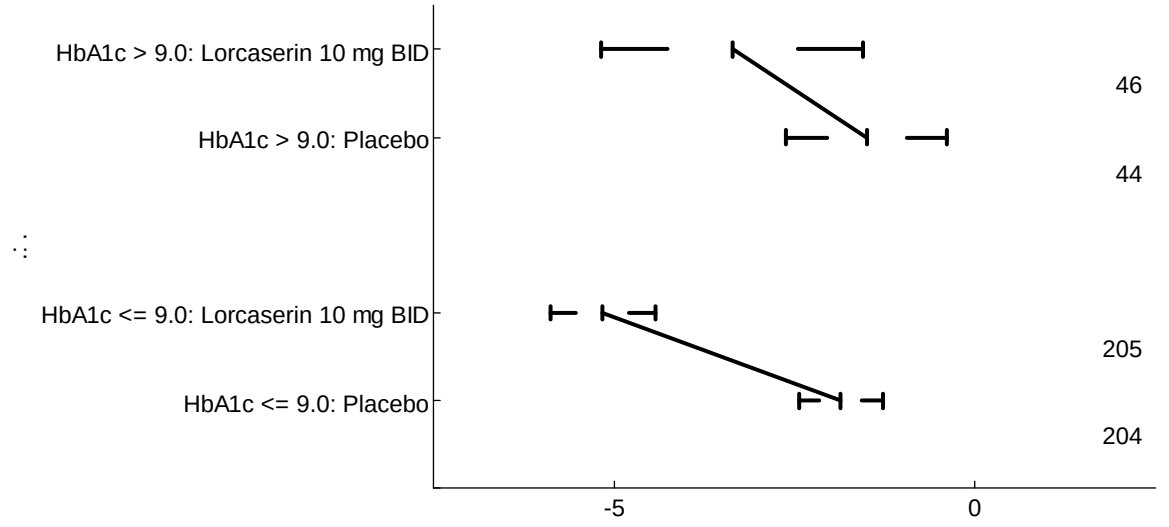
Note: The means and 95% confidence intervals are depicted for each subgroup and treatment arm. The p-values are from the analysis of covariance model based on the primary analysis model, with the following general form: baseline weight, HbA1c stratification factor, diabetes medication stratification factor, treatment arm, and diabetes medication factor by treatment arm interaction.

Source: Analysis by this reviewer

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

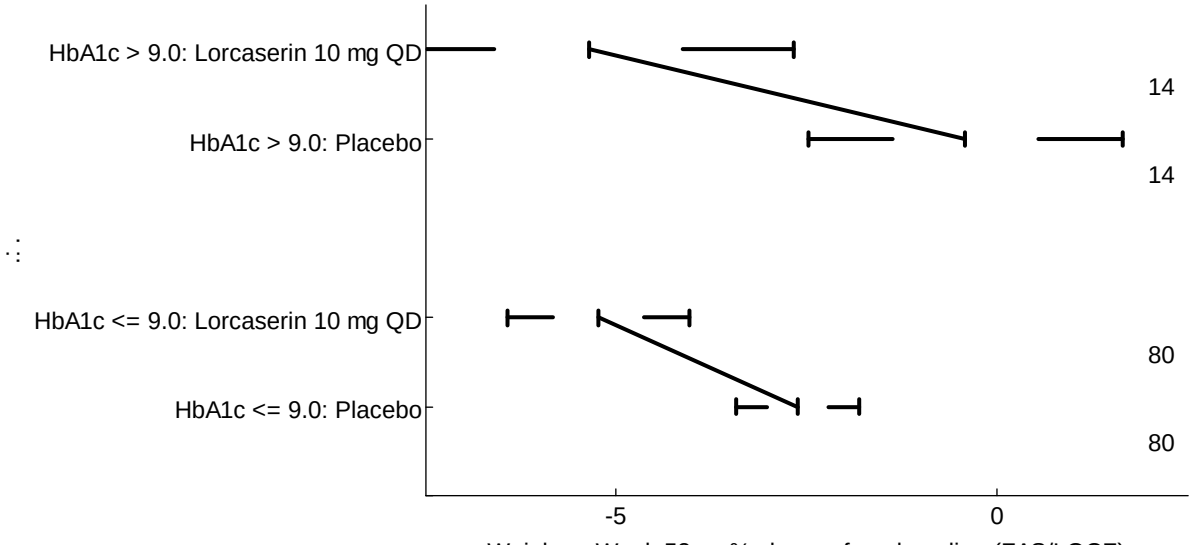
Mean weight at week 52 as % change from baseline by HbA1c at baseline (MITT/LOCF)

A. Full Enrollment Set: Lorcaserin 10 mg BID vs Placebo



HbA1c baseline 9.0 cutpoint x treatment: p=0.2097

B. Enrollment Prior to Protocol Amendment 3: Lorcaserin 10 mg QD vs Placebo



HbA1c baseline 9.0 cutpoint x treatment: p=0.2324

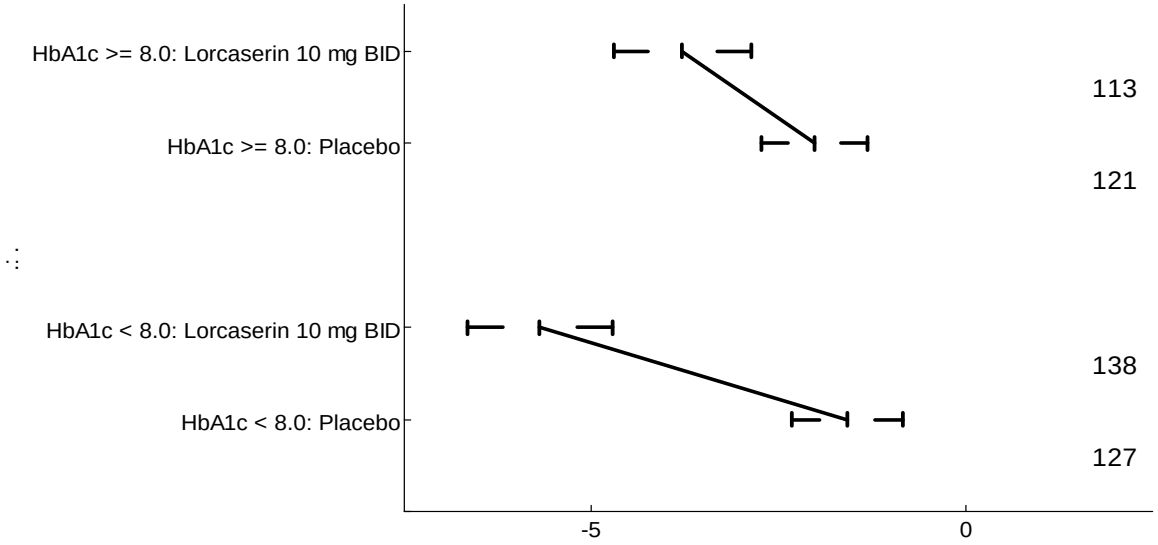
Note: The means and 95% confidence intervals are depicted for each subgroup and treatment arm. The p-values are from the analysis of covariance model based on the primary analysis model, with the following general form: baseline weight, HbA1c stratification factor (with a cutpoint of 9.0), diabetes medication stratification factor, treatment arm, and HbA1c factor by treatment arm interaction.

Source: Analysis by this reviewer

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

Mean weight at week 52 as % change from baseline by HbA1c at baseline, with a revised cutpoint of 8.0, (MITT/LOCF)

Full Enrollment Set: Lorcaserin 10 mg BID vs Placebo



HbA1c baseline (8.0 cutpoint) x treatment: p=0.0209

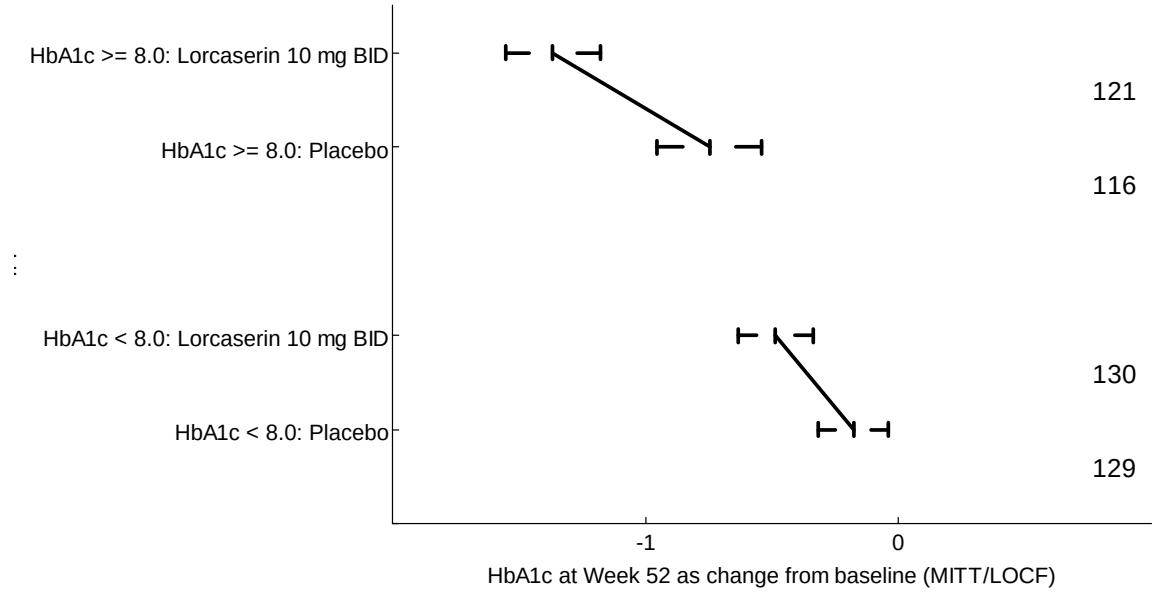
Note: The means and 95% confidence intervals are depicted for each subgroup and treatment arm. The p-values are from the analysis of covariance model based on the primary analysis model, with the following general form: baseline weight, baseline HbA1c with a cutpoint of 8.0, diabetes medication stratification factor, treatment arm, and baseline HbA1c cutpoint of 8.0 by treatment arm interaction.

Source: Analysis by this reviewer

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

Mean weight at week 52 as % change from baseline by HbA1c at baseline, with a revised cutpoint of 8.0, (MITT/LOCF)

Full Enrollment Set: Lorcaserin 10 mg BID vs Placebo



HbA1c baseline (8.0 cutpoint) x treatment: p=0.0603

Note: The means and 95% confidence intervals are depicted for each subgroup and treatment arm. The dependent variable is HbA1c at week 52, expressed as a change from baseline. The p-values are from the analysis of covariance model based on the primary analysis model, with the following terms: baseline HbA1c factor with a cutpoint of 8.0, diabetes medication stratification factor, treatment arm, and the interaction of baseline HbA1c cutpoint of 8.0 by treatment arm.

Source: Analysis by this reviewer

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.