FDA Briefing Document

NDA 22529

Lorqess (lorcaserin hydrochloride) Tablets, 10 mg

Sponsor: Arena Pharmaceuticals

Advisory Committee – September 16, 2010

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Section:

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 19 August 2010

FROM: Eric Colman, MD
Deputy Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food & Drug Administration

TO: Members and Consultants,
Endocrinologic & Metabolic Drugs Advisory Committee

SUBJECT: 16 September 2010, Advisory Committee meeting for lorcaserin

Background

Thank you for agreeing to participate in the September 16, 2010, advisory committee meeting. This meeting is being held to discuss the efficacy and safety of lorcaserin. Lorcaserin is a 5HT2c receptor agonist being developed by Arena Pharmaceuticals for the treatment of obesity. The sponsor is seeking approval of lorcaserin 10 mg BID.

The FDA briefing document contains reviews of lorcaserin's pharmacology, preclinical carcinogenic profile, and clinical efficacy and safety. The conclusions from the FDA's Executive Carcinogenicity Assessment Committee's review of the lorcaserin carcinogenicity studies in rodents are also included the briefing document.

The 5HT2c receptor subtype, expressed in the hypothalamus and choroid plexus, plays a role in appetite regulation, activation of the HPA axis, locomotion, anxiety, and in the modulation of dopamine release. The 5HT2b receptor subtype, expressed in the central nervous system and in various peripheral tissues, is involved in motor behavior, cerebrovascular tone and mitogenesis of cardiac valves, among other things. The 5HT2a receptor subtype, expressed in the cortex, hypothalamus, cerebellum, and amygdale and the liver, coronary vasculature, adipocytes, platelets, the kidney, and the gastrointestinal tract, functions in the modulation of neurotransmitters and peptides, adipocyte differentiation, platelet aggregation, and enteric neurotransmission.

In-vitro assays indicate that lorcaserin's binding affinity and activation of the 5HT2c receptor subtype is greater than its affinity and activation of the 5HT2a or 5HT2b subtypes. When assessed by calcium release, the EC50s for lorcaserin are 6 nM, 52 nM, and 350 nM for the 2c, 2a, and 2b receptor subtypes, respectively.

In 2007 the Division of Metabolism and Endocrinology Products issued a draft guidance entitled Developing Products for Weight Management. The guidance stipulates that a drug will be considered effective if at least one of the following criteria is satisfied after one year of treatment:

1 Mean efficacy criterion - 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

or

2 Categorical efficacy criterion - 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

Efficacy of Lorcaserin

The efficacy of lorcaserin was evaluated in two phase 3 trials comprising approximately 7200 individuals. The BLOSSOM trial was a one-year, placebo-controlled study that randomized 4008 overweight (BMI 27-29.9 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2) nondiabetic adult male and female subjects to lorcaserin 10 mg BID, lorcaserin 10 mg QD, or placebo in a 2:1:2 fashion. The BLOOM trial was a two-year, placebo-controlled study that randomized 3182 overweight and obese adult males and females to lorcaserin 10 mg BID or placebo in a 1:1 fashion. At the end of one year of treatment, the lorcaserin group was re-randomized in a 2:1 fashion to lorcaserin 10 mg BID or placebo. Subjects originally randomized to placebo remained on placebo during the second year of the study.

The mean percent change in body weight from baseline to Year 1 was approximately -2.5% in the placebo groups and approximately -5.8% in the lorcaserin 10 mg BID groups ($p<0.001$ vs. placebo). The mean percent change in body weight in the lorcaserin 10 mg QD group was nearly -5% ($p<0.001$ vs placebo). In the categorical analyses, approximately 23% of subjects in the placebo groups lost $\geq$ 5% of baseline body weight during Year 1 compared with 47% and 40% of subjects in the lorcaserin 10 mg BID and lorcaserin 10 mg QD groups, respectively ($p<0.001$ both lorcaserin vs. placebo).

The weight loss observed in the lorcaserin-treated groups was associated with improvements in systolic and diastolic blood pressure, lipoprotein lipid levels, fasting glucose and insulin levels, and levels of hsCRP.

When gauged by the standards of the Division's 2007 draft guidance for Developing Products for Weight Management, the mean weight loss associated with the lorcaserin 10 mg QD and BID dose was about 3% greater than the mean weight loss with placebo. Therefore lorcaserin did not satisfy the guidance's mean efficacy criterion. However, the lorcaserin 10 mg BID dose did, by a slim margin, satisfy the categorical efficacy criterion.

Safety of Lorcaserin

Valvular heart disease, neuro-psychiatric and cognitive-related adverse events, and preclinical tumor development are three noteworthy safety issues discussed in the FDA background documents.

Valvular Heart Disease: The weight-loss drugs fenfluramine and dexfenfluramine were removed from the U.S. market in 1997 due to the occurrence of left-sided valvular heart disease (VHD). Recent research suggests that activation of the 5HT2b receptor is the mechanism responsible for fenfluramine- and dexfenfluramine-associated VHD. Lorcaserin's affinity for the 5HT2c receptor is greater than its affinity for the 5HT2b receptor. To evaluate if lorcaserin increases the risk for VHD, subjects in the phase 3 studies were evaluated with serial echocardiograms. Valvular heart disease was defined as mild or greater aortic insufficiency and/or moderate or greater mitral insufficiency. This is referred to as FDA-defined valvulopathy or FDA-defined VHD.

A mutually-agreed upon non-inferiority margin of 1.5 for the development of VHD was used to determine the sample size for the phase 3 lorcaserin development program. While arbitrary, the Division considered this margin reasonable for the initial evaluation of lorcaserin.

In the BLOOM trial, the incidence of FDA-defined VHD over the course of one year was 2.35% in the placebo group and 2.66% in the lorcaserin 10 mg BID group [RR 1.13 95% CI (0.69, 1.85)]. In the BLOSSOM trial, the incidence of FDA-defined VHD over the course of one year was 1.99% in both the lorcaserin 10 mg BID and placebo groups [RR 1.00 95% CI (0.57, 1.75)]. In an analysis of pooled data, the RR was 1.07 (0.74, 1.55) for FDA-defined valvulopathy in the lorcaserin 10 mg BID group versus the placebo group. These data allow one to rule out a 55% or greater increase in the relative risk for FDA-defined VHD with lorcaserin.

Neuro-psychiatric and Cognitive-Related Adverse Events: In the phase 3 clinical trials, perceptual- or dissociative-related adverse events were reported by 21% of subjects treated with lorcaserin 10 mg BID compared with 12% of subjects treated with placebo. A wide variety of individual adverse event terms including dizziness, fatigue, paresthesias, and abnormal dreams, contributed to the overall imbalance between treatment groups. Although a greater percentage of subjects randomized to the lorcaserin 10 mg BID group (2.7%) versus the placebo group (1.4%) reported adverse events mapped to a broad categorization of depression, when confined to a narrower categorization, there was no imbalance between treatment groups in depression-related adverse events. Memory impairment, disturbance in attention, amnesia and other cognitive-related adverse events were reported infrequently overall; however, three times more subjects treated with lorcaserin 10 mg BID reported these types of events compared with subjects treated with placebo.

Malignancies in Rats: A number of malignant tumor types developed in rats treated with lorcaserin for up to two years. An excess number of malignant mammary tumors

developed in female rats treated with lorcaserin at doses within 7-fold of the proposed clinical dose of 10 mg BID. Male rats developed malignant mammary tumors when treated with lorcaserin at doses 17-fold higher than the proposed clinical dose. Although the sponsor believes that lorcaserin-mediated increases in serum prolactin explain the excess risk for malignant breast tumors, FDA reviewers do not believe that the available data support this hypothesis. In addition to breast tumors, lorcaserin-treated rats had an excess number of malignant astrocytomas, squamous carcinomas of the subcutis, and malignant schwannomas. There were no imbalances in reports of cancer between lorcaserin and placebo-treated subjects in the phase 3 clinical studies.

Draft Points for Discussion and Regulatory Question

As you read the background documents from the FDA and Arena Pharmaceuticals please keep in mind the following draft discussion points and regulatory question.

Taking into account the material provided in the background documents and presented at the advisory committee meeting, please comment on whether you believe that the sponsor has:

1. Provided adequate evidence to establish lorcaserin's efficacy as a weight-loss drug
    a. are there additional studies that you would recommend pre- or post-approval to further evaluate lorcaserin's efficacy?

2. Adequately assessed the potential risk for lorcaserin-induced valvular heart disease.
    a. are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk?
    b. if approved, please discuss need for monitoring and possible monitoring strategies.

3. Provided adequate evidence to assess the potential risk to human subjects of lorcaserin-related neoplasms in rats of the:

    - mammary tissue
    - brain
    - skin
    - subcutis
    - nerve sheath tissue

    a. are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk?

b. if approved, please discuss need for monitoring and possible monitoring strategies.

4. Adequately assessed and characterized the potential risk for psychiatric adverse events, such as dissociative disorders and depression/suicidality.
    a. are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk
    b. if approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

5. Adequately assessed and characterized the potential risk for adverse events related to disorders of attention, memory, and other cognitive disorders.
    a. are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk
    b. if approved, please discuss need for monitoring and possible monitoring strategies.

6. Taking into account the clinical and preclinical information provided in the background documents and the presentations made at this advisory committee meeting, please vote whether you believe that the available data adequately demonstrate that the potential benefits of lorcaserin outweigh the potential risks when used long-term in a population of overweight and obese individuals.

If voting ‘Yes’, please provide your rationale and comment on the need for and approach to post-approval risk management.

If voting ‘No’, please provide your rationale and comment on what additional clinical or preclinical information would 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

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Abstract

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, is reasonably demonstrated to underlie the anorexigenic effect of lorcaserin. An important aspect of the preclinical 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 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 considers, off-target activation of 5HT2A and 2B appears unlikely (2002/04 data) or plausible (2009 data) when compared to clinically relevant plasma drug levels based on the *in vitro* estimates of receptor potency. Cross-activation of these receptors may be more likely in the CNS, where the lorcaserin concentration is 10 to 25-fold higher than in plasma of rats and monkeys, but is unknown in human subjects.

The neurological and cardiac assessments did not identify major toxicities that would be anticipated if 5HT2A and 2B were activated by lorcaserin, even at doses that provide drug concentrations that substantially exceed the *in vitro* receptor potency data. The degree to which the *in vitro* receptor studies may have over-predicted the potency of lorcaserin *in vivo* is not well-defined. Short-comings in some of the neurological

assessments and limitations in the ability to screen for drug-induced valvulopathy in animals are additional considerations precluding a definitive prediction that lorcaserin will be devoid of such toxicities should it be approved for marketing.

Role of 5HT2C receptor in appetite regulation by serotonin

Serotonin as a therapeutic target for weight loss is well supported by non-clinical and clinical experience with several serotonergic compounds. Agents that promote serotonin release, inhibit serotonin uptake, or directly interact with serotonin receptors promote pre- & post-meal satiety and reduce meal size and caloric intake, resulting in various degrees of body weight loss. Serotonin activity contributes to short-term or 'episodic' regulation of appetite in large part by suppressing orexigenic and promoting anorexigenic neuropeptide release within appetite regulatory centers of the hypothalamus[1,2]. Clinically significant weight loss sufficient to support FDA approval was demonstrated for sibutramine[a] (serotonin/norepinephrine reuptake inhibitor) and fenfluramine/dexfenfluramine[b] (serotonin releaser and receptor agonist). Evidence of weight loss has also been documented with other serotonergic compounds[1], such as fluoxetine (SSRI), meta-chlorophenylpiperazine (5HT1B/2C agonist), and sumatriptan (5HT1D/1B agonist).

Studies into the mechanism of satiation with serotonergic compounds suggest a central role for neuronal 5HT2C and 5HT1B receptors within the arcuate nucleus of the hypothalamus[1,2]. Activation of the 5HT2C receptor on pro-opiomelanocortin (POMC) neurons promotes satiety and reduced energy intake via release of α-melanocyte stimulating hormone (αMSH) and activation of melanocortin receptors 3 and 4 on neurons located within hypothalamic paraventricular nuclei (PVN). The anorectic POMC/MC pathway is negatively regulated by AgRP/NPY (agouti-related peptide/neuropeptide Y) neurons also located within the arcuate nucleus. Activation of 5HT1B receptors and release of NPY from these neurons suppresses POMC activity, promoting appetite and energy intake. Activation of anorexigenic POMC neurons and suppression of orexigenic AgRP/NPY neurons is postulated to underlie the satiation properties of serotonin and serotonergic pharmaceutical compounds[3,4]. As a 'selective' 5HT2C agonist, lorcaserin would be expected to interact with POMC but not AgRP/NPY neurons[5], and to increase satiety and reduce food intake, resulting in a net anorexigenic effect.

Serotonin acts in a milieu of other episodic and chronic regulatory signals that converge on central sites of appetite control, including the arcuate nucleus. These signals convey information about energy balance and can come from the periphery (e.g., choleycystikinin, leptin, insulin, ghrelin) and from central sites (e.g., orexin, melanin concentrating hormone, pituitary adenylate cyclase-activating peptide). Activation of 5HT2C contributes to, but is not the sole determinant of, serotonin's anorexigenic properties. Consistent with the role of 5HT2C in appetite regulation, lorcaserin effectively reduces food intake and body weight in obese and non-obese rodent models.

[a] NDA 20632
[b] NDA 20344

In general, the majority of lorcaserin's anorexic effect in rodents was short-lived (≤ 10 days) with a lesser effect upon sustained treatment. Cessation of dosing rapidly resulted in a rebound of food intake and weight gain.

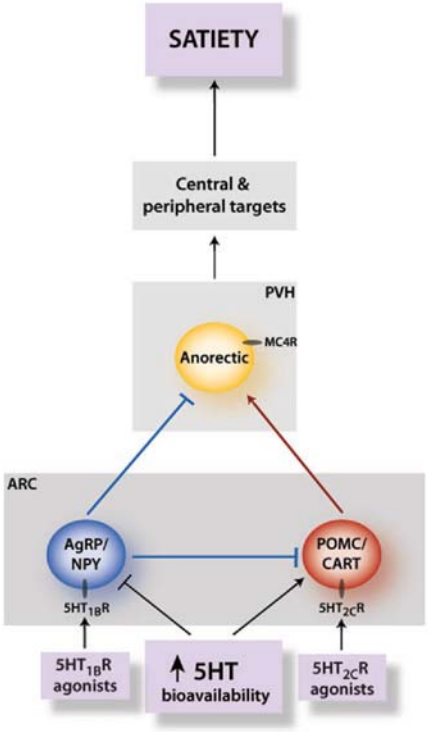


Figure 1. Proposed model of a serotonergic pathway modulating food intake.
Serotonin acts at 5HT2C receptors on POMC/CART neurons in the arcuate nucleus to release α-melanocyte stimulating hormone, which acts on MC4R receptors on neurons in the paraventricular nucleus to promote satiety. Serotonin also acts at 5HT1B receptors to suppress activity of counter-regulatory AgRP/NPY neurons, further promoting POMC/MC activity and satiety. ARC, arcuate nucleus; PVN, paraventricular nucleus; AgRP/NPY, agouti-related protein/neuropeptide Y; POMC/CART, pro-opiomelanocortin/cocaine and amphetamine regulated transcript; MC4R, melanocortin receptor-4.
Reproduced from Garfield and Heisler (J Physiol 2009; 587).

Importance of Serotonin Receptor Selectivity

Serotonin has pleiotropic effects on central and peripheral biological functions beyond its role in appetite regulation[6]. Serotonergic compounds are approved for numerous medical conditions including depression, migraine, irritable bowel syndrome and, previously, obesity. Serotonin achieves its biological diversity by interacting with fourteen receptors (5HTR) that are categorized into seven families (5HTR1-5HTR7) based on similarities in sequence and signaling pathways[7]. Some aspects of the toxicological profile of serotonergic agents might reasonably be anticipated from its profile of 5HT receptor selectivity.

The desired anorexigenic properties of dexfenfluramine and other serotonergic compounds involve activation of 5HT2C[4,5]. That the satiation properties of serotonergic agents might be divisible from adverse effects associated with activation of related 5HT receptors has propelled interest in developing weight loss compounds that selectively activate 5HT2C. However, high sequence homology among the 5HT2A, B, and C receptors has hampered development of 5HT2C selective agonists.

Lorcaserin was designed to target the 5HT2C receptor which is one of three recognized subtypes in the 5HT2 family, the others identified as 5HT2A and 5HT2B. **Table 1**

summarizes the general tissue distribution and function of 5HT2A, 2B, and 2C in the CNS and peripheral tissues[6,8]. The table is not comprehensive, but is included to demonstrate the diversity of expression and function among the 5HT2 receptor subtypes. Of particular note, and relative to adverse drug action, 5HT2A is implicated in the hallucinogenic and addictive properties of psychedelic drugs such as lysergic acid (LSD), and activation of 5HT2B is thought to underlie drug-induced cardiac valvulopathy, including that associated with use of fenfluramines in human subjects[6]. Off-target activation of 5HT2A or 2B is not desirable and would present a safety concern for any anorexic drug candidate.

Table 1: Summary of Distribution and Function of 5HT2 Receptor Family Members

5HT2R subtype	Distribution	Function
2A	**CNS** Cortex, hypothalamus, cerebellum, amygdale, ventral striatum (NAcc) **Periphery** Liver, Pulmonary/coronary vasculature, adipocytes, platelets, Kidney, GI	**CNS** Anxiety, behavior, locomotion, addiction Modulates other neurotransmitters/peptides **Periphery** Hepatocellular mitogen Vasoactive and pro-mitogenic Adipocyte differentiation Platelet aggregation Renal mesangial proliferation/matrix production Enteric neurotransmitter
2B	**CNS** Cerebellum, amygdale, hypothalamus **Periphery** Cardiac tissue and valves Pulmonary vasculature Liver	**CNS** Motor behavior, Anxiety, cerebrovascular tone **Periphery** Cardiac development, mitogenesis in valves Pulmonary vascular remodeling Hepatocellular mitogen
2C	**CNS** Hypothalamus (PVN, ArcN, VMN) Choroid Plexus **Periphery** Little to no expression	**CNS** Locomotion, Anxiety Appetite suppression (POMC/MSH/MCR) Activation of HPA axis (CRH/ACTH) Modulation of dopamine output

Serotonin receptor selectivity profile of Lorcaserin

Lorcaserin's selectivity for serotonin receptors was addressed by receptor binding and activation studies *in vitro*, by dedicated *in vivo* neurobehavioral studies, and by investigator observations made in the course of chronic toxicology studies. Being a primary concern in lorcaserin's development, the potential for cardiac valvulopathy was also addressed by an expanded histological evaluation in rodents and monkeys.

In Vitro Receptor Selectivity Studies: 5HT2A, 2B, and 2C

Summary

The *in vitro* receptor selectivity studies demonstrate that lorcaserin binds to and activates the 5HT2C receptor with greater affinity and potency than to the 5HT2A and 2B receptors. Lorcaserin's selectivity for 5HT2C is driven primarily by the functional receptor activation assays which defined a range of selectivity for 5HT2C of 8 to 15-fold versus 5HT2A, and 45 to 90-fold versus 5HT2C. Based on the range of functional EC50 values across studies, off-target activation of 5HT2A and 2B appears plausible (2009 data) or unlikely (2002/04 data) when compared to clinically relevant plasma drug levels. Activation of off-target 5HT2A and 2B receptors appears more likely in the CNS than in the periphery, as levels of lorcaserin are potentially 10 to 25-fold higher in the CNS compared to systemic plasma levels. Lorcaserin did not significantly interact with other 5HT receptor subtypes, monoamine transporters, or an extensive panel of other off-target receptors, channels, and transporters. Active and non-active metabolites of lorcaserin have been identified but are unlikely to contribute to pharmacodynamic activity based on limited plasma exposure.

5HT2 Receptor Binding

Binding affinity of lorcaserin for 5HT2 receptors was assessed using a radioligand competition binding assay conducted with human embryonic kidney epithelial cells (HEK293) that express recombinant human 5HT2A, 2B, or 2C. Lorcaserin competed for binding with radiolabeled demethoxy-iodoamphetamine (^{125}I-DOI). Binding affinities for lorcaserin expressed as Ki values were 92, 147, and 13nM for 5HT2A, 2B, and 2C, respectively (**Table 2**). Lorcaserin's affinity for 5HT2C was within 7- to 10-fold the affinity for 5HT2A and 2B.

5HT2 Receptor Activation

The ability of lorcaserin to activate 5HT2 receptors was assessed by measuring events in the phospholipase C pathway, specifically the accumulation of ^{3}H-inositol phosphate and release of calcium in HEK293 cells expressing recombinant human 5HT2A, 2B, or 2C.

Lorcaserin increased phosphoinositol (PI) hydrolysis with an EC_{50} of 133, 811, and 9nM for the 5HT2A, B, and C receptors (**Table 2**), demonstrating selectivity for the 5HT2C subtype. Lorcaserin was a full agonist at the 5HT2B and 2C receptors (93-100% as active as serotonin), and a partial agonist at the 5HT2A receptors (80% serotonin activity). Similar results were obtained for calcium release, with potencies (EC50) of 52, 350, and 6nM for 5HT2A, 2B, and 2C, respectively.

The selectivity of lorcaserin for 5HT2C is driven by the functional receptor activation assays rather than the binding assays.

Table 2: Lorcaserin binding (Ki) and activation (EC50) of human serotonin receptors 5HT2A, 2B, and 2C *in vitro*.			
	5HT2A	**5HT2B**	**5HT2C**
Receptor Binding[1,2] (Ki, nM)	92	147	13
PI Hydrolysis[3] (EC50, nM)	133	811	9
Calcium release[4] (EC50, nM)	52	350	6

[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 from 2002-2009
[3]PI hydrolysis data (inositol phosphate accumulation) from 2002-2004 studies.
[4]Calcium release measured by FLIPR in HEK293 cells preloaded with calcium 4 dye.

Difference in 5HT2 receptor activation data from 2002/2004 and 2009 studies
The 5HT2 receptor activation studies presented above were conducted in 2002/2004 and submitted to the FDA in support of clinical development during the IND phase. Arena conducted another receptor activation study in 2009 to assess selectivity of lorcaserin and its enantiomer and metabolites. The two studies, while separated in time, followed the same basic protocol using HEK293 cells expressing recombinant human 5HT2A, 2B, or 2C receptors. Results of the 2009 studies were submitted in support of the NDA.

The 2009 data resulted in 5- to 10-fold greater potency compared to the 2002/04 study (**Table 3**). Arena noted that all dose response curves in the 2009 study were left-shifted, including data for the positive control, DOI. Estimates of potency from the 2009 study are consistent with a published independent analysis of lorcaserin's potency for calcium release[c]. This shift in potency decreased by half the estimated relative selectivity of lorcaserin for 5HT2C, from 15x to 8x for 5HT2A, and from 90x to 45x for 5HT2B (**Table 4**). This revised range of selectivity (8x-15x for 2A, and 45x-90x for 2B) is consistent with the selectivity range defined by the sponsor's calcium release studies (9x for 2A, and 58x for 2B).

Table 3: Activation of human 5HT2A, B, C receptors by lorcaserin (PI Hydrolysis from 2002/04 and 2009 studies)			
	Lorcaserin, EC50, nM		
Study date	**5HT2A**	**5HT2B**	**5HT2C**
2002/04	133	811	9
2009	14	82	1.8

[c] Kozikowski AP et al (2010) Chem Med Chem (5) 1221.

Table 4: Fold Selectivity of Lorcaserin for 5HT2C receptor activation[1]		
Study data	**vs. 5HT2A**	**vs. 5HT2B**
2002/04	15x	90x
2009	8x	45x

[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 and 2009 studies.

The sponsor considers the 2002/04 data the more definitive estimate of lorcaserin's potency, explaining that higher expression of the 5HT2 receptors in the transiently transfected HEK293 cells may have left-shifted the results in the 2009 study. Binding affinity constants did not change substantially from the earlier studies (Ki for 5HT2A, B, C: 81nM, 131nM, 10nM, respectively, n=6, conducted 24 June to 8 July 2009). 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[d]. Efforts to normalize the potency data to receptor density (e.g., eliminate receptor reserve) were not made or were not described in the NDA. Nevertheless, putative higher receptor density in the 2009 studies is a plausible reason for the left-ward shift in potency. This implies that the actual drug concentration required to activate each 5HT2 receptor in different tissues *in vivo* may be similar to or higher than those predicted by the *in vitro* studies, but the magnitude of the potential difference is undefined. The FDA therefore viewed the data from the 2002/04 and 2009 studies as a potential range of functional potency for lorcaserin, rather than favoring one set of studies over the other, while recognizing that actual *in vivo* potency of lorcaserin may be lower.

5HT Receptor Selectivity compared to clinical exposure to lorcaserin

A substantial change in the absolute potency of lorcaserin for 5HT2 receptors may impact the assessment of receptor selectivity *in vivo*. The 'functional selectivity' of lorcaserin would only be advantageous when 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 exceeds the EC50 for all three 5HT2 receptor subtypes, which could reasonably result in partial or full receptor activation. **Figure 4** compares plasma 'free' drug levels of lorcaserin at clinical exposure (10mg bid) to the *in vitro* receptor activation data for 5HT2A, 2B, and 2C, as measured by PI hydrolysis, from the 2002/04 study **(Fig 4A)** and the 2009 study **(Fig 2B)**. As might be expected, plasma concentrations of lorcaserin over a 24 hour period substantially exceed the EC50 for activation of 5HT2C, regardless of which study is considered. Relative to the 2002/04 study, lorcaserin is unlikely to result in significant activation of 5HT2A or 2B because plasma concentrations largely fall below the EC50 for both these receptors, most notably the 2B receptor. However, relative to the 2009 study, the potential for lorcaserin to result in at least partial

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

activation of 5HT2A and 2B becomes apparent, as plasma concentrations approximate or exceed the EC50 for both receptors, most notably the 2A receptor.

Figure 4: Comparison of plasma drug concentration in obese/overweight subjects to in vitro 5HT receptor activation data. EC50 values from the 2002/04 study (A) and 2009 study (B) for receptor activation, measured as phosphoinositol hydrolysis in vitro and shown as horizontal red lines, were plotted against the predicted and observed lorcaserin concentrations (expressed as free drug fraction) of 10mg lorcaserin bid in obese/overweight individuals. The pharmacokinetic data, corrected for 70% protein binding, comes from clinical study APD356-011 of NDA 22529. Predicted plasma drug levels are depicted by the dotted and solid lines; actual measured drug levels are depicted by the symbols.

Fig 4(A): 2002/2004 data

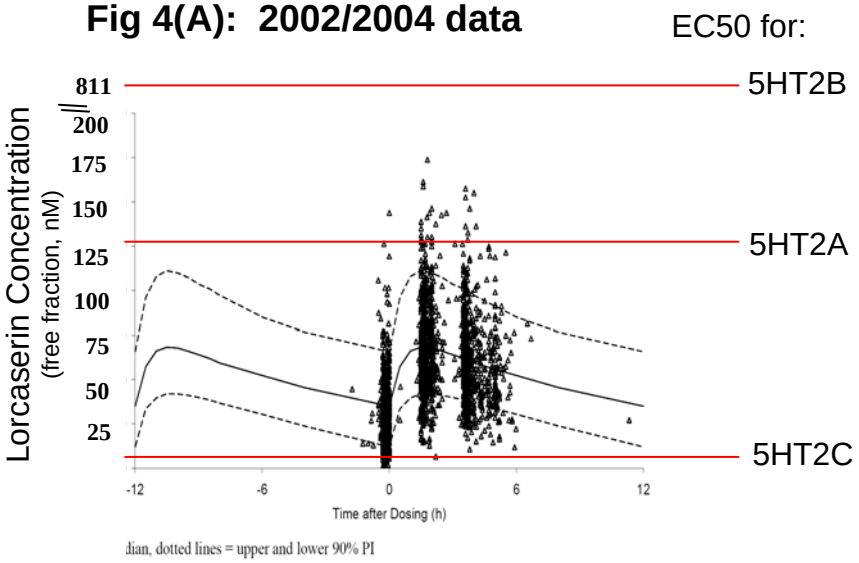
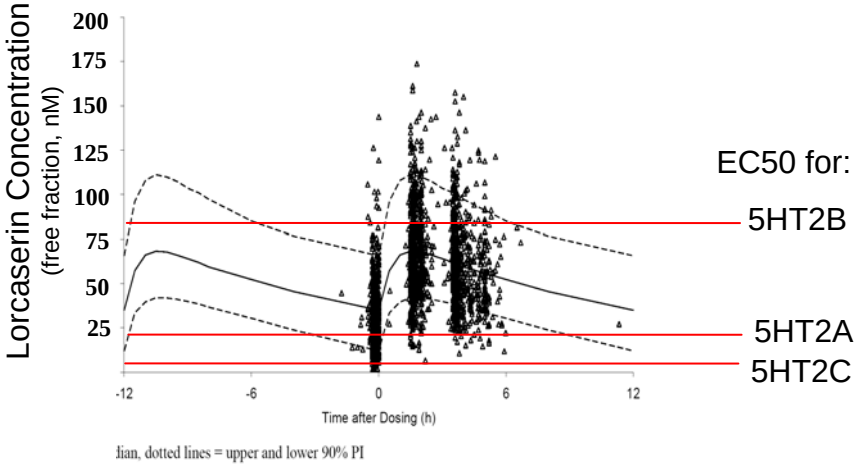


Fig 4(B): 2009 data



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[8,9]. Levels of lorcaserin in the CNS were not determined in human subjects, but were investigated in rodents and monkeys. After dosing to steady state, lorcaserin was present in brain tissue an average of 25-fold and 10-fold higher compared to plasma in rodents and monkeys, respectively. Drug levels in the cerebrospinal fluid, by comparison, were $1/10^{th}$ to $1/20^{th}$ of plasma. This profile is consistent with other 5HT2C agonist compounds that the FDA has reviewed, and may reflect slower clearance of drug from brain tissue than from the plasma compartment. Distribution in the brain of monkeys appears uniform, with similar levels of lorcaserin present in the cortical, hypothalamic/thalamic, and subcortical regions. Assuming that distribution of lorcaserin in monkeys and humans is most comparable, brain levels of lorcaserin may reach 430ng/ml or 1.7μM from the clinical dose of 10mg bid. This concentration of lorcaserin would be expected to activate central 5HT2A and potentially 2B receptors, assuming that lorcaserin has access to receptor sites in the CNS.

Lorcaserin Interaction with other 5HTRs and transporters
Lorcaserin showed poor binding affinity for other serotonin receptor subtypes and for a large panel of unrelated G-protein coupled receptors and ion channels. The most notable interaction was for binding and activation of 5HT1A, with observed binding affinities of 50 to 724nM and an activation EC50 of 1.4μM (GTPγS assay).

Lorcaserin did not interact with relevant potency to transporters for norepinephrine, dopamine, or serotonin *in vitro*. Functional studies demonstrated that lorcaserin did not interfere in the uptake or release of norepinephrine, dopamine, or serotonin in preparations of rat synaptosomes.

These assays support the view that lorcaserin has highest affinity for the 5HT2 family of serotonin receptors, and would not be expected to *directly* interact with other serotonin receptors or with monoamine transporters.

Receptor Pharmacology of Lorcaserin Metabolites
Lorcaserin is converted to a sulfated metabolite (lorcaserin sulfamate, or M1) in humans and in animals. Exposure to M1 exceeds exposure to the parent compound by several fold in all species. M1 is considered a major but pharmacodynamically inactive metabolite, as M1 did not interact with relevant potency to 5HT1 or 2 receptor subtypes or with monoamine transporters. Distribution of M1 was restricted to the systemic circulation and was not found in appreciable quantities in the CNS.

The only metabolite with pharmacodynamic activity comparable to lorcaserin is M2, a hydroxylated metabolite formed in the liver. Exposure to M2 in the systemic circulation is very low (< 2% of parent) and would contribute minimally to the pharmacodynamic or toxic effects of lorcaserin.

Lorcaserin is produced as a racemate and then further processed to enantiomeric purity. The excluded enantiomer, termed AR226175, was evaluated and found to have a similar 5HT2 receptor binding and activation profile as lorcaserin. The lorcaserin drug substance contains <0.1% AR226175 and chiral inversion *in vivo* does not appear to occur, so there is little if any contribution of AR226175 to lorcaserin's effects.

The metabolites and enantiomer of lorcaserin are not expected to contribute to the pharmacodynamic activity of lorcaserin because they are either inactive (M1 sulfamate, M5 N-carbomyl glucoronide) or are active but present in very small quantities (M2, AR226175 enantiomer).

Assessment of Neurological effects in Animals

Summary:
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. Despite reaching plasma and brain drug levels theoretically sufficient to activate 5HT2A, lorcaserin did not clearly elicit 5HT2A-related behavior in rats but did elicit 5HT2C-related behaviors. Though portrayed as evidence of receptor selectivity *in vivo*, limitations of these studies preclude definitive conclusions regarding elicitation of 5HT2A-related behaviors by lorcaserin.

Dedicated Neurological Studies
Central 5HT2A receptors are broadly expressed in the CNS, including the amygdale, cortex, and ventral striatum (nucleus accumbens). Activation of 5HT2A can modulate anxiety, locomotion, and addictive behaviors associated with hallucinogenic compounds[8]. Aside from regulation of appetite, activation of 5HT2C is also linked to modulation of locomotion and anxiety[9]. Lorcaserin activates rat and monkey 5HT2A and 2C receptors with reasonably similar potency to the human receptors, which allows for screening of major adverse neurological effects in these species (**Table 5**).

Table 5: Lorcaserin activation of human, rat, and monkey 5HT2A and 2C receptors (EC50, nM)

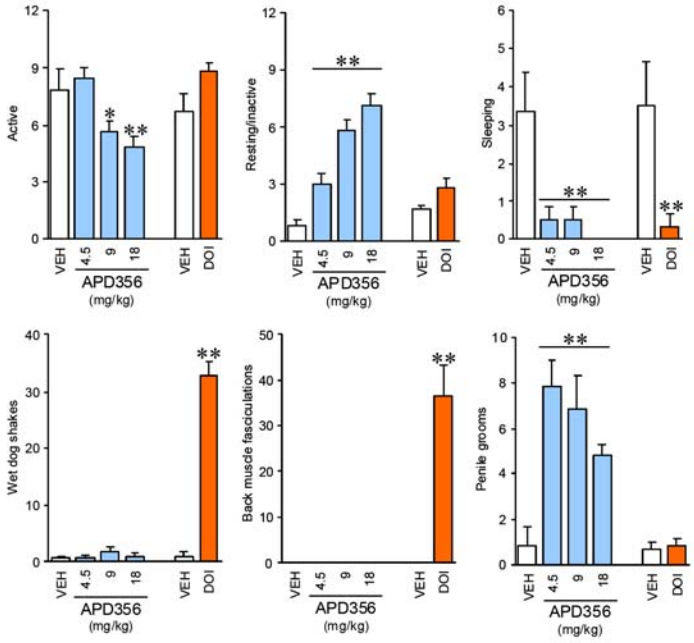
	5HT2 A	5HT2 C
Human	14	1.8
Rat	31	5
Monkey	23	2

Functional IP accumulation from expressed receptors on HEK cells
EC50 values as determined in the 2009 study, NDA 22529

Arena investigated the neurobehavioral response of rats to lorcaserin compared to the response to demethoxyiodoamphetamine (DOI), a non-selective 5HT2A and 2C agonist. A single dose of DOI provoked behaviors considered typical of 5HT2A activation, specifically 'wet-dog shakes' and back fasiculations, but a single dose of lorcaserin did

not provoke these behaviors (**Figure 5**). Conversely, lorcaserin provoked penile grooming and reduced locomotor activity which is considered reflective of 5HT2C activation, but DOI was less active in provoking these behaviors.

Figure 5: The effect of single dose lorcaserin (APD356) and DOI on behavior in the rat. Data excerpted from NDA 22529.



Arena concluded that this data supports the *in vivo* selectivity of lorcaserin for 5HT2C versus 5HT2A. Limitations of this study have tempered FDA's interpretation of this data. Of note, the behavioral responses to DOI and to lorcaserin appear to have been evaluated *one year apart* and not concomitantly within the same study. A robust comparison of lorcaserin to DOI is not feasible under these conditions when one considers that different study animals and different personnel were involved in assessing a set of behavioral endpoints. Arena acknowledges this point in NDA 22529, noting that DOI and lorcaserin must be compared to their respective vehicle controls, and not to each other. Also of concern, the highest dose of lorcaserin used in this study is estimated to result in brain levels of 14μM, greatly exceeding the EC50 of 632nM (2002/04 data) for activation of the rat 5HT2A receptor. Yet, behavior typical of 5HT2A activation was not reported at this dose level. Arena suggests that higher drug concentrations that those predicted by the *in vitro* data are required to activate 5HT2A, which is plausible, but demonstration of this prediction is lacking. Given these concerns, this study suggests but is not definitive evidence for a qualitative difference in behavioral responses of rats to lorcaserin and DOI.

Arena also assessed the potential of lorcaserin to induce release of serotonin and dopamine from the nucleus accumbens of rats *in vivo* by means of a microdialysis probe. The 5HT2A and 2C receptors are reported to have somewhat oppositional effects on striatal and accumbal dopamine release, with 5HT2A agonists facilitating release and

5HT2C agonists inhibiting basal and stimulated release of dopamine[8,9]. A single dose of lorcaserin to rats did not increase levels of serotonin or alter levels of dopamine. Lorcaserin's lack of effect on serotonin release is consistent with its mechanism of action as a 5HT receptor agonist rather than a serotonin-releasing agent such as dexfenfluramine. Indeed, dexfenfluramine increased release of serotonin in this study. However, lorcaserin's lack of effect on dopamine release appears inconsistent with reports in the literature[9,10] that show 5HT2C agonists inhibiting dopamine release using the same microdialysis methodology. Moreover, activation of 5HT2A is reported to enhance stimulated but not basal dopamine release[8,11]. Lorcaserin's effect was evaluated under basal but not stimulated conditions (e.g., haloperidol, cocaine), so potential cross-reactivity of lorcaserin with accumbal 5HT2A receptors was not fully assessed by this study.

Neurological Effects in Toxicology Studies

In additional studies in rats, Arena demonstrated that lorcaserin reduced locomotor activity (ambulations) after acute dosing and prolonged the latency of tail flick in rats. The acute suppressive effect on locomotion was lost with continued dosing of lorcaserin, consistent with the known tachyphylaxis resulting from continued stimulation of the 5HT2C receptor.

When compared to the maximum proposed human dose, the findings of reduced locomotion in rodents occurred at ~2-fold higher plasma drug levels (**Table 6**). Brain levels of lorcaserin in rodents are approximately 25-times higher than in plasma. If one assumes that brain levels of lorcaserin in human subjects are 10-fold higher than in plasma (similar to monkeys), then these centrally-mediated effects on locomotion in rodents occur ~6-fold higher drug exposure.

Table 6: Comparison of exposure at the maximum proposed human dose to exposure causing adverse neurobehavioral responses in SD rats.

Neurobehavioral Response in Rats	Estimated Cmax* Associated with Finding			
		NOAEL	LOAEL	Clinical Cmax (10mg bid)
↓ Activity, ↑ Resting, ↑ Tail Flick Latency	Plasma	208nM	416nM	179nM
	Brain**	5200nM	10400nM	1790nM (est.)

*Estimated from Fed/Fasted PK study in SD rats, 10mg/kg fed conditions
**Estimated from distribution studies in SD rats (25x) and cynomolgus monkeys (10x)
NDA 22529

NOAEL= No Observed Adverse Effect Level; LOAEL= Lowest Observed Adverse Effect Level

Some information regarding neurobehavioral responses to lorcaserin can also be extracted from the cageside clinical observations and physical exams obtained in the course of general toxicology studies in rats and monkeys. Reduced activity, tremor, and convulsions were observed in rats during shorter term studies but apparently resolved with longer term dosing (6 months). This is consistent with the tolerance noted with repeated dosing of rats in the targeted neurobehavioral studies discussed above. In monkeys, decreased activity described as lethargy and drowsiness was reported in 1, 3, and 12 month duration studies. The dose at which decreased activity occurred was lower with increasing study duration, but still occurred with a 3-fold safety margin after 12 months of dosing relative to maximum human exposure (**Table 7**). More severe neurobehavioral signs such as tremor and convulsion were also observed, but occurred at a low incidence after initial exposure to lorcaserin and occurred with a reasonable safety margin (≥ 11x) to human exposure.

Table 7: Clinical safety margin to decreased activity in cynomolgus monkeys administered lorcaserin

	Study Duration		
	1 month	3 months	12 months
Decreased Activity (lethargy/drowsy)	14x	11x	3x
Tremor	14x	11x	69x

'Safety margin' reflects the fold multiple between the no-observed adverse effect level (NOAEL) in monkeys to maximum clinical exposure, based on maximal plasma drug concentration (clinical Cmax, 0.18μM)
NDA 22529

Assessment of Valvular Heart Disease in Animals

Approved in 1996, dexfenfluramine was voluntarily withdrawn a year later over documented cases of pulmonary hypertension (PPH) and cardiac valvular heart disease (VHD) [12]. Dexfenfluramine at that time was shown to increase synaptic serotonin by inhibiting serotonin reuptake and promoting its release from neurons. Subsequently, dexfenfluramine and more so its metabolite norfenfluramine was shown to have potent agonist properties for 5HT2B as well as 5HT2C receptors[13,14]. Comparative binding affinity and potency of lorcaserin, fenfluramine, norfenfluramine, and pergolide for 5HT2 A, B, and C are shown in Appendix I.

Several lines of evidence persuasively argue that among the 5HT2 receptors, activation of 5HT2B is the culprit mechanism underlying dexfenfluramine-induced VHD[15]: 1) Cardiac valves express 5HT2A & B but not 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.

The mechanism by which dexfenfluramine increases the risk of pulmonary hypertension is less clear, but the pulmonary vasoconstriction and vascular remodeling associated with PPH appears to involve multiple serotonergic mechanisms including chronic interference in serotonin transporters and activation of 5HT1B, 2A and 2B[16].

Preclinical 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 suggesting that rodents may provide some useful information on the potential of a drug to induce VHD. For example, the cardiac valves in rats are enriched for expression of 5HT2B as are valves from humans, pigs, and monkeys[15,17]. Cardiac alterations suggestive of VHD were produced in rats administered serotonin[18], pergolide[19], and the experimental 5HT2C agonist RO3013[20]. The pathology noted in these studies was described as fibrotic and proliferative lesions on the cardiac leaflets, papillary muscle, and the subendocardium. Functionally, thickened valves with evidence of regurgitation on echocardiography were observed in the studies with serotonin and pergolide. The lesions were observed within a few days to 5 months of dosing. On the other hand, the results with serotonin in rats have been criticized as being consistent with spontaneous age-related cardiac disease[21], and have not been uniformly reproduced in the literature[22]. Also, the FDA is unaware of any prospective toxicology study that persuasively demonstrates cardiac findings consistent with VHD in adult animals administered dexfenfluramine. Pregnant rats administered dexfenfluramine produced litters with apparent valvulopathy[23], but this finding was not reproduced in a similar study in pregnant mice[24].

Extensive echocardiographic monitoring was conducted in the course of clinical studies with lorcaserin. For the preclinical 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 activates rat 5HT2B with approximately 4-fold greater potency than the human receptor (**Table 7**). Also, lorcaserin was tested over a concentration range that substantially exceeded the *in vitro* activation potency for 5HT2B in rats and monkeys (**Table 7**), so there was a reasonable expectation that cardiac lesions would 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. No adverse cardiac lesions were observed at ~100-times the clinical dose of lorcaserin. This result appears reassuring, but it is concerning 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 be less than that predicted by the *in vitro* activation studies. This explanation is plausible, but has not been adequately demonstrated. Other limitations of the evaluation 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 cannot be excluded. Additionally, published studies that detected drug-induced VHD 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. A low propensity of lorcaserin to activate 5HT2B *in vivo* is also plausible; however, given the experimental limitations stated above, the FDA has not definitively concluded that lorcaserin is devoid of valvulopathy-related cardiac effects in animals.

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

	Binding, Ki (nM)	**Activation, EC50 (nM)**	**Approx. plasma concentration range of lorcaserin in toxicology studies**
Human	147	811	na
Rat	114	226	150 to 20,000 nM
Monkey	127	61*	400 to 20,000 nM

'Activation' refers to inositol phosphate accumulation in vitro
Binding and activation data from 2002/04 study
*2009 activation data. For comparison, EC50 for human 5HT2B: 82nM from 2009 data

References

1. Halford JCG, Harrold JA, Boyland EJ, Lawton CL, Blundell JE. 2007. Serotonergic Drugs: Effects on appetite expression and use for the treatment of obesity. Drugs, 67 (1): 27-55.

2. Garfield AS and Heisler LK. 2009, Pharmacological targeting of the serotonergic system for the treatment of obesity. J Physiol, 587: 49-60.

3. Heisler LK, Cowley MA, Kishi T, et al. 2003. Central serotonin and melanocortin pathways regulating energy homeostasis. NY Acad Sci, 994: 169-174.

4. Heisler LK, Cowley MA, Tecott LH, et al. 2002. Activation of central melancortin pathways by fenfluramine. Science, 297: 609-611.

5. Lam DD, Przydzial MJ, Ridley SH, et al. 2008. Serotonin 5HT2C receptor agonist promotes hypophagia via downstream activation of melanocortin 4 receptors. Endocrinology, 149: 1323-1328.

6. Berger M, Gray JA, Roth BL. 2009. The expanded biology of serotonin. Annu Rev Med. 60: 355-366.

7. Kroeze WK, Kristiansen K, Roth BL. 2002. Molecular biology of serotonin receptors- structure and function at the molecular level. Curr Topics Med Chem. 2: 507-528.

8. Filip M and Bader M. 2009. Overview of 5HT receptors and their role in physiology and pathology of the central nervous system. Pharm Reports. 61: 761-777.

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

10. Di Giovanni G, Di Matteo V, Di Mascio, et al. 2000. Preferential modulation of mesolimbic vs. nigrostriatal dopaminergic function by serotonin 2C/2B receptor agonists: a combined in vivo electrophysiological and microdialysis study. Synapse, 35: 53-61.

11. Kuroki T, Meltzer HY, Ichikawa J. 2003. 5HT2A receptor stimulation by DOI, a 5HT 2A/2C receptor agonist, potentiates amphetamine-induced dopamine release in rat medial prefrontal cortex and nucleus accumbens. Brain Res. 972: 216-221.

12. Connolly HM, Crary JL, McGoon MD, et al. 1997. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med, 337: 581-588.

13. Rothman RB, Baumann MH, Savage JE, et al. 2000. Evidence for possible involvement of 5HT2B receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. Circulation. 102: 2836-2841.

14. Fitzgerald LW, Burn TC, Brown BS, et al. 2000. Possible role of valvular serotonin 5HT2B receptors in the cardiopathy associated with fenfluramine. Mol Pharmacol, 57: 75-81.

15. Huang XP, Setola V, Yadav PN, et al. 2009. Parallel functional activity profiling reveals valvulopathogens are potent 5-hydroxytryptamine 2B receptor agonists: implications for drug safety assessment. Mol Pharmacol, 76: 710-722.

16. Maclean M and Dempsie Y. 2010. The serotonin hypothesis of pulmonary hypertension revisited. Adv Exp Med Biol, 661: 309-322.

17. Elangbam CS, Lightfoot RM, Yoon LW, et al. 2005. 5HT receptors in the heart valves of cynomolgus monkesy and sprague-dawley rats. J Histochem Cytochem, 53(5): 671-677.

18. Gustafsson BI, Tommeras K, Nordrum I, et al. 2005. Long-term serotonin administration induces heart valve disease in rats. Circulation. 111: 1517-1522.

19. Droogmans S, Franken PR, Garbar C, et al. 2007. In vivo model of drug-induced valvular heart disease in rats: pergolide-induced valvular heart disease demonstrated with echocardiography and correlation with pathology. Eur Heart J, 28: 2156-2162.

20. Fielden MR, Hassani M, Uppal H, et al. 2009. Mechanism of subendocardial cell proliferation in the rat and relevance for understanding drug-induced valvular heart disese in humans. Exp Toxicol Path [Epub ahead of print] doi:10.1016/j.etp.2009.08.009

21. Donnelly KB. 2008. Cardiac valvular pathology: comparative pathology and animal models of acquired cardiac valvular diseases. Toxiol Path, 36: 204-217.

22. Hauso O, Gustafsson BI, Loennechen JP, et al. 2007. Long-term serotonin effects in the rat are prevented by terguride. Reg Peptides, 143: 39-46.

23. Bratter J, Gessner IH, and Rowland NE. 1999. Effects of prenatal co-administration of phentermine dexfenfluramine in rats. Eur J Pharmacol, 369: R1-R3

24. Rayburn WF, Sienko AE, Gonzalez CL, et al. 2000. Impact of antenatal exposure of mice to fenfluramine on cardiac development and long-term growth of the offspring. Drug Chem Toxicol, 23: 419-431.

Appendix I

Comparative binding affinity of lorcaserin, fenfluramine, and norfenfluramine for human 5HT2A, 2B, and 2C receptors, (Ki, nM)				
Drug	**5HT2 A**	**5HT2 B**	**5HT2 C**	**Source**
(+) fenfluramine	2316	52	557	Ref #14 (competitive ligand, DOI A&C; LSD B)
(+) norfenfluramine	187	56	27	
Lorcaserin	**92**	**147**	**13**	NDA 22529 (DOI ligand)

Comparative potency of lorcaserin, fenfluramine, and norfenfluramine for human 5HT2B and 2C receptor activation **(Inositol phosphate accumulation, EC50, nM)**			
Drug	**5HT2 C**	**5HT2 B**	**Clinical exposure**
(+) fenfluramine	362	379	350 nM
(+) norfenfluramine	13	18	110 nM (total) 44 nM (free%)
Pergolide	--	53	1000 nM (total) 100 nM (free%)
Lorcaserin	2-9	82-811	178 nM (total) 53 nM (free%)

EC50 values for fenfluramine, norfenfluramine, pergolide from references #13-14.
% free indicates approximate non-protein bound drug concentration at maximum clinical exposure

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

Advisory Committee Briefing Document: Statistical Review of Efficacy
Advisory Committee Date: September 16, 2010

NDA/Serial Number:	022529/0
Drug Name:	Lorcaserin tablets
Indication(s):	Weight management
Applicant:	Arena Pharmaceuticals Inc
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
Project Manager:	Patricia Madara

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1. EXECUTIVE SUMMARY

1.1 Conclusions

Confirmation of efficacy: The results of two Phase 3 studies are consistent and confirm the efficacy of lorcaserin 10 mg bid and 10 mg qd compared to placebo after 52 weeks of treatment, in the co-primary weight loss endpoints of average weight loss compared to baseline, the percentage of subjects who lost at least 5% of baseline body weight, and the percentage of subjects who lost at least 10% of baseline body weight. Results of alternate analysis models and other versions of the analysis population were consistent with the results from the primary analysis. However, the placebo-adjusted weight loss was relatively low, compared to the benchmark of 5% described in the February 2007 draft *Guidance for Industry: Developing Products for Weight Management*. The results from the primary analyses are shown below:

TABLE 1 Efficacy results from Study 009 and Study 011; primary analyses (MITT/LOCF)

1. Weight loss at week 52 as a % of baseline weight					
Treatment groups	N	Baseline mean (kg) ± SE	Adjusted mean % change from baseline at Week 52 ± SE	Difference in adjusted mean % change, Lorcaserin - Placebo (95% CI)	P-value vs. Placebo
Study APD356-009 BLOOM					
Lorcaserin 10 mg bid	1538	100.4 ± 0.4	-5.9 ± 0.2	-3.7 (-4.1, -3.3)	<0.0001
Placebo	1499	99.7 ± 0.4	-2.2 ± 0.1		
Study APD356-011 BLOSSOM					
Lorcaserin 10 mg bid	1561	100.3 ± 0.4	-5.8 ± 0.2	-3.0 (-3.4, -2.6)	<0.0001
Lorcaserin 10 mg qd	771	100.1 ± 0.6	-4.7 ± 0.2	-1.9 (-2.5, -1.4)	<0.0001
Placebo	1541	100.8 ± 0.4	-2.8 ± 0.2		
2. Percentage of subjects achieving ≥ 5% weight loss at week 52					
Treatment groups	N	Number of responders (%)	Difference in proportions (95% CI)	Odds ratio (95% CI)	p-value vs. placebo
Study APD356-009 BLOOM					
Lorcaserin 10 mg bid	1538	731 (47.5%)	27.2 (24.0, 30.5)	3.6 (3.1, 4.2)	<0.001
Placebo	1499	304 (20.3%)			
Study APD356-011 BLOSSOM					
Lorcaserin 10 mg bid	1561	737 (47.2%)	22.2 (18.9, 25.5)	2.7 (2.3, 3.1)	<0.0001
Lorcaserin 10 mg qd	771	310 (40.2%)	15.2 (11.1, 19.3)	2.0 (1.7, 2.4)	<0.0001
Placebo	1541	385 (25.0%)			
3. Percentage of subjects achieving ≥ 10% weight loss at week 52					
Study APD356-009 BLOOM					
Lorcaserin 10 mg bid	1538	347 (22.6%)	14.9 (12.4, 17.4)	3.5 (2.8, 4.4)	< 0.001
Placebo	1499	115 (7.7%)			
Study APD356-011 BLOSSOM					
Lorcaserin 10 mg bid	1561	353 (22.6%)	12.9 (10.3, 15.4)	2.7 (2.2, 3.3)	< 0.0001
Lorcaserin 10 mg qd	771	134 (17.4%)	7.6 (4.6, 10.7)	2.0 (1.5, 2.5)	< 0.0001
Placebo	1541	150 (9.7%)			

Considerations that may limit the extension of study conclusions to the intended target population are as follows:

1. A substantial percentage of randomized subjects in each study and study arm, between 40% and 55%, withdrew prior to week 52. At any given time during the study, subjects who had lost less weight were more likely to withdraw than subjects who had lost more weight.

2. Subjects in the African American/ Black and Hispanic/ Latino minority subgroups were more likely to withdraw than subjects in the majority Caucasian / White subgroup. These minority subgroups also had less average weight loss in the placebo and lorcaserin arms compared to the majority subgroup.

Other key findings are as follows:

1. The results from secondary efficacy endpoints, such as LDL-cholesterol, systolic and diastolic blood pressure, fasting plasma glucose, total body fat, and total quality of life score, supported the efficacy of lorcaserin compared to placebo.

2. Patients who withdrew early were likely to be within 5% of their baseline weight at the time of withdrawal. This is consistent with classifying early withdrawals as 5% non-responders. A reasonable measure of efficacy to extend the study conclusions to the intended target population is the placebo-adjusted odds of being classified as a 5% responder. This measure can encompass the intention-to-treat population by classifying early dropouts as 5% non-responders.

1.2 Brief Overview of Clinical Studies

The long-term efficacy of lorcaserin was evaluated in two Phase 3 studies: APD356-009 (BLOOM; Study 009) and APD356-011 (BLOSSOM; Study 011). Both studies enrolled adults between ages 18 and 65 years who were either obese (BMI $\geq$30 kg/m^2), or overweight with at least one weight related co-morbid condition (BMI 27-30 kg/m^2). The two studies were designed to evaluate the effect of lorcaserin administered in conjunction with behavior modification for 52 weeks as a primary endpoint period. Both studies were conducted at sites within the US. The mean baseline weight was approximately 100 kg in each study (TABLE 3)[1]. The large majority of subjects were female (81%). The largest racial group was Caucasian/ white (67%), followed by African American/ black (19%) and Hispanic/ Latino (12%). The co-morbid conditions of dyslipidemia and hypertension occurred in 30% and 23% of subjects, respectively.

In Study 009, 3182 subjects were randomized in a 1:1 ratio to lorcaserin 10 mg bid: placebo. In Study 011, 4008 subjects were randomized in a ratio of 2:1:2 to lorcaserin 10 mg bid: lorcaserin

[1] Table and figure references in the Executive Summary refer to tables and figures in the main body of this report.

10 mg qd: placebo. Participants in both studies were treated with a behavior modification program, which was considered to be the standard of care for obese and overweight subjects.

Study 009 was continued for a second year, with a re-randomization of lorcaserin subjects to either continue with lorcaserin or to switch to placebo in a 2:1 ratio. Subjects who had been randomized to placebo in the first year were continued on placebo.

1.3 Statistical Issues and Findings

Disposition: A substantial percentage of randomized subjects in each study and study arm, between 40% and 55%, withdrew prior to week 52 (TABLE 2). This level of discontinuation is typical of weight loss studies. The efficacy of lorcaserin in the intended target population needs to be evaluated in the context of this high level of discontinuation.

Most of the subjects who withdrew early did so before the week 26 mid-point (FIGURE 1, TABLE 2). On average, subjects who withdrew early had lost less weight at the time of withdrawal, compared to the average weight loss at the same study week in subjects who completed the study (FIGURE 3). This trend was apparent in both the placebo and the lorcaserin arms. My interpretation of this finding is that at any given time throughout the study, subjects who were less successful at losing weight were more likely to drop out than subjects who were more successful. Based on this interpretation, the completers are likely to be different from the non-completers with respect to the efficacy endpoint.

Analysis of efficacy: The applicant pre-specified three co-primary efficacy endpoints, and used a gate-keeping strategy to control the overall Type I error, in the order shown below:

(1) the proportion of subjects achieving ≥ 5% reduction in body weight at the end of year 1 ("5% responders")
(2) the change from baseline to the end of year 1 in body weight
(3) the proportion of subjects achieving ≥ 10% reduction in body weight at the end of year 1 ("10% responders")

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

The applicant used several versions of the analysis population and different analysis models in order to evaluate the sensitivity of estimates for each of the co-primary efficacy endpoints. The analysis models included both analysis of covariance and mixed model repeated measures for the continuous endpoint, and logistic regression for the categorical endpoints. The analysis populations included a modified intention-to-treat population, both with and without last

observation carried forward, a per protocol population, a completers population, and a returning dropout population that included off-treatment weights from subjects who dropped out but returned for a final weight.

Efficacy at week 52: The primary results for the three co-primary endpoints are as follows:

(1) 5% responders: After 52 weeks of treatment in Study 009, 48% of subjects treated with lorcaserin 10 mg bid had lost at least 5% of their baseline body weight, compared to 20% of subjects treated with placebo (TABLE 6). The odds of being classified as a 5% responder with lorcaserin compared to placebo were 3.6 (95% CI 3.1 to 4.2).

The results for Study 011 were similar, with 47% in the lorcaserin bid arm, 40% in the lorcaserin 10 mg qd arm, and 25% in the placebo arm classified as 5% responders (TABLE 8). The odds of being classified as a 5% responder with lorcaserin compared to placebo were 2.7 (95% CI 2.3 to 3.1) for the 10 mg bid arm and 2.0 (95% CI 1.7, 2.4) for the 10 mg qd arm.

These results are based on the primary analysis of the MITT population, carrying forward the last on-study weight prior to dropout. In both studies, the majority of dropouts had lost less than 5% of their baseline body weight at the time of dropout (FIGURE 5, FIGURE 9). This means that carrying forward the last observation was reasonably close to classifying study withdrawals as non-responders. In a sensitivity analysis, which classified dropouts as non-responders in the 5% endpoint, the results were very similar to those from the primary analysis with the MITT/LOCF population (TABLE 6, TABLE 8).

Results from sensitivity analyses using the completers population and the per protocol population supported the results from the primary analysis.

(2) *Change from baseline in body weight:* The placebo-adjusted mean weight loss with lorcaserin 10 mg bid was 3.7% of baseline body weight (95% CI 3.3% to 4.1%) in Study 009 and 3.0% (95% CI 2.6% to 3.4%) in Study 011 (TABLE 5, TABLE 7). The placebo-adjusted mean weight loss with lorcaserin 10 mg qd was 1.9 (95% CI 1.4% to 2.5%) in Study 011. These estimates are from the primary analysis of the MITT population with last observation carried forward. Results from different versions of the analysis population and different analysis methods were reasonably consistent in both studies. The primary analysis and several supportive analyses resulted in placebo-adjusted effects that were statistically significantly less than 5% of baseline body weight. Because a weight loss of 5% is a benchmark described in the weight loss guidance, the clinical review division should evaluate whether or not the weight loss associated with lorcaserin is clinically significant.

(3) *10% responders:* In both studies, the results for the 10% weight loss responders were consistent with the results for the 5% weight loss responders, with a smaller overall percentage of subjects in this category compared to 5% responders (TABLE 5, TABLE 7).

Subgroups:

Sex: Males and females were fairly similar in the mean placebo-adjusted effect of lorcaserin 10 mg bid in Study 009. However, results from Study 011 suggested that males may not show additional benefit with the 10 mg bid dose compared to the 10 mg qd dose, whereas females did have a greater mean weight loss with the higher dose compared to the lower dose (TABLE 18, FIGURE 15).

Race: The placebo-adjusted effect of lorcaserin 10 mg bid in the two minority subgroups African American/ Black and Hispanic/ Latino was fairly similar to the majority subgroup Caucasian/ White. However, the unadjusted mean weight loss in the placebo and lorcaserin arms was less in the minority subgroups compared to the majority subgroup (TABLE 19, FIGURE 16). This finding corresponds to a lower retention of subjects in the minority subgroups compared to the majority subgroup (TABLE 20). In addition, subjects in the Hispanic/ Latino subgroup in Study 011 did not appear to respond to the lower lorcaserin dose, but did have a response to the higher dose.

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

Baseline BMI: The average weight loss was fairly similar across baseline BMI subgroups (TABLE 21, TABLE 22).

Other efficacy endpoints: The results from secondary efficacy endpoints supported the efficacy of lorcaserin compared to placebo. In general, the mean difference between lorcaserin and placebo was relatively small but statistically significant. This review provides summaries for LDL-cholesterol, systolic and diastolic blood pressure, fasting plasma glucose, total body fat, and total quality of life score (TABLE 9 - TABLE 14). These were pre-specified as key secondary efficacy endpoints in one or both studies.

Year 2 of Study 009: The results from year 2 of Study 009 may be challenging to interpret with respect to the intended target population of lorcaserin, because only 50% of the initially randomized population completed year 1 and participated in year 2. In addition, the primary comparison involved the subgroup of subjects who were 5% responders to lorcaserin from year 1. Both of these considerations describe subjects who were more likely to be successful in weight loss compared to the general target population. The primary finding that more 5% responder subjects from year 1 remained as 5% responders when maintained for a second year on lorcaserin (67.9%) than when switched to placebo for the second year (50.3%) should be described carefully with respect to the limitations of inference to the intended target population (TABLE 16, TABLE 17).

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. Lorcaserin is a selective serotonin 2C receptor agonist. Serotonin and certain serotonin agonists decrease food intake and reduce body weight through activation of centrally located 5-HT$_{2C}$ receptors. The applicant developed lorcaserin with the intention of activating 5-HT$_{2C}$ receptors without initiating the heart valve toxicity seen in the historical weight management products fenfluramine and dexfenfluramine.

2.2 Scope of Statistical Review of Efficacy for Advisory Committee Meeting on September 16, 2010

The purpose of this portion of the briefing document is to provide the statistical review perspective of the efficacy of lorcaserin, based on the results from two Phase 3 studies: APD356-009 (BLOOM; Study 009) and APD356-011 (BLOSSOM; Study 011).

Enrollment: Studies 009 and 011 both included 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). The highest allowable BMI was 45 kg/m^2 at screening. Pregnant or lactating women were excluded from enrollment, as were subjects who had undergone prior bariatric surgery. Study 009 was conducted from November 2006 (first subject enrolled) to February 2009 (last subject completed). Study 011 was conducted from January 2008 to July 2009.

Study arms: The two Phase 3 studies were designed to evaluate the effect of lorcaserin administered in conjunction with behavior modification for 104 weeks (Study 009) and 52 weeks (Study 011). In Study 009, 3182 subjects were randomized in a 1:1 ratio to lorcaserin 10 mg BID : placebo. In Study 011, 4008 subjects were randomized in a ratio of 2:1:2 to lorcaserin 10 mg BID : lorcaserin 10 mg QD : placebo. Participants in both studies were treated with a behavior modification program, which was considered to be the standard of care for obese and overweight subjects.

Number of subjects in each study: The applicant planned to enroll 3100 subjects in Study 009 and 3000 subjects in Study 011, making the assumption that 60% would complete year 1. The size of each study was developed to address several considerations: (1) a specific evaluation of the occurrence of cardiac valvulopathy; (2) a general evaluation of safety; and (3) the evaluation of efficacy from three co-primary endpoints. A key resource was the February 2007 draft *Guidance for Industry: Developing Products for Weight Management*. Under the topic "Efficacy benchmarks," the guidance recommends:

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

- *The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant*

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

As part of my review activities, I confirmed the calculations of statistical power that the applicant used in developing the size of each study.

3. STATISTICAL EVALUATION OF EFFICACY

3.1. Subject disposition

A substantial percentage of randomized subjects in each study and study arm, between 40% and 55%, withdrew prior to week 52 (TABLE 2A). This finding is typical of weight loss studies. Investigators in this field have proposed and evaluated different ways to evaluate weight loss programs and/or drugs, given that a large percentage of subjects are likely to discontinue before the primary endpoint period[2]. The weight management guidance recommends estimating the effect of a drug by several different methods. This sensitivity analysis should reflect the time dynamics and reasons for early discontinuation.

The percentage of subjects who withdrew prior to week 52 was somewhat greater in the placebo group in each study than in the lorcaserin arm(s) (TABLE 2A). In all study arms, the reason for early withdrawal given by the greatest percentage of subjects was "withdrawal of consent," followed by "lost to follow-up." A summary of attempts to reach subjects who were lost to follow-up was included in the disposition database. I reviewed a selection of these summaries to gain an appreciation of the several failed attempts to reach these subjects by phone and registered letter. Early withdrawal due to an adverse event accounted for less than 10% of randomized subjects in each study arm.

Subjects who withdrew early were more likely to do so before the week 26 mid-point of the study (TABLE 2B). This pattern is also illustrated in (FIGURE 1). The shortest average time on study was in subjects who were lost to follow-up. Subjects with higher BMI at baseline were somewhat more likely to withdraw early from the study than subjects with a lower baseline BMI (FIGURE 2). This effect was small but consistent between the studies and across study arms. However, the correlation between baseline BMI and number of weeks on the study was low (-0.02 in the lorcaserin arm and -0.07 in the placebo arm of Study 009), suggesting that baseline BMI may not contribute substantially to a subject's decision to withdraw.

[2] For example, see Gadbury, GL, CS Coffee and DB Allison, 2003: Modern statistical methods for handling missing repeated measurements in obesity trial data: beyond LOCF. Obesity Reviews 4: 175-184.

On average, subjects who withdrew early lost less weight at the time of withdrawal, compared to the average weight loss at the same study week in subjects who completed the study. To assess this pattern, I created five subgroups of subjects, according to their last week on the study, as follows:

- week 0-6 subgroup: dropped out on or before week 6
- week 6-12 subgroup: dropped out after week 6, up to and including week 12
- week 12-24 subgroup: dropped out after week 12, up to and including week 24
- week 24-52 subgroup: dropped out after week 24 but before week 52
- completers: completed the study

The time course of average weight loss in each dropout subgroup and in the completers is depicted in FIGURE 3. The average weight loss at weeks 4, 12, 24 and 52 is also tabulated for each cohort and study arm. The average weight loss in dropout cohort 6 is less than the average weight loss in the completers at week 4, for both the lorcaserin and placebo arms (FIGURE 3; week 4 is the final visit for this dropout subgroup). This finding is consistent across the final visits for dropout cohorts 12, 24 and 52 compared to the completers at the same visit. One interpretation of this finding is that subjects who are less successful at losing weight at any given time throughout the study are more likely to drop out than subjects who are more successful.

Subjects who withdrew early from the study had the opportunity to return for a weight measurement at week 52. These weights were not used in the primary efficacy analysis, but they were used in one of the sensitivity analyses. The largest percentage of subjects returning for a week 52 weight had withdrawn because of an adverse event, and, perhaps not surprisingly, the smallest percentage came from subjects who were lost to follow-up (TABLE 2C).

TABLE 2 Disposition of subjects in Study 009 and Study 011 at week 52

	Study 009		Study 011		
	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Lorcaserin 10 mg QD	Placebo
A. Disposition[1]					
Number randomized	1595	1587	1603	802	1603
No. (%) who completed	883 (55.4)	715 (45.1)	917 (57.2)	473 (59.0)	834 (52.0)
No. (%) who withdrew prior to week 52	712 (44.6)	872 (54.9)	686 (42.8)	329 (41.0)	769 (48.0)
Reason for withdrawal:					
Withdrawal of consent	307 (19.2)	439 (27.7)	293 (18.3)	162 (20.2)	376 (23.5)
Lost to follow-up	191 (12.0)	226 (14.2)	198 (12.4)	83 (10.3)	234 (14.6)
Adverse event	113 (7.1)	106 (6.7)	115 (7.2)	50 (6.2)	74 (4.6)
Combined other reasons[2]	101 (6.3)	100 (6.3)	80 (5.0)	34 (4.2)	85 (5.3)
B. Average time on study (weeks) prior to withdrawal					
Reason for withdrawal:					
Withdrawal of consent	20.0	18.8	17.7	16.9	17.3
Lost to follow-up	12.7	11.2	14.0	17.1	12.7
Adverse event	17.4	17.1	19.7	18.0	15.9
Combined other reasons[2]	21.2	15.8	23.8	27.7	27.3
C. Returning dropouts: Subjects who withdrew but returned for a final weight					
No. (%) of returning dropouts	154 (9.7)	191 (12.0)	114 (7.1)	54 (6.7)	119 (7.4)
Reason for withdrawal n (%):					
Withdrawal of consent	76 (4.8)	128 (8.1)	46 (2.9)	26 (3.2)	66 (4.1)
Lost to follow-up	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Adverse event	51 (3.2)	37 (2.3)	42 (2.6)	20 (2.5)	30 (1.9)
Combined other reasons[2]	26 (1.6)	26 (1.6)	26 (1.6)	8 (1.0)	22 (1.4)

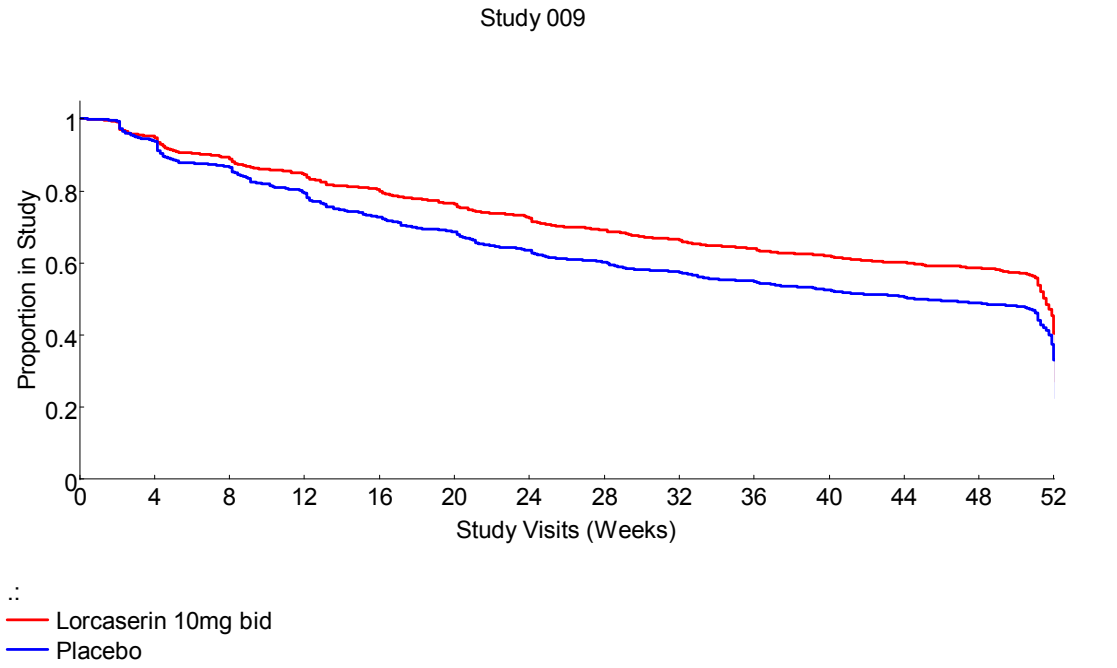
Notes

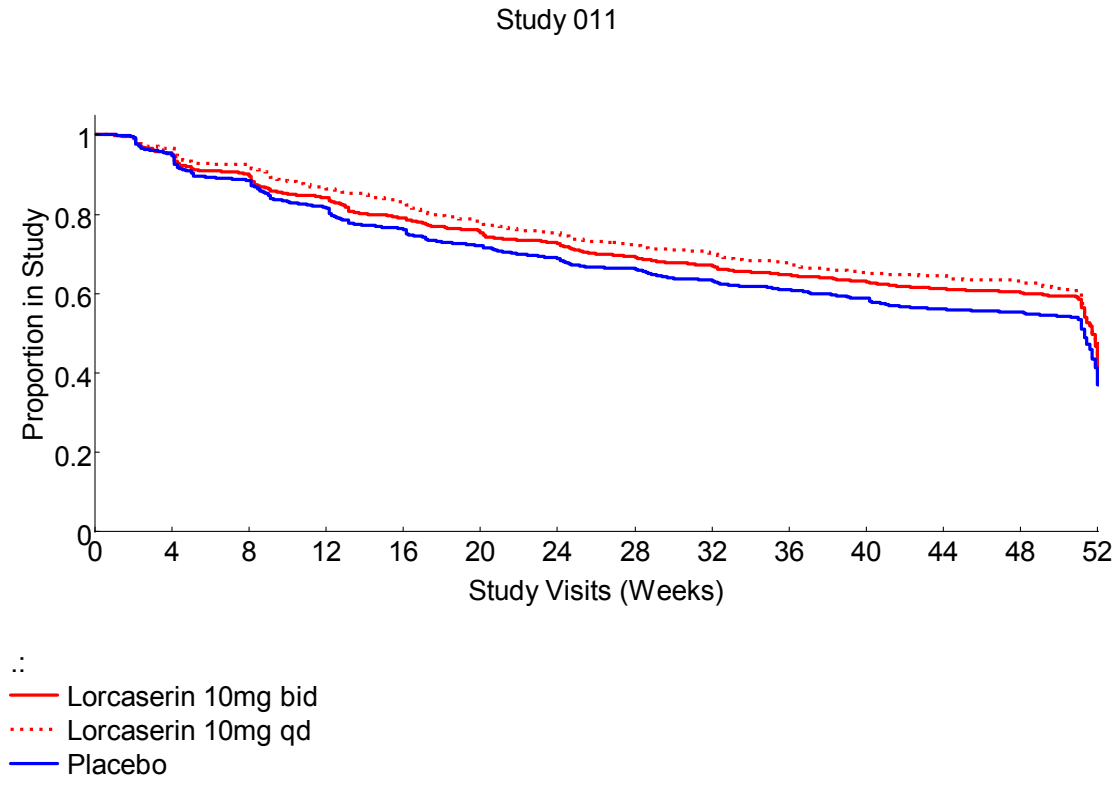
[1] For percentages, the number of subjects randomized was used as the denominator.

[2] For "Combined other reasons," the following discontinuation categories were combined: Protocol deviation / noncompliance, Sponsor decision, PI decision and Other discontinuation reason

Source: Integrated Summary of Efficacy, Table 4, and additional analysis by this reviewer.

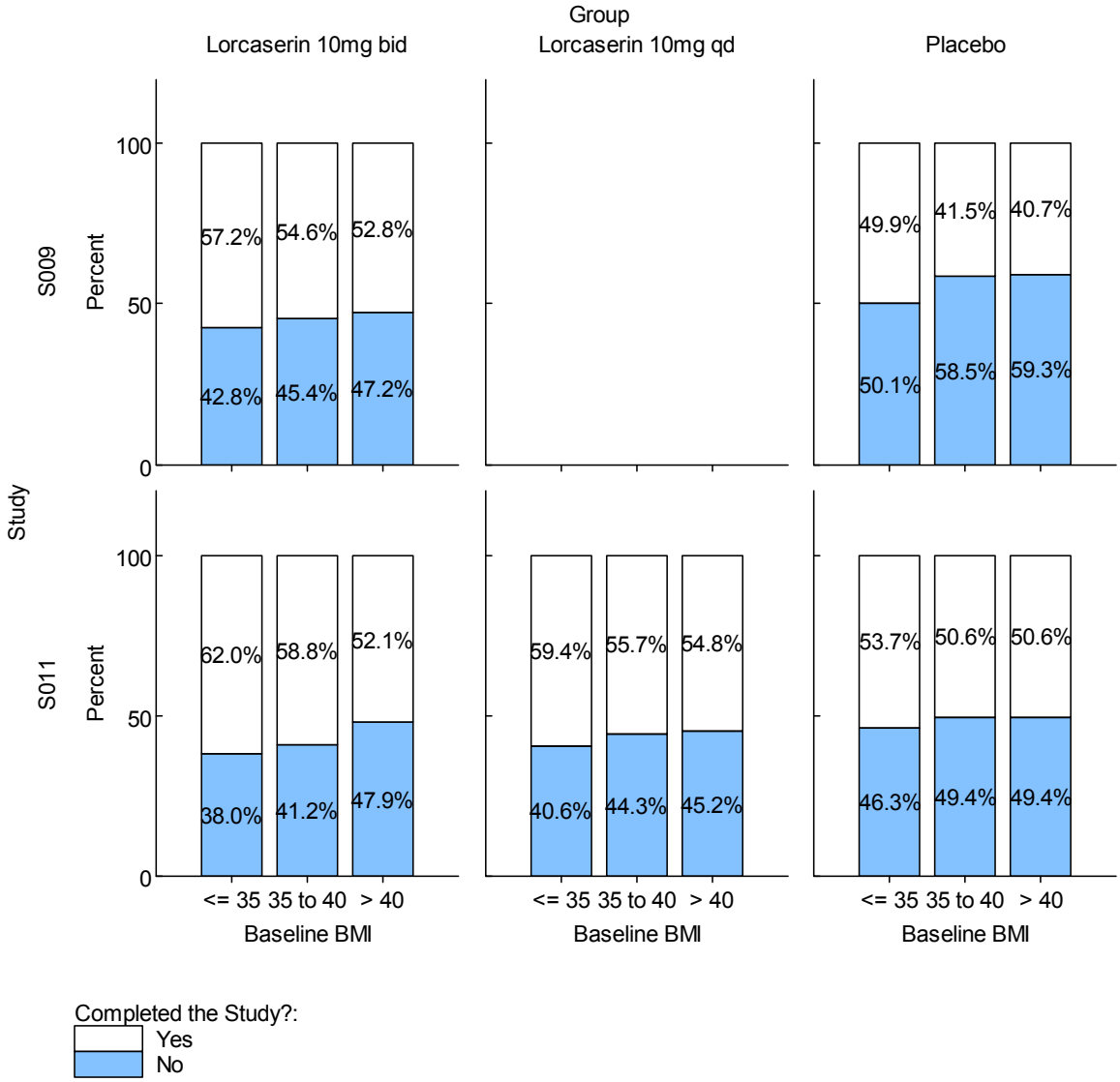
FIGURE 1 Disposition of subjects in Study 009 and Study 011 by week 52





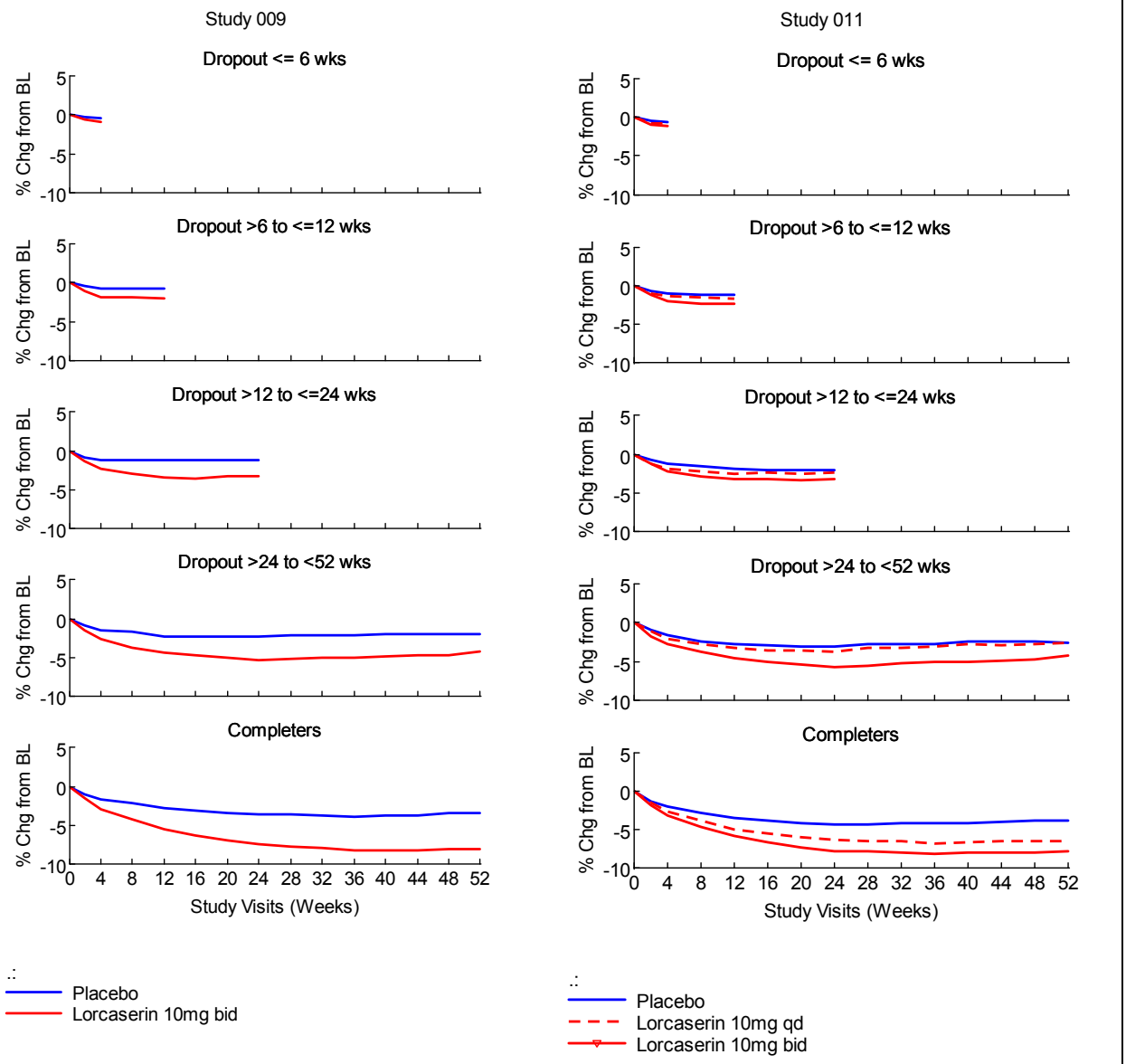
Source: Analysis by this reviewer

FIGURE 2 Percentage of early withdrawals (before week 52) in Study 009 and 011, and the relationship to baseline BMI



Source: Analysis by this reviewer

FIGURE 3 Body weight, mean percent change from baseline (MITT) in subgroups defined by week of dropout, and in completers



Average % change from baseline in body weight
in final visit for each dropout subgroup, and comparable visit for completers subgroup

		Study 009				Study 011			
	Visit (week)	4	12	24	52	4	12	24	52
Subgroups by final visit before dropping out	Placebo	-0.4	-0.7	-1.2	-2.0	-0.6	-1.2	-2.0	-2.5
	Lorcaserin 10mg qd					-0.8	-1.7	-2.3	-2.5
	Lorcacerin 10mg bid	-0.8	-2.0	-3.2	-4.2	-1.1	-2.4	-3.2	-4.2
Completers	Placebo	-1.6	-2.7	-3.6	-3.3	-2.0	-3.5	-4.3	-3.9
	Lorcaserin 10mg qd					-2.7	-4.9	-6.4	-6.5
	Lorcacerin 10mg bid	-2.9	-5.4	-7.4	-8.0	-3.1	-5.8	-7.8	-7.9

Notes: Within each subgroup, the weight at the subject's final visit before dropping out was carried forward to the final visit for that subgroup. *Source:* Analysis by this reviewer.

3.2. Subject demographic and baseline characteristics

Studies 009 and 011 were fairly similar in the distribution of subject demographic and baseline characteristics (TABLE 3). The enrollment criteria of both studies excluded subjects over 65 years of age. The large majority of subjects (approximately 80%) were female. Approximately two-thirds of the subjects were Caucasian. The average baseline weight was approximately 100 kg, and the distribution of subjects across obesity categories defined by levels of body mass index was fairly similar between the two studies and among the arms within each study (TABLE 3).

TABLE 3 Subject demographic and baseline characteristics in the randomized subjects in Study 009 and Study 011

	Study 009		Study 011		
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**
Age (years)					
Mean ± SD	43.7 ± 11.3	44.4 ± 11.1	43.7 ± 11.7	43.8 ± 11.8	43.7 ± 11.8
Median	44.0	45.0	44.0	44.0	44.0
Range	18 to 66	18 to 66	18 to 65	18 to 65	18 to 65
Sex					
Female (n, %)	1323 (82.9%)	1334 (84.1%)	657 (81.9%)	1290 (80.4%)	1251 (78.0%)
Male (n, %)	272 (17.1%)	253 (15.9%)	145 (18.1%)	313 (19.5%)	352 (22.0%)
Race[1]					
Caucasian/White	1081 (67.8%)	1048 (66.0%)	539 (67.2%)	1081 (67.4%)	1066 (66.5%)
African American/ Black	300 (18.8%)	299 (18.8%)	160 (20.0%)	306 (19.1%)	319 (19.9%)
Hispanic/Latino	181 (11.3%)	213 (13.5%)	86 (10.7%)	174 (10.9%)	181 (11.3%)
Asian	12 (0.8%)	9 (0.6%)	3 (0.4%)	12 (0.7%)	10 (0.6%)
Native Hawaiian / Pacific Islander	1 (0.0%)	1 (0.0%)	4 (0.5%)	10 (0.6%)	6 (0.4%)
American Indian / Alaska Native	11 (0.7%)	4 (0.3%)	7 (0.9%)	7 (0.4%)	10 (0.6%)
Other	9 (0.6%)	11 (0.7%)	3 (0.4%)	13 (0.8%)	11 (0.7%)
Baseline comorbid conditions					
Dyslipidemia	534 (33.5%)	525 (33.1%)	218 (27.2%)	455 (28.4%)	439 (27.4%)
Hypertension	335 (21.0%)	342 (21.6%)	175 (21.8%)	388 (24.2%)	383 (23.9%)
Sleep apnea	72 (4.5%)	55 (3.5%)	27 (3.4%)	72 (4.5%)	73 (4.6%)
Glucose intolerance	18 (1.1%)	14 (0.9%)	15 (1.9%)	29 (1.8%)	18 (1.1%)
Weight (kg)					
Mean ± SD	100.4 ± 15.7	99.7 ± 15.6	100.1 ± 16.7	100.5 ± 15.6	100.8 ± 16.2
Median	99.0	98.3	97.5	99.1	99.0
Range	62.6 to 156.9	62.7 to 156.0	64.9 to 185.4	64.1 to 159.3	63.9 to 165.9
BMI (kg/m^2)					
Mean ± SD	36.2 ± 4.3	36.1 ± 4.3	35.9 ± 4.3	36.1 ± 4.3	36.0 ± 4.2
Median	35.8	35.7	35.2	35.6	35.5
Range	26.8 to 46.2	26.7 to 46.5	26.4 to 46.8	26.7 to 52.5	27.1 to 46.6
BMI categories					
< 30	75 (4.7%)	65 (4.1%)	30 (3.7%)	75 (4.7%)	66 (4.1%)

	Study 009		Study 011		
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
≥ 30 to ≤ 35	615 (38.6%)	653 (41.1%)	362 (45.1%)	649 (40.5%)	664 (41.4%)
> 35 to ≤ 40	570 (35.7%)	537 (33.8%)	243 (30.3%)	549 (34.2%)	557 (34.7%)
> 40	335 (21.0%)	332 (20.9%)	167 (20.8%)	330 (20.6%)	316 (19.7%)

Source: Analysis by this reviewer, from 0000\...\ISS-ISE\Analysis\DM.xtp for randomized subjects

3.3. Analysis populations

The applicant used the same definitions in the analysis of each study separately. Differences in terminology pertain to the distinction between year 1 and year 2 for Study 009. These definitions are as follows:

Modified Intent-to-Treat (MITT) Population: The MITT population consisted of all randomized subjects who had a baseline measurement, who received at least one dose of study medication, and who had a post-randomization measurement. Subject data was analyzed according to the treatment assigned at randomization, regardless of the treatment received during the course of the trial. Data collected after subjects discontinued from treatment was not included in the primary analysis. The last observation on or prior to discontinuation (LOCF) was carried forward and used in the analysis. At least 95% of randomized subjects were in the MITT populations (TABLE 4).

In Study 009, the MITT1 population for Year 1 was as defined above. The MITT2 population for Year 2 consisted of all randomized subjects who completed Year 1, were re-randomized at week 52, took at least one dose of study medication after re-randomization, and had at least one weight measurement post re-randomization. The last post re-randomization observation on or prior to discontinuation was carried forward and used in the analysis.

Week 52 (W52) Population: The W52 population included all randomized subjects who had a post-baseline body weight recorded within 2 weeks of the scheduled 52-week visit. This included subjects who withdrew from the study prior to week 52, and returned for a body weight measurement within 2 weeks of their scheduled week 52 visit. Approximately 60% of randomized subjects were in the W52 population (TABLE 4).

Per-Protocol Population: The PP population excluded subjects and/or data points with clinically important protocol deviations based on a set of pre-specified criteria. The PP population did not include estimates for missing data. Study 009 had a PP1 population for Year 1 and a PP2 population for Year 2. The per-protocol criteria were similar in both studies, and in both years of Study 009, and included the following:

- The subject had a baseline body weight measurement recorded.

- The subject had a body weight recorded within 2 weeks (days 357-371) of the scheduled 52-week visit.
- If the subject was a tobacco user at baseline, he/she did not stop tobacco use at week 52.
- The subject's compliance in taking study medication over 52 weeks of the study was 80-120%.
- The subject provided body weights for at least 10 of the 14 scheduled visits during year 1.

Safety Analysis Population: The safety population included all subjects who were randomized and received at least one dose of study drug. Missing or invalid data was not imputed.

The combined analysis of Study 009 and Study 011 used the same definition of the MITT population at year 1 as in the separate analyses. In addition, the applicant defined an MITT2 population. The MITT2 population included all subjects in the MITT population. However, if subjects who had withdrawn early returned for a week 52 weight measurement, this value was used instead of the LOCF value. Subjects who did not return for a week 52 weight did have the LOCF value used to estimate their final weight. The term "MITT2" was used differently in the combined analysis than it was in the analysis of year 2 data from Study 009.

In the combined analysis of the two studies, the applicant defined the Returning Dropout Population (RDP) instead of using the Week 52 Population. The two definitions are very similar, but the criteria for including week 52 weights from "returning dropouts" was specified to be within 2 weeks (days 357-371) of the scheduled 52-week visit. This excluded a small number of subjects in Study 009 who were in the W52 population but not the RDP (TABLE 4). The applicant also defined a Completers Population (CP) to include all subjects who had completed the study at year 1. The analyses of the CP population and RDP population did not estimate missing data.

As an additional sensitivity analysis, I used the following approach to estimating week 52 weight for study dropouts: (1) if a subject dropped out but returned for a final weight, I used this weight for week 52; (2) if a subject dropped out and did not return for a final weight, I estimated the week 52 weight by adding 0.3 kg per month to the last measured weight, based on the number of months between the drop-out date and week 52. This method incorporates the rate of regain that is expected after discontinuation of a weight loss effort, as described in Fabricatore et al. (2009)[3].

[3] Fabricatore, A.N., T.A. Wadden, R.H. Moore, M.L. Butryn, S.B. Heymsfield and A.M. Nguyen, 2009. Predictors of attrition and weight loss success: Results from a randomized controlled trial. *Behaviour Research and Therapy* 47: 685-691.

TABLE 4 Analysis populations defined for Study 009 and Study 011, primary endpoint (Year 1 for Study 009)

	Study 009		Study 011		
	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Lorcaserin 10 mg QD	Placebo
Number randomized	1595	1587	1603	802	1603
Safety population, n (%)	1593(99.9)	1584 (99.8)	1602 (99.9)	801 (99.9)	1601 (99.9)
Separate analysis of each study[1]					
MITT population, n (%)	1538 (96.5)	1499 (94.5)	1561 (97.4)	771 (96.1)	1541 (96.1)
Week 52 population, n (%)	1031 (64.6)	901 (56.8)	1028 (64.1)	524 (65.3)	951 (59.3)
Per Protocol population, n (%)	737 (46.2)	583 (36.7)	846 (52.8)	418 (52.1)	764 (47.7)
Combined analysis of Study 009 and Study 011					
Returning Dropout population, n (%)	1015 (63.6)	888 (56.0)	1028 (64.1)	524 (65.3)	951 (59.3)
Completers population, n (%)	883 (55.4)	716 (45.1)	917 (57.2)	473 (59.0)	834 (52.0)
MITT2 population, n (%)[2]	1538 (96.5)	1499 (94.5)	1561 (97.4)	771 (96.1)	1541 (96.1)

Notes

[1] Study 009, the Year 1 terms for the MITT and PP analysis populations are MITT1 and PP1

[2] For the combined analysis, MITT2 refers to an analysis population, as described in Part 3.1.3 of this review. Note that for the separate analysis of Study 009, MITT2 refers to the MITT population in Year 2.

Sources: Study 009 report, Figure 2; Study 011 report, Table 5; and analysis by this reviewer

3.4. Co-primary efficacy endpoints

For both Study 009 and Study 011, the sponsor defined three co-primary efficacy endpoints in the following order: (1) the proportion of subjects achieving ≥ 5% reduction in body weight at the end of year 1 ("5% responders"); (2) the change from baseline to the end of year 1 in body weight; and (3) the proportion of subjects achieving ≥ 10% reduction in body weight at the end of year 1 ("10% responders"). This order is important in the approach to controlling Type I error (described at the end of this section).

This set of co-primary endpoints is somewhat different from those recommended in the 2007 weight management guidance. The continuous endpoint is the absolute change in body weight from baseline rather than the percentage change as described in the guidance. The 5% responder endpoint is the same as is described in the guidance. The applicant also included a 10% responder endpoint. In my opinion, the differences are not substantial enough to cause discrepancies in study conclusions based on the applicant's endpoints compared to the guidance's endpoints. This is due to several considerations: (1) the third endpoint, the 10% responder endpoint, is evaluated at the end of the closed testing procedure (see below) and therefore does not influence gate-keeping decisions from the first two endpoints; (2) the 10% responder endpoint is obtained from a subset of subjects who are 5% responders, and so statistical conclusions about both categorical endpoints are likely to be similar; (3) in these study populations where the average baseline weight is approximately 100 kg, the continuous endpoint may be fairly similar when expressed either as an absolute change or as a percentage change. However, for extension of inference to the target population, it is important to know whether the drug effect is best expressed as a percentage change or an absolute change. The results of these studies should inform subjects in the target population about the weight loss they can expect after one year of treatment. The weight management guidance expresses the continuous endpoint as a percentage change in part because the health effects of a 5% or greater weight loss from baseline have been described in the literature: "In overweight and obese individuals, particularly individuals with comorbidities such as hypertension, dyslipidemia, and type 2 diabetes, long-term weight loss greater than or equal to 5 percent following diet, exercise, and in some cases, drug treatment, is associated with improvement in various metabolic and cardiovascular risk factors (Douketis and Macie et al. 2005)"[4]. For this reason, I evaluated the continuous endpoint as a percentage change from baseline in this review.

Approach to multiplicity: Control of Type I error in the co-primary endpoints: Based on the 2007 guidance, the efficacy of lorcaserin would be supported if either one or both of the co-primary endpoints described in the guidance were statistically significant. The guidance does not comment on the control of Type I error in the co-primary endpoints. However, the ICH-E9 guidance advises that in the event that a protocol identifies more than one primary endpoint, "the effect on the Type I error should be explained because of the potential for multiplicity problems …; the method of controlling Type I error should be given in the protocol."[5]

[4] Douketis, JD, C Macie, L Thabane, and DF Williamson, 2005, Systematic Review of Long-Term Weight Loss Studies in Obese Adults: Clinical Significance and Applicability to Clinical Practice, *International Journal of Obesity*, 29:1153-1167; the quotation is from Part IIIA of the weight management guidance (2007 draft).

[5] Part II.B.5., *Guidance for Industry, E9 Statistical Principles for Clinical Trials*, September 1998

The protocols for studies 009 and 011 describe a gate-keeping strategy to control the Type I error for three co-primary endpoints. This strategy also gives priority to the continuous endpoint and to the 5% responder endpoint, which are either similar (in the case of the continuous endpoint) or the same as (in the case of the 5% responder endpoint) the two endpoints described in the weight management guidance. The gate-keeping strategy is a closed testing procedure, with the following steps:

Step 1: Test the proportion of 5% responders at a two-tailed α of 0.05. If the result is significant, conclude that the results support the efficacy of lorcaserin compared to placebo. Continue to step 2.

Step 2: Test the change from baseline to the end of year 1 in body weight at a two-tailed α of 0.05. If the result is significant, continue to step 3.

Step 3: Test the proportion of 10% responders at a two-tailed α of 0.05.

3.5. Statistical analysis methods for primary efficacy endpoint

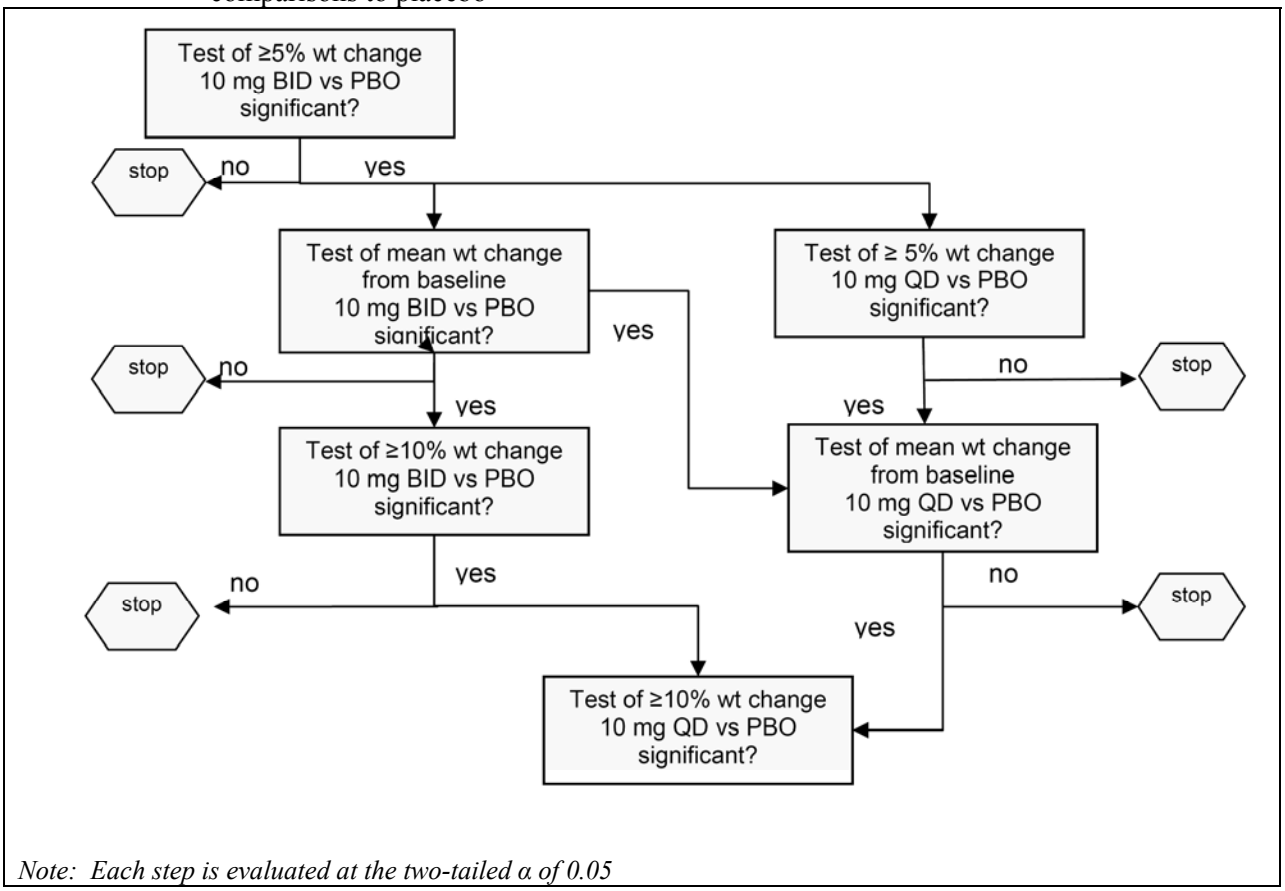
Continuous endpoint: Change in weight was analyzed with analysis of covariance (ANCOVA) models with treatment and gender as the factors, and baseline body weight as covariate. The primary analysis for year 1 used the MITT1 population with LOCF estimation for subjects who dropped out before the end of year 1. The applicant also analyzed the percent change from baseline with the same analysis model.

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

Approach to multiplicity: Control of Type I error between dose levels of lorcaserin (Study 011):

The applicant described a closed testing procedure that included the three co-primary efficacy endpoints and the comparisons of two lorcaserin dose arms against placebo. This process is depicted in FIGURE 4.

FIGURE 4 Study 011; closed testing procedure for 3 co-primary endpoints and 2 dose level comparisons to placebo



Note: Each step is evaluated at the two-tailed α of 0.05

Source: Study 011 Statistical Methods, Figure 2

3.6. Results of the statistical analysis of efficacy: Weight endpoints

Study 009

Continuous endpoint: After 1 year of treatment with lorcaserin 10 mg bid, subjects lost a statistically significant amount of weight. Expressed as a % change from baseline, the placebo-adjusted average weight loss was 3.7%, with a 95% confidence interval of 3.3% to 4.1% (TABLE 5, result 1). I confirmed this result. This outcome supports one of the benchmarks for clinical significance in the weight management guidance. Expressed as weight loss in kg, the placebo-adjusted average weight loss was 3.6 kg, with a 95% confidence interval of 3.2 to 4.0. These two expressions are similar (with a correlation of 0.98) because the average baseline was close to 100 kg in each arm. Because of this similarity, I will use the "% change from baseline" expression in further review comments about the continuous endpoint.

This result was consistent across different versions of the analysis population and different methods of analysis (TABLE 5). However, the average weight loss was statistically significantly less than 5% in the primary analysis and most of the supportive analyses. This result does not support one of the benchmarks for clinical significance for the continuous endpoint, as described in the weight management guidance.

The majority of subjects who dropped out prior to the end of the study remained within ± 5% of their baseline body weight (FIGURE 5; top two portions of each bar). These are the subjects whose final weight was estimated by LOCF in the primary analysis. Some of these subjects returned for a final week 52 weight ("returning dropouts"; FIGURE 5, middle porttion of each bar). Using the week 52 weight of the returning dropouts instead of LOCF did not appreciably affect the distribution of weight change (FIGURE 6) or the results of the statistical analysis (TABLE 5, result 9). Estimating the final weight of non-returning dropouts by a weight gain algorithm also did not greatly affect the percentage of subjects who had gained more than 5% of their baseline weight (FIGURE 7), and did not greatly affect the results of the statistical analysis (TABLE 5, result 8). A longitudinal profile of weight change from baseline is given in FIGURE 8.

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 6). This finding meets one of the criteria for clinical significance in the 5% responder endpoint, as described in the weight management guidance. The results from the analysis of the MITT population are supported by the results of the analyses of the per protocol population (PP) and the completers population (CP).

Subjects who dropped out were more likely to stay within ± 5% of their baseline body weight compared to subjects who completed the study (FIGURE 5). For this reason, a sensitivity analysis that classified dropouts as non-responders produced results that were very similar to the primary analysis (TABLE 6).

The results for the 10% weight loss responders were consistent with the results for the 5% weight loss responders, with a smaller overall percentage of subjects in this category compared to 5% weight loss responders (TABLE 6).

TABLE 5 Study 009; Weight as a % change from baseline at year 1; results from primary and supportive analyses

Study 009 Treatment groups	N	Baseline mean (kg) ± SE	Adjusted mean % change from baseline at Week 52 ± SE[1]	Difference in adjusted mean % change, Lorcaserin - placebo (95% CI)	P-value vs. placebo
Analyses with MITT1 population					
Lorcaserin 10 mg bid	1538	100.4 ± 0.4			
Placebo	1499	99.7 ± 0.4			
1. Primary analysis: LOCF estimation for dropouts; primary ANCOVA model; sponsor's analysis					
Lorcaserin 10 mg bid			-5.9 ± 0.2	-3.7 (-4.1, -3.3)	<0.0001
Placebo			-2.2 ± 0.1		
2. MITT1 population with no estimation for missing data; MMRM model; sponsor's analysis					
Lorcaserin 10 mg bid			-6.8 ± 0.1	-4.2 (-4.6, -3.8)	<0.001
Placebo			-2.6 ± 0.1		
3. MITT1 population with LOCF estimation for dropouts; ANCOVA model including factor for site; this reviewer's analysis					
			-5.9 ± 0.2	-3.6 (-4.1, -3.2)	<0.0001
			-2.3 ± 0.2		
Analysis with PP1 population					
4. no LOCF estimation (dropouts were not included in this population); primary ANCOVA model; sponsor's analysis					
Lorcaserin 10 mg bid	737	100.7 ± 0.6	-8.2 ± 0.3	-4.9 (-5.7, -4.2)	<0.001
Placebo	583	99.0 ± 0.7	-3.3 ± 0.3		
Analysis with Completers population					
5. no LOCF estimation (dropouts were not included in this population); primary ANCOVA model; sponsor's analysis					
Lorcaserin 10 mg bid	861	100.6 ± 0.5	-8.0 ± 0.3	-4.8 (-5.4, -4.1)	<0.001
Placebo	697	99.3 ± 0.6	-3.2 ± 0.3		
Other Analyses					
6. Returning dropouts and completers (non-returning dropouts were not included in this population); primary ANCOVA model; this reviewer's analysis [A]					
Lorcaserin 10 mg bid	1015	100.2 ± 0.5	-6.9 ± 0.3	-4.0 (-4.7, -3.4)	<0.0001
Placebo	888	99.1 ± 0.5	-2.9 ± 0.3		
7. MITT1 population with (a) weight regain estimation for non-returning dropouts; (b) week 52 weights for returning dropouts; primary ANCOVA model; this reviewer's analysis [A]					
Lorcaserin 10 mg bid	1569	100.4 ± 0.4	-4.9 ± 0.2	-3.6 (-4.1, -3.1)	<0.0001

Placebo	1517	99.7 ± 0.4	-1.3 ± 0.2		
8. MITT1 population with (a) LOCF imputation for non-returning dropouts and (b) week 52 weight for returning dropouts; this reviewer's analysis [A]					
Lorcaserin 10 mg bid	1569	100.4 ± 0.4	-5.6 ± 0.2	-3.4 (-3.8, -2.9)	<0.0001
Placebo	1517	99.7 ± 0.4	-2.2 ± 0.2		

Notes:

[A] The group totals in this analysis represent a small percentage of cases with duplicate records in the analysis database; this analysis database represented a combination of variables from several databases provided by the applicant. I was not able to fully resolve this issue, but I do not believe that the inaccuracies that resulted from the analysis of this database affected the interpretation of results.

Sources:

1. Study report, Table 11, which references Tables 14.2.1.1 and 14.2.3, and Table E4.0 submitted 4/2/2010 (0008)
2. Table E4.10 submitted 4/2/2010 (0008)
3. Analysis by this reviewer
4. Table E4.11 submitted 4/2/10 (0008)
5. Table E4.1 submitted 4/2/10 (0008)

6, 7, 8. Analysis by this reviewer

TABLE 6 Study 009; 5% and 10% weight loss responders; results from primary and supportive analyses

Treatment groups	N	Number of responders (%)	Difference in proportions[1] (95% CI)	Odds ratio[3] (95% CI)	p-value[3] vs. placebo
% of subjects achieving ≥ 5% weight loss at week 52					
1. Primary analysis: MITT1; LOCF[2]					
Lorcaserin 10 mg bid	1538	731 (47.5%)	27.2 (24.0, 30.5)	3.6 (3.1, 4.2)	<0.001
Placebo	1499	304 (20.3%)			
2. Supportive analysis: PP; LOCF					
Lorcaserin 10 mg bid	737	489 (66.4%)	34.2 (29.2, 39.4)	4.2 (3.3, 5.3)	< 0.001
Placebo	583	187 (32.1%)			
3. Supportive analysis: Completers					
Lorcaserin 10 mg bid	861	567 (65.9%)	33.9 (29.2, 38.6)	4.0 (3.3, 5.0)	< 0.001
Placebo	697	223 (32.0%)			
4. Supportive analysis: Non-responder imputation (baseline carried forward); ITT/BOCF					
Lorcaserin 10 mg bid	1595	731 (45.8%)	26.7 (23.6, 29.8)	3.6 (3.1, 4.2)	<0.001
Placebo	1587	304 (19.2%)			

Treatment groups	N	Number of responders (%)	Difference in proportions[1] (95% CI)	Odds ratio[3] (95% CI)	p-value[3] vs. placebo
% of subjects achieving ≥ 10% weight loss at week 52					
5. Primary analysis: MITT1; LOCF					
Lorcaserin 10 mg bid	1538	347 (22.6%)	14.9 (12.4, 17.4)	3.5 (2.8, 4.4)	< 0.001
Placebo	1499	115 (7.7%)			
6. Supportive analysis: PP; LOCF					
Lorcaserin 10 mg bid	737	267 (36.2%)	22.7 (18.2, 27.1)	note 4	< 0.001
Placebo	583	79 (13.6%)			
7. Supportive analysis: Completers					
Lorcaserin 10 mg bid	861	303 (35.2%)	21.6 (17.5, 25.6)	3.5 (2.7, 4.5)	< 0.001
Placebo	697	95 (13.6%)			

Notes:

[1] The difference in proportions and 95% CI were calculated using normal approximation.

[2] Although the applicant did not include a sensitivity analysis with non-responder imputation for dropouts, the results from the primary analysis should be fairly close to this analysis, because most of the dropouts had final on-study weights that were within 5% of their baseline weight and would be classified by LOCF as non-responders.

[3] 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.

[4] I did not find this odds ratio in the applicant's materials; this is on request from the applicant.

Sources:

1. Study 009 Clinical Report, Table 10 (references Tables 14.2.1 and 14.2.1.2)
2. Study 009 Clinical Report, Table 14.2.73
3. Study 009 Table E72.10 (submitted 4/2/10 0008)
4. Advisory Committee briefing document Table 24
5. Study 009 Clinical Report, Table 12 (references Table 14.2.5.1); Advisory Committee briefing document Table 19
6. Study 009 Clinical Report, Table 14.2.5.1
7. Study 009 Table E73.10 (submitted 4/2/10 0008)

FIGURE 5 Study 009; Distribution of weight change at week 52; MITT population with primary imputation method (LOCF)

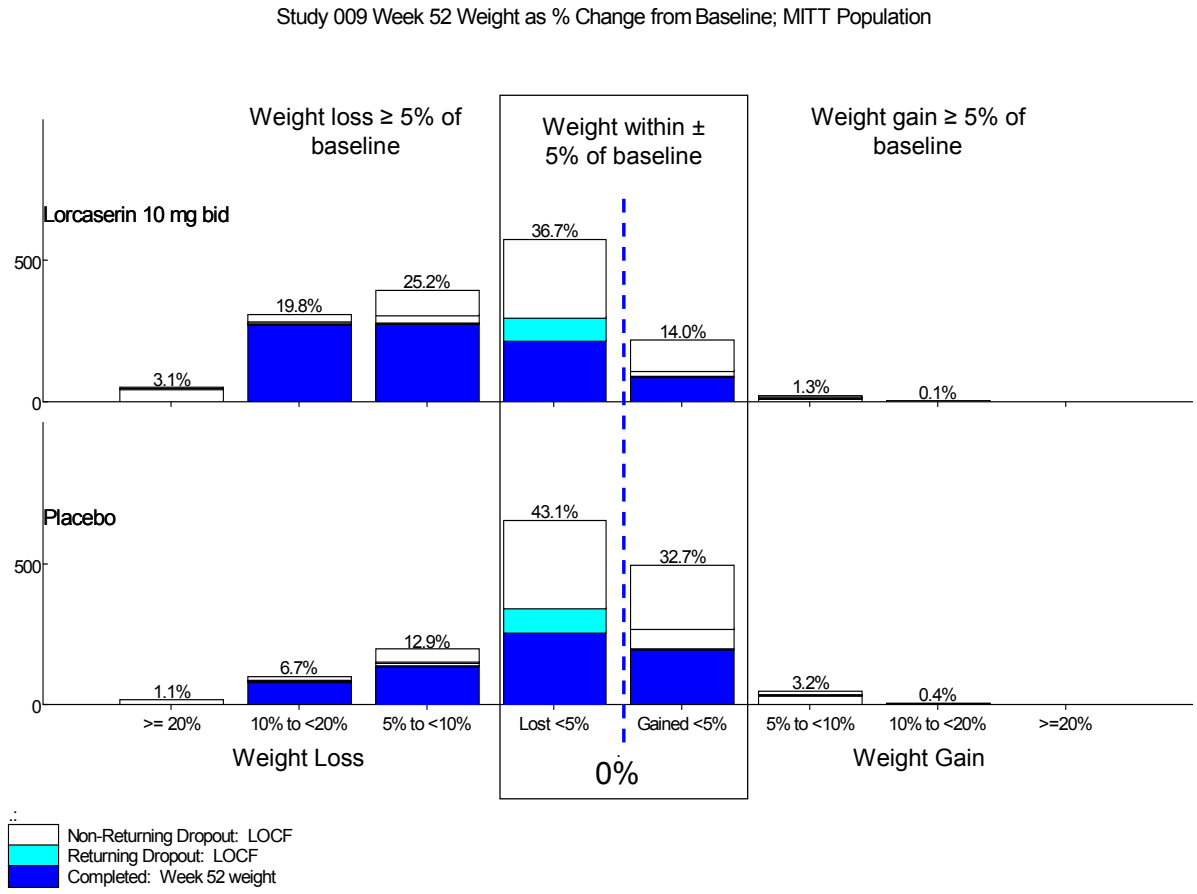


FIGURE 6 Study 009; Distribution of weight change at week 52; MITT population with week 52 weights for returning dropouts

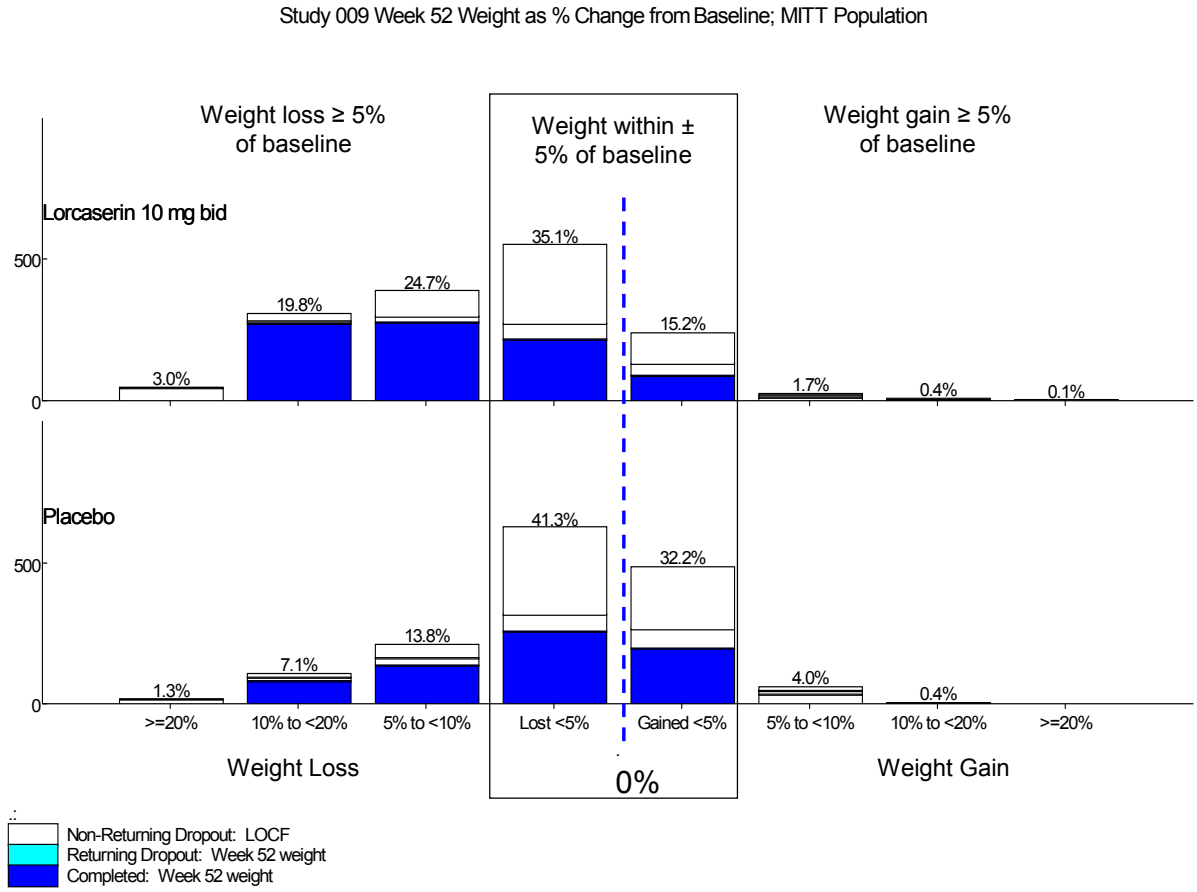


FIGURE 7 Study 009; Distribution of weight change at week 52; MITT population with week 52 weights for returning dropouts and weight regain estimation for non-returning dropouts

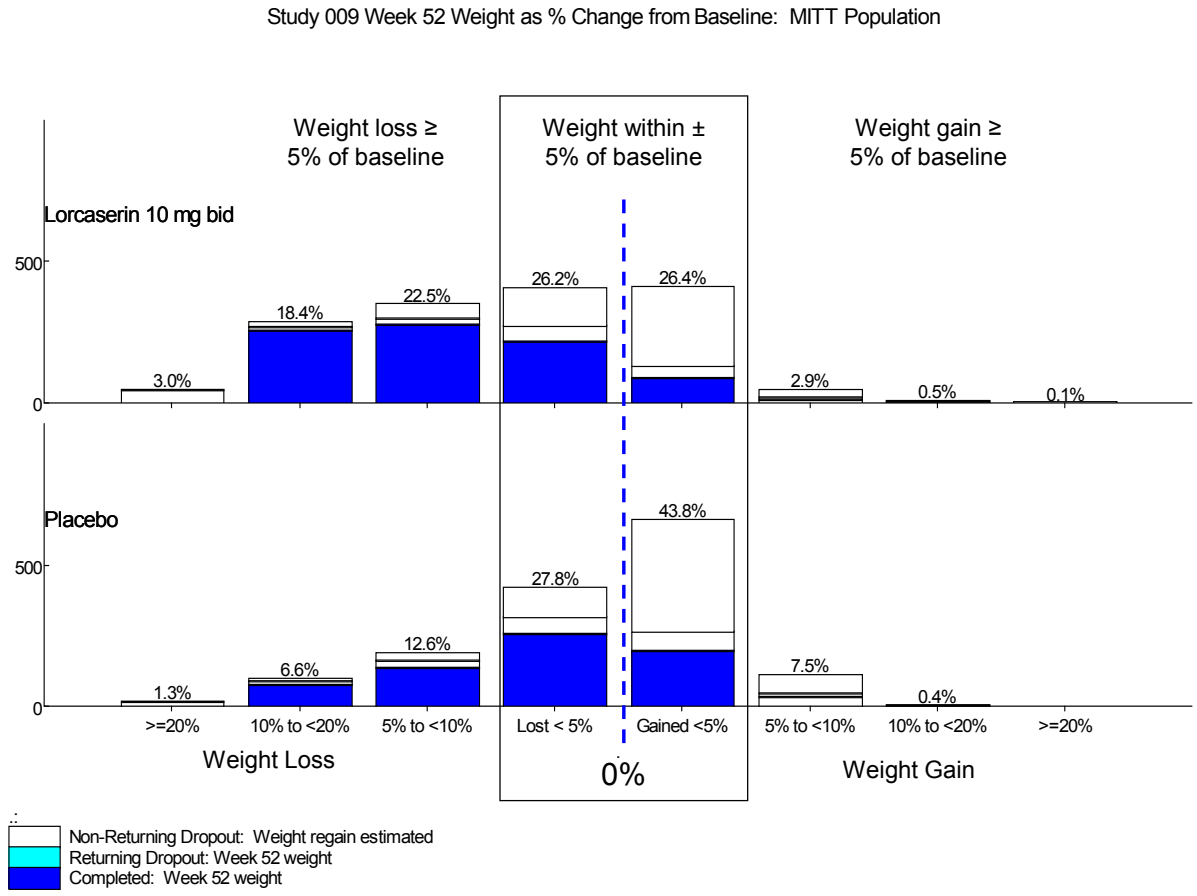
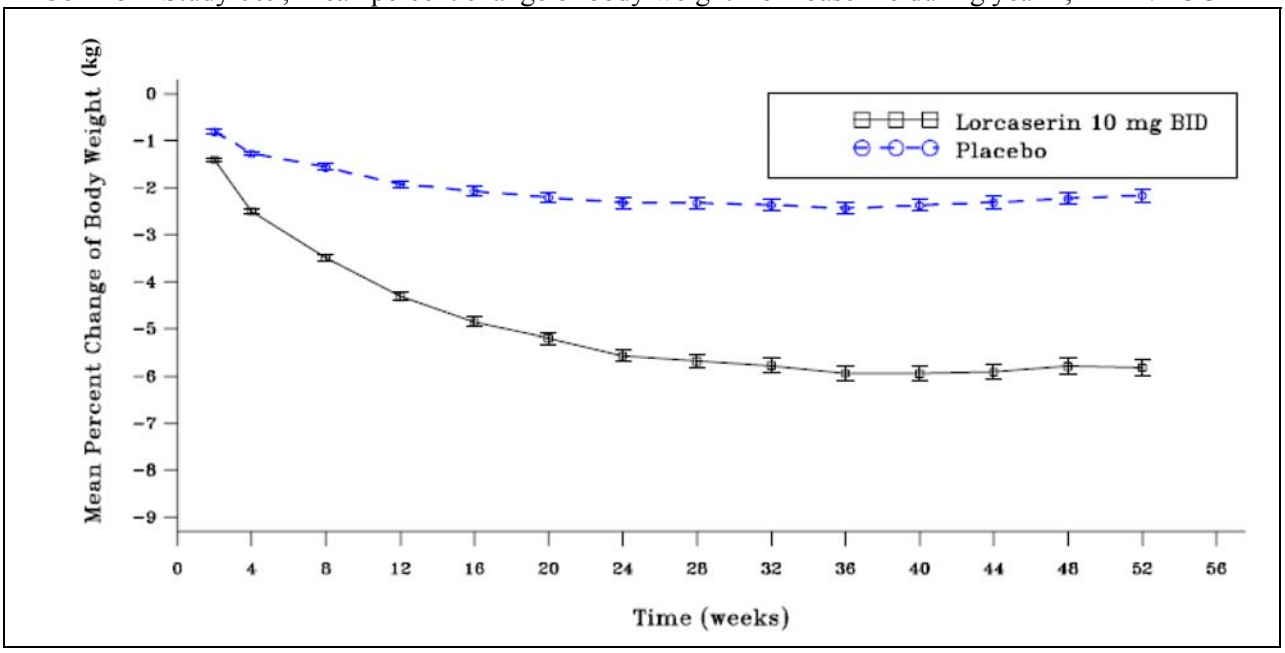


FIGURE 8 Study 009; Mean percent change of body weight from baseline during year 1; MITT/LOCF



Note: This figure from the Study 009 report (Figure 14.4.3) depicts the longitudinal profile of the MITT/LOCF population; however, for review purposes a longitudinal profile of the completers population is preferable and will be requested from the applicant.

Study 011

Continuous endpoint: After 1 year of treatment with either lorcaserin 10 mg bid or 10 mg qd, subjects lost a statistically significant amount of weight (TABLE 7). Results from different versions of the analysis population and different methods of analysis were consistent. This finding meets one of the criteria for clinical significance described in the weight management guidance. However, as in Study 009, the average weight loss was statistically significantly less than 5%. Expressed as a % change from baseline, the placebo-adjusted average weight loss with lorcaserin 10 mg bid was 3.0%, with a 95% confidence interval of 2.6% to 3.4% (TABLE 7, result 1). I confirmed this result. The average amount of weight lost in the lorcaserin 10 mg bid arm was greater than the average weight loss in the lorcaserin 10 mg qd (TABLE 7). This result supports a dose-response relationship between these two dosages.

Most of the subjects who dropped out before the end of the study remained within ± 5% of their baseline body weight at the time of dropout (FIGURE 9; top two portions of each bar). A small percentage of these dropouts returned for a week 52 weight. Using the week 52 weight of the returning dropouts instead of LOCF did not appreciably affect the distribution of weight change (FIGURE 10) or the results of the statistical analysis (TABLE 7, result 9). Estimating the final weight of non-returning dropouts by a weight gain algorithm did not greatly affect the percentage of subjects who had gained more than 5% of their baseline weight (FIGURE 11), and did not greatly affect the results of the statistical analysis (TABLE 7, result 8). A longitudinal profile of weight change over time is shown in FIGURE 12.

Categorical endpoints: After one year of treatment with lorcaserin, a statistically significantly greater percentage of subjects lost at least 5% of their baseline body weight, compared to placebo (TABLE 8). This result is supported by results from analyses of the per protocol population and the completers population. This finding meets one of the criteria for clinical significance described in the weight management guidance. Another sensitivity analysis, which classified dropouts as non-responders, produced results that are very similar to the primary analysis with the MITT/LOCF population. The results are similar because the LOCF imputation classifies most of the dropouts as non-responders (FIGURE 9).

The percentage of 5% weight loss responders in the lorcaserin 10 mg qd arm was lower than in the 10 mg bid arm, and not all odds ratios were significantly greater than 2 (TABLE 8). This finding supports the dose-response relationship between the two dosages.

The results for the 10% weight loss responders were consistent with the results for the 5% weight loss responders, with a smaller overall percentage of subjects in this category compared to 5% weight loss responders (TABLE 8).

TABLE 7 Study 011; Weight as a % change from baseline at year 1; results from primary and supportive analyses

Study 011 Treatment groups	N	Baseline mean (kg) ± SE	Adjusted mean % change from baseline at Week 52 ± SE[1]	Difference in adjusted mean % change, Lorcaserin - placebo (95% CI)	P-value vs. placebo
Analyses with MITT1 population					
Lorcaserin 10 mg bid	1561	100.3 ± 0.4			
Lorcaserin 10 mg qd	771	100.1 ± 0.6			
Placebo	1541	100.8 ± 0.4			
1. Primary analysis: LOCF estimation for dropouts; primary ANCOVA model					
Lorcaserin 10 mg bid			-5.8 ± 0.2	-3.0 (-3.4, -2.6)	<0.0001
Lorcaserin 10 mg qd			-4.7 ± 0.2	-1.9 (-2.5, -1.4)	<0.0001
Placebo			-2.8 ± 0.2		
2. MITT1 population with no estimation for missing data; MMRM model					
Lorcaserin 10 mg bid			-6.7 ± 0.1	-3.4 (-3.8, -3.1)	<0.001
Lorcaserin 10 mg qd			-5.3 ± 0.2	-2.1 (-2.5, -1.6)	<0.001
Placebo			-3.2 ± 0.1		
Analysis with PP1 population					
3. primary ANCOVA model					
Lorcaserin 10 mg bid	846	100.2 ± 0.5	-7.8 ± 0.2	-3.9 (-4.6, -3.2)	<0.0001
Lorcaserin 10 mg qd	418	99.3 ± 0.8	-6.5 ± 0.3	-2.5 (-3,4, -1.7)	<0.0001
Placebo	764	101.3 ± 0.6	-4.0 ± 0.3		
Analysis with Completers population					
4. no LOCF estimation (dropouts were not included in this population); primary ANCOVA model; sponsor's analysis					
Lorcaserin 10 mg bid	1050	100.4 ± 0.5	-7.1 ± 0.2	-3.7 (-4.3, -3.0)	<0.001
Lorcaserin 10 mg qd	534	99.3 ± 0.7	-5.6 ± 0.3	-2.1 (-2.9, -1.4)	<0.001
Placebo	832	100.9 ± 0.5	-3.4 ± 0.3		
Other Analyses					
5. Returning dropouts and completers (non-returning dropouts were not included in this population); primary ANCOVA model; this reviewer's analysis [A]					
Lorcaserin 10 mg bid	1030	100.4 ± 0.5	-6.6 ± 0.2	-3.3 (-3.9, -2.7)	<0.0001
Lorcaserin 10 mg qd	576	99.3 ± 0.7	-5.1 ± 0.3	-1.8 (-2.5, -1.1)	<0.0001
Placebo	1064	100.8 ± 0.5	-3.3 ± 0.3		
6. MITT1 population with (a) weight regain estimation for non-returning dropouts; (b) week 52 weights for returning dropouts; primary ANCOVA model; this reviewer's analysis [A]					
Lorcaserin 10 mg bid	1579	100.3 ± 0.4	-5.0 ± 0.2	-3.1 (-3.6, -2.6)	<0.0001
Lorcaserin 10 mg qd	777	100.0 ± 0.6	-3.9 ± 0.3	-2.0 (-2.3, -1.6)	<0.0001
Placebo	1558	100.7 ± 0.4	-1.9 ± 0.2		
7. MITT1 population with (a) LOCF imputation for non-returning dropouts and (b) week 52 weight for returning dropouts [A]					
Lorcaserin 10 mg bid	1579	100.3 ± 0.4	-5.8 ± 0.2	-3.0 (-3.4, -2.5)	<0.0001
Lorcaserin 10 mg qd	777	100.0 ± 0.6	-4.6 ± 0.2	-1.8 (-2.3, -1.2)	<0.0001

Placebo	1558	100.7 ±0.4	-2.9 ± 0.2

Notes:
[A] The group totals in this analysis represent a small percentage of cases with duplicate records in the analysis database; this analysis database represented a combination of variables from several databases provided by the applicant. I was not able to fully resolve this issue, but I do not believe that the inaccuracies that resulted from the analysis of this database affected the interpretation of results.

Sources:
1. Study 011 report, Table 11
2. Study 011 Table E4.10 submitted 4/2/2010 (0008)
3. Study 011 report, Table 14.2.3.1
4. Study 011 Table E2.1 submitted 4/2/10 (0008)
5, 6, 7 Analysis by this reviewer

TABLE 8 Study 011; 5% and 10% weight loss responders; results from primary and supportive analyses

Treatment groups	N	Number of responders (%)	Difference in proportions vs. placebo[1] (95% CI)	Odds Ratio vs. placebo (95% CI)[3]	p-value vs. placebo[3]
% of subjects achieving ≥ 5% weight loss at week 52					
1. Primary analysis: MITT1; LOCF					
Lorcaserin 10 mg bid	1561	737 (47.2%)	22.2 (18.9, 25.5)	2.7 (2.3, 3.1)	<0.0001
Lorcaserin 10 mg qd	771	310 (40.2%)	15.2 (11.1, 19.3)	2.0 (1.7, 2.4)	<0.0001
Placebo	1541	385 (25.0%)			
2. Supportive analysis: PP; LOCF					
Lorcaserin 10 mg bid	846	535 (63.2%)	28.3 (23.6, 33.0)	3.2 (2.6, 3.9)	< 0.0001
Lorcaserin 10 mg qd	418	222 (53.1%)	18.2 (12.3, 24.0)	2.1 (1.6, 2.7)	<0.0001
Placebo	764	267 (34.9%)			
3. Supportive analysis: Completers					
Lorcaserin 10 mg bid	914	568 (62.1%)	27.4 (22.9, 31.9)	3.1 (2.5, 3.8)	< 0.001
Lorcaserin 10 mg qd	470	247 (52.6%)	17.8 (12.3, 23.4)	2.1 (1.6, 2.6)	<0.001
Placebo	832	289 (34.7%)			
4. Supportive analysis: Non-responder imputation (baseline carried forward); ITT/BOCF					
Lorcaserin 10 mg bid	1603	737 (46.0%)	22.0 (18.8, 25.2)	2.7 (2.3, 3.1)	<0.001
Lorcaserin 10 mg qd				note 4	
Placebo	1603	385 (24.0%)			
% of subjects achieving ≥ 10% weight loss at week 52					
5. Primary analysis: MITT1; LOCF					
Lorcaserin 10 mg bid	1561	353 (22.6%)	12.9 (10.3, 15.4)	2.7 (2.2, 3.3)	< 0.0001
Lorcaserin 10 mg qd	771	134 (17.4%)	7.6 (4.6, 10.7)	2.0 (1.5, 2.5)	< 0.0001
Placebo	1541	150 (9.7%)			

Treatment groups	N	Number of responders (%)	Difference in proportions vs. placebo[1] (95% CI)	Odds Ratio vs. placebo (95% CI)[3]	p-value vs. placebo[3]
6. Supportive analysis: PP; LOCF					
Lorcaserin 10 mg bid	846	297 (35.1%)	19.0 (14.9, 23.2)	2.8 (2.2, 3.6)	< 0.0001
Lorcaserin 10 mg qd	418	110 (26.3%)	10.2 (5.3, 15.2)	1.9 (1.4, 2.5)	< 0.0001
Placebo	764	123 (16.1%)			
7. Supportive analysis: Completers					
Lorcaserin 10 mg bid	914	313 (34.3%)	18.7 (14.8, 22.7)	2.8 (2.2, 3.6)	< 0.001
Lorcaserin 10 mg qd	470	122 (26.0%)	10.5 (5.8, 15.1)	1.9 (1.4, 2.5)	< 0.001
Placebo	832	129 (15.5%)			

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] Although the applicant did not include a sensitivity analysis with non-responder imputation for dropouts, the results from the primary analysis should be fairly close to this analysis, because most of the dropouts had final on-study weights that were within 5% of their baseline weight and would be classified by LOCF as non-responders.

[4] The applicant did not provide the results for lorcaserin 10 mg qd vs placebo; this is on request.

Sources:

1. Study 011 Clinical Report, Table 9
2. Study 011 Clinical Report, Table 14.2.1
3. Study 011 Table E72.10 (submitted 4/2/10 0008)
4. Advisory Committee briefing document, Table 24
5. Study 011 Clinical Report, Table 12
6. Study 011 Clinical Report, Table 14.2.5
7. Study 011 Table E73.11 (submitted 4/2/10 0008)

FIGURE 9 Study 011; Distribution of weight change at week 52; MITT population with primary imputation method (LOCF)

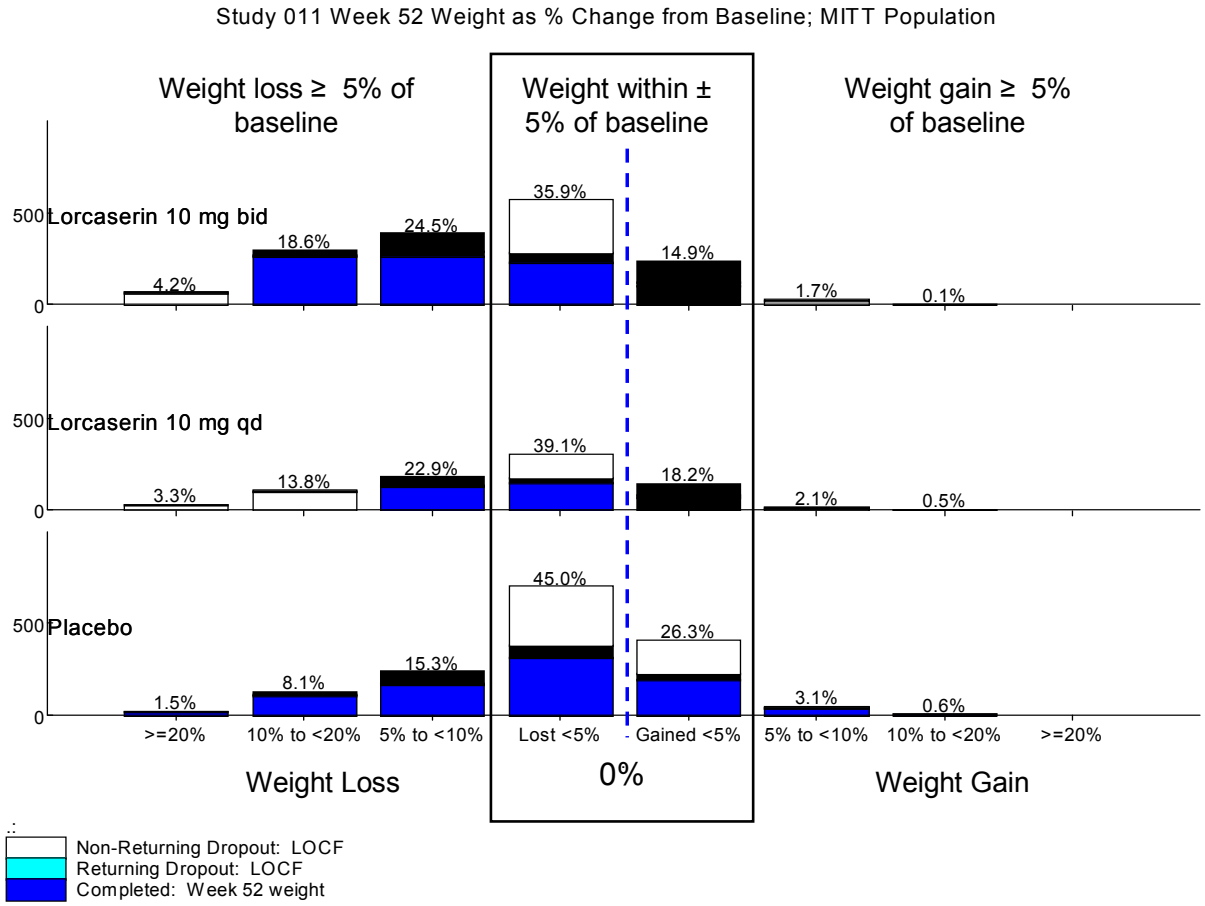


FIGURE 10 Study 011; Distribution of weight change at week 52; MITT population with week 52 weights for returning dropouts

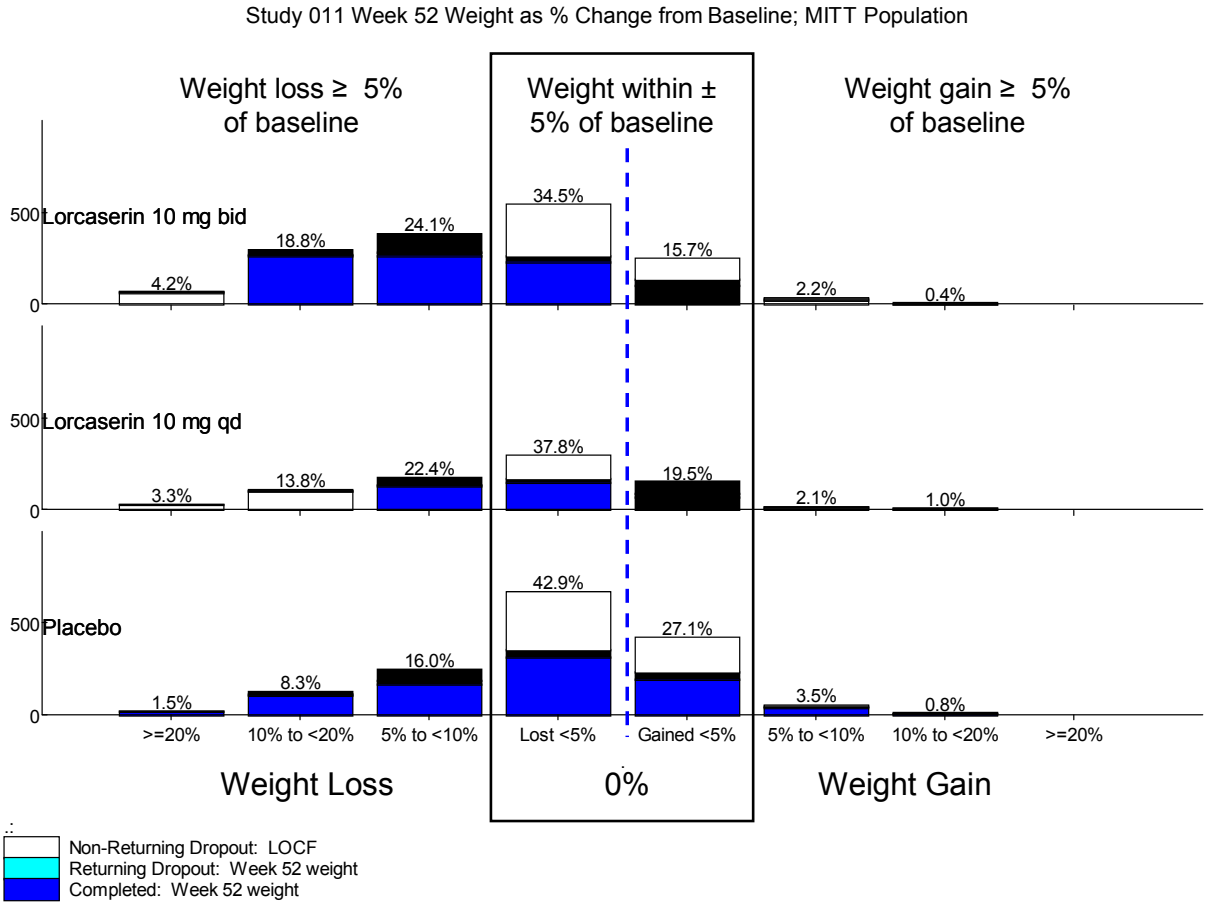


FIGURE 11 Study 011; Distribution of weight change at week 52; MITT population with week 52 weights for returning dropouts and weight regain estimation for non-returning dropouts

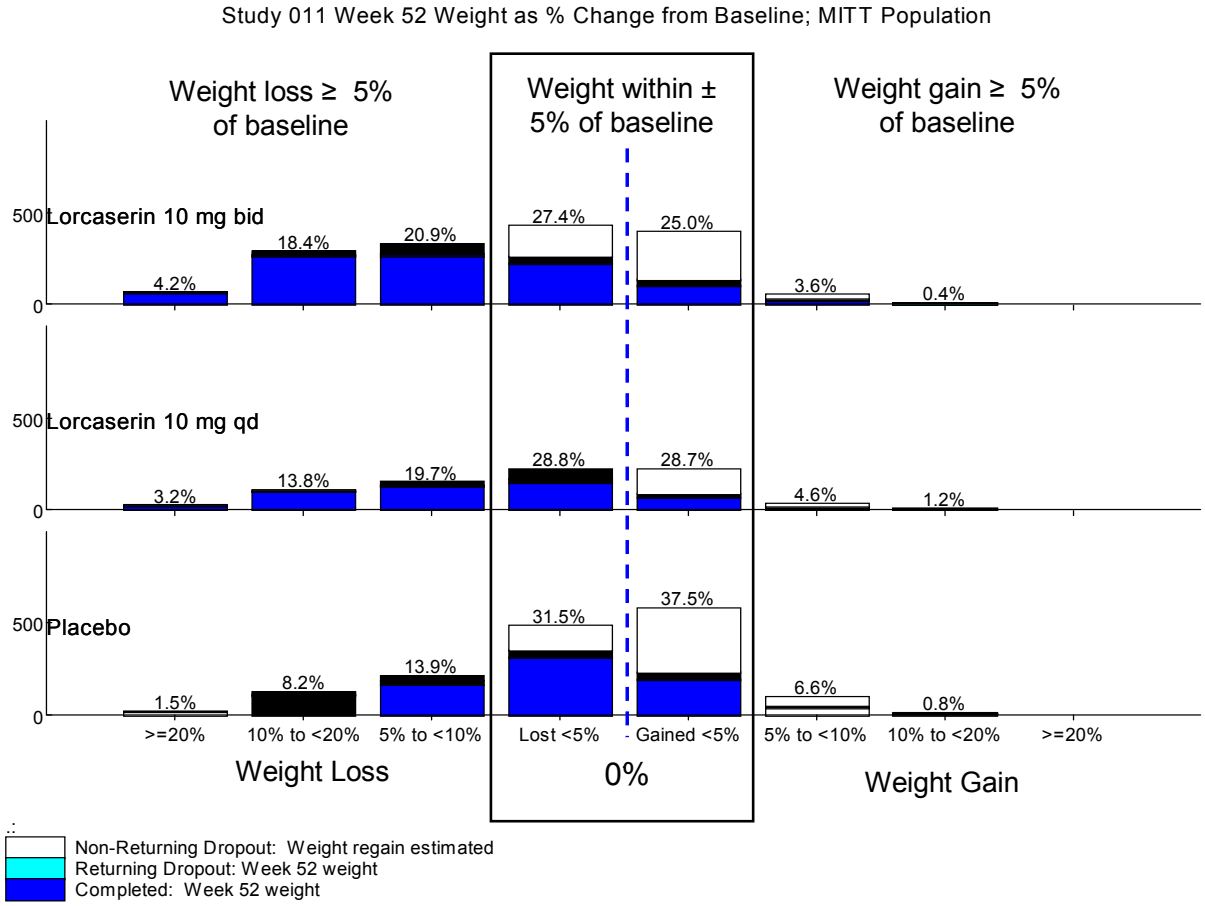
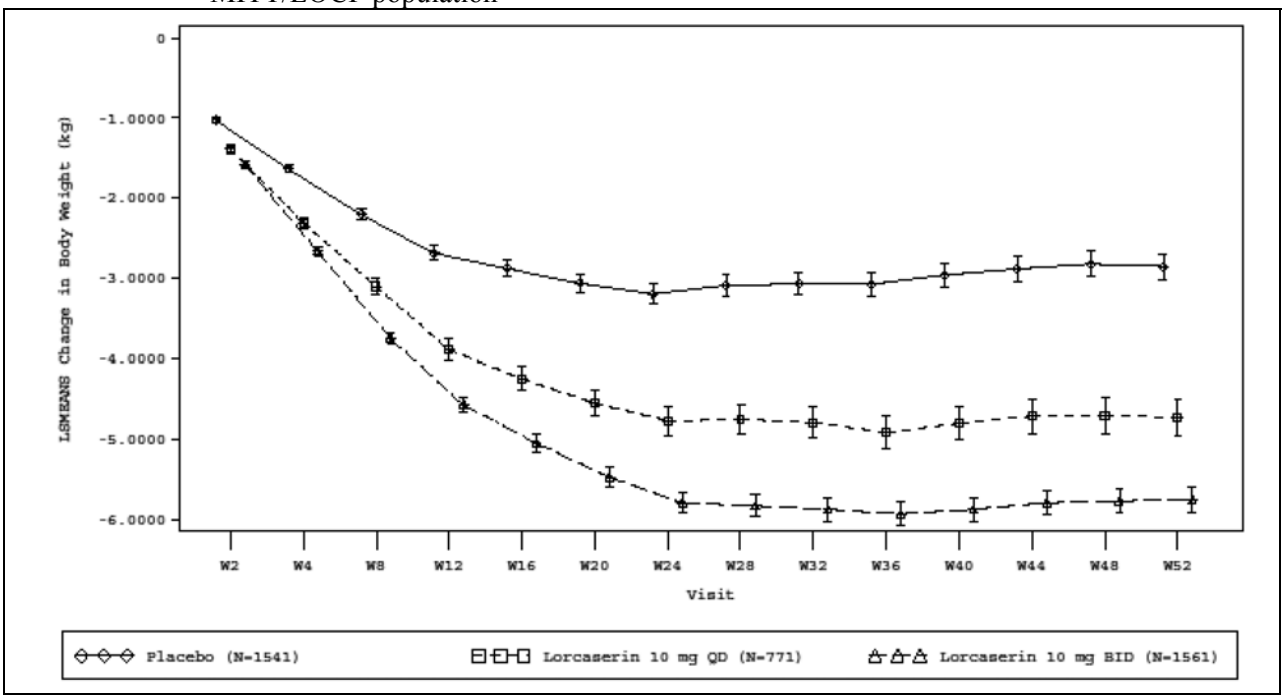


FIGURE 12 Study 011; Mean change from baseline (kg) over time (mean ± SE) by treatment group; MITT/LOCF population



Note: This figure from the Study 011 report (Figure 4) depicts the longitudinal profile of the MITT/LOCF population; however, for review purposes a longitudinal profile of the completers population is preferable and will be requested from the applicant.

3.7. Other Efficacy Endpoints

3.7.1. Key secondary efficacy endpoints

For each study, the statistical analysis plan identified groups of key secondary efficacy endpoints. Within each group, endpoints were prioritized in pre-specified order. Each group of endpoints was evaluated only if the primary comparison of the proportion of 5% weight loss responders was significant.

Both studies identified a group of lipid profile variables and a group of blood pressure variables. Within the lipid group, both studies identified LDL-cholesterol as the key variable or first variable to be evaluated. Within the blood pressure group, both studies identified systolic (SBP) and diastolic blood pressure (DBP) as key variables. Because both studies had a similar approach to the analysis of the lipid group and the blood pressure group, this review includes the results from the applicant's analysis of LDL-cholesterol, SBP and DBP from the data pooled across studies. For the pooled analysis, the applicant used an analysis of covariance model, with baseline value of the endpoint as a covariate, treatment arm and study as factors. Only the lorcaserin 10mg arm and the placebo were included as treatment arms in these pooled analyses.

The statistical analysis plan for Study 009 identified one additional group, consisting of glycemic control variables, in which fasting glucose was specified as the key variable. The statistical analysis plan for Study 011 identified two additional groups, one group consisting of body composition endpoints, in which body fat was identified as the key variable, and the other group consisting of quality of life endpoints, in which the total score was identified as the key variable. this review includes the results from the applicant's analysis of these endpoints from their respective studies.

The results from the secondary efficacy endpoints supported the efficacy of lorcaserin compared to placebo. In general, the mean difference between lorcaserin and placebo was relatively small, but the mean difference was statistically significant.

LDL-Cholesterol (pooled analysis): The mean difference in change in LDL-cholesterol from baseline at week 52 was relatively small (-1.30 mg/dL with 95% confidence interval of -2.4 to -0.3) between the lorcaserin 10 mg bid arm and the placebo arm, but in the direction of an improved level of LDL-cholesterol in the lorcaserin arm compared to placebo (TABLE 9).

SBP and DBP (pooled analysis): The mean difference in change in SBP and DBP was also relatively small, but the difference was in the direction of lowered blood pressure in the lorcaserin arm compared to placebo (TABLE 10, TABLE 11).

Fasting Plasma Glucose (analysis from Study 009): The mean difference in change in fasting plasma glucose (FPG) was relatively small, but the difference was in the direction of lowered FPG in the lorcaserin arm (TABLE 12).

Total body fat (analysis from Study 011): Both lorcaserin groups and the placebo group had an average reduction in body fat by a small amount between week 52 and baseline. The two lorcaserin dose groups had a greater average reduction than placebo (TABLE 13).

Quality of life (analysis from Study 011): The lorcaserin groups had an average increase in total quality of life score and the placebo group had an average decrease between week 52 and baseline (TABLE 14).

TABLE 9 Analysis of percent change from baseline in LDL (mg/dL) at week 52 (MITT/LOCF), pooled data from Study 009 and Study 011

Treatment	N	Mean (SD)		Percent Change from Baseline (%)			
		Baseline	Week 52	Mean (SE)	Median	Min	Max
Pooled Placebo	2764	114.14 (29.71)	115.46 (30.82)	2.96 (0.40)	1.18	-82.95	209.76
Pooled Lorcaserin 10 mg BID	2869	114.25 (31.17)	113.93 (32.23)	1.63 (0.40)	-0.75	-72.65	217.86

Treatment	Percent Change from Baseline (%)		
	LS Mean (SE)	95% CI for LS Mean	p-Value
Pooled Placebo	2.92 (0.38)	(2.17, 3.67)	<0.001
Pooled Lorcaserin 10 mg BID	1.62 (0.38)	(0.88, 2.35)	<0.001

Between Treatment Difference	Difference in LS Means (95% CI) (%)	p-Value
Lorcaserin 10 mg BID vs. Placebo	-1.30 (-2.35, -0.25)	0.015

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment	0.015
Protocol	<0.001

Root Mean Square Error of Change = 20.10

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error

Source: ISE-Statistical-Report, Table E6.0

TABLE 10 Analysis of change from baseline in systolic blood pressure (mmHg) at week 52 (MITT/LOCF), pooled data from Study 009 and Study 011

		Mean (SD)		Change from Baseline			
Treatment	N	Baseline	Week 52	Mean (SE)	Median	Min	Max
Pooled Placebo	3039	121.51 (11.74)	120.46 (12.46)	-1.05 (0.21)	-1.00	-58.00	51.00
Pooled Lorcaserin 10 mg BID	3096	121.39 (11.86)	119.66 (12.66)	-1.73 (0.22)	-2.00	-59.00	58.00

	Change from Baseline		
Treatment	LS Mean (SE)	95% CI for LS Mean	p-Value
Pooled Placebo	-1.02 (0.20)	(-1.41, -0.64)	<0.001
Pooled Lorcaserin 10 mg BID	-1.76 (0.19)	(-2.14, -1.38)	<0.001

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Lorcaserin 10 mg BID vs. Placebo	-0.74 (-1.27, -0.20)	0.007

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment	0.007
Protocol	0.966

Root Mean Square Error of Change = 10.77

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error

Source: ISE-Statistical Report, Table E11.0

TABLE 11 Analysis of change from baseline in diastolic blood pressure (mmHg) at week 52 (MITT/LOCF), pooled data from Study 009 and Study 011

		Mean (SD)		Change from Baseline			
Treatment	N	Baseline	Week 52	Mean (SE)	Median	Min	Max
Pooled Placebo	3039	77.71 (8.09)	76.67 (8.75)	-1.04 (0.16)	-1.00	-44.00	48.00
Pooled Lorcaserin 10 mg BID	3096	77.44 (8.05)	75.94 (8.70)	-1.50 (0.16)	-2.00	-40.00	50.00

	Change from Baseline		
Treatment	LS Mean (SE)	95% CI for LS Mean	p-Value
Pooled Placebo	-0.97 (0.14)	(-1.24, -0.69)	<0.001
Pooled Lorcaserin 10 mg BID	-1.57 (0.14)	(-1.84, -1.29)	<0.001

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Lorcaserin 10 mg BID vs. Placebo	-0.60 (-0.99, -0.21)	0.003

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment	0.003
Protocol	0.340

Root Mean Square Error of Change = 7.83

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error

Source: ISE-Statistical-Report, Table E12.0

TABLE 12 Study 009; Summary of change from baseline in fasting plasma glucose (mg/dL) at week 52: MITT population

Treatment	**N**	**Fasting Plasma Glucose (mg/dL) Mean (SEM)**			**p-Value**
		Baseline	**Week 52**	**Change from Baseline at Week 52**	
Lorcaserin	1538	94.3 (0.26)	93.5 (0.26)	-0.8 (0.27)	< 0.0001
Placebo	1499	94.1 (0.27)	95.3 (0.28)	1.1 (0.26)	

Source: Study 009 report, Table 26

TABLE 13 Study 011; Summary of change from baseline in total body fat (%) at week 52: MITT population

Treatment	N	n[a]	Mean (SD)		Change from Baseline			
			Baseline	Week 52	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-value
Lorcaserin 10 mg BID	1561	85	46.73 (5.744)	44.40 (6.483)	-2.33 (0.380)	-2.335 (0.332)	(-2.99, -1.68)	<0.0001
Lorcaserin 10 mg QD	771	35	47.06 (6.349)	45.78 (7.479)	-1.28 (0.565)	-1.284 (0.517)	(-2.30, -0.26)	0.0139
Placebo	1541	69	45.61 (5.761)	44.44 (6.448)	-1.16 (0.261)	-1.153 (0.369)	(-1.88, -0.42)	0.0021

Between Treatment Difference	Difference in LS Means (95% CI)	p-value
Lorcaserin 10 mg BID vs. Placebo	-1.183 (-2.16, -0.20)	0.0184
Lorcaserin 10 mg QD vs. Placebo	-0.131 (-1.39, 1.12)	0.8368
Lorcaserin 10 mg QD vs. Lorcaserin 10 mg BID	1.051 (-0.16, 2.26)	0.0886

p-value for ANCOVA Effects	
Baseline Value	0.7867
Treatment	0.0409
Root Mean Square Error of Change=3.06	

Source: Study 011 report, Table 28

TABLE 14 Study 011; Change from baseline in overall converted score of the quality of life questionnaire at week 52: MITT population

Treatment	N	n[a]	Mean (SD)		Change from Baseline			
			Baseline	Week 52	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-value
Lorcaserin 10 mg BID	1561	1291	74.7 (16.07)	86.7 (12.77)	12.0 (0.36)	11.82 (0.28)	(11.26, 12.37)	<0.0001
Lorcaserin 10 mg QD	771	658	75.5 (15.98)	86.6 (13.38)	11.1 (0.49)	11.32 (0.40)	(10.54, 12.10)	<0.0001
Placebo	1541	1217	75.3 (15.58)	85.1 (13.60)	9.9 (0.36)	9.96 (0.29)	(9.38, 10.53)	<0.0001

Between Treatment Difference	Difference in LS Means (95% CI)	p-value
Lorcaserin 10 mg BID vs. Placebo	1.86 (1.06, 2.66)	<0.0001
Lorcaserin 10 mg QD vs. Placebo	1.37 (0.40, 2.33)	0.0057
Lorcaserin 10 mg QD vs. Lorcaserin 10 mg BID	-0.49 (-1.45, 0.47)	0.3146

p-value for ANCOVA Effects	
Baseline Value	<0.0001
Treatment	<0.0001

Root Mean Square Error of Change=10.21

Source: Study 011 report, Table 30

3.7.2. Year 2 of Study 009

Study 009 extended into a second year. Subjects who completed the initial 52 weeks of treatment (n=1599) were eligible to continue the second year. The start of the second year included a randomization, stratified according to whether or not the subject had been classified as a 5% responder at the end of year 1. Subjects who received placebo during year 1 remained on placebo for year 2. Subjects who received lorcaserin during year 1 were re-randomized within each of the two strata in a 2:1 ratio to either remain on lorcaserin 10 mg bid or switch to placebo, respectively for year 2 (FIGURE 13). The percentage of subjects who completed the second year was 72.6% overall, and was relatively similar among groups (TABLE 15). This percentage is higher than the completion percentage from the first year, which was 50.1% overall (TABLE 2). Subjects who completed the first year appeared to be more likely to remain in the study for the entire second year as well.

The primary endpoint at the end of year two was the percentage of subjects who were 5% responders with respect to their baseline body weight at entrance into the study (i.e., at the start of year 1). The applicant specified that the primary comparison involved the stratum of subjects who entered year 2 as 5% responders in year 1 (groups C and D in FIGURE 13). In this stratum, lorcaserin subjects from year 1 who were randomized to remain on lorcaserin in year 2 were compared to the lorcaserin subjects from year 1 who were randomized to switch to placebo in year 2. The modified intention-to-treat population, MITT2, defined as all randomized subjects

who completed year 1, were re-randomized at week 52 and took at least one dose of study medication after re-randomization, had at least one weight measurement post re-randomization. The last post re-randomization observation on or prior to discontinuation was carried forward and used in the analysis. An additional analysis population was the per-protocol population for year 2 (PP2), which excluded subjects and/or data points with clinically important protocol deviations. Additional analyses also used the weight at the start of year 2 as the reference baseline for the weight endpoint.

Based on the pre-specified primary comparison, I believe that the applicant's main interest in year 2 was to assess the extent to which subjects on lorcaserin who had achieved a 5% or greater weight loss in year 1 could remain as a 5% responder during a second year of treatment with lorcaserin. As a comparison group, the applicant chose subjects who were 5% responders with lorcaserin in year 1 who had been randomized to change to placebo in year 2. This comparison does demonstrate that more 5% responder subjects remained as 5% responders when maintained for a second year on lorcaserin (67.9%) than when switched to placebo for the second year (50.3%; TABLE 16). On average, subjects in the MITT2 population gained weight during the second year: 1.0 kg in the placebo→placebo group, 4.8 kg in the lorcaserin→placebo group, and 2.5 kg in the lorcaserin→lorcaserin group (TABLE 17). Even with these weight gains during year 2, each group had an average weight loss over the two year period, and the lorcaserin→lorcaserin group had a greater average weight loss than the lorcaserin→placebo group or the placebo→placebo group (TABLE 17). A profile of average weight change in the three groups over the two-year period is shown in FIGURE 14.

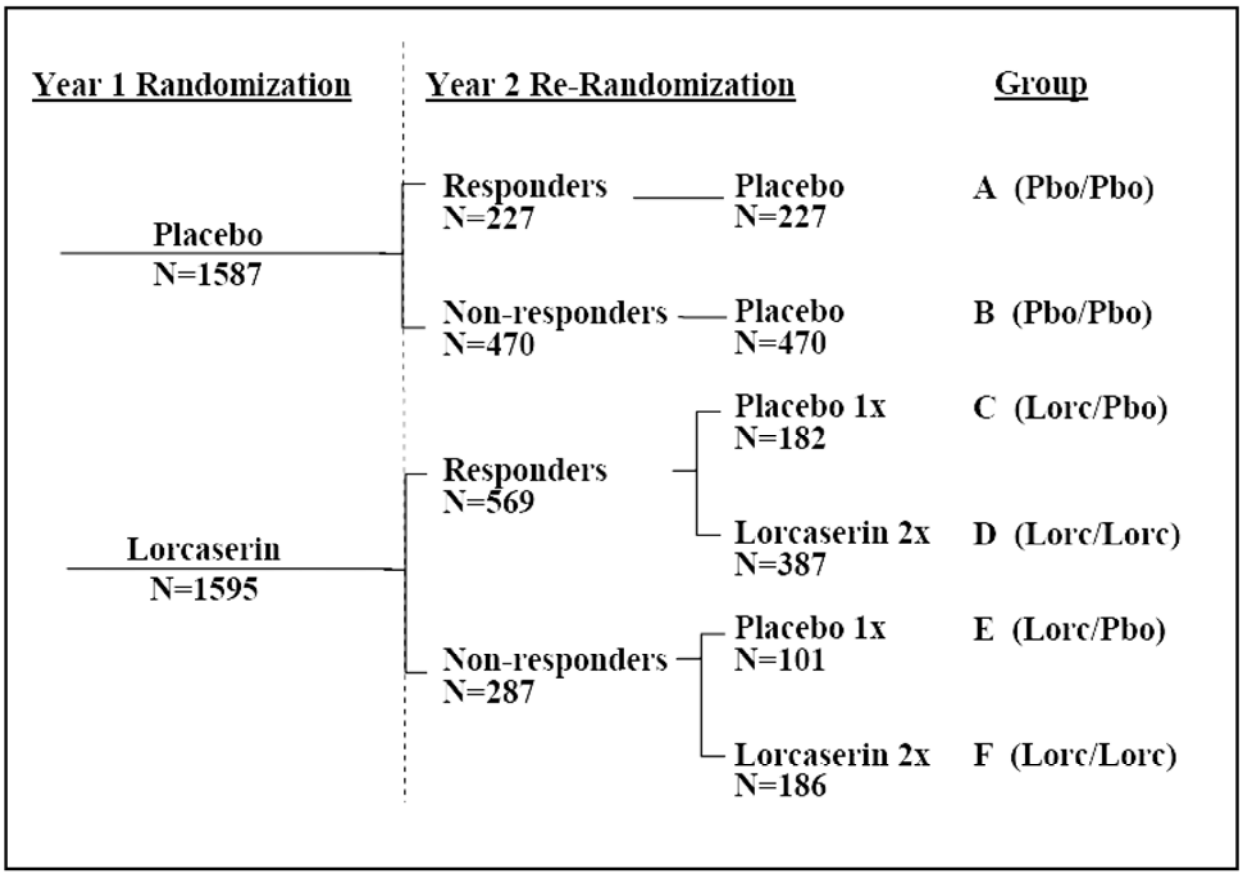
I believe that the results from year 2 of Study 009 are challenging to interpret with respect to the intended target population of lorcaserin, for the following reasons:

(1) Only 50% of the initially randomized population completed year 1 and participated in year 2. As I have discussed in other parts of this review, the tendency to complete year 1 of the study was related at least in part to a subject's ongoing experience of weight loss. This means that subjects who were randomized in year 2 were likely to be different from the target population in terms of tendency to lose weight.

(2) The applicant focused attention on the 5% responders to lorcaserin from year 1. This subgroup is based on the response to treatment in year 1. For this reason, this subgroup is one more step removed from the target population. Although the applicant was careful not to make formal statistical comparisons between the lorcaserin responder subgroup and the placebo responder subgroup, less careful readers may not realize that these two subgroups are not comparable.

For these reasons, I believe that claims based on the results from year 2 of Study 009, if included in the label at all, need to be very carefully expressed in order to avoid over-generalization to the intended target population of lorcaserin.

FIGURE 13 Study 009 design, showing year 1 and year 2 randomizations



Source: Study 009 report, Figure 1

TABLE 15 Study 009; Disposition in year 2

Year 1 randomization	Lorcaserin n=1595				Placebo n=1587
Week 52 primary outcome (in Week 52 completers)	Lorcaserin Responders[1] (C and D) n=856		Lorcaserin Non-Responders (E and F) n=287		Placebo Responders and Non-Responders n=697
Year 2 randomization[2]	Group C Lorcaserin → Placebo	Group D Lorcaserin → Lorcaserin	Group E Lorcaserin → Placebo	Group F Lorcaserin → Lorcaserin	Group A+B Placebo → Placebo
Year 2 number randomized	182	387	101	186	697
No. (%) in MITT2 population	175 (96.2)	380 (98.2)	100 (99.0)	184 (98.9)	684 (98.1)
No. (%) who completed	128 (70.3)	304 (78.6)	67 (66.3)	122 (65.6)	507 (72.7)
No. (%) in PP2 population	93 (51.1)	221 (57.1)	47 (46.5)	87 (46.8)	344 (49.4)
No. (%) who withdrew prior to week 104	54 (29.7)	83 (21.4)	34 (33.7)	64 (34.4)	190 (27.3)
Reason for withdrawal:					
Withdrawal of consent	31 (17.0)	44 (11.4)	23 (22.8)	30 (16.1)	105 (15.1)
Lost to follow-up	14 (7.7)	25 (6.5)	9 (8.9)	17 (9.1)	37 (5.3)
Adverse event	7 (3.8)	10 (2.6)	2 (2.0)	7 (3.8)	21 (3.0)
Combined other reasons[3]	2 (1.1)	4 (1.0)	0 (0.0)	10 (5.4)	27 (3.9)

Notes

[1] Responders were subjects who lost ≥ 5% of baseline body weight by week 52.

[2] For percentages, the number of subjects randomized in year 2 was used as the denominator.

[3] For "Combined other reasons," the following discontinuation categories were combined: Protocol deviation / noncompliance, Sponsor decision, PI decision and Other discontinuation reason

Source: Study 009 report, Table 14.1.2

TABLE 16 Study 009 Year 2; results from the primary analysis (MITT2/LOCF): The proportion of lorcaserin subjects achieving ≥ 5% reduction in body weight after week 52 of treatment (5% responders) who maintained at least 5% weight loss based on baseline weight at the end of week 104.

Treatment	N	n (%) Yes		
Lorc/Lorc	380	258 (67.9%)		
Lorc/Pbo	175	88 (50.3%)		
Between Treatment Comparison	**Difference in Proportion (%) (95% CI[a])**	**p-Value[b]**		
		Treatment	**Gender**	**Baseline Body Weight**
Lorc/Lorc vs. Lorc/Pbo	17.6 (8.8, 26.4)	< 0.0001	0.8224	0.8595

[a] 95% Confidence Interval for difference in proportions were calculated using normal approximation

[b] p-Values were calculated by using logistic regression model with effects for baseline body weight, treatment and gender.

Source: ISE report, Table 61

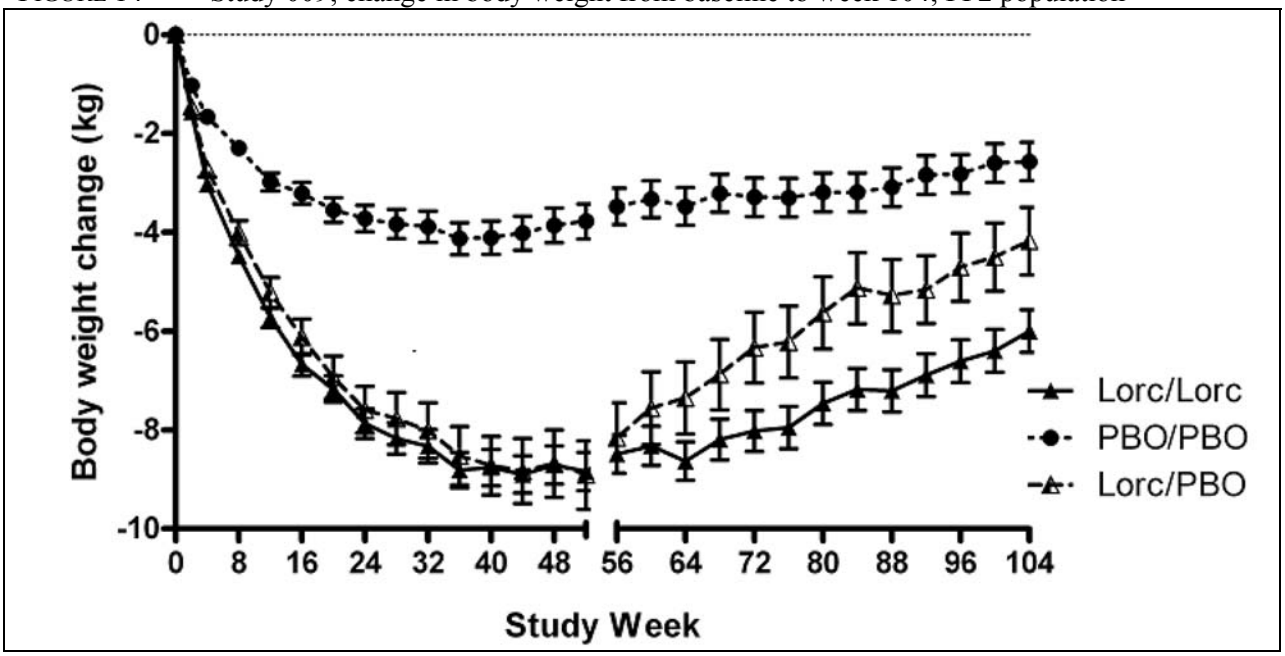
TABLE 17 Study 009; Summary of change in weight (kg) from week 52 to week 104; MITT2 population

Treatment	N	Body Weight (kg) Mean (SE)					p-Value
		Baseline	Week 52	Week 104	Change from Week 52 at Week 104	Change from Baseline at Week 104	
Lorc/Lorc	553	100.6 ±0.7	92.4 ±0.7	95.0 ±0.7	2.53 ±0.186	-5.56 ±0.31	
Lorc/Pbo	267	100.6 ±1.0	92.5 ±1.1	97.2 ±1.1	4.76 ±0.310	-3.30 ±0.42	< 0.0001[a]
Pbo/Pbo	665	99.3 ±0.6	95.7 ±0.6	96.7 ±0.7	1.00 ±0.161	-2.43 ±0.28	< 0.0001[b]

SE=Standard Error
[a] Comparison of change in weight in Lorc/Lorc Group versus Lorc/Pbo Group
[b] Comparison of change in weight in Lorc/Lorc Group versus Pbo/Pbo Group

Source: ISE report, Table 62

FIGURE 14 Study 009; change in body weight from baseline to week 104; PP2 population



Note: This figure from the ISE report (Figure 33) depicts the longitudinal profile of the per protocol population; however, for review purposes a longitudinal profile of the completers population is preferable and will be requested from the applicant.

4. EFFICACY FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Race and Age

Sex: Females made up the large majority of each study (about 80%). However, the studies were large enough to evaluate the placebo-adjusted effect of lorcaserin in males and females. In Study 009, males and females were relatively similar in the mean placebo-adjusted effect of lorcaserin 10 mg bid (FIGURE 15, TABLE 18). In Study 011, males and females were relatively similar in the effect of lorcaserin 10 mg qd; however, in the higher dose arm, the two sexes were different. The effect of both dose levels was relatively similar in males, while females had a greater average weight loss at the higher dose (FIGURE 15, TABLE 18).

A larger percentage of males completed each study compared with females, although the difference is not very great (FIGURE 15, TABLE 20). For this reason, it does not appear that the different response of males to the two dose arms compared with females in Study 011 was related to differential retention in the study.

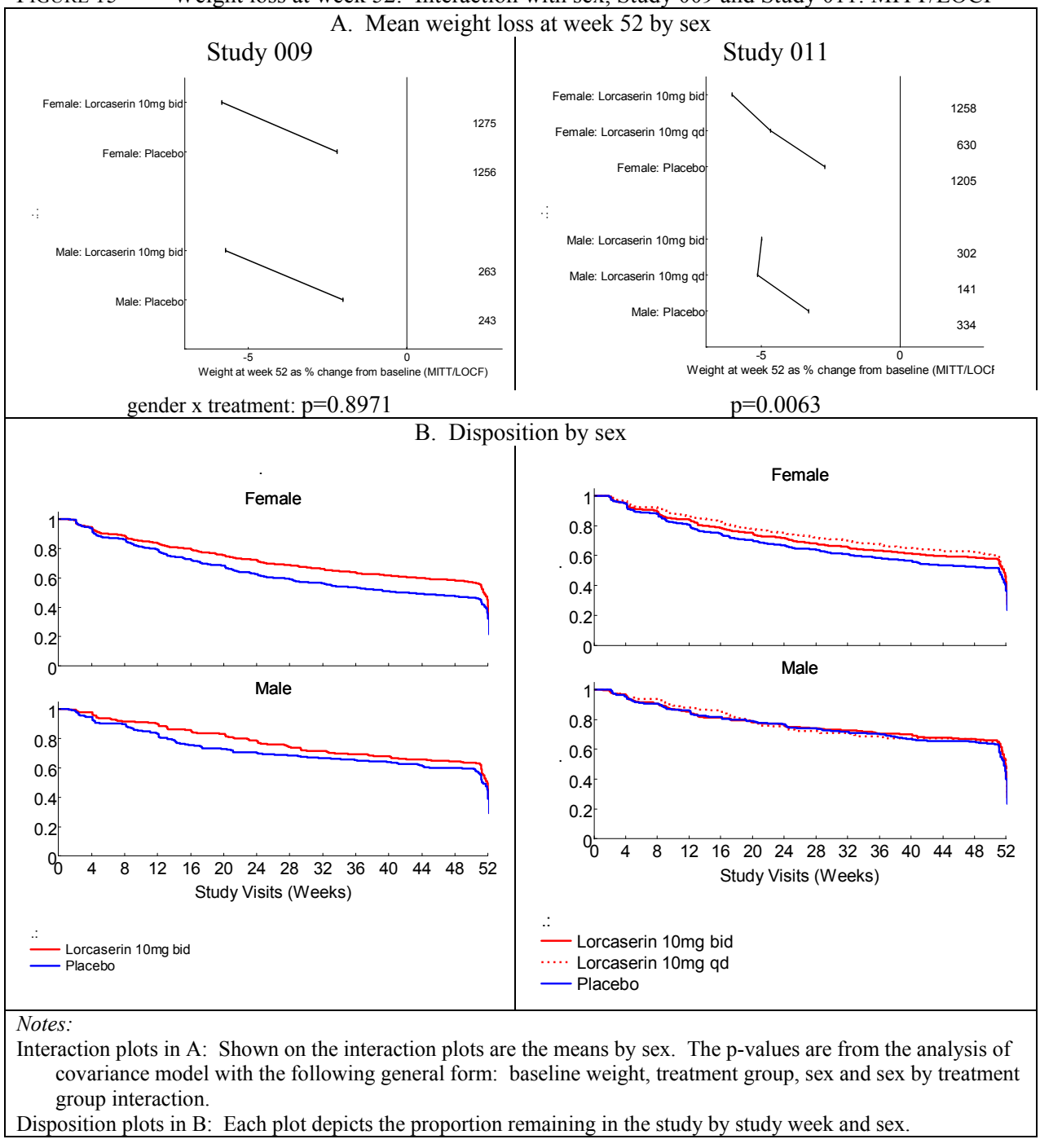
Race: Subjects in the Caucasian/White subgroup made up the large majority of each study (about 66%). However, the studies were large enough to evaluate the placebo-adjusted effect of lorcaserin in African American/Black and Hispanic/Latino subgroups. In Study 009, the three subgroups were relatively similar in the mean placebo-adjusted effect of lorcaserin 10 mg qd (FIGURE 16, TABLE 19). However, the unadjusted mean weight loss in the placebo and the lorcaserin arms was less in the African American/Black and the Hispanic/Latino subgroups compared to the Caucasian/White subgroup (FIGURE 16, TABLE 19). This finding corresponds to a lower retention of subjects in the African American/Black and the Hispanic/Latino subgroups (FIGURE 16, TABLE 20). The applicant, in describing these findings, noted "These data indicate that the phase 3 behavior modification program was less effective in Black and Hispanic subjects than in White subjects. This program, in either design or administration, may be inherently more effective in certain ethnic groups."[6]

This pattern is also apparent in the results from Study 011, with additional information concerning response of racial subgroups to the 10 mg qd dose of lorcaserin. Subjects in the Caucasian/White subgroup had a dose-response relationship between the two dose arms of lorcaserin and placebo (FIGURE 16, TABLE 19). Subjects in the African American/Black subgroup had a relatively similar response to each dose (FIGURE 16, TABLE 19). Subjects in the Hispanic/Latino subgroup did not appear to respond to the lower dose compared to placebo, but did have a response to the higher dose (FIGURE 16, TABLE 19).

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.

[6] ISE-Report, Part 5.1.1, p. 103/174

FIGURE 15 Weight loss at week 52: Interaction with sex, Study 009 and Study 011: MITT/LOCF

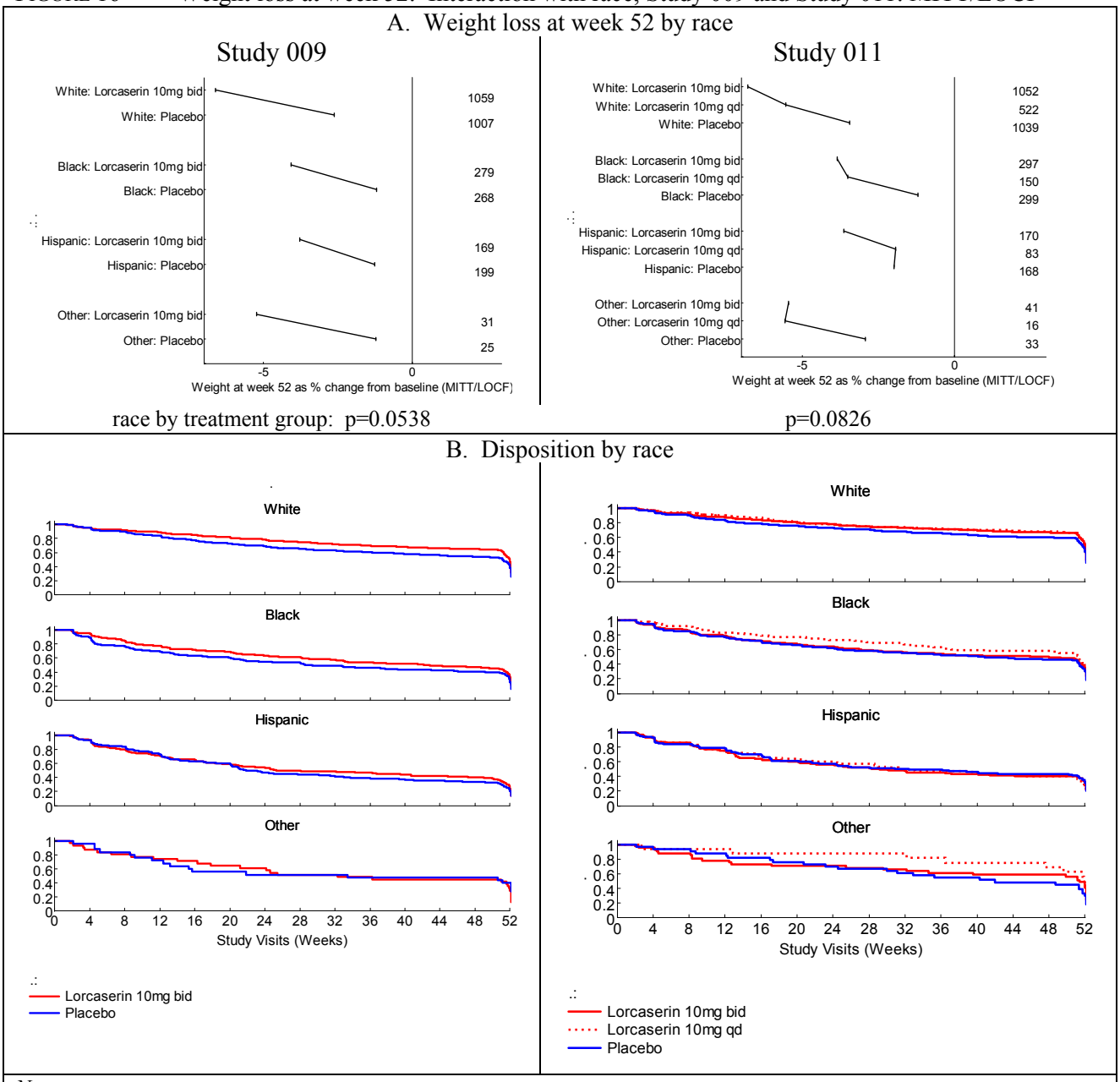


Notes:

Interaction plots in A: Shown on the interaction plots are the means by sex. The p-values are from the analysis of covariance model with the following general form: baseline weight, treatment group, sex and sex by treatment group interaction.

Disposition plots in B: Each plot depicts the proportion remaining in the study by study week and sex.

FIGURE 16 Weight loss at week 52: Interaction with race, Study 009 and Study 011: MITT/LOCF



Notes:

Interaction plots in A: Shown on the interaction plots are the means for each race category. The p-values are from the analysis of covariance model with the following general form: baseline weight, treatment group, race and race by treatment group interaction. The race category of "other" includes subgroups with small numbers of subjects as well as the "other" category designated by the applicant.

Disposition plots in B: Each plot depicts the proportion remaining in the study by study week and race.

TABLE 18 Mean weight loss in MITT population by sex; Study 009 and 011

	Treatment Arm	Sex	LS Mean change Baseline ± SE	Lorcaserin – Placebo LSMean (95% CI)
Study 009	Lorcaserin 10mg bid	Female	-5.8 ± 0.2	-3.6 (-4.1, -3.2)
		Male	-6.0 ± 0.4	-3.7 (-4.7, -2.7)
	Placebo	Female	-2.1 ± 0.2	
		Male	-2.2 ± 0.4	
Study 011	Lorcaserin 10mg bid	Female	-6.0 ± 0.2	-3.3 (-3.8, -2.8)
		Male	-5.3 ± 0.4	-1.7 (-2.7, -0.7)
	Lorcaserin 10 mg qd	Female	-4.6 ± 0.3	-2.0 (-2.6, -1.3)
		Male	-5.5 ± 0.5	-2.0 (-3.1, -0.6)
	Placebo	Female	-2.6 ± 0.2	
		Male	-3.6 ± 0.4	

Source: Analysis by this reviewer

TABLE 19 Mean weight loss in MITT population by race; Study 009 and 011

Study	Treatment Arm	Race	LS Mean change from baseline ± SE	Lorcaserin – Placebo LSMean (95% CI)
Study 009	Lorcaserin 10mg bid	White	-6.6 ± 0.2	-4.0 (-4.5, -3.5)
		Black	-4.1 ± 0.3	-2.9 (-3.9, -1.9)
		Hispanic	-3.7 ± 0.4	-2.5 (-3.7, -1.3)
		Other	-5.1 ± 1.0	-3.8 (-6.9, -0.8)
	Placebo	White	-2.6 ± 0.2	
		Black	-1.2 ± 0.4	
		Hispanic	-1.2 ± 0.4	
		Other	-1.2 ± 1.2	
Study 011	Lorcaserin 10mg bid	White	-6.8 ± 0.2	-3.3 (-3.9, -2.8)
		Black	-3.9 ± 0.4	-2.7 (-3.7, -1.7)
		Hispanic	-3.5 ± 0.5	-1.5 (-2.9, -0.2)
		Other	-5.4 ± 1.0	-2.6 (-5.4, 0.3)
	Lorcaserin 10 mg qd	White	-5.5 ± 0.3	-2.1 (-2.7, -1.4)
		Black	-3.6 ± 0.5	-2.3 (-3.6, -1.1)
		Hispanic	-1.8 ± 0.7	0.1 (-1.5, 1.8)
		Other	-5.5 ± 1.5	-2.6 (-6.3, 1.0)
	Placebo	White	-3.5 ± 0.2	
		Black	-1.2 ± 0.4	
		Hispanic	-1.9 ± 0.5	
		Other	-2.8 ± 1.1	

Source: Analysis by this reviewer

TABLE 20 Study completion in MITT population by sex and by race; Study 009 and 011

Treatment Arm	Sex	Study 009 N completed in MITT (%)	Study 011 N completed in MITT (%)
Lorcaserin 10mg bid	Female	717/1275 (56.2%)	718/1258 (57.1%)
	Male	166/263 (63.1%)	199/302 (65.9%)
Lorcaserin 10 mg qd	---		381/630 (60.4%)
	---		92/141 (65.2%)
Placebo	Female	572/1256 (45.5%)	622/1205 (51.6%)
	Male	144/243 (59.3%)	212/334 (63.5%)
Treatment Arm	Race	N completed in MITT (%)	N completed in MITT (%)
Lorcaserin 10mg bid	White	674/1059 (63.6%)	688/1052 (65.4%)
	Black	129/279 (46.2%)	141/297 (47.5%)
	Hispanic	66/169 (39.1%)	66/170 (38.8%)
	Other	14/31 (45.2%)	22/41 (53.7%)
Lorcaserin 10 mg qd	---		346/522 (66.3%)
	---		83/150 (55.3%)
	---		33/83 (39.8%)
	---		11/16 (68.8%)
Placebo	White	534/1007 (53.0%)	611/1039 (58.8%)
	Black	107/268 (39.9%)	137/299 (45.8%)
	Hispanic	64/199 (32.2%)	71/168 (42.3%)
	Other	11/25 (44.0%)	15/33 (45.5%)

Source: Analysis by this reviewer

4.2 Other Special/Subgroup Populations

Baseline BMI: Baseline BMI: The average weight loss was fairly similar across baseline BMI subgroups (TABLE 21, TABLE 22). Based on the results of the smallest and the largest BMI subgroup, the weight loss may be more constant across BMI subgroups when expressed as a percentage change from baseline rather than as a change in kg. However, the results across all BMI subgroups are not entirely consistent with this interpretation.

TABLE 21 Weight loss (kg) from baseline to week 52 by baseline BMI subgroups, combined data from Study 009 and 011 (MITT/LOCF); summary statistics

		Baseline	Week 52	Change from Baseline		
Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Median	Range
BMI <30 kg/m2						
Pooled Placebo	122	79.44 (7.52)	77.63 (8.81)	-1.80 (0.41)	-1.30	-19.30 to 12.90
Pooled Lorcaserin 10 mg BID	144	79.37 (8.75)	73.77 (10.54)	-5.60 (0.45)	-4.70	-24.30 to 7.10
BMI 30 - <35 kg/m2						
Pooled Placebo	1235	90.63 (10.55)	88.16 (11.56)	-2.47 (0.15)	-1.40	-35.10 to 14.40
Pooled Lorcaserin 10 mg BID	1205	90.73 (10.21)	85.29 (11.57)	-5.44 (0.18)	-4.30	-32.30 to 11.70
BMI 35 - <40 kg/m2						
Pooled Placebo	1060	103.39 (11.57)	101.16 (12.51)	-2.22 (0.17)	-1.10	-56.10 to 14.80
Pooled Lorcaserin 10 mg BID	1092	103.62 (11.47)	97.71 (13.13)	-5.91 (0.20)	-4.70	-36.00 to 14.80
BMI >=40 kg/m2						
Pooled Placebo	621	118.00 (13.34)	114.79 (14.57)	-3.21 (0.29)	-1.70	-42.80 to 20.00
Pooled Lorcaserin 10 mg BID	657	117.20 (12.78)	111.07 (14.78)	-6.13 (0.28)	-4.40	-37.20 to 9.90
SD=Standard Deviation; SE=Standard Error;						

Source: ISE-Statistical Report, Table E19.4

TABLE 22 Weight loss (kg) from baseline to week 52 by baseline BMI subgroups, combined data from Study 009 and 011 (MITT/LOCF); analysis results

				Comparison with Placebo	
Treatment	N	LS Mean (SE)	95% CI	Difference in LS Means	95% CI
BMI <30 kg/m2					
Pooled Placebo	122	-1.80 (0.46)	(-2.70, -0.91)	---	---
Pooled Lorcaserin 10 mg BID	144	-5.59 (0.42)	(-6.42, -4.77)	-3.79	(-5.01, -2.57)
BMI 30 - <35 kg/m2					
Pooled Placebo	1235	-2.47 (0.16)	(-2.78, -2.15)	---	---
Pooled Lorcaserin 10 mg BID	1205	-5.43 (0.16)	(-5.75, -5.12)	-2.97	(-3.41, -2.52)
BMI 35 - <40 kg/m2					
Pooled Placebo	1060	-2.22 (0.19)	(-2.58, -1.85)	---	---
Pooled Lorcaserin 10 mg BID	1092	-5.91 (0.18)	(-6.27, -5.55)	-3.69	(-4.21, -3.18)
BMI >=40 kg/m2					
Pooled Placebo	621	-3.21 (0.29)	(-3.77, -2.64)	---	---
Pooled Lorcaserin 10 mg BID	657	-6.14 (0.28)	(-6.69, -5.59)	-2.93	(-3.72, -2.14)
p-Value for Treatment by Subgroup Interaction is = 0.138					
Root Mean Square Error of Change from Baseline is = 6.11					
CI=Confidence Interval; LS=Least Squared; SE=Standard Error;					

Source: ISE-Statistical-Report, Table E56.4

5. CONCLUSIONS ABOUT EFFICACY OF LORCASERIN

The results of two Phase 3 studies are consistent and confirm the efficacy of lorcaserin 10 mg bid and 10 mg qd compared to placebo after 52 weeks of treatment, in the co-primary weight loss endpoints of average weight loss compared to baseline, the percentage of subjects who lost at least 5% of baseline body weight, and the percentage of subjects who lost at least 10% of baseline body weight. Results of alternate analysis models and other versions of the analysis population were consistent with the results from the primary analysis. However, the placebo-adjusted weight loss was relatively low, compared to the benchmark of 5% described in the February 2007 draft *Guidance for Industry: Developing Products for Weight Management*. The clinical review division should evaluate whether or not the weight loss associated with lorcaserin is clinically significant.

A significant review issue that affects the extension of study results to the intended target population is the occurrence of a substantial percentage of randomized subjects who withdrew from each study prior to week 52. As part of my evaluation of this issue, I found that, on average, subjects who withdrew early had lost less weight at the time of withdrawal, compared to the average weight loss at the same study week in subjects who completed the study. This trend was apparent in both the placebo and the lorcaserin arms. My interpretation of this finding is that at any given time throughout the study, subjects who were less successful at losing weight were more likely to drop out than subjects who were more successful. Based on this interpretation, the completers are likely to be different from the non-completers with respect to the efficacy endpoint.

Continuing my analysis, I found that 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. Because of this relationship, I believe that a reasonable measure of efficacy that extends 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. A logistic regression model is a reasonable approach to estimating the placebo-adjusted effect of the active drug, allowing for factors and covariates of the study design.

The placebo-adjusted effect of lorcaserin on average weight loss (the continuous endpoint) was also fairly consistent across different analysis models and versions of the analysis populations. This consistency, even with a substantial proportion of withdrawals, may reflect the modest efficacy of lorcaserin, and may not extend in general to other weight loss products.

Advisory Committee Nonclinical Briefing Document

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

Re: Genotoxicity and Carcinogenicity Assessment for Lorcaserin

Table of Contents

Abstract
Lorcaserin was identified as a non-genotoxic carcinogen in a two-year bioassay conducted 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, skin, subcutis, peripheral nerves, and liver and thyroid gland of males. The tumor response to lorcaserin is not considered secondary to generalized toxicity, as tumor burden was the primary cause of excess mortality. Weight loss, specifically in high dose males, is not considered evidence of generalized toxicity, as weight loss with other investigational anti-obesity agents have generally prolonged survival and lessened tumor burden in two-year rat bioassays. Lorcaserin did not increase tumors in mice, but this is considered a reflection of lower drug exposure achieved in mice compared to rats.

No safety margin was identified in female rats for mammary tumors, which emerged within 7-fold of the proposed clinical dose of 10mg bid. Lorcaserin-emergent mammary tumors were generally lethal and reduced survival time at all doses in females. Mammary tumors emerged in male rats at 17-fold the clinical dose. Studies addressing the mechanism of tumorigenesis failed to demonstrate a robust or sustained elevation in prolactin, providing weak evidence for prolactin as a key event in lorcaserin-emergent mammary tumors. No alternative mechanism of action was addressed to aid in risk assessment.

Lorcaserin increased the incidence of brain astrocytoma in male rats by an unidentified mechanism of action. The cellular lineage of spontaneous astrocytoma in rats compared to other species is unresolved in the literature, but is of secondary concern to the finding that lorcaserin increased brain tumors in rats by an unknown pathway. Without a plausible tumorigenic mechanism identified, risk assessment is based primarily on the difference in exposure between doses in rats and the clinical dose in humans. Comparing brain levels of lorcaserin is most appropriate given the anatomical location of astrocytoma. Lorcaserin preferentially partitions to the brain in rats, mice, and monkeys, but the brain-to-plasma ratio varies across the species. Brain partitioning in human subjects was not determined. Thus, estimating safety margins based on assumptions of partitioning in human subjects is not entirely reliable. Assuming that the monkey best models human partitioning, the estimated safety margin to a non-tumorigenic dose in rats may range from 11x to 17x, with tumors associated with brain exposures that are 40x to 59x higher than clinical exposure. More conservatively, safety margins based on plasma drug levels, which is known for rats and humans, yields a safety margin to the non-tumorigenic dose in rats of 5x, with brain tumors occurring at doses of lorcaserin 17-fold higher than the clinical dose.

Other tumors including benign fibroma of the skin, squamous carcinoma of the subcutis, and malignant schwannoma occurred in male rats with a safety margin to the non-tumorigenic dose of 5x, with lorcaserin increasing the incidence of these tumors at a dose 17-fold higher than the clinical dose. No studies were conducted to address the mechanism by which lorcaserin induced these tumors. Liver and thyroid neoplasms occurred at a high exposure multiple (55-fold) of the clinical dose, and reasonable evidence was provided supporting a rodent-specific mode of action involving induction of hepatic drug-metabolizing enzymes.

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.

Mouse Carcinogenicity study
The carcinogenicity study in mice was initiated with 25, 50 and 100 mg/kg of lorcaserin and a vehicle control. Each dose group consisted of 65 mice/sex/group, and lorcaserin was administered daily by oral gavage. Despite selection of doses thought to be tolerable over a two year dosing period, excessive mortality resulted within the first 16 days of dosing at 100mg/kg. The deaths were clearly related to lorcaserin, but necropsies did not identify a definitive cause of death. With no evidence of tissue damage, and because lorcaserin can accumulate up to 25-times higher in the brain vs. plasma in mice, it is plausible that the deaths had a neural origin. However, only one case of convulsion was reported in a male on Day 1 at 100 mg/kg, with no apparent detrimental consequence.

In consultation with the FDA, the doses of lorcaserin were decreased to 5, 25 and 50 mg/kg starting on Day 19. The lowered doses were tolerated and survival in lorcaserin-dosed groups was similar to the control group for the remainder of the 2 year study (Table 1). The high dose of 50mg/kg in the mouse provided exposure 4- to 7-times higher than the clinical dose of 10mg BID (based on AUC, total drug exposure; Figure 1).

Table 1: Survival of mice at lowered doses of lorcaserin in the 2 year bioassay

2-Year mouse study	Sex	Lorcaserin Dose, mg/kg/d			
		Control (H_2O)	5	25	50
Survival rate, %	M	41%	37%	28%	37%
	F	35%	32%	38%	33%

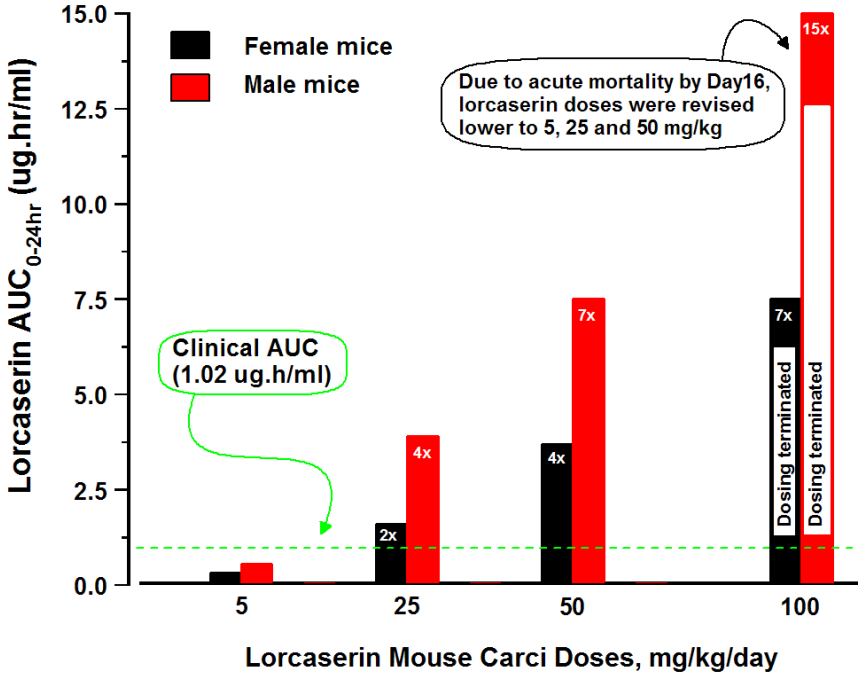
Study Findings in Mice:
Lorcaserin had no substantial effect on body weight or food intake in male or female mice. Lorcaserin effectively reduces food intake and body weight in rodents in shorter term studies, so the lack of effect on body weight after two years of dosing may reflect a loss of pharmacodynamic sensitivity to 5HT2C agonism in appetite regulatory centers.

Review of the study results by the Division and the Executive Carcinogenesis Assessment Committee of FDA is consistent with the Sponsor's conclusion that no drug-related tumors were

observed in mice (see 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.

The primary safety concern in the mouse study was the apparent and unanticipated steep dose response curve for toxicity not related to tumors. Whereas mice tolerated a 50mg/kg dose for 2 years without apparent adverse effects, a doubling of exposure to 100mg/kg resulted in rapid and unexplained deaths in a number of mice. This was unanticipated because prior studies had shown minimal mortality in the first few days of treatment with higher doses of lorcaserin, including 250 mg/kg in a 13-week study and 350 mg/kg in a 2-week study.

Figure 1: Lorcaserin exposure achieved in mice (bars) compared to the clinical dose of 10mg BID (green horizontal line). The ratio of mouse to human exposure is noted within the bars. Comparisons are based on AUC drug exposure (Area Under the Curve). Dosing was terminated for the 100mg/kg dose group due to excess mortality within the first 16 days of dosing.



Rat Carcinogenicity Study

The two-year carcinogenicity study in Sprague-Dawley rats evaluated lorcaserin at doses of 10, 30 and 100 mg/kg, and included a vehicle control. The high dose groups consisted of 75 rats/sex, with other dose groups consisting of 65/sex (Table 2). The toxicokinetic (TK) groups were used to measure drug exposure and were dosed for 52 weeks. Due to the emergence of mammary tumors in the study, several TK rats were dosed an additional 2 to 4 weeks to allow for serum analysis of prolactin and estradiol and for immunohistochemical staining of prolactin.

Table 2: Group assignments for 2 year rat carcinogenicity study

Group Assignments			
Group Number	Dose Level (mg/kg/day)	Number of Animals	
		Male	Female
Main Study			
1 Control (C)	0	65	65
2 Low dose (LD)	10	65	65
3 Mid dose (MD)	30	65	65
4 High dose (HD)	100	75	75
Toxicokinetic			
5	0	6	6
6	10	15	15
7	30	15	15
8	100	15	15

Drug exposure in rats substantially exceeded that achieved in mice (Table 3). Drug exposure in male rats achieved a 5x, 17x, and 55x multiple at the LD, MD, and HD compared to the clinical dose. Exposure in female rats was higher, achieving a 7x, 24x, and 82x multiple of the clinical dose.

Table 3: Multiples of clinical exposure to lorcaserin achieved in 2yr rat study			
	Dose, mg/kg	**Males**	**Females**
104-week Rat Carci Study	10 (LD)	5x	7x
	30 (MD)	17x	24x
	100 (HD)	55x	82x
Exposure multiples calculated as AUC exposure in rats divided by average AUC exposure of the clinical dose of lorcaserin, 10mg BID, 1.02 ug*h/ml AUC			

Rat Tumor Findings

A summary of tumors associated with lorcaserin in rats is presented in Table 4. Of particular note, the combined incidence of mammary adenocarcinoma and fibroadenoma increased at all doses in females and in the mid and high dose males. Numerous other tumors were observed in male rats but not in female rats. These include tumors of the brain, peripheral nerves (Schwannoma), skin and subcutis, liver, and thyroid.

Table 4: Incidence of lorcaserin-induced tumors in the 2 year rat carcinogenicity study.
(n= 65/sex for Control, 10, 30mg/kg and n=75/sex for 100mg/kg)

Male rats Incidence of tumors		**Lorcaserin dose, mg/kg/day**			
		Control	**10**	**30**	**100**
Brain	astrocytoma	1	0	4 NS	8[a] SS
Mammary	adenocarcinoma	0	0	2	2 NS
	fibroadenoma	0	1	4 NS	6 NS
	combined	**0**	**1**	**6** SS	**8** SS
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

Female rats Incidence of tumors		**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
	combined	**40**	**56** SS	**61** SS	**70** SS

[a] One case of astrocytoma in an HD male was reclassified as infarct due to lymphocytic leukemia in an amendment to the NDA

Statistical analysis provided by the FDA statistician, Dr. Matthew Jackson.
NS = not significant ($p > 0.05$ rare tumor; $p > 0.01$ common tumor)
SS = Statistical significance ($p \leq 0.05$ rare tumor; $p \leq 0.01$ common tumor; pairwise comparison)
Shaded boxes indicate FDA's conclusion of a lorcaserin-related tumor increase, including numerical and 'statistically significant' increases.

Lorcaserin-related tumors other than mammary neoplasms were observed only in male rats. This is not due to a sex difference in exposure; indeed, males had lower overall AUC exposure than females. This is also not interpreted as evidence of a robust tumor response in just one sex. Rather, the lack of other tumor types in females likely reflects the greater and earlier mortality in females compared to males (see Survival, below). For example, half of the high dose females were dead by ~week 67 compared to week 75 for high dose males, and half of the mid-dose females were dead by ~week 80 compared to week 95 for mid-dose males. Had females survived similarly to males, it is reasonable to expect that other tumor types may have emerged.

Survival

Lorcaserin-emergent tumors had a substantial impact on survival in the male and female rats. (Table 5, Figure 2). Surviving females of all dose groups and the high dose (HD) males were necropsied at ~ week 96/99, after consultation with FDA's Executive Carcinogenesis Assessment Committee. Overall, lorcaserin-treated males survived for a longer period than females.

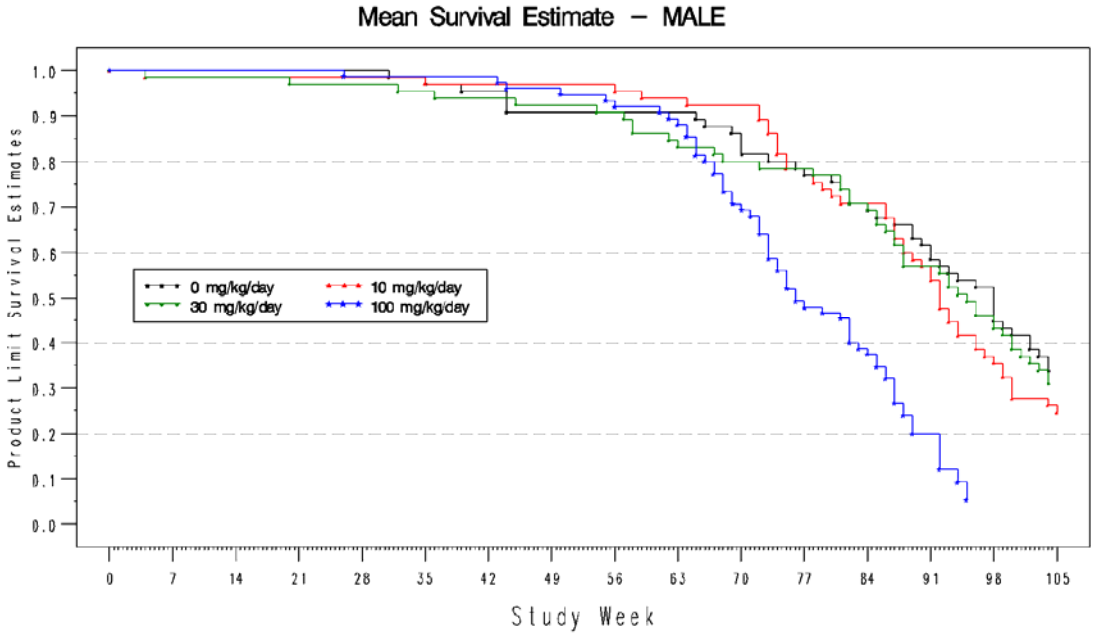
Survival declined significantly at all doses in females due to the emergence of drug-related mammary fibroadenoma and adenocarcinoma. According to the sponsor's study report, survival also declined significantly in HD males, with the excess deaths due to the emergence of drug-related tumors in the brain,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

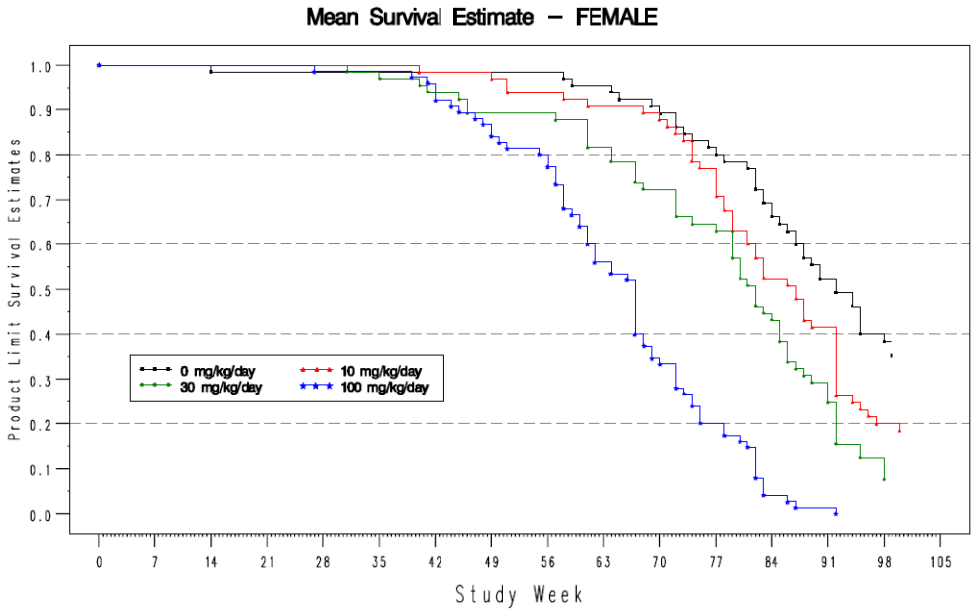
Excess mortality in carcinogenicity studies is considered evidence that drug exposure has exceeded the maximum tolerated dose (MTD), *but only when* the cause of mortality is related to something other than drug-induced tumors. In those cases, any tumors associated with that dose are not necessarily 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.

Table 5: The number of live rats and survival rate at the end of the 2-year carcinogenicity study

2-Year Rat study	Sex	Lorcaserin Dose, mg/kg/d			
		Control (H_2O)	10	30	100
Number animals alive	M	22/75	16/65	20/65	4/75
	F	23/75	12/65	5/65	0/75
Survival rate, %	M	33.8%	24.6%	30.7%	5.3%
	F	35%	18.4%	7.7%	0%

Figure 2: Kaplan-Meir survival estimates in male and female rats treated with 10, 30 and 100 mg/kg of lorcaserin for up to 2 years.

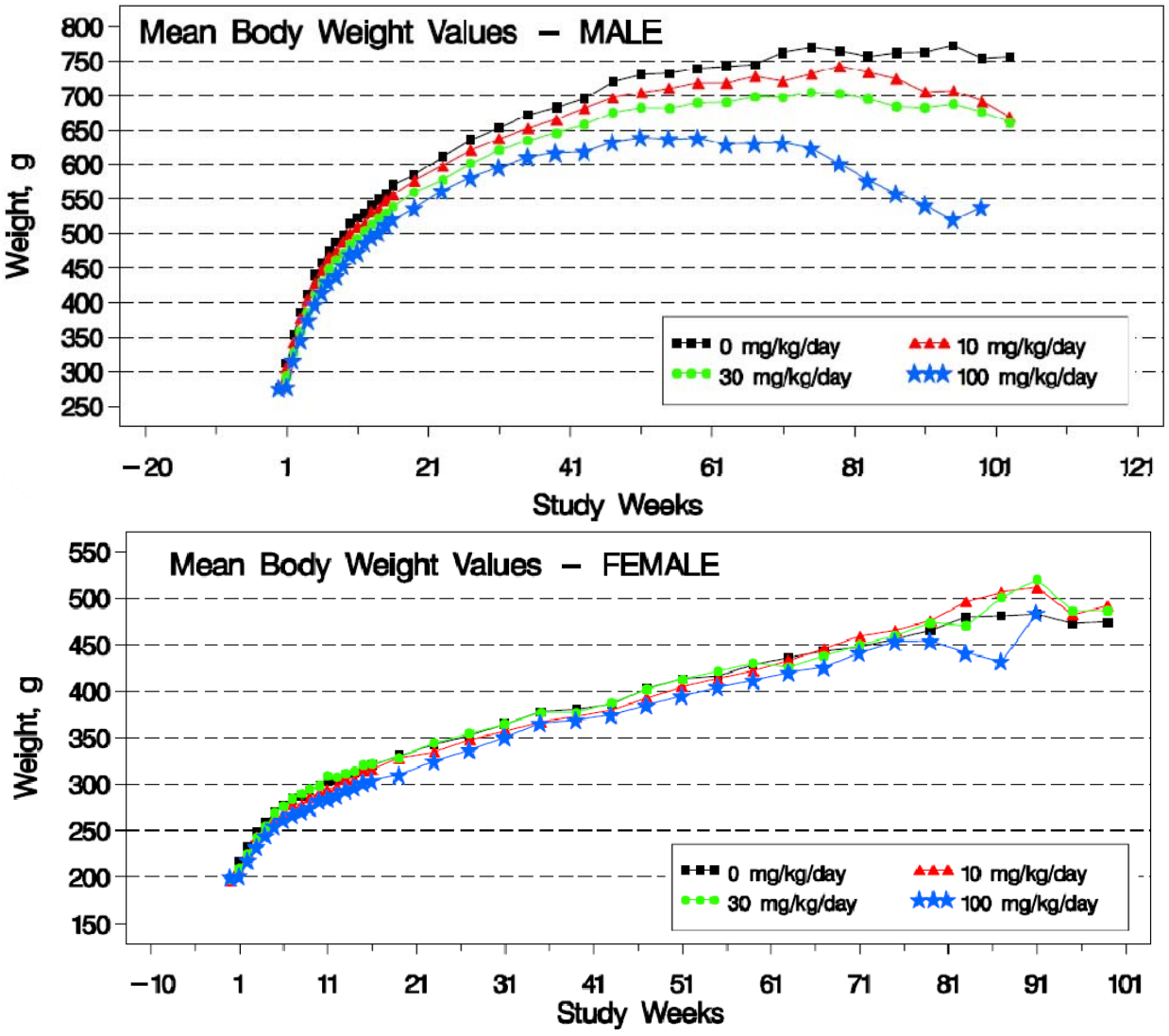




Body Weight changes

Body weight declined in males, most notably at 100 mg/kg, but did not substantially change in females (Figure 3). Decreased food intake was variable in both sexes but slightly lower in males. 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 generalized toxicity, and is not interpreted as a reason for reduced survival or for tumor induction. Rather, the reduced weight in high dose males was likely skewed by the greater tumor burden and earlier mortality in this group.

Figure 3: Mean body weight measurements in the 2 year rat carcinogenicity study.



Mammary tumors

Summary: Lorcaserin significantly increased mammary fibroadenoma alone or combined with adenocarcinoma in females at all doses and at the mid and high doses in males. No safety margin was established in the females (tumors occurred ~7x clinical dose), whereas a safety margin of 5x was identified in males (tumors occurred 17x clinical dose). Lorcaserin-induced mammary tumors, both benign and malignant, were lethal and decreased survival over the 2 year study. The mechanistic studies provide weak support for the hypothesis that lorcaserin-induced mammary tumors are secondary to elevations in prolactin, as occurs with approved anti-dopaminergic agents. No other hypotheses were addressed to identify an alternative mechanism of lorcaserin-induced mammary tumors in rats. Given the lack of a safety margin, an unresolved tumorigenic mechanism of action, and a patient population already at increased risk of breast cancer, the relevance of these finding in rats to human risk cannot be dismissed.

Mammary tumors in rats consisted of fibroadenoma and adenocarcioma. Statistically, the increased incidence of adenocarcinoma was significant only in high dose females. When combined with fibroadenoma, statistical significance is achieved at all doses in females and at mid- and high doses for males (Table 6). A safety margin, defined by a non-tumorigenic dose, was not identified in females because an increased incidence of fibroadenoma was observed at the low dose, or ~7x the clinical dose.

The historical incidence of mammary tumors in male rats is relatively low, so the observation that mammary adenocarcinoma and fibroadenoma combined was significantly increased in mid- and high-dose males is notable (Table 6). The histological data identified a degree of feminization in males, defined as partial or complete replacement of typical lobulo-alveolar appearance of the mammary gland with a ductulo-alveolar appearance in all treated males (LD: 64%, MD: 69% and HD: 63%) as well as controls (48%). Although no mammary tumors were reported for the control group, this degree of feminization may have increased the susceptibility of the male rats to develop mammary tumors in response to lorcaserin.

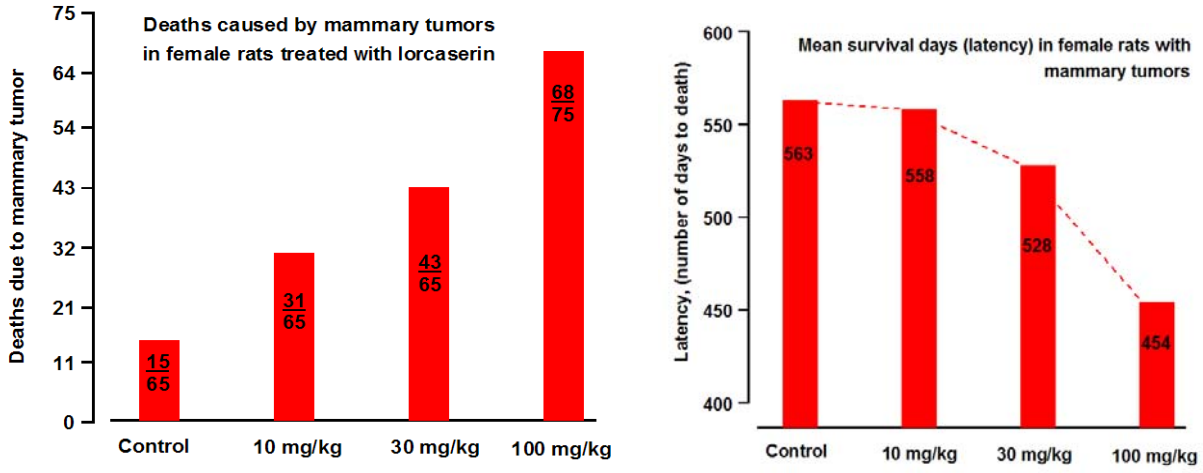
Table 6: Mammary Tumor Incidence in 2 year rat study

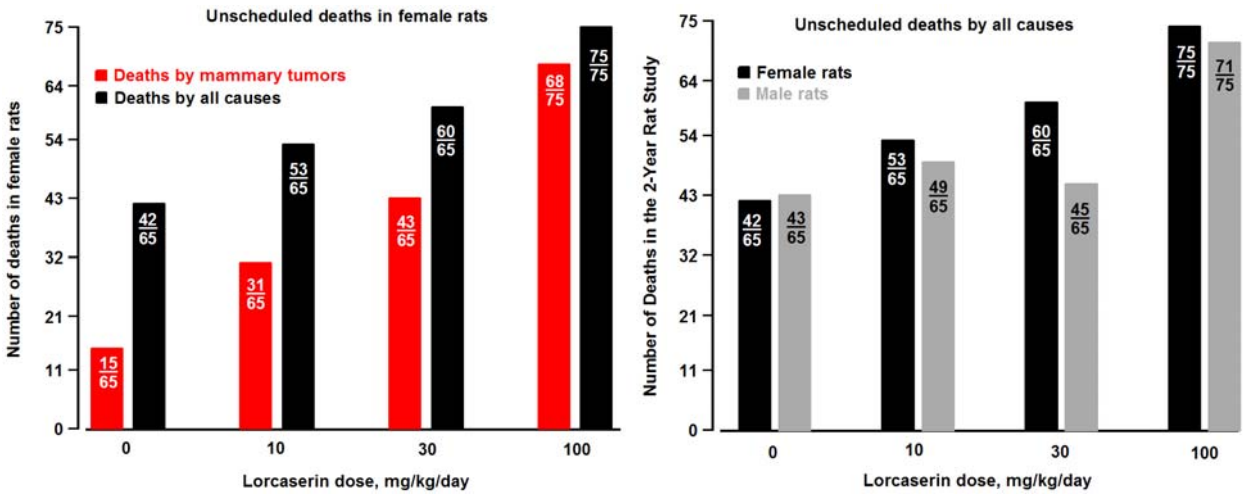
Mammary Tumor Incidence **# animals effected (% incidence)** **SS, statistical significance**		**Lorcaserin dose, mg/kg/day**			
		Control **n=65**	**10** **n=65**	**30** **n=65**	**100** **n=75**
Males	adenocarcinoma	0	0	2 (3%)	2 (2.6%) NS
	fibroadenoma	0	1 (1.5%)	4 (6%) NS	6 (8%) NS
	combined	**0**	**1**	**6** SS	**8** SS
Females	adenocarcinoma	28 (43%)	34 (52%) NS	35 (54%) NS	60 (80%) SS
	fibroadenoma	20 (31%)	47 (72%) SS	53 (81%) SS	45 (60%) SS
	combined	40	56 SS	61 SS	70 SS

Historical control data for mammary tumor incidence in SD rats for study site (compiled from 11 studies, conducted 2002-2007)			
	Mammary tumor type	Range	Average
Males	Adenocarcinoma	0-2%	0.3%
	Fibroadenoma	0-3.3%	0.9%
Females	Adenocarcinoma	8.3-37%	24%
	Fibroadenoma	22-54%	36%

The FDA's risk assessment is based on the combined incidence of mammary fibroadenoma and adenocarcinoma, and is not substantially swayed by the argument that statistically significant malignant adenocarcinoma was confined to high dose females. As demonstrated in Figure 4, the number of deaths caused by mammary tumors increased in females at all doses, not just the high dose, and mean survival time for females with mammary tumors (latency) decreased with an increase in lorcaserin. As the dose of lorcaserin increased, the more females died of mammary tumors and at an earlier time at all doses. Confining the analysis to the final incidence of mammary tumors without consideration of tumor-related mortality is not justified. Among the deaths attributed to mammary tumors, approximately 1/15, 6/31, 14/43 and 10/68 deaths were attributed to fibroadenoma in the control, LD, MD and HD female rats, respectively, suggesting that fibroadenoma as well as adenocarcinoma were fatal.

Figure 4: Deaths of female rats related to lorcaserin-induced mammary tumors.





An additional reason that the FDA risk assessment is not substantially weighted toward malignant adenocarcinoma is the uncertainty apparent in the course of diagnosing adenocarcinoma from fibroadenoma in the study (Table 7a,b). The high incidence of mortality and palpable tumors in female rats observed during the course of the study prompted the FDA to request periodic updates from the Sponsor regarding the incidence of observed tumors, particularly mammary and brain tumors. The entire female high dose group and the majority of mid-dose females were evaluated histologically by week 96. In subsequent updates and in the final study report, the incidence of adenocarcinoma in the MD and HD females was lower than that reported at week 96 (Table 7a). The incidence of adenocarcinoma increased in the controls and stayed consistent in the low dose group over the same period. The incidence of fibroadenoma increased in all dose groups from week 96 to the final study report, though the numbers notably varied in the mid- and high dose groups (Table 7b). It appears that some of the decrease in the number of adenocarcinoma after week 96 was accompanied by an increase in fibroadenoma, potentially a consequence of the sponsor/CRO reclassifying the observed tumor types.

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

Table 7b: Mammary Fibroadenoma Incidence over time in Female Rats (main study)				
Data Update (Week)	Control	10 mg/kg/d	30 mg/kg/d	100 mg/kg/d
Week 88 update	4/28	16/38	24/45	35/74
Week 96 update	10 / 39	27 / 50	36 / 57	36 / 75
Week 104 update	20 / 65	47 / 65	60 / 65	53 / 75
Final update	20 / 65	48 / 65	56 / 65	51 / 75
Final NDA	20 / 65	47 / 65	53 / 65	45 / 75

Mechanism of Lorcaserin-related Mammary Tumors in Rats

Summary: The primary hypothesis addressed by the Sponsor was that lorcaserin-induced mammary tumors occurs via a mechanism similar to that demonstrated for compounds with direct or indirect anti-dopaminergic activity, including many approved anti-psychotic medications. Specifically, suppression of dopamine promotes an increase in prolactin levels, which is a known intermediary of mammary tumorigenesis in rodents but of unresolved significance to human breast cancers. Evidence supporting this pathway in the mechanism of lorcaserin-induced mammary tumors is not persuasive. Lorcaserin repeatedly failed to increase serum prolactin or prolactin staining of the pituitary or mammary tissue of intact female rats. A modest increase in serum prolactin after single dose exposure in male rats was not sustained after prolonged exposure. Efforts to reduce perceived variability in the prolactin data by ovariectomizing female rats also did not yield evidence of a lorcaserin-induced increase in prolactin. The experimental condition required to demonstrate even a modest increase with lorcaserin in female rats was ovariectomy plus pharmacologic treatment with ovarian hormones, conditions that bear little resemblance to the 2 year study in which lorcaserin increased mammary tumors. By comparison, haloperidol, an anti-dopaminergic agent associated with rodent mammary tumors, robustly increased serum prolactin regardless of experimental conditions. The serotonergic agent dexfenfluramine modestly increased serum prolactin regardless of experimental condition. Of note, the modest increase in serum prolactin with dexfenfluramine does not result in mammary tumors (Redux NDA 20344). No other hypotheses were addressed to identify an alternative mechanism of lorcaserin-induced mammary tumors in rats, which the FDA considers as yet unresolved.

Prolactin is known to be an intermediary hormone in development of mammary tumors in rodents. Several CNS active drugs (anti-dopaminergic compounds or drugs indirectly affecting dopamine) result in mammary tumors in rodents secondary to increased pituitary output of prolactin. Because serotonin is reported to negatively regulate dopamine release, potentially via activation of 5HT2C receptors, a similar mechanism may exist in lorcaserin-treated rats. To test this hypothesis, the Sponsor conducted several mechanistic studies in males and intact and ovariectomized female rats to demonstrate increased prolactin production or perturbation in hormone status in response to lorcaserin.

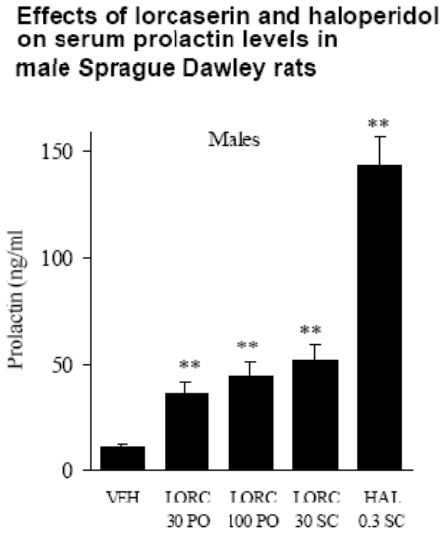
Prolactin responses in male rats

A single dose of lorcaserin increased plasma prolactin in male rats (Figure 5a). Haloperidol is an anti-dopaminergic compound associated with mammary tumors in rodents, which robustly increased prolactin after a single dose in males. However, after one year exposure to lorcaserin,

serum prolactin in treated males was reduced by 50% relative to the control (Figure 5b). Also, prolactin immunoreactivity in the pituitary and mammary tissue showed no change in treated versus control. Thus, the acute but modest increase in prolactin after a single dose of lorcaserin was not observed after repeated doses in males. This was also the case in humans where a single dose of lorcaserin appeared to result in small increases of serum prolactin but not in multiple dose clinical studies (please refer to Dr. Golden's review). This profile is consistent with published data showing that repeated dosing with a 5HT2A/C agonist can quickly lead to rapid tolerance regarding prolactin release in rats[1] and humans[2], suggesting that an increase in prolactin with lorcaserin would be acute with no long lasting change to produce the outcome seen in the carcinogenicity study.

Figure 5: Serum prolactin response in male rats after (A) single dose or (B) 55 weeks of lorcaserin administration. Hal, haloperidol; lorc, lorcaserin (study DBR-08-031, NDA 22529)

(A) Single Dosing



(B) 55 week dosing

MPI Research Study Number 900-063
A 2-Year Carcinogenicity Study of APD356 Given by Oral Gavage to Rats

Summary of Toxicokinetic Neuroendocrine Hormone Values - MALE

Endpoint	Interval of Study	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Prolactin ng/mL	Week 55	57.87	32.562	6	28.24[b]	12.479	14	29.93[b]	10.908	10	23.69[b]	16.140	14

[1] Aulakh CS et al. JPET (271) 1994
[2] Benjamin J et al. Psychopharmacology (127) 1996

Prolactin responses in female rats

Lorcaserin increased mammary tumors in sexually intact female rats in the 2 year bioassay. Several studies failed to demonstrate a persuasive increase in prolactin or estradiol under comparable conditions (i.e., non-ovariectomized, intact female rats). Figure 6 demonstrates that single dose haloperidol increases serum prolactin, but single dose lorcaserin does not. Table 8A demonstrates that serum estradiol and prolactin do not increase in response to lorcaserin after 1, 15, or 28 days of dosing relative to the control group. Table 8B demonstrates that prolactin immunoreactivity in the pituitary and mammary gland is similar to control after 28 days of exposure to lorcaserin. Consistent with the shorter duration studies, 56 weeks of exposure to lorcaserin did not result in increased serum prolactin or estradiol relative to controls, although a slight increase in prolactin immunoreactivity was reported in the pituitary of treated females (Table 9A, B). The positive pituitary finding did not correlate with findings in the mammary tissue, however. According to the sponsor, "*The incidence and the severity of prolactin immunohistochemistry stain* (of mammary tissue) *were similar among control, low dose, and mid-dose animals and were decreased by 40% at the highest dose. There were no correlations between the incidence of mammary gland prolactin stain and the incidence of pituitary gland prolactin stain in females at all dose levels." (page 900-063, study #TX05071, NDA 22529).*

Figure 6: Effect of single dose lorcaserin or haloperidol on serum prolactin in intact female rats (study DBR-08-031, NDA 22529)

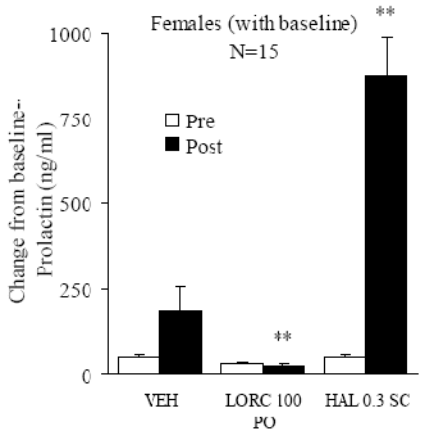


Table 8A: Serum estradiol and prolactin levels in intact female rats in response to lorcaserin after 1, 15, and 28 days administration. (study MPI 900-101, NDA 22529)

Day and time of measurements	Estradiol, pg/ml		Prolactin, ng/ml	
	0 mg/kg	100 mg/kg	0 mg/kg	100 mg/kg
Day 1, at 2hr	< 2 to 6	< 2 to 6	49	62
Day 1, at 6 hr	< 2 to 18	< 2 to 33	378	213
Day 1, 12 hr	< 2 to 6	< 2 to 8	59	95
Day 1, 24 hr	< 2 to 15	< 2 to 3	87	215
Day 15, 2 hr	< 2 to 26	< 2 to 13	109	31
Day 15, at 6 hr	<2 to 18	< 2 to 24	659	505
Day 15, at 24 hr	<2 to 13	< 2	76	109
Day 28, 2 hr	< 2 to 15	<2 to 16	569	167
Day 28, at 6hr	< 2 to 20	< 2 to 13	409	882

Day 28, at 24 hr	< 2	<2 to 11	294	205

Table 8B: Prolactin immunoreactivity in mammary and pituitary gland from intact female rats after 28 days lorcaserin administration. (study MPI 900-101, NDA 22529)

MPI Research Study Number 900-101
APD356: Assessment of Serum Prolactin and Estradiol in Female Rats During Daily Dosing for 28 Days

Summary of Microscopic Observations - FEMALE

Tissue / Observation	Severity	0 mg/kg/day	100 mg/kg/day
Number of Animals Examined		20	20
mammary gland (ihc)		(19)	(18)
prolactin stain, increased	- minimal	9	9
within normal limits		10	9
pituitary gland (ihc)		(19)	(20)
prolactin stain, decreased	- mild	0	1
within normal limits		19	19
vagina		(20)	(20)
diestrus		4	2
estrus		5	6
metestrus		6	6
proestrus		5	6

Table 9A: Serum prolactin and estradiol levels in toxicokinetic female rats after 56 weeks administration of lorcaserin. (study 900-063, 2 yr rat carcinogenicity study)

Summary of Toxicokinetic Neuroendocrine Hormone Values - FEMALE

Endpoint	Interval of Study	0 mg/kg/day Mean	0 mg/kg/day SD	0 mg/kg/day N	10 mg/kg/day Mean	10 mg/kg/day SD	10 mg/kg/day N	30 mg/kg/day Mean	30 mg/kg/day SD	30 mg/kg/day N	100 mg/kg/day Mean	100 mg/kg/day SD	100 mg/kg/day N
Prolactin ng/mL	Week 56	114.78	79.726	5	129.91	55.678	14	106.12	67.995	13	116.62	62.920	10
Estradiol pg/mL	Week 56	2.0	0.00	5	3.7	3.10	14	2.2	0.60	13	2.0	0.00	10

N - Number of measures used to calculate mean
SD - Standard Deviation
[b]Significantly different from control; (p<0.01)

Table 9B: Prolactin immunoreactivity in pituitary gland of toxicokinetic female rats after 56 weeks administration of lorcaserin. (study 900-063, 2 yr rat carcinogenicity study)

MPI Research Study Number 900-063
A 2-Year Carcinogenicity Study of APD356 Given by Oral Gavage to Rats

Summary of Prolactin Positive Stained Cell Counts in the Pituitary Gland - FEMALE

		0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Estrous Stage	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Prolactin Labeling Index (%)	All Stages	60.56	7.566	5	70.42	13.442	14	79.01[a]	14.942	14	79.82[a]	11.268	10

N - Number of measures used to calculate mean
SD - Standard Deviation
[a]Significantly different from control; ($p<0.05$)

Baseline levels of prolactin are higher in females than in males primarily due to the presence of estrogen and progesterone. The sponsor contends that prolactin levels were variable in the intact females and therefore those studies showing lorcaserin's lack of effect on prolactin were 'inconclusive'. That haloperidol robustly increased prolactin in the intact female rats contradicts the sponsor's concern. Nevertheless, to address this perceived shortcoming in the studies, female rats were ovariectomized to reduce levels of sex hormones in an effort to demonstrate a lorcaserin-induced increase in prolactin. Ovariectomy reduced baseline levels of prolactin, but lorcaserin failed to increase serum prolactin or immunoreactivity in the pituitary of ovariectomized females either acutely or after 9 or 20 days of dosing (Table 10). By comparison, the serotonergic agonist dexfenfluramine increased serum prolactin in both intact and ovariectomized females, most likely as a consequence of increasing brain levels of serotonin and suppressing dopamine output. This is of particular interest, because dexfenfluramine *did not* result in mammary tumors in Sprague Dawley rats (NDA 20344), despite the increase in prolactin demonstrated herein.

Table 10: Prolactin release in intact and ovariectomized female rats after administration of lorcaserin (APD356) or dexfenfluramine (D-FEN) for 10 and 21 days (study WIL670002/TX08007). Similar results were obtained in a separate study (WIL670001/TX08001).

Prolactin Analysis.

	Sexually Intact Females			Ovariectomized Females		
Group:	Vehicle	APD356	D-FEN	Vehicle	APD356	D-FEN
Prolactin (ng/mL)						
Day 9 Mean	15.0	6.2	42.1	10.7	3.1	21.5
% Difference		-58.7	180.7		-71.0	100.9
SD	16.42	6.05	41.75	8.73	1.96	15.42
Range	0.4-47.8	1.1-18.1	3.8-105.4	2.2-28.8	0.4-7.0	4.2-38.1
N	10	10	5	10	10	5
Day 20 Mean	11.7	9.1	98.1*	4.6	4.7	12.6*
% Difference		-22.2	738.5		2.2	173.9
SD	17.03	6.73	143.74	2.79	3.06	11.92
Range	0.8-44.7	0.4-18.3	14.3-354.2	0.4-9.1	0.4-9.8	1.7-27.8
N	10	10	5	10	10	5

* = Significantly different from the control group at 0.05 using Dunnett's test

The lack of lorcaserin's effect on prolactin in intact and ovariectomized female rats prompted the sponsor to further hypothesize that '*controlled levels of ovarian hormones might be required to facilitate the detection of a lorcaserin-stimulated increase in serum prolactin in female rats*." (Section 2.4.4.8, NDA 22529). That dexfenfluramine readily increased prolactin in intact and ovariectomized females again contradicts the sponsor's reasoning. Nevertheless, to address this issue the sponsor ovariectomized female rats and then implanted pellets to replenish ovarian hormones. The replenishment consisted of 'low' and 'high' doses of an estradiol/progesterone combination. The implanted hormones significantly increased serum prolactin by 10- to 20-fold in ovariectomized females (Figures 7a, b). Lorcaserin had little effect on serum prolactin in ovariectomized females as before, but modestly increased prolactin in the hormone-treated groups (Figure 7a). Expressed as a fold-change to baseline prolactin in ovariectomized rats, the effect of lorcaserin appears particularly minimal (Figure 7b). By comparison, the anti-dopaminergic agent haloperidol robustly increased prolactin regardless of hormone status, with a fold-change similar to that induced by estradiol/progesterone. The conditions required to demonstrate even a minimal increase in serum prolactin with lorcaserin (i.e., ovariectomy + high dose hormones) bears little resemblance to the conditions under which lorcaserin induced mammary tumors in the 2 year bioassay.

Figure 7a: Serum prolactin in response to lorcaserin and haloperidol in ovariectomized females with and without hormonal implantation (study DBR09001). Similar results were obtained in a separate study (DBR08032). Figure 7b depicts the fold change to baseline prolactin in ovariectomized rats without hormone implantation.

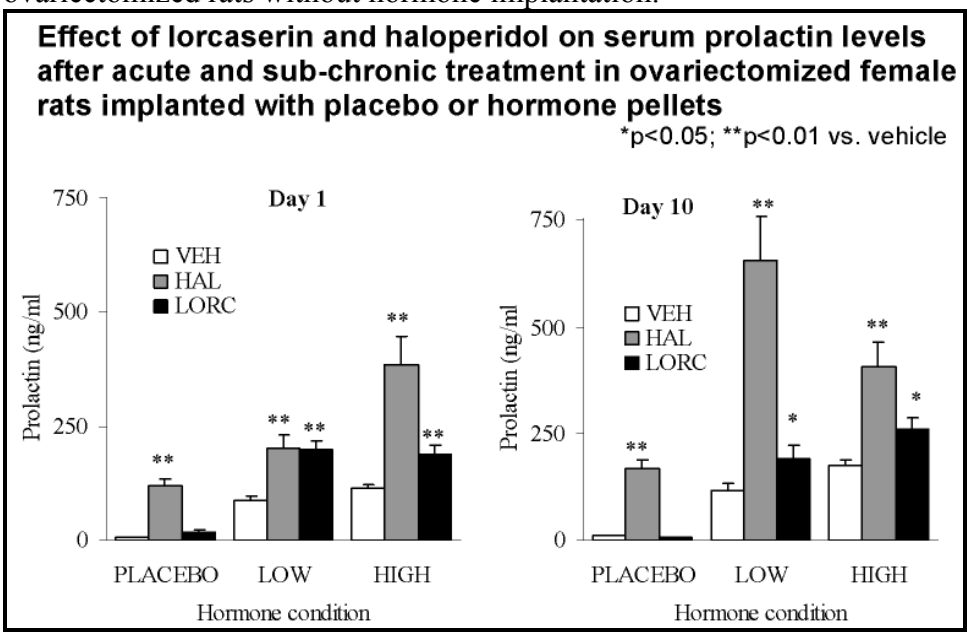
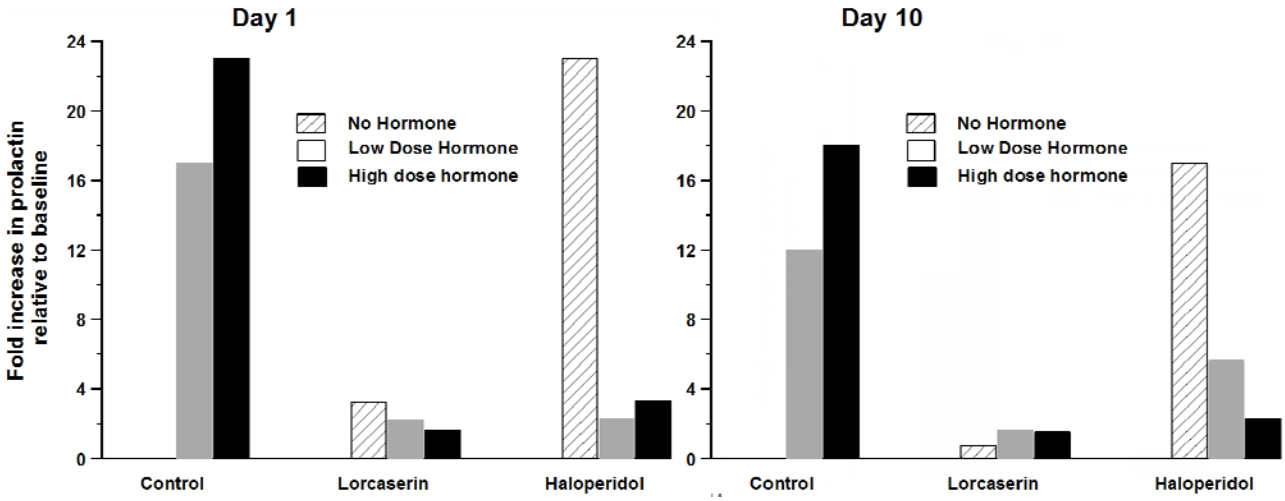


Figure 7b: Fold-change of serum prolactin in ovariectomized female rats administered lorcaserin or haloperidol in the absence or presence of low or high dose hormone pellet implantation. Fold-changes are relative to serum prolactin in ovariectomized rats without hormone implantation on day 1 (5.2ng/ml) and on day 10 (9.8ng/ml). Figure constructed by FDA

based on data from study DBR09001, NDA 22529. Figure 7a depicts the absolute serum prolactin values.



Brain astrocytoma

Lorcaserin increased the incidence of brain astrocytoma in male rats in a dose-dependent manner (Table 11). The numerical increase at the mid dose and the statistically significant increase at the high dose are both considered related to lorcaserin treatment. There was no statistically significant increase in brain tumors in female rats, although when main study and toxicokinetic groups are combined the incidence of astrocytoma in females is observed only in the lorcaserin-treated groups and not in the concurrent control group (Table 12). The incidence of astrocytoma in males exceeds the historical control range for the study site. In females, the incidence of astrocytoma is above the average historical incidence in all lorcaserin-treated groups though still within the historical range of the study site. Astrocytoma appeared within a year of treatment and was fatal in most cases.

Table 11: Incidence of brain astrocytoma in 2 yr rat study, main study groups

	Lorcaserin dose, mg/kg/day			
	Control n=65	**10 n=65**	**30 n=65**	**100 n=75**
Males	1 (1.5%)	0	4 (6.1%) NS	8 (10.7%) SS
Females	0	2 (3.0%)	0	1 (1.3%)

Historical control data for astrocytoma incidence in SD rats for study site (compiled from 11 studies, conducted 2002-2007)		
	Range	Average
Males	0-5%	2.7%
Females	0-3.3%	1%

Table 12: Incidence of brain astrocytoma in female rats, main study + toxicokinetic groups

Brain astrocytoma in SD rats		Lorcaserin dose, mg/kg/day			
		0	10	30	100
Females	Main Study	0/65	2/65	0/65	1/75
	TK study	0/5	0/14	1/14	2/10
	Combined	0/70 (0%)	2/79 (2.5%)	1/79 (1.3%)	3/85 (3.5%)

The sponsor has argued that the astrocytomas identified in male rats may stem from a macrophage/microglial cellular lineage rather than astrocytes as occurs in human astrocytoma. They further argue that the rat astrocytomas are of minimal human relevance because immune cell tumors in the CNS of humans are rare, and that 'generalized toxicity' may provide a mechanism of brain tumor formation with lorcaserin in rats. Among the thirteen astrocytomas evaluated further by the sponsor, all stained positive for ED1 (anti-CD68 macrophage marker), one stained positive for MHCII, and none stained for GFAP (astrocyte marker). This immunoreactive profile is consistent with literature[3] dating back 20 years that rat astrocytoma is consistently negative for GFAP staining, unlike astrocytoma in other species including humans. Non-neoplastic astrocytes are GFAP-positive in rats and in other species. A recent publication by Nagatani et al[4] suggests that rat astrocytoma may share a lineage with malignant reticulosis, concluding that "*These two tumors most likely originate from the same cell lineage, namely, microglia, macrophage, or radial glia*." Note that the authors of this paper did not exclude the possibility that rat astrocytoma may also derive from radial glia, which is a recognized neuronal progenitor cell type. Alternatively, the lack of GFAP in rat astrocytoma may reflect a less differentiated state of rodent vs. human neoplasms[5], consistent with down-regulation of GFAP in stage III/IV human astrocytoma[6].

Evidence over the past 5 years indicates that astrocytoma can initiate from neural stem cells, which may lead directly to tumor cells at various stages of differentiation within an astrocytoma mass[7,8]. Although expression of GFAP, a glial differentiation marker was examined, markers of

[3] Boorman GA et al. Pathology of the Fischer Rat (1990)
[4] Nagatani M, et al. Toxicol Path (37) 2009
[5] Krinke GJ et al. Toxicol Path (28) 2000
[6] Chumbalkar VC, et al. Proteomics (5) 1005
[7] Zhu Y, et al. Cancer Cell (8) 2005

more poorly differentiated astro-glial cells involved in gliomas, such as NG2, vimentin and nestin[6], were not investigated. An astrocytoma mass can also be comprised of additional cell types due to the very diffuse and migratory nature of the astrocytoma cells. There is also evidence showing that astrocytoma can be infiltrated by inflammatory cells, such as macrophages[9], which could explain the presence of positively-stained ED1 and MHCII cells within an astrocytoma neoplastic region. Thus, it is important to identify which cell types are actively dividing within the neoplasm by using proliferation markers, such as Ki67, in addition to looking at cell-specific markers. Since more histological characterization is required to define the brain neoplasms in question, it is not possible to overrule initial astrocytoma pathological classifications with only evidence from GFAP-negative immunohistochemistry and without investigation of other immunohistochemical markers.

The unresolved lineage of the rat astrocytoma is much less important than the lack of an identified molecular mechanism that leads to the lorcaserin-related increase in brain tumors. Elucidation of a drug-induced tumorigenic mechanism provides a basis to evaluate whether key events in that mechanism are operative in human biology. The sponsor's proposal that 'generalized toxicity' may be a mechanism for tumors of monocytic lineage is rejected because excess mortality was related to tumors, not generalized toxicity, other monocytic tumor types were not increased with treatment. Also, in a screen of 250 approved and non-approved drugs with rodent tumor data[10], only one is associated with brain malignancy (malignant glioma induced by a nucleoside reverse transcriptase inhibitor), despite drug levels that often exceed tolerability. It is relevant that serotonin 5-HT receptors, including 5HT2 subtypes, have been shown to be expressed in normal astrocytes, upregulated in human glioma cells, and can positively modulate glioma cell proliferation, migration, and invasion[11]. However, other potential mechanisms for the increase in brain astrocytoma with lorcaserin were not addressed. Without a plausible tumorigenic mechanism supported by experimental studies, human risk assessment is primarily based on the difference in exposure between the dose causing the brain tumors in rats to the clinical dose of lorcaserin.

Because astrocytoma is located within the brain compartment, comparison of exposure to lorcaserin in rats and humans is most appropriately based on brain levels of drug, not plasma levels. This comparison is complicated because lorcaserin preferentially partitions to the brain compared to the plasma, and the degree of partitioning varies across species (Table 13). Brain partitioning after a single dose of lorcaserin is alarmingly variable, but steady state brain-to-plasma partitioning is less variable with an average partitioning of 29x in rats and 10x in monkeys. Brain-to-plasma partitioning in human subjects was not reported by the sponsor and therefore remains unknown. The sponsor argues that brain partitioning in human subjects would resemble that in monkeys and not rats, which appears reasonable but is nevertheless still an assumption given the absence of data.

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[8] Sakariassen PO, et al. Neoplasia (9) 2007
[9] Kielian et al. Journal of Neuro-Oncology (56) 2002
[10] Internal FDA database of approved/non-approved drugs that tracks results of 2 year rodent carcinogenicity studies.
[11] Merzak et al. Brain Res Mol Brain Res (41) 1996

Table 13: Brain partitioning of lorcaserin in rats and monkeys			
Species	Day of sampling	Brain to Plasma ratio (based on AUC)	
		Range	Average
Rats[1]	Day 1	13x - 35x	26x
	Day 14	24x - 35x	29x
Monkeys[2]	Day 1	10x - 23x	15x
	Day 14	8x - 12x	10x
Humans	--	Unknown	

[1]Data source studies PDR-08218, 080097, & 08014
[2]Data source study ARN-20080419

If one accepts that brain-to-plasma partitioning of lorcaserin in humans would be more like monkeys, then the estimated safety margin to a non-tumorigenic dose may range from 11x to 17x, with tumors associated with brain exposures that are 40x to 59x higher than clinical exposure (Table 14). While these margins may appear reassuring, they are based on assumptions, not data, of brain partitioning in human subjects. Therefore, actual margins may be higher or lower than those presented here.

Given the absence of brain-to-plasma partitioning data in human subjects, the most conservative approach is to disregard estimated brain levels and rather calculate safety margins based on plasma drug levels, which is known for rats and humans. The safety margin to the non-tumorigenic dose would then be 5x, with brain tumors occurring at doses of lorcaserin 17x higher than clinical exposure.

Table 14: Estimated Safety Margins to Astrocytomas, based on estimated brain exposure to lorcaserin			
Estimated Brain Exposure in Male Rats, ug*h/ml		Multiple to Estimated Brain Exposure in Humans at Clinical Dose (10mg bid)	
10mg/kg (No brain tumors)	30mg/kg (brain tumors)	10mg/kg (No brain tumors)	30mg/kg (brain tumors)
115 - 168	405 - 591	11x - 17x	40x - 59x

Estimated brain exposure in rats assumes 24x - 35x brain:plasma partitioning
Estimated brain exposure in humans assumes 10x brain:plasma partitioning.

Skin fibroma, Squamous cell carcinoma, Malignant schwannomas
Lorcaserin increased the incidence of benign subcutis fibroma, squamous carcinoma of the skin, and malignant schwannoma in male rats at the mid- and high doses (Table 15). Arguably, the numerical increase in benign fibroma at the low dose is also drug-related. These tumors were not observed in female rats. No studies were conducted to address the mechanism by which lorcaserin increases these tumors. Therefore, risk assessment is again based on the difference in exposure between rats and the clinical dose in humans. Exposure at the non-tumorigenic low dose provides a safety margin of 5x, with lorcaserin increasing the incidence of these tumors at a dose 17x higher than the clinical dose.

Table 15: Incidence of neoplasms of the skin, subcutis, and nerve sheath in 2 year rat study

Tumors in male rats		Lorcaserin dose, mg/kg/day			
		Control	10	30	100
Skin, subcutis	benign fibroma	3 (4.6%)	7 (11%) NS	11 (17%) SS	17 (22%) SS
Skin	squamous carcinoma, primary	0	0	4 (6%) NS	5 (6.6%) SS
Nerve Sheath	Malignant schwannoma, all sites	0	0	2 (3%) NS	9 (10%) SS

Historical Range from study site:
Subcutis fibroma: 0-5%
Squamous carcinoma: 0-1.7%
Schwannoma: 0-3.3% (subcutis)

Liver and Thyroid Tumors
Lorcaserin increased the incidence of hepatocellular adenoma and carcinoma and thyroid follicular cell adenoma in male rats with statistical significance being reached at the high dose, or approximately 55x higher than the clinical dose. There was no increase in hepatic or thyroid tumors in females, although pre-neoplastic findings of basophilic foci of cellular alteration were reported. The highest non-tumorigenic dose provides a safety margin of 17x higher than the clinical dose.

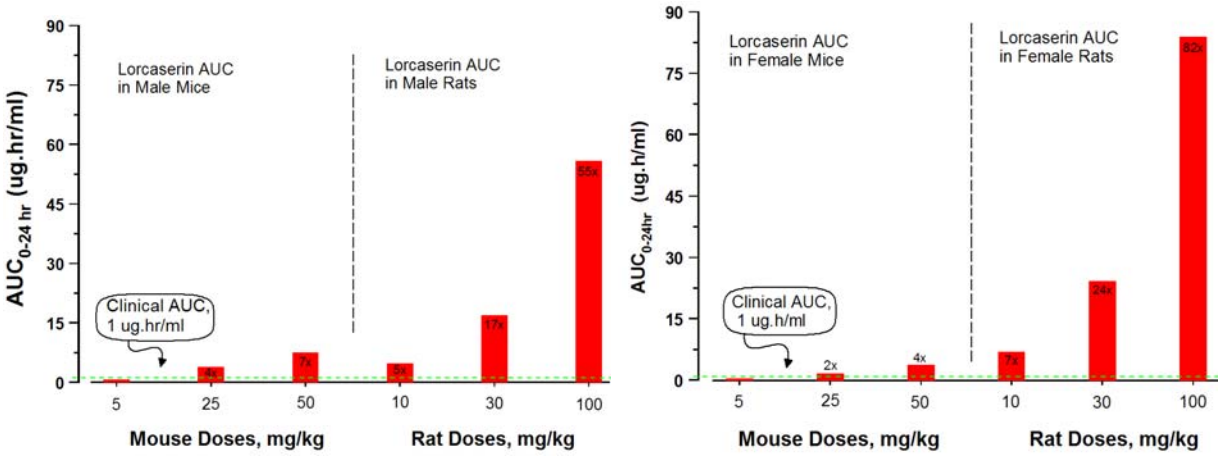
Sufficient evidence suggests that lorcaserin increased liver tumors by a known mechanism in rodents involving chronic induction of liver drug-metabolizing enzymes. Lorcaserin induced UGT and cytochrome p450 enzymes and resulted in a greater degree of hepatocellular hypertrophy in males than in females. Also, overall drug levels were lower in male than in female rats, a likely consequence of higher induction of drug-metabolizing enzymes in males. Thyroid follicular cell tumors often accompany hepatic tumors that arise from induction of drug-metabolizing enzymes, a likely consequence of increased triiodothyronine turnover by the liver with secondary chronic thyroid follicular cell stimulation. Induction of drug-metabolizing enzymes in the liver of human subjects is not known to lead to hepatic carcinogenesis, as typified by clinical experience with phenobarbital.

With a reasonable safety margin to non-tumorigenic exposure and, more significantly, a recognized mechanism of tumorigenesis, the potential risk of hepatic and thyroid tumors to humans is considered minimal.

Difference in Tumor Response of Mice and Rats

Lorcaserin increased multiple tumor types in rats but not in mice. However, this is not interpreted as evidence of a 'single species' tumor response but rather a reflection of the large difference in drug exposure achieved in the two species. As shown in Figure 8, drug exposure at the highest dose in mice is similar to that achieved with the lowest dose in rats (4x to 7x the clinical dose). Thus, the lack of a tumor response in mice more reasonably reflects insufficient drug exposure rather than a species-specific difference in tumor susceptibility. Pre-neoplastic or neoplastic lesions were also not reported in monkeys up to 12 months of lorcaserin exposure; however, the absence of evidence of preneoplasia in a short term study is not evidence of absence of risk from chronic or lifetime exposure.

Figure 8: Comparison of lorcaserin exposure in mice and rats from the 2 year carcinogenicity studies (*left panel*, males; *right panel*, females)



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

Clinical Briefing Document
Endocrine and Metabolic Drugs Advisory Committee Meeting
September 16, 2010

New Drug Application 22529
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 5HT2C receptor agonist for obesity treatment. The 5HT2C receptor is concentrated in the central nervous system (CNS) where it regulates feeding behavior. The endogenous ligand is serotonin.

Lorcaserin has been developed by Arena Pharmaceuticals ("the sponsor") with 2 pivotal placebo-controlled safety and efficacy trials that evaluated > 7000 patients with body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with at least 1 weight-related co-morbidity (hypertension, dyslipidemia, glucose intolerance, cardiovascular disease, and/or sleep apnea). The first trial, BLOOM, was a 104-week trial that evaluated lorcaserin 10 mg twice daily (BID) versus placebo. In the second year of BLOOM, the lorcaserin-treated patients were re-randomized 2:1 to lorcaserin or placebo. The second trial, BLOSSOM, was a 1-year trial that evaluated 2 lorcaserin doses, 10 mg once daily (QD) and 10 mg BID versus placebo.

The proposed lorcaserin dose for marketing is 10 mg BID.

1.1 Efficacy Summary

In the first year of the 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 5.8 ± 0.16 kg body weight as compared to 2.2 ± 0.14 kg in the placebo group ($p < 0.001$)
- 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 ($p < 0.001$)

In the 1-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 5.76 ± 0.17 kg, 4.72 ± 0.240, and 2.86 ± 0.154 kg body weight, respectively ($p<0.001$ for lorcaserin 10 mg BID vs. placebo; $p<0.001$ 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)

In the second year of the 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

The 1-year pooled data from BLOOM and BLOSSOM demonstrated that the placebo-subtracted mean body weight change in the lorcaserin 10 mg BID treatment group was -3.25 kg. The summary of the 5 and 10 percent weight loss categorical pooled analyses are shown in the table below.

Table 1. Categorical Weight Loss, Pooled Phase 3 Trials

	LOCF		**Completers**		**Returning Drop-Outs**	
	≥ 5% wt loss	**≥ 10% wt loss**	**≥ 5% wt loss**	**≥ 10% wt loss**	**≥ 5% wt loss**	**≥ 10% wt loss**
Lorc 10 BID	47% (1460/3098)	22% (695/3098)	64% (1135/1775)	35% (616/1775)	59% (1197/2043)	31% (638/2043)
Pbo	23% (687/3038)	9% (264/3038)	33% (512/1529)	15% (224/1529)	32% (584/1839)	13% (248/1839)
Difference	25%	14%	30%	20%	27%	18%

Lorc=lorcaserin, Pbo=placebo, LOCF=last observation carried forward, wt=weight

Source: NDA 22529, ISE Tables 11 and 15

Modest improvements in metabolic- and cardiovascular-related secondary efficacy endpoints were seen in the lorcaserin 10 mg BID group as compared to placebo. These changes generally appeared commensurate with the degree of weight loss, although in some weight loss responder subgroup analyses changes in the lorcaserin-treated group appeared less favorable than those in the placebo-treated group.

1.2 Safety Summary

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 (e.g., carcinogenicity).

- Valvular Heart Disease: Fenfluramine and dexfenfluramine are thought to cause valvular heart disease (VHD) via activation of the 5HT2B receptor. Lorcaserin activates the 5HT2C receptor with 45- to 90-fold selectivity over the 5HT2B receptor in *in vitro* assays. Using echocardiographic assessments, the clinical development program was designed to rule out a 50% or greater increase in the relative risk (RR) for FDA-defined VHD (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation). The RR in patients from the pooled Phase 3 trials without baseline FDA-defined VHD at Week 52 was 1.07 (95% C.I.: 0.74, 1.55). No

lorcaserin-treated patient developed severe aortic or mitral regurgitation or required heart valve surgery or replacement during the trials.

- Pulmonary Hypertension: Anorexigenic drugs that act on the serotonergic system have been associated with the development of primary pulmonary hypertension (PPH). The rarity of this condition makes it unlikely that drug-related PPH could be identified in a clinical trial setting. Furthermore, because the pathophysiology of PPH with anorexigenic drugs is somewhat undefined (most authors consider it likely that increase of serotonin release via the serotonin transporter is involved, although activation of 5HT1B, 5HT2A, and 5HT2B receptors have been implicated as well), the absolute risk to patients treated with lorcaserin is unclear. Patients were screened in the lorcaserin program for PPH with measurement of pulmonary systolic pressure (PASP) by echocardiogram. Two patients in the trial were found to have new-onset PASP values > 50 mmHg, both treated with lorcaserin 10 mg BID. One patient was diagnosed with potential confounders of sleep apnea and possible pulmonary disease and the other reportedly did not have the elevated PASP confirmed by a cardiologist external to the trial.

- Psychosis and other Dissociative-Related Adverse 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, primarily at supratherapeutic doses in normal-weight individuals in the early phase trials. In the Phase 3 program, 6 patients (0.2%) treated with lorcaserin 10 mg BID developed euphoria, as compared with 1 patient (<0.1%) treated with placebo.

- Depression and Suicidality: Although the proportion of patients in the Phase 3 trials with adverse events specific for depression (such as preferred terms of depression or depressed mood) 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. There were 2 suicide attempts in the development program: 1 patient randomized to lorcaserin and 1 patient re-randomized in Year 2 from lorcaserin to placebo. Formal suicidality assessment was limited to a single question on the depression inventory (Beck Depression Inventory-II, BDI-II). No firm conclusions regarding depression or suicidality could be drawn from the BDI-II results.

- 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 effects (AEs) were primarily identified from the Phase 3 database, in which AEs such as impairments in attention and memory were seen 3 times as frequently in the lorcaserin 10 mg BID treated group as compared to placebo.

- Malignancies: Lorcaserin was associated with the development of multiple tumor types in a carcinogenicity study in rats. A neoplastic risk determination from the clinical data cannot be assessed, given the limited number of cancer diagnoses and the

relatively short study durations. A potential association between prolactin and mammary carcinogenesis in the rat was suggested by the sponsor. Prolactin concentrations were therefore evaluated in a subset of patients from a Phase 3 trial. Prolactin concentrations appear to be acutely increased after lorcaserin administration; however, from the data available lorcaserin does not appear to be associated with large or chronic increases over time.

2 5HT2 Agonists for Obesity

The 5-hydroxytryptamine 2 (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, and differences in receptor affinity and activity may predict a particular drug's desired action as well as its toxicity.

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 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]

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[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.

[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.

Fenfluramine and dexfenfluramine, nonspecific 5HT2 agonists, were FDA-approved for the treatment of obesity in 1973 and 1996, respectively. The drugs' association with 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]

Lorcaserin hydrochloride is a 5HT2C receptor agonist that has been developed for the treatment of obesity. Lorcaserin is formulated as a 10 mg tablet and is recommended for twice a day administration.

3 General Discussion of Endpoint

As described in the FDA draft guidance for developing weight management drugs,[10] weight change has historically been the endpoint of interest in clinical trials for the development of obesity drugs. Weight is an easily measured surrogate for body adiposity and long-term weight loss of 5 percent or more is associated with improvements in cardiovascular risk factors.[11]

There are currently 2 obesity medications approved for long-term use in the United States: sibutramine and orlistat. The weight loss efficacy of 2 other obesity medications have been recently described at a recent Endocrinology and Metabolism Drug Advisory Committee (EMDAC) meeting (Qnexa, 15 July 2010) and in the literature (naltrexone/bupropion).[12] Table 2 presents the weight changes in active drug and placebo groups from various Phase 3 trials that are available for comparison.

---

[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.
[10] FDA Draft Guidance for Industry: Developing Products for Weight Management. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf Accessed 27 July 2010.
[11] Van Gaal LF, et al. The beneficial effects of modest weight loss on cardiovascular risk factors. Int J Obes Relat Metab Disord 1997 Mar; 21 Suppl 1: S5-9.
[12] Greenway FL, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. www.thelancet.com Published online 30 July 2010.

Table 2. Mean Weight Change at One Year for Various Obesity Drugs Studied for Long-Term Use

	Active	Placebo	Data Source
Orlistat 120 mg TID	-6.1 kg	-2.6 kg	Xenical prescribing information
Sibutramine 15 mg QD	-6.4 kg	-1.6 kg	Meridia prescribing information
Qnexa (phentermine/topiramate) 15/92 mg QD	-10.6 kg	-1.7 kg	NDA 22580, FDA Briefing Package, EMDAC meeting, 15 July 2010
NB32 (naltrexone 32 mg/bupropion 360 mg) QD	-6.1 kg	-1.4 kg	Reference 12
Lorcaserin 10 mg BID	-5.8 kg	-2.5 kg	NDA 22529, ISE Table 13

4 Pharmacology of Lorcaserin

Please see Dr. Todd Bourcier's review for a full discussion of lorcaserin pharmacology. Lorcaserin is a selective 5HT2C receptor agonist with *in vitro* assays demonstrating 8- to 15-fold selectivity over the 5HT2A receptor and 45- to 90-fold selectivity over the 5HT2B receptor (Table 3). Lorcaserin is considered a full agonist at the 2C and 2B receptors, and a partial agonist at the 2A receptor.

Table 3. Lorcaserin Potency at Recombinant Human 5HT2 Receptors Measured in Inositol Phosphate Accumulation Assays

Receptor	Assay 1 EC_{50}, nM (95% CI, nM)	Assay 2 EC_{50}, nM (95% CI, nM)
5HT2A	133 (113, 157)	14 (7, 30)
5HT2B	811 (678, 969)	82 (62, 110)
5HT2C	9 (8, 10)	1.85 (1, 3)
CI=confidence interval		

Source: NDA 22529, DBR-090-004 Tables 9 and 14

Lorcaserin and its enantiomer stimulate serotonin, dopamine, and norepinephrine release via transporters only at high concentrations and weakly stimulate neurotransmitter uptake.

5 Pharmacokinetics and Pharmacodynamics of Lorcaserin

5.1 Pharmacokinetics

5.1.1 Absorption, Distribution, Metabolism, and Elimination

Lorcaserin reaches peak concentrations approximately 2 hours following a dose, and its half-life is approximately 11 hours (see Table 4). After BID dosing, steady state occurs within 3 days and drug accumulation is approximately 70%. Lorcaserin exposure is unaffected by a high fat meal as compared to the fasting state; time to reach maximum plasma concentration (T_{max}) is delayed approximately 1 hour in the fed state.

Preclinical studies of cynomolgus monkeys and rats demonstrated that lorcaserin is concentrated in the brain relative to plasma, with steady state brain to plasma ratio of 10

in the monkey and 24-35 in the rat. Lorcaserin is bound approximately 70% to human plasma proteins.

Lorcaserin is extensively metabolized in the liver by multiple enzymatic pathways. The majority of a single radioactively labeled dose of lorcaserin was recovered in urine (92.3%) and feces (2.2%). The major circulating metabolite is the sulfamate of lorcaserin (M1); the major urinary metabolite is the *N*-carbamoyl glucuronide (M5). Neither M1 nor M5 was shown to have significant binding activity at a panel of receptors, transporters and ion channels. All circulating lorcaserin metabolites identified in humans are also present in at least 1 toxicology species.

Table 4. Lorcaserin and Lorcaserin Sulfamate (M1) Plasma Pharmacokinetic Parameters after Administration of a Single-Dose (10 mg) of Lorcaserin to Healthy Subjects, Mean (SD)

Pharmacokinetic Parameters	**Lorcaserin**	**M1**
C_{max} (ng/mL)	46.0 (12.8)	45.1 (13.2)
T_{max} (h)	2.34 (0.98)	3.34 (0.82)
AUC_{0-t} (ng·h/mL)	680 (191)	2500 (1200)
AUC_{0-inf} (ng·h/mL)	692 (192)	2600 (1280)
$t_{1/2}$ (h)	11.1 (1.9)	41.3 (10.0)
C_{max}=maximum plasma concentration; T_{max}=time to reach maximum plasma concentration; AUC=area under the plasma concentration-time profile; $t_{1/2}$=plasma half-life		

Source: NDA 22529, Summary of Clinical Pharmacology Studies Table 26

Lorcaserin plasma concentrations were measured in a subgroup of patients in the two Phase 3 trials. Population pharmacokinetic (PK) modeling indicated that sex, race, and BMI did not affect lorcaserin exposure. Baseline body weight was a significant covariate on both apparent clearance and apparent volume of distribution of lorcaserin. Patients in the highest body weight quartile had 27% lower mean exposures than the patients in the lower body weight quartiles. In addition, patients in the higher body weight quartiles tended to lose less weight than patients in the lower body weight quartiles. Patients assigned to lorcaserin in the lowest body weight quartiles tended to report dizziness and nausea more often than did those with higher baseline body weight (see section 8).

5.1.2 Specific Populations

The PK properties of lorcaserin were evaluated in individuals with mild (N=8, creatinine clearance 51-80 mL/min), moderate (N=8, creatinine clearance 31-50 mL/min), severe (n=8, creatinine clearance 5-30 mL/min), or end-stage (N=8, requiring hemodialysis) renal disease. Creatinine clearance was calculated by Cockgroft-Gault equation based on ideal body weight (IBW). AUC and C_{max} of lorcaserin were not meaningfully affected by renal function. Lorcaserin sulfamate (M1) increased approximately 1.7-fold and *N*-carbamoyl-lorcaserin (M5) increased approximately 2.8-fold in patients with moderate renal impairment. Metabolites M1 and M5 increased by approximately 4-fold and 6-fold, respectively, in patients with severe renal impairment and increased 3-fold and 26-fold, respectively, in patients with end-stage renal disease. Lorcaserin and M1 were not removed from the circulation by hemodialysis, and M5 was only modestly extracted

(18%). Based on the exposure changes of M1 and M5 in moderate and severe renal impairment and end-stage renal disease the sponsor is proposing that lorcaserin should be used with caution in patients with moderate renal impairment and should not be used in patients with severe renal impairment or end-stage renal disease.

In patients with mild or moderate hepatic impairment, AUC and C_{max} were not meaningfully affected. Lorcaserin C_{max} was 7.8% (mild hepatic impairment) and 14.3% (moderate hepatic impairment) lower than in healthy matched controls. Mean AUC values were 24% and 30% higher, respectively, than in the healthy controls. Plasma half-life was increased from 12 hours in healthy controls to 17 hours and 19 hours in patients with mild or moderate hepatic impairment, respectively. The sponsor is not recommending a dose adjustment for patients with mild or moderate hepatic impairment. The sponsor did not evaluate the effect of severe hepatic impairment on lorcaserin PK.

An open-label single-dose study was conducted to compare the PK parameters of lorcaserin in obese or overweight elderly patients (> 65 years) to those obtained from obese or overweight adults (18-65 years). The lorcaserin AUC of the elderly group was found to be equivalent to that of the adult group and C_{max} was 17% lower in elderly patients.

5.1.3 Drug-Drug Interactions

Because preclinical assays predicted that significant PK interactions between lorcaserin and other drugs would be observed with agents metabolized by CYP2D6, the sponsor only conducted formal drug-drug interaction (DDI) clinical studies that evaluated potential CYP2D6 inhibition. The APD356-012 study indicated that lorcaserin is a mild to moderate inhibitor of CYP2D6, as indicated by a ~2-fold increase in dextromethorphan exposure in patients dosed concurrently with the proposed clinical dose of lorcaserin.

Of note, 631 patients took dextromethorphan concurrently with lorcaserin during Phase 3 trials. A single instance of a potential interaction characterized by vertigo, nausea, vomiting, diarrhea, and elevated blood pressure was reported as serotonin syndrome (see section 8.4.6).

Reviewer comment: Our clinical pharmacology colleagues note that in vitro *studies indicate that there is an interaction potential with CYP2C9 substrates for patients exhibiting high steady state concentrations of the major circulating metabolite of lorcaserin (lorcaserin sulfamate). There are a variety of drugs metabolized by CYP2C9 likely to be coadministered in this patient population, i.e., sulfonylureas, thiazolidinediones, rosuvastatin, and narrow therapeutic index drugs such as warfarin. The sponsor did not evaluate this interaction potential in an* in vivo *study.*

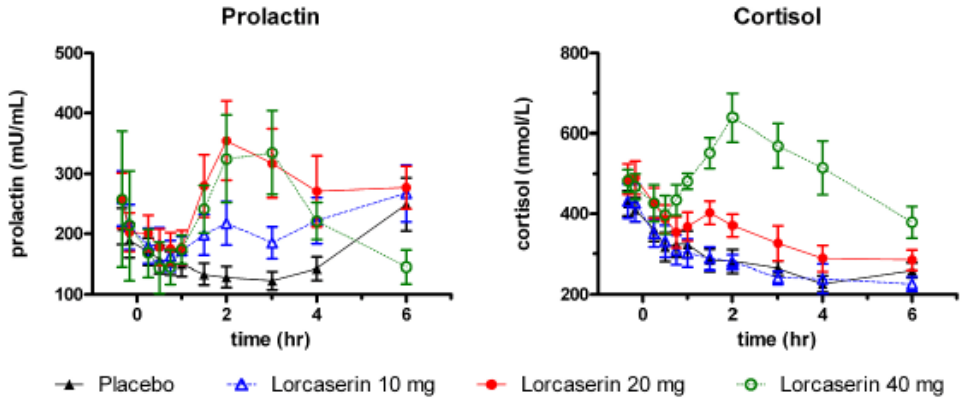
5.2 Pharmacodynamics

The intended pharmacological effect of lorcaserin is decreased food intake due to activation of 5HT2C receptors in the central nervous system. In the single-dose Phase 1 study APD356-001a in which single doses of lorcaserin 10 mg, 20 mg, and 40 mg were

administered, hunger scores from a Hunger/Appetite Visual Analog Scale only significantly decreased after administration of the 40 mg dose.

There is evidence that activation of serotonin receptors, including 5HT2C, promote the secretion of prolactin and cortisol due to pituitary stimulation in rodents and humans.[13] Plasma and cortisol concentrations can therefore be measured in order to establish the CNS activity of the drug. Plasma prolactin and cortisol concentrations were measured at several time points following single doses of lorcaserin (10 mg, 20 mg, and 40 mg) in the Phase 1 study APD356-001a. Both prolactin and cortisol were significantly increased as compared to placebo following lorcaserin doses of 20 mg or 40 mg, but not lorcaserin 10 mg (Figure 1).

Figure 1. Effect of a Single Dose of Lorcaserin on Prolactin and Cortisol in Healthy Subjects



Normal ranges: Prolactin 414 mIU/mL men, 523 mIU/mL women; cortisol 681nmol/L men and women

Source: NDA 22529, ISS Figure 28

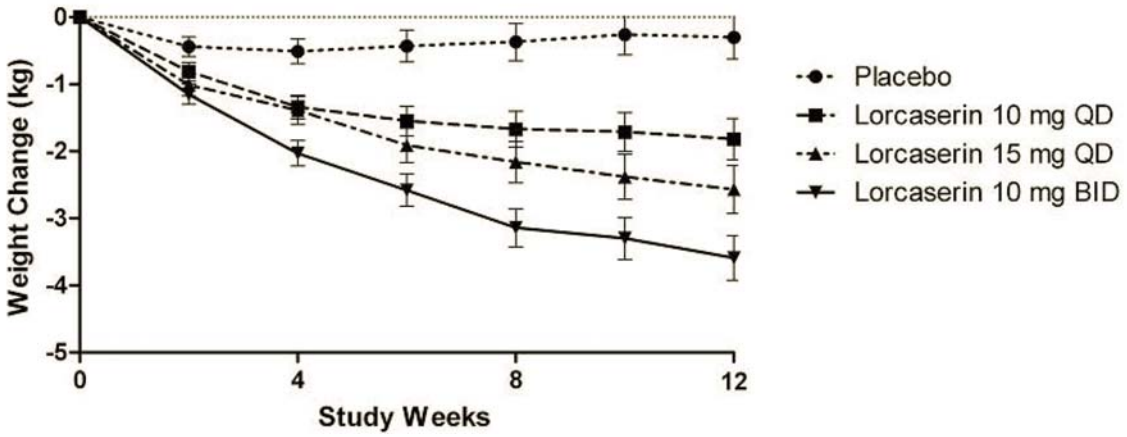
Chronic lorcaserin dosing on prolactin concentrations and its potential human relevance is addressed in section 8.4.5.1.

Reviewer comment: Although cortisol increases with lorcaserin were only seen at higher than therapeutic single doses, it is unknown how chronic lorcaserin dosing would impact cortisol concentrations or the regulation of the hypothalamic-pituitary-adrenal axis.

The sponsor conducted two Phase 2 dose-finding trials, APD356-003 and APD356-004 with a total duration of 28 days and 3 months, respectively. APD356-003 assessed doses of 1 mg, 5 mg, and 15 mg given once daily, and placebo. APD356-004 evaluated doses of 10 mg and 15 mg given once daily, 10 mg given twice daily, and placebo. APD356-004 demonstrated that the 10 mg dose given twice daily resulted in the highest weight loss compared to placebo over a period of 3 months (Figure 2).

[13] Meltzer HY and Maes M. Pindolol pretreatment blocks stimulation by meta-chlorophenylpiperzine of prolactin but not cortisol secretion in normal men. Psych Res 1995; 58: 89-98.

Figure 2. Change in Body Weight from Baseline to Week 12 in APD356-004, Completer Analysis



Source: NDA 22529, Summary of Clinical Efficacy Figure 3

6 Lorcaserin Clinical Program

6.1 Background

The lorcaserin program was designed to conform to the February 2007 FDA draft guidance for developing weight management drugs.[10] 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 1 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%.

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 8.4.3.2.

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 (see Appendix D for details).

The division was alerted to cancer signals in animal carcinogenicity studies during development. This issue is addressed in depth by Dr. Fred Alavi, and clinical findings are presented in section 8.4.5. 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. These results are presented in section 8.4.5.1.

It should also be noted that the Phase 3 program did not include patients who have diabetes mellitus. BLOOM-DM is the third Phase 3 trial in the lorcaserin program, and is evaluating the safety and efficacy of lorcaserin in patients with type 2 diabetes. However, because of difficulties with enrollment, the division agreed that the NDA could be submitted prior to the completion of this trial. If lorcaserin is approved prior to the completion of BLOOM-DM, the sponsor was informed that labeling will need to convey that the safety and efficacy of lorcaserin has not been established in patients with diabetes until these data are available.

6.2 Patient Population

A total of 4919 individuals were exposed to at least 1 dose of lorcaserin: 421 individuals were exposed to lorcaserin at doses ranging from 0.1 mg to 60 mg during the Phase 1 clinical development program, and 4613 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, 2135 patients were exposed > 180 days and 1589 patients were exposed > 360 days. In the lorcaserin 10 mg QD treatment group, 560 patients were exposed > 180 days and 400 patients were exposed > 360 days. A total of 426 patients completed 2 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 5. 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
Phase 3								
BLOOM	Obese/overweight with co-morbidities	1587					1595	52
BLOSSOM	Obese/overweight with co-morbidities	1603			802		1603	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 22529, ISS Table 4 and APD356-011 CSR Table 14.1.1

6.3 Phase 1 and 2 Program

6.3.1 Single Dose – Healthy Subjects

Seven single dose studies were performed in healthy subjects. A total of 132 subjects were exposed to lorcaserin (0.1 mg [n=20], 1 mg [n=20], 10 mg [n=114], 20 mg [n=12], and 40 mg [n=6]) and 35 subjects received placebo across these studies. Twenty of the 132 subjects exposed to lorcaserin received lorcaserin at three different dose levels (0.1 mg, 1 mg, and 10 mg).

- APD356-001A was a double-blind, placebo-controlled, randomized, dose-escalation study to define the maximum tolerated dose of lorcaserin following single oral administration.
- APD356-001B was an open-label, two period, crossover study to evaluate the safety and PK profile of a single oral dose of 10 mg lorcaserin administered to healthy male (n=6) and female (n=6) subjects under fasted (Period 1) and fed (Period 2) conditions.
- APD356-001C was a double-blind, placebo-controlled, randomized, four period, cross-over study to evaluate the pharmacodynamic effects of lorcaserin on food intake and subjective measures of satiety in 20 healthy male subjects.
- APD356-005 was an open-label, randomized, 2-way crossover, 2-sequence, comparative bioavailability design under fasting conditions to assess the single-dose relative bioavailability of lorcaserin 10 mg tablets compared to the lorcaserin 10 mg hard gelatin capsules.
- APD356-006 was an open-label study to assess the mass balance of lorcaserin following a single 10 mg oral dose of lorcaserin containing 100 μCi 14C-lorcaserin in healthy male subjects.
- APD356-015 was an open-label, single-dose, crossover study to evaluate the PK properties of a single 10 mg oral dose of lorcaserin in the fed versus fasted state.

- APD356-018 was an open-label, single dose, parallel-group study to compare the PK parameters of lorcaserin 10 mg in obese or overweight elderly (> 65 years) to those obtained from obese or overweight adults (18-65 years).

6.3.2 Single Dose – Specific Populations

- APD356-013 was a randomized, double-blind, double-dummy, placebo- and active-controlled, 7-way crossover study to evaluate the abuse potential of single doses of lorcaserin (20 mg, 40 mg, and 60 mg) compared to placebo, zolpidem, and ketamine in healthy male and female recreational polydrug users.
- APD356-016 was a multicenter, open-label, single-dose, parallel group study of adult men and women designed to evaluate the PK properties of lorcaserin in subjects with mild, moderate, severe, or end-stage (requiring hemodialysis) renal disease as compared to subjects with normal function.
- APD356-017 was a multi-site, open-label, parallel-group study designed to evaluate the PK properties of lorcaserin in subjects with mild or moderate hepatic impairment as compared to subjects with normal hepatic function.

6.3.3 Multiple Dose – Healthy Subjects

- APD356-002 was a double-blind, placebo-controlled, randomized, dose-escalation study to define the maximum tolerated dose following multiple oral doses. Twenty-seven healthy male and female subjects were enrolled into the study and randomized into one of three dose levels of lorcaserin (3 mg, 10 mg, or 20 mg). Nine subjects were randomized into each dose level and received lorcaserin (6 subjects) or placebo (3 subjects) once a day for 14 days.
- APD356-007 was a double-blind, randomized, parallel design study in healthy male and female subjects to determine whether lorcaserin had any effect on ECG parameters. Two hundred forty-four subjects were randomized to 1 of 4 treatment groups: placebo, moxifloxacin 400 mg Day 7 (positive control) and placebo on Days 1-6, lorcaserin 15 mg, or lorcaserin 40 mg. Study drug was administered for 7 days.

6.3.4 Drug-Drug Interaction – Healthy Subjects

- APD356-008 was an open-label, single- and multiple-dose, 1-sequence DDI study evaluating the impact of 4 days of lorcaserin 20 mg QD on dextromethorphan 30 mg. Twenty-four healthy female and male subjects were enrolled and received at least 1 dose of study drug. Eleven subjects completed the study and were included in the PK analyses.
- APD356-012 was an open-label, single- and multiple-dose, 1-sequence DDI study evaluating the impact of 4 days of lorcaserin 10 mg BID on long-acting dextromethorphan 60 mg. Twenty-four healthy female and male subjects were enrolled and received at least 1 dose of study drug. Twenty-three subjects completed the study and were included in the PK analyses.

6.3.5 Phase 2

- APD356-003 was a double-blind, placebo-controlled, randomized, parallel group study to assess the effects of lorcaserin on body weight after 4 weeks of study drug

administration to obese male and female patients. A total of 352 patients were randomized to 1 of 4 treatment groups (placebo or lorcaserin 1 mg, 5 mg, or 15 mg).

- APD356-004 was a double-blind, placebo-controlled, randomized, parallel-group study to assess the effect of lorcaserin on body weight after 12 weeks of administration to obese patients. A total of 469 patients were randomized to 1 of 4 treatment groups (placebo or lorcaserin 10 mg QD, 15 mg QD, or 10 mg BID).

6.4 Phase 3 – Summary of Study Designs

The lorcaserin development program included 2 pivotal Phase 3 trials, with similar patient populations and endpoints. Inclusion and exclusion criteria for the two trials are included in Appendix A. Details of study designs are in Appendix B.

- Study APD356-009 (Behavioral modification and Lorcaserin for Overweight and Obesity Management; BLOOM) was a placebo-controlled 2-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 1 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. The primary endpoints were: 1) to assess the weight loss effect of lorcaserin at the end of the first year of treatment (Week 52), and 2) to assess the ability of lorcaserin to maintain body weight loss achieved during Year 1, as assessed at the end of Year 2 (Week 104). Secondary endpoints included: changes in heart valve regurgitation and pulmonary artery pressure, additional weight loss in the second year of treatment, changes in cardiovascular risk factors (e.g., dyslipidemia, insulin sensitivity, hypertension, and central fat distribution), changes in mood as assessed by the BDI-II, and population PK.

- Study APD356-011 (Behavioral modification and Lorcaserin Second Study for Obesity Management; BLOSSOM) was a placebo-controlled 1-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. The primary endpoint was to assess the weight loss effect of lorcaserin after 1 year of treatment. Secondary endpoints included: changes in heart valve regurgitation and pulmonary artery pressure, changes in cardiovascular risk factors (e.g., dyslipidemia, insulin sensitivity, hypertension, and central fat distribution), changes in mood as assessed by the BDI-II, and population PK. A substudy evaluating prolactin concentrations was also conducted.

6.5 Phase 3 – Demographics and Baseline Information

The following table enumerates the demographics and baseline weight and comorbidity data for the pooled Phase 3 patient population. Treatment groups were generally well-matched. The majority of the patients were white (66-67%) and female (81-82%). Mean BMI was 36 kg/m^2 and mean weight was 100 kg. A total of 40-44% of patients was

diagnosed with a weight-related comorbidity; the majority of diagnosed comorbidities were hypertension and dyslipidemia.

Table 6. Patient Demographics and Baseline Characteristics, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
Age, years mean +/- SD	43.8 +/- 11.6	43.8 +/- 11.7	44.0 +/- 11.4
Sex, % female	81.7	81.9	81.0
Race White, % Black, % Hispanic, %	 67.7 18.9 11.1	 67.2 20.0 10.7	 66.2 19.4 12.4
BMI, kg/m² mean +/- SD	36.1 +/- 4.3	35.8 +/- 4.3	36.1 +/- 4.2
Weight, kg mean +/- SD	100.4 +/- 15.7	99.8 +/- 16.6	100.2 +/- 15.9
Any Comorbidity, % *	44.3	40.1	43.7
Hypertension, %	22.6	21.8	22.7
Dyslipidemia, %	30.9	27.2	30.2
CVD, %	0.6	0.5	0.9
Glucose intolerance, %	1.5	1.9	1.0
Sleep apnea, %	4.5	3.4	4.0
* Denominators used for comorbidity percentages were numbers of patients randomized CVD=cardiovascular disease			

Source: NDA 22529, ISE Table 3 and Reviewer created from datasets

The following table describes demographics and baseline comorbidities by trial; the following variables are similar and generally support data pooling for safety (see section 8):

Table 7. Patient Demographics and Baseline Comorbidities by Trial

	BLOOM N=3177	**BLOSSOM N=4004**
Age, years mean +/- SD	44.1 +/- 11.2	43.8 +/- 11.8
Sex, % female	83.5	79.8
Race White, % Black, % Hispanic, %	 66.9 18.8 12.4	 67.0 19.6 11.0
Any Comorbidity, %	45.5	42.0
Hypertension, %	21.3	23.6
Dyslipidemia, %	33.3	27.7
CVD, %	0.3	1.1
Glucose intolerance, %	1.0	1.5
Sleep apnea, %	4.0	4.3

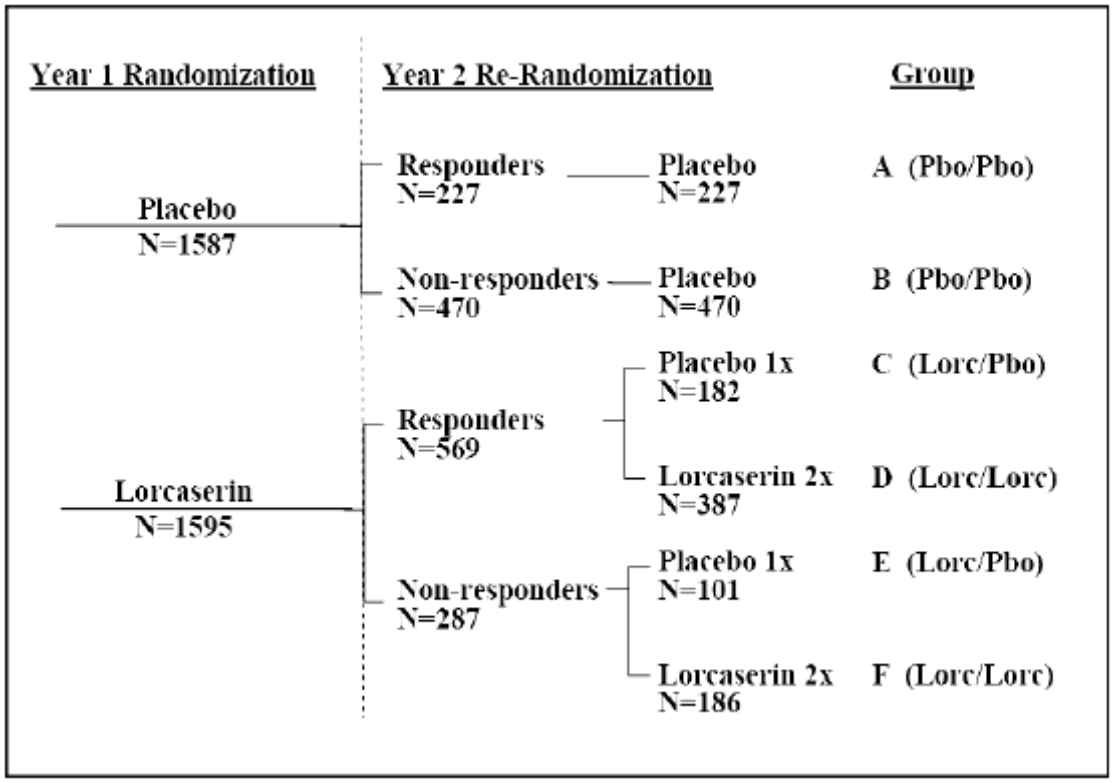
Source: NDA 22529, APD356-009 CSR Tables 14.1.6 and 14.1.7, APD356-011 CSR Tables 14.1.4 and 14.1.5

6.6 Phase 3 – Patient Disposition

6.6.1 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.

Figure 3. Patient Disposition, BLOOM Trial



Source: NDA 22529, APD356-009 CSR Figure 1

6.6.2 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.

6.6.3 Early Terminations

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 (includes pregnancy, study site closure, and errors). The following table describes the reasons for discontinuation in the Phase 3 trials:

Table 8. Reasons for Discontinuation, Phase 3 Trials

	BLOOM		BLOSSOM		
	Lorc 10 BID N=1595	**Pbo N=1587**	**Lorc 10 BID N=1603**	**Lorc 10 QD N=802**	**Pbo N=1603**
Withdrawn early during Year 1	712 (44.6)	871 (54.9)	686 (42.8)	329 (41.0)	769 (48.0)
Patient Decision	307 (19.2)	439 (27.7)	293 (18.3)	162 (20.2)	376 (23.5)
Lack of Efficacy	27 (1.7)	88 (5.5)	39 (2.4)	25 (3.1)	62 (3.9)
Other	280 (17.6)	351 (22.1)	254 (15.8)	137 (17.1)	314 (19.6)
Adverse Event	113 (7.1)	106 (6.7)	115 (7.2)	50 (6.2)	74 (4.6)
Lost to Follow-Up	191 (12.0)	226 (14.2)	198 (12.4)	83 (10.3)	234 (14.6)
Non-compliance	47 (2.9)	44 (2.8)	59 (3.7)	20 (2.5)	49 (3.1)
Investigator Decision	9 (0.6)	6 (0.4)	11 (0.7)	4 (0.5)	6 (0.4)
Sponsor Decision	25 (1.6)	26 (1.6)	9 (0.6)	10 (1.2)	30 (1.9)
Other	20 (1.3)	24 (1.5)	1 (0.1)	0	0

Source: NDA 22529, ISE Table 4

A significant proportion of patients were discontinued under the 'other' category under 'patient decision' category in both studies. After review, a large proportion of the discontinuations in this category appear to be due to scheduling conflicts and family or personal reasons. Some patients cited that they were discontinuing the study to pursue bariatric surgery. In many instances, reasons were not provided, and would have been considered loss-to-follow-up, except that the certified letter that was sent after attempting to contact the patients was signed.

Reviewer comment: The overall incidence of discontinuation in these studies is high, and is similar to or higher than has been reported in other obesity drug trials.[15]

The sponsor identified several withdrawals that could have been attributable to adverse events; such cases occurred at a similar incidence in lorcaserin and placebo groups (0.2% of lorcaserin BID patients, 0.3% of lorcaserin QD patients, and 0.3% of placebo patients).

7 Efficacy

7.1 Proposed Indication

The sponsor provided draft labeling text in the NDA submission. The proposed indication is as follows:

- [Lorcaserin] is a selective serotonin 2C agonist indicated for weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced-calorie diet and a program of regular exercise. [Lorcaserin] is indicated for obese patients with an initial body mass index ≥ 30 kg/m^2, or overweight patients with a body mass index ≥ 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).

[15] Fabricatore AN, et al. Attrition from randomized controlled trials of pharmacological weight loss agents: a systematic review and analysis. Obes Rev 2009; 10: 333-41.

7.2 Methods

This efficacy review focuses on the 2 pivotal Phase 3 trials, BLOOM and BLOSSOM. Two Phase 2 trials were conducted as well, the 4-week APD356-003 and the 12-week APD356-004. These were primarily proof-of-concept studies and were used to establish the appropriate dose for the pivotal trials (see section 5.2), and were not otherwise reviewed for efficacy.

Because BLOOM and BLOSSOM both had 1:1 randomization schemes for lorcaserin 10 mg BID and placebo and background lifestyle treatment and study designs were similar, some of the efficacy data presented are pooled. Second year data from BLOOM are presented separately as are lorcaserin 10 mg QD data from BLOSSOM. Please see Dr. Janice Derr's statistical review for a comprehensive analysis of the efficacy data.

7.3 Results

7.3.1 Primary Efficacy Endpoints

7.3.1.1 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 studies, BLOOM and BLOSSOM.

Table 9. BLOOM 5% Responder, Modified Intent to Treat (MITT) LOCF

Treatment	**N**	**n (%)**
Lorc 10 BID	1538	731 (47.5)
Pbo	1499	304 (20.3)
Between Treatment Comparison	**Difference in Proportion (percentage)**	**p-value**
Lorc 10 BID vs. Pbo	27.2 (24.0, 30.5)	< 0.0001

Source: NDA 22529, APD356-009 CSR Table 10

Table 10. BLOSSOM 5% Responder, 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 (percentage)**	**p-value**
Lorc 10 BID vs. Pbo	22.23 (18.94, 25.52)	< 0.0001
Lorc 10 QD vs. Pbo	15.19 (11.11, 19.27)	< 0.0001
Lorc 10 QD vs. Lorc 10 BID	-7.04 (-11.29, -2.78)	0.0012

Source: NDA 22529, APD356-011 CSR Table 9

Table 11. Pooled Phase 3 Trials 5% Responder, MITT LOCF

Treatment	**N**	**n (%)**
Lorc 10 mg BID	3098	1460 (47.13)
Pbo	3038	687 (22.61)
Between Treatment Comparison	**Difference in Proportion (percentage)**	**p-value**
Lorc 10 BID vs. Pbo	24.52 (22.22, 26.82)	< 0.001

Source: NDA 22529, ISE Statistical Report Table E1.0

Findings were similar in the completer and return dropout (RDP) populations. In this analysis, RDP includes completers and patients who returned for a Week 52 weight after premature discontinuation.

Table 12. Pooled Phase 3 Trials 5% Responder, Other Analysis Populations

Treatment	**Completer**		**RDP**	
	N	**n (%)**	**N**	**n (%)**
Lorc 10 mg BID	1775	1135 (63.94)	2043	1197 (58.59)
Pbo	1529	512 (33.49)	1839	584 (31.76)
Between Treatment Comparison	**Difference in Proportion (percentage)**	**p-value**	**Difference in Proportion (percentage)**	**p-value**
Lorc 10 BID vs. Pbo	30.44 (27.18, 33.69)	<0.001	26.85 (23.83, 29.86)	<0.001

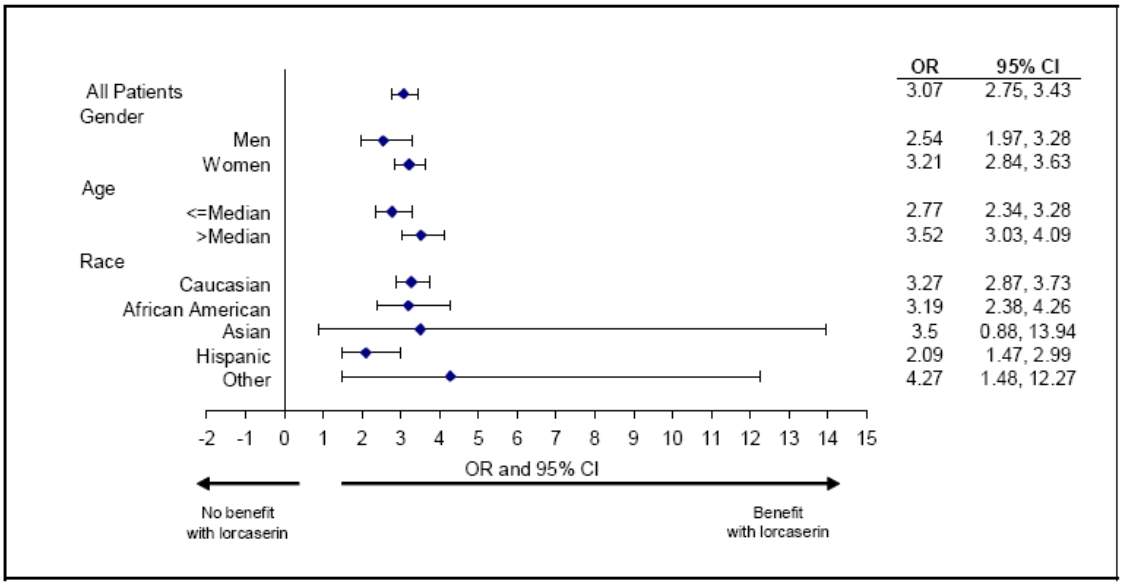
Source: NDA 22529, ISE Statistical Report Tables E1.1 and E1.2

Reviewer comment: The sponsor was asked to bring patients back for a Week 52 weight even if patients had discontinued prematurely (return drop-out population, RDP). FDA has asked to see such data in weight loss trials in order to conduct sensitivity analyses and support the efficacy of the drug; however, ideally, such a population would include a large proportion of drop-outs.[16] *In this program, the RDP is still considered a select group of patients.*

Figure 4 presents the proportion of patients achieving 5% weight loss at Week 52 by sex, age, and race. In general, all subgroups benefit from lorcaserin, although men, individuals less than the median age, and Hispanics appear to benefit less than women, older individuals, and other races, respectively. See Dr. Derr's statistical review for further detailed subgroup analyses.

[16] Simons-Morton DG, et al. Obesity research – limitations of methods, measurements, and medications. JAMA 2006; 295(7): 826-8.

Figure 4. Odds Ratios for the Proportion of Patients Achieving 5% Weight Loss at Week 52 by Subgroup



Source: NDA 22529, ISE Figure 17

7.3.1.2 Mean Weight Change

In the pooled intent-to-treat analysis, patients treated with lorcaserin 10 mg BID lost 5.8 kg of body weight compared to 2.5 kg lost by patients receiving placebo at Week 52; a between treatment mean difference of -3.25 kg.

Table 13. Change in Mean Body Weight (kg) at Week 52 LOCF, Pooled Phase 3 Trials

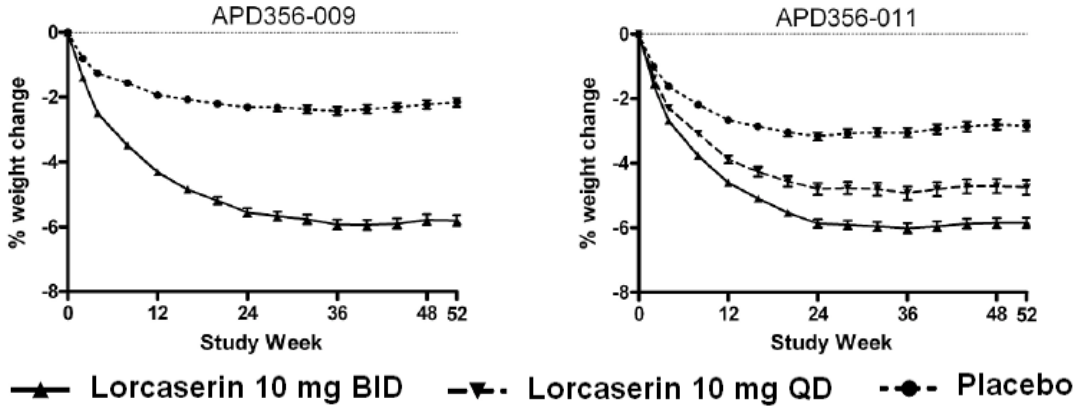
Treatment	**N**	**Mean (SD)**		**Change from Baseline**		
		Baseline	**Week 52**	**LS Mean (SE)**	**95% CI**	**p value**
Lorc 10 BID	3098	100.36 (15.67)	94.60 (16.71)	-5.76 (0.11)	(-5.97, -5.54)	<0.001
Lorc 10 QD	771	100.11 (16.74)	95.39 (17.38)	-4.73 (0.23)	(-5.18, -4.28)	<0.001
Pbo	3038	100.22 (15.92)	97.72 (16.50)	-2.51 (0.11)	(-2.72, -2.29)	<0.001
Between treatment difference				**Difference in LS means (95% CI)**		**p value**
Lorc 10 BID vs. Pbo				-3.25 (-3.56, -2.94)		<0.001
Lorc 10 QD vs. Pbo[a]				-1.88 (-2.43, -1.33)		<0.001
Lorc 10 QD vs. Lorc 10 BID[a]				1.03 (0.48, 1.58)		<0.001
[a] Results from the BLOSSOM trial						

Source: NDA 22529, ISE Statistical Report Table E2.0 and APD356-011 CSR Table 10

In the completer population, mean weight loss from baseline was greater in all treatment groups, as was the mean difference between groups: the mean change difference between lorcaserin 10 mg BID and placebo was -4.23 kg in the pooled Phase 3 trials.

Figure 5 graphically demonstrates the mean percent weight loss in the individual Phase 3 trials. Weight loss tended to plateau by Weeks 24 – 36 in the lorcaserin-treated groups and approximately by Weeks 16 – 24 in the placebo-treated group.

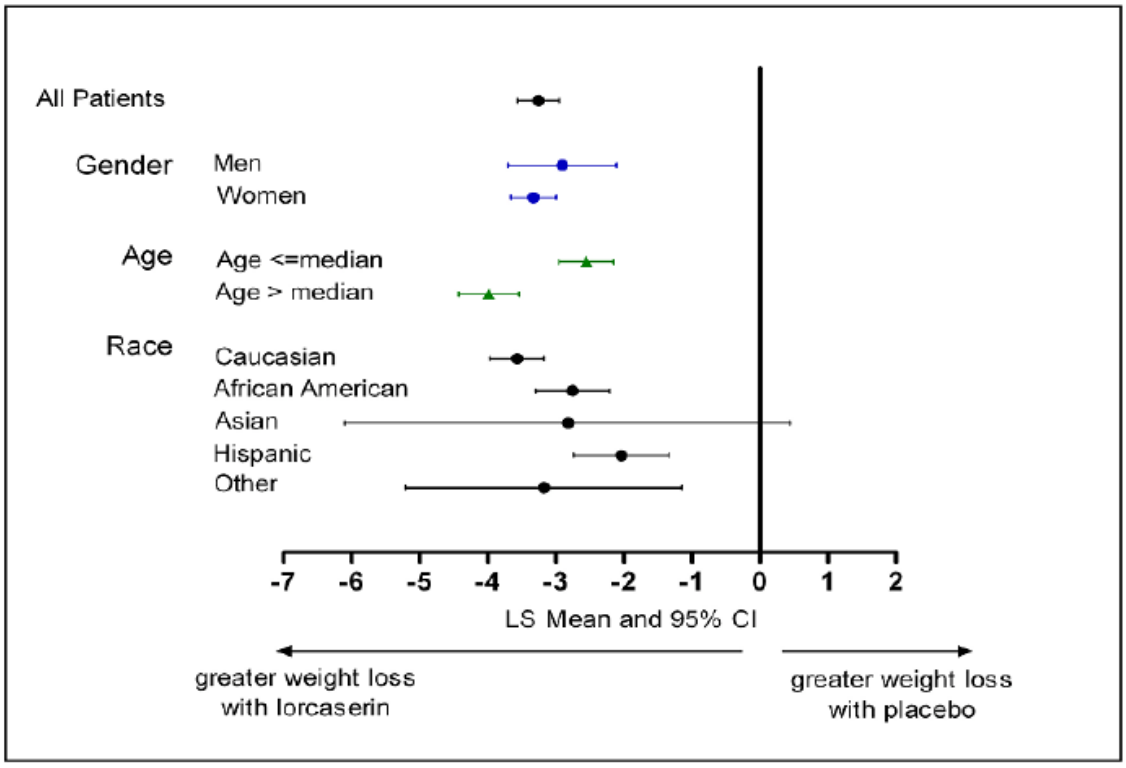
Figure 5. Mean Percent Weight Loss, BLOOM (APD356-009) and BLOSSOM (APD356-011), MITT LOCF



Source: NDA 22529, ISE Figure 5

Subgroup analyses of mean weight loss are fairly consistent with the subgroups of responder analyses (see Figure 4 and Figure 7), in that women, older individuals, and Caucasians/Whites appear to benefit from lorcaserin more so than others. As described in section 5.1, sex, age, and race did not significantly impact lorcaserin PK.

Figure 6. Difference in Mean Change from Baseline in Body Weight (kg) at Week 52 by Subgroup, MITT



Source: NDA 22529, ISE Figure 18

7.3.1.3 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%, $p < 0.001$). Findings were similar in the individual studies, BLOOM and BLOSSOM.

Table 14. BLOOM 10% Responder, MITT LOCF

Treatment	**N**	**n (%)**
Lorc 10 BID	1538	347 (22.6)
Pbo	1499	115 (7.7)
Between Treatment Comparison	**Difference in Proportion (percentage)**	**p-value**
Lorc 10 BID vs. Pbo	14.9 (12.4, 17.4)	< 0.0001

Source: NDA 22529, APD356-009 CSR Table 12

Table 15. BLOSSOM 10% Responder, 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 (percentage)**	**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
Lorc 10 QD vs. Lorc 10 BID	-5.25 (-8.63, -1.86)	0.0031

Source: NDA 22529, APD356-011 CSR Table 12

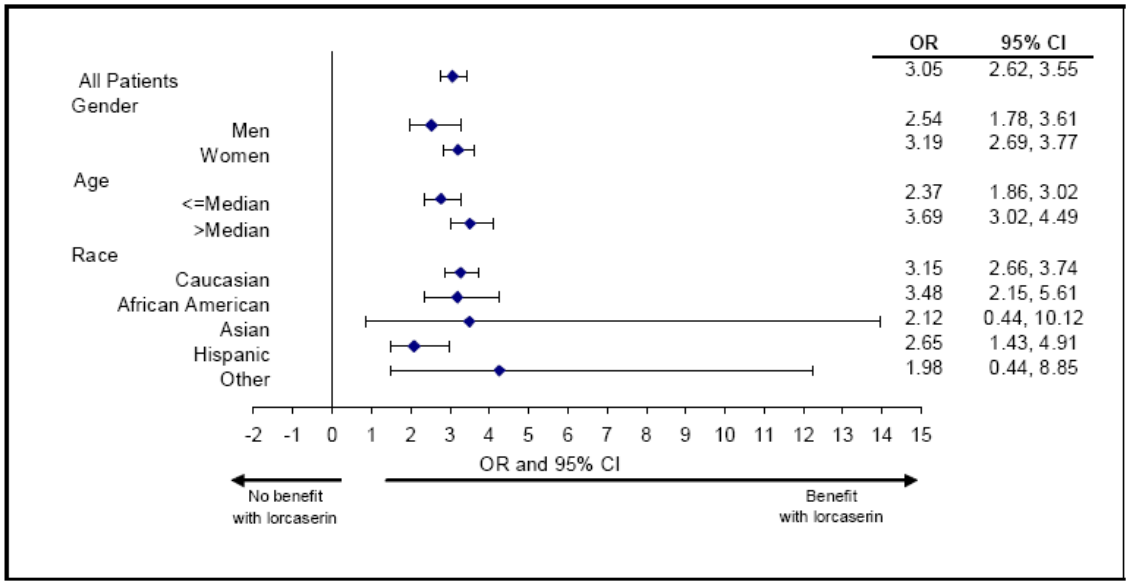
Table 16. Pooled Phase 3 Trials 10% Responder, MITT LOCF

Treatment	**N**	**n (%)**
Lorc 10 BID	3098	695 (22.43)
Pbo	3038	264 (8.69)
Between Treatment Comparison	**Difference in Proportion (percentage)**	**p-value**
Lorc 10 BID vs. Pbo	13.75 (11.97, 15.52)	< 0.001

Source: NDA 22529, ISE Statistical Report Table E3.0

As shown in Figure 7, 10% responders by subgroup demonstrated a similar pattern to the 5% responders by subgroup.

Figure 7. Odds Ratios for the Proportion of Patients Achieving 10% Weight Loss at Week 52 by Subgroup



Source: NDA 22529, ISE Figure 19

7.3.2 Secondary Efficacy Endpoints

7.3.2.1 Week 104 weight

The subset of patients who continued into the second year of the BLOOM trial was evaluated for weight changes over the second year (populations: modified intent-to-treat 2, MITT2 and per protocol 2, PP2).

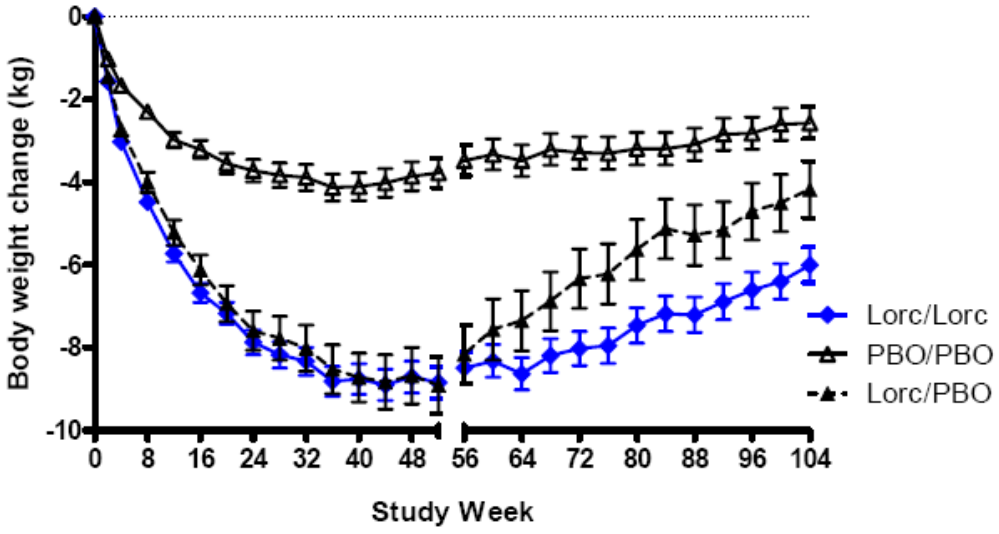
Table 17 demonstrates that patients who were re-randomized to placebo from lorcaserin in Year 2 regained significantly more weight than those who remained on lorcaserin. This finding is consistent with what has been seen with orlistat upon re-randomization to placebo,[17] and underscores the rationale for the use of obesity medications long-term. By contrast, those who remained on placebo regained statistically significantly less weight than those on lorcaserin in the second year of treatment (1.00 kg vs. 2.53 kg, $p < 0.0001$).

Table 17. Change in Body Weight to Week 104, MITT2, BLOOM trial

Treatment	N	Body Weight (kg) Mean ± SE			p-value vs. Lorc/Lorc
		Week 52	Week 104	Change from Week 52 at Week 104	
Lorc/Lorc	553	92.4 ± 0.7	95.0 ± 0.7	2.53 ± 0.186	
Lorc/Pbo	267	92.5 ± 1.1	97.2 ± 1.1	4.76 ± 0.310	< 0.0001
Pbo/Pbo	665	95.7 ± 0.6	96.7 ± 0.7	1.00 ± 0.161	< 0.0001

Source: NDA 22529, APD356-009 CSR Table 20

Figure 8. Change in Body Weight from Baseline to Week 104, PP2, BLOOM trial



Source: NDA 22529, APD356-009 CSR Figure 7

[17] Davidson MH, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. JAMA. 1999 Jan 20;281(3):235-42.

Patients who were 5% weight loss responders on lorcaserin in Year 1 of BLOOM were more likely to maintain a ≥ 5% weight loss at Week 104 if they were randomized to remain on lorcaserin (67.9%) than if they were re-randomized to placebo (50.3%).

7.3.2.2 Anthropometric measures

7.3.2.2.1 Waist circumference and BMI

Consistent with the weight changes observed, waist circumference and BMI decreased to a greater extent with lorcaserin treatment in a dose related fashion as compared with placebo.

Table 18. Change from Baseline in Waist Circumference (cm) at Week 52, Pooled Phase 3 Trials, 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 22529, ISE Statistical Report Table E14.0

It is noted that mean BMI at Week 52 in the lorcaserin-treated group is approximately 34 kg/m^2, suggesting that a significant proportion of treated patients remained obese (Table 19).

Table 19. Change from Baseline in Body Mass Index (kg/m^2) at Week 52, Pooled Phase 3 Trials, 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 22529, ISE Statistical Report Table E15.0

7.3.2.2.2 DEXA

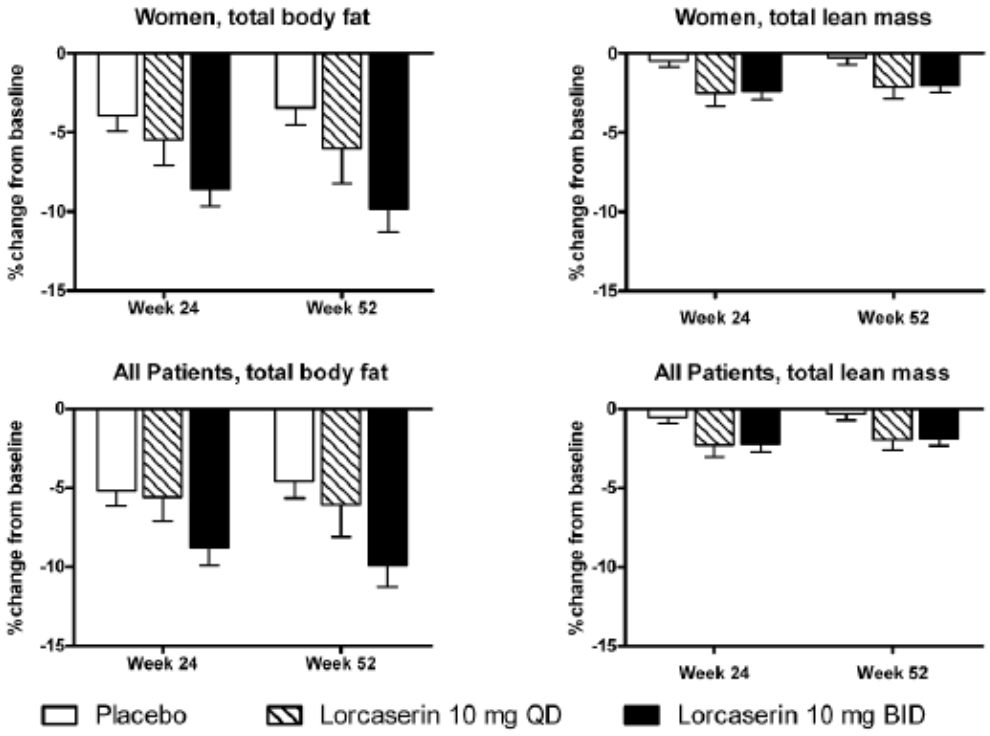
A subset of patients in the BLOSSOM study had body composition measured by dual energy X-ray absorptiometry (DEXA) at baseline, Week 24, and Week 52. Total body fat and total body lean mass was calculated for the group as a whole, as well as by gender and proportion of weight lost.

The decreases in total body fat were greater in patients randomized to receive lorcaserin 10 mg BID as compared to those receiving placebo. Lorcaserin 10 mg QD also produced

greater decreases in percent body fat than placebo in the overall population, but not in the small subgroup of men (n=4). The decrease in body fat paralleled the increasing body weight loss in all treatment groups. In patients losing ≥ 5% of body weight at Week 52, percent body fat decreased by 18.4% in patients treated with lorcaserin 10 mg BID compared to 13.8% in patients treated with placebo. There were only a small number of male patients for evaluation, so these results should be interpreted cautiously; however, the data suggest that men achieve greater decreases in percent body fat than women, particularly in the placebo group (males: Pbo -8.5%, Lorc 10 BID -10.4%; females: Pbo -3.4%, Lorc 10 BID -9.9%).

Patients treated with lorcaserin 10 mg BID tended to lose somewhat more lean body mass than patients treated with placebo (Week 52 Lorc 10 BID vs. Pbo difference in mean lean body mass -0.66, p=0.024).

Figure 9. 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 22529, ISE Figure 12

7.3.2.3 Metabolic- and cardiovascular-related endpoints

Additional secondary efficacy endpoints of interest to FDA include blood pressure, lipids, and fasting glucose and insulin measures.[10]

7.3.2.3.1 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, but the difference was only

statistically significant in the BLOOM trial. Similarly for diastolic blood pressure (DBP), a statistically significant difference in was seen in the BLOOM study but not in the BLOSSOM study for either dose of lorcaserin vs. placebo.

Table 20. Change from Baseline in Systolic and Diastolic Blood Pressure to Week 52, Pooled Phase 3 Trials, MITT LOCF

	BLOOM		BLOSSOM			Pooled	
	Lorc 10 BID N=1538	Pbo N=1499	Lorc 10 BID N=1561	Lorc 10 QD N=771	Pbo N=1541	Lorc 10 BID N=3096	Pbo N=3039
SBP, mmHg							
Baseline Mean (SD)	120.7 (11.37)	121.2 (11.62)	122.1 (12.16)	121.2 (12.18)	121.9 (11.91)	121.39 (11.86)	121.51 (11.74)
Mean Change (SE)	-1.4 (0.30)	-0.8 (0.31)	-2.0 (0.32)	-1.1 (0.43)	-1.2 (0.30)	-1.73 (0.22)	-1.05 (0.21)
p-value vs. Pbo	0.04		0.07	0.79		0.01	
DBP, mmHg							
Baseline Mean (SD)	76.8 (7.84)	77.1 (8.13)	78.1 (8.13)	78.0 (8.43)	78.3 (8.06)	77.44 (8.05)	77.71 (8.09)
Mean Change (SE)	-1.1 (0.23)	-0.6 (0.23)	-1.9 (0.23)	-1.0 (0.32)	-1.5 (0.22)	-1.50 (0.16)	-1.04 (0.16)
p-value vs. Pbo	0.01		0.08	0.42		<0.01	

Source: NDA 22529, ISE Table 31 and APD356-011 CSR Tables 11.16 and 11.17

In Year 2 of the BLOOM trial, treatment with lorcaserin significantly reduced systolic blood pressure (-2.5 vs. -1.4, p=0.04) and diastolic blood pressure (-1.7 vs. -0.7, p=0.01) as compared to placebo.

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, although statistical testing was not performed.

Table 21. Change in Blood Pressure at Week 52 by Responder Groups, 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 22529, ISE Statistical Report Tables E69.0 and E70.0

The following table 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.

Table 22. Number (%) of Patients who Changed the Total Daily Dose of or Initiated Antihypertensive Medications from Baseline to Week 52, Pooled Phase 3 Trials (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 22529, 2 Apr 2010 Response to 74-Day Filing Letter Appendix 9 Tables 32.3 and 33.3

7.3.2.3.2 Lipids

Treatment with lorcaserin decreased triglyceride (TG) concentrations by Week 4; TG remained decreased throughout the 52-week treatment period.

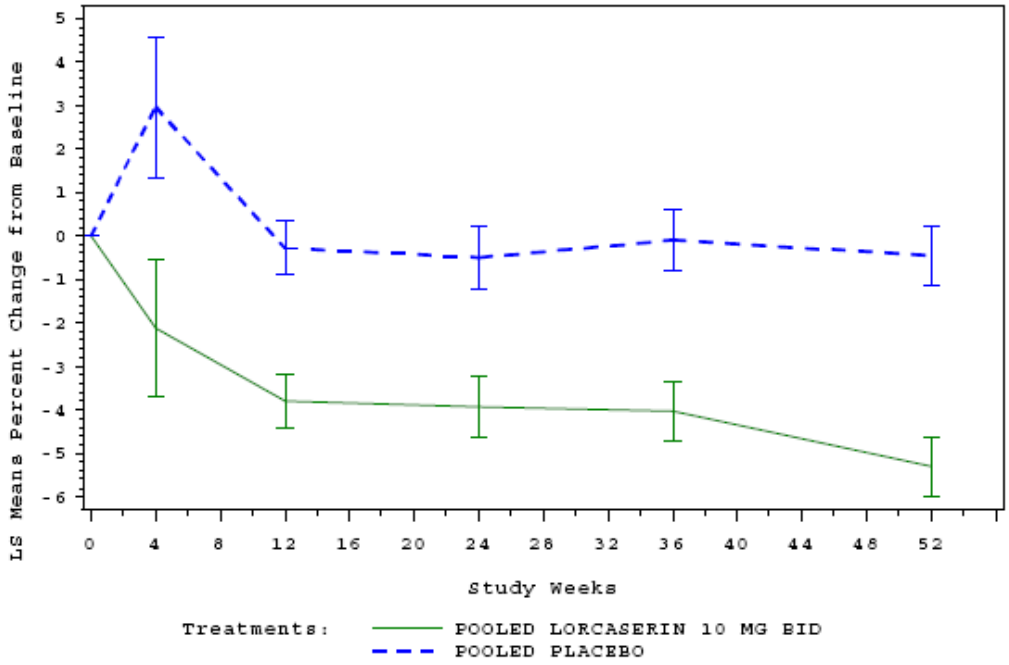
HDL cholesterol initially decreased from baseline in lorcaserin and placebo treatment groups before returning to baseline values and increasing in the lorcaserin group. These changes are consistent with HDL-C changes that occur with active weight loss and weight maintenance.[18,19]

The lowest mean LDL cholesterol and total cholesterol values were observed after 4 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.

The following figures illustrate the lipid excursions over the course of 52 weeks of treatment:

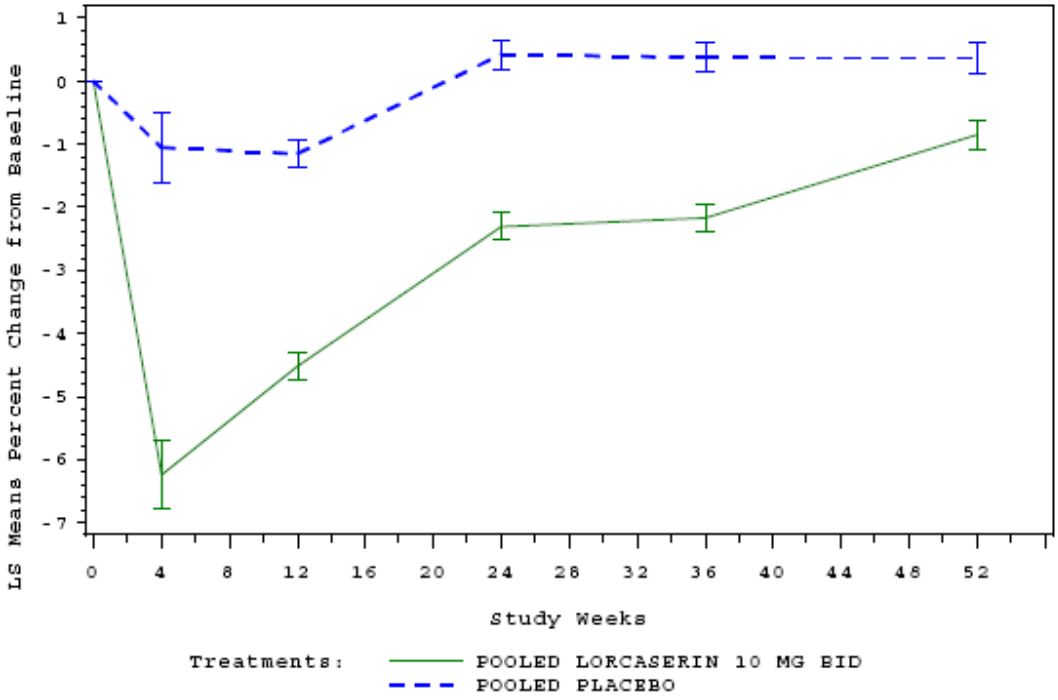
[18] Dattilo AM and Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr 1992; 56:320-8.
[19] Thompson PD, et al. Unexpected decrease in plasma high density lipoprotein cholesterol with weight loss. Am J Clin Nutr 1979; 32: 2016-21.

Figure 10. Mean Percent Change from Baseline in Triglycerides, MITT LOCF



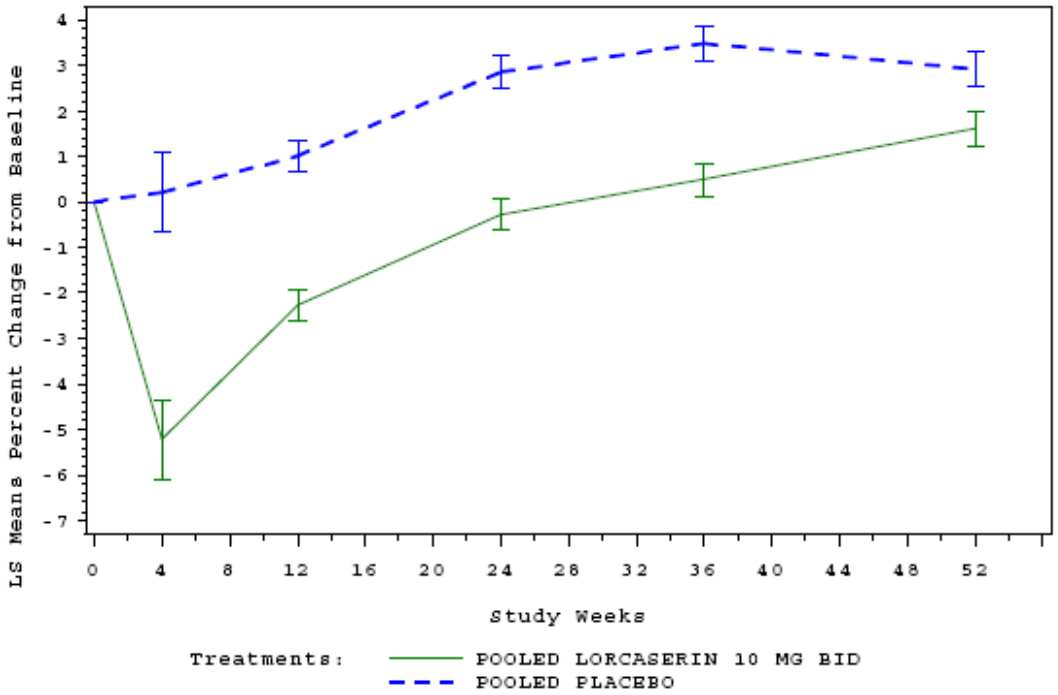
Source: NDA 22529, ISE Statistical Report Figure 7

Figure 11. Mean Percent Change from Baseline in Total Cholesterol, MITT LOCF



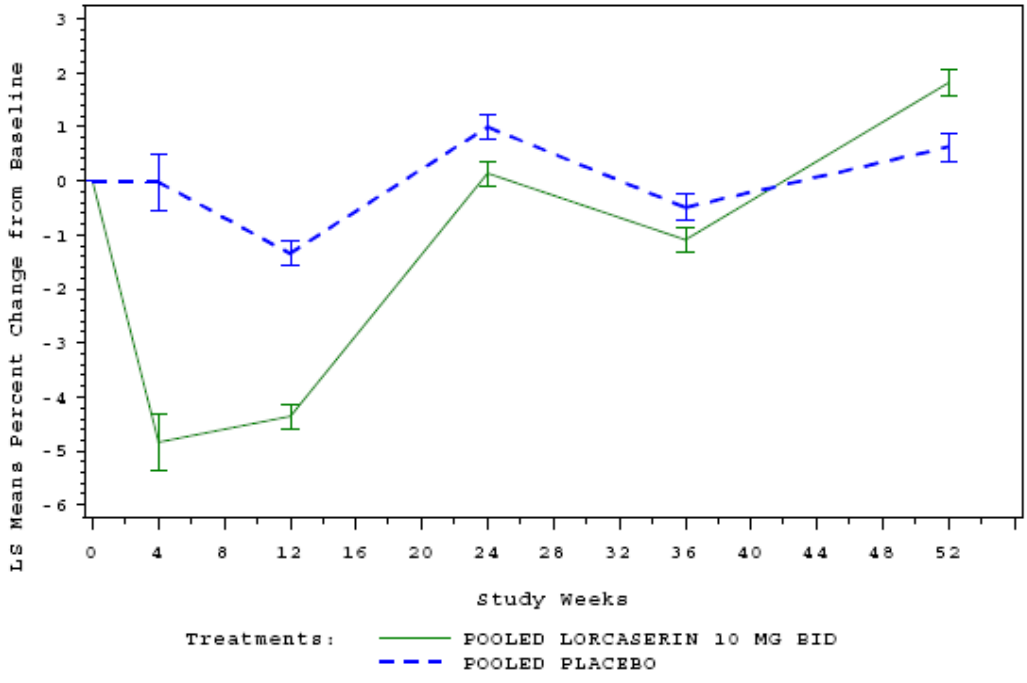
Source: NDA 22529, ISE Statistical Report Figure 8

Figure 12. Mean Percent Change from Baseline in LDL-C, MITT LOCF



Source: NDA 22529, ISE Statistical Report Figure 9

Figure 13. Mean Percent Change from Baseline in HDL-C, MITT LOCF



Source: NDA 22529, ISE Statistical Report Figure 10

Table 23 presents the changes in lipids in the 5% weight loss responders versus non-responders. (As with the responder analysis for blood pressure, results should be considered exploratory only; statistical analysis was not conducted.) 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.

Table 23. Mean Percent Change from Baseline in Lipids at Week 52, Pooled Phase 3 Trials MITT: Responders and Non-Responders

	Responders		**Non-Responders**	
	Lorc 10 BID	**Pbo**	**Lorc 10 BID**	**Pbo**
Triglycerides				
N	1444	682	1438	2098
Mean (SD) Baseline, mg/dL	136.04 (76.78)	139.63 (75.35)	134.81 (74.57)	136.11 (79.52)
% (SE) Change from Baseline	-14.45 (0.84)	-12.88 (1.22)	4.12 (1.15)	3.43 (0.82)
Total Cholesterol				
N	1444	682	1438	2098
Mean (SD) Baseline, mg/dL	195.62 (35.61)	196.21 (35.43)	193.08 (36.57)	194.33 (35.65)
% (SE) Change from Baseline	-2.11 (0.36)	-1.14 (0.53)	0.47 (0.34)	0.84 (0.28)
LDL Cholesterol				
N	1439	679	1430	2085
Mean (SD) Baseline, mg/dL	115.01 (30.72)	114.21 (29.09)	113.48 (31.60)	114.11 (29.92)
% (SE) Change from Baseline	0.55 (0.60)	2.01 (0.87)	2.72 (0.54)	3.27 (0.45)
HDL Cholesterol				
N	1444	682	1438	2098
Mean (SD) Baseline, mg/dL	53.68 (13.18)	54.06 (13.76)	52.81 (13.37)	53.26 (13.98)
% (SE) Change from Baseline	4.04 (0.40)	4.31 (0.60)	-0.44 (0.34)	-0.65 (0.29)

Source: NDA 22529, ISE Table 22

The following table suggests that fewer patients treated with lorcaserin 10 mg BID than placebo required initiation or an increase in dose of anti-dyslipidemia medication.

Table 24. Number (%) of Patients who Changed the Total Daily Dose of or Initiated Anti-Dyslipidemia Medication from Baseline to Week 52, Pooled Phase 3 Trials (Safety Population)

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
Decrease	43 (1.3)	14 (1.7)	23 (0.7)
No Change	484 (15.1)	108 (13.5)	474 (14.9)
Increase	83 (2.6)	24 (3.0)	109 (3.4)
Initiated Anti-Dyslipidemia Medication	62 (1.9)	21 (2.6)	80 (2.5)

Source: NDA 22529, 2 Apr 2010 Response to 74-Day Filing Letter Appendix 9 Tables 32.3 and 33.3

7.3.2.3.3 Glucose- and Insulin-Related Parameters

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 the analysis of blood glucose, the mean change from baseline at Week 52 was not significantly different in the lorcaserin-treated group and significantly increased in the placebo-treated group.

Table 25. Analysis of Change from Baseline in Fasting Glucose (mg/dL) at Week 52, MITT LOCF

Treatment	**N**	**Mean (SD)**		**Change from Baseline**		
		Baseline	**Week 52**	**LS Mean (SE)**	**95% CI**	**p value**
Lorc 10 BID	2934	92.08 (10.60)	91.89 (10.80)	-0.23 (0.17)	(-0.56, 0.11)	0.182
Pbo	2861	92.37 (10.55)	92.87 (11.00)	0.60 (0.17)	(0.26, 0.94)	<0.001
Between treatment difference				**Difference in LS means (95% CI)**		**p value**
Lorc 10 BID vs. Pbo				-0.82 (-1.30, -0.35)		<0.001

Source: NDA 22529, ISE Statistical Report Table E9.0

In this patient population that did not have diabetes mellitus, both treatment groups experienced small statistically significant decreases in HbA1c, with a significantly greater decrease in the lorcaserin-treated group.

Table 26. Analysis of Change from Baseline in HbA1c (%) at Week 52, MITT LOCF

Treatment	**N**	**Mean (SD)**		**Change from Baseline**		
		Baseline	**Week 52**	**LS Mean (SE)**	**95% CI**	**p value**
Lorc 10 BID	2466	5.63 (0.38)	5.51 (0.43)	-0.12 (0.01)	(-0.13, -0.11)	<0.001
Pbo	2290	5.64 (0.39)	5.59 (0.45)	-0.05 (0.01)	(-0.06, -0.04)	<0.001
Between treatment difference				**Difference in LS means (95% CI)**		**p value**
Lorc 10 BID vs. Pbo				-0.07 (-0.09, -0.05)		<0.001

Source: NDA 22529, ISE Statistical Report Table E10.0

Fasting insulin concentrations were only measured in the BLOOM trial. Fasting insulin decreased to a greater degree (more favorably) in the lorcaserin-treated group versus the placebo-treated group (-3.33 vs. -1.28 μIU/mL, $p<0.001$).

Patients who were diagnosed with diabetes mellitus during the Phase 3 trials were permitted to remain in the study unless an injectable agent was required.

In the BLOOM trial, 2 patients developed type 2 diabetes while taking lorcaserin, 2 while taking placebo, and 1 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. Remaining patients were treated with diet and exercise, with the exception of one patient on lorcaserin who was treated with sitagliptin at Week 12 and remained in the trial through Week 31 (the patient was discontinued for an unrelated reason). No hypoglycemia was reported in any patient with diabetes mellitus.

In the BLOSSOM trial, 3 patients treated with placebo, 4 treated with lorcaserin BID, and 2 treated with lorcaserin QD were diagnosed with type 2 diabetes during the trial. One patient on placebo was started on metformin; the others received no concomitant medications for diabetes during the trial. No hypoglycemia was reported in any patient with diabetes.

Within the pooled Phase 3 studies, approximately 5% of patients had fasting glucose ≥ 110 mg/dL. Lorcaserin 10 mg BID did not appear to benefit this subgroup with respect to change in fasting glucose as compared to placebo.

Table 27. Mean Change in Fasting Glucose from Baseline to Week 52 in Patients with Fasting Glucose ≥ 110 mg/dL

	Lorc 10 BID	**Pbo**
Baseline FG < 110 mg/dL	n=2780	n=2712
Change from Baseline, mean (SE)	0.37 (0.18)	1.12 (0.18)
Change from Baseline, range	-51.00 to 150.00	-48.00 to 82.00
Baseline FG ≥ 110 mg/dL	n=154	n=149
Change from Baseline, mean (SE)	-10.31 (1.42)	-10.73 (1.43)
Change from Baseline, range	-103.00 to 91.00	-74.00 to 57.00

Source: NDA 22529, ISE Statistical Report Table E24.0

Similarly, although 5% weight loss responders 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.

Table 28. Change in Fasting Glucose by Responder Group, MITT LOCF

	Lorc 10 BID	**Pbo**
Responders	n=1451	n=685
Change from Baseline, mean (SE)	-1.48 (0.27)	-2.29 (0.40)
Change from Baseline, range	-103.00 to 46.00	-74.00 to 44.00
Non-Responders	n=1483	n=2176
Change from Baseline, mean (SE)	1.08 (0.28)	1.38 (0.22)
Change from Baseline, range	-46.00 to 150.00	-68.00 to 82.00

Source: NDA 22529, ISE Statistical Report Table E24.1

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, Pooled Phase 3 Trials (Safety Population)

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
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)
Initiated Anti-Diabetes Medication	4 (0.1)	0	6 (0.2)

Source: NDA 22529, 2 Apr 2010 Response to 74-Day Filing Letter Appendix 9 Tables 32.3 and 33.3

8 Safety

This review primarily focuses on the Phase 3 trials; these results are discussed in detail. Some discussions of safety issues include summaries of adverse events and other safety outcomes from the Phase 1 and 2 trials. In general, the Year 1 results will be presented for BLOOM and BLOSSOM combined (pooled analysis), as the design and patient populations were similar. This analysis will include lorcaserin 10 mg BID and placebo data pooled as well as lorcaserin 10 mg QD data from the BLOSSOM trial. Re-randomized second year data from the BLOOM trial will be presented separately, unless stated otherwise.

8.1 Deaths

Two deaths occurred in the development program, both in patients randomized to placebo. The first patient was a 52-year-old White female who was involved in a motor vehicle accident on Study Day 558 of the BLOOM trial and died from multiple injuries, and the second was a 45-year-old White female with a history of asthma, who experienced an acute exacerbation of asthma and died from cardiac and respiratory arrest on Study Day 160 of the BLOSSOM trial.

8.2 Other Serious Adverse Events

8.2.1 Phase 1

No serious adverse events (SAEs) were reported during Phase 1 or PK studies of lorcaserin, nor were any SAEs reported during the thorough QT or abuse liability trials.

8.2.2 Phase 2

There were no SAEs reported during the 4-week Phase 2 trial APD356-003.

There were 5 SAEs reported in 4 patients during the 12-week Phase 2 trial APD356-004 in 2 patients receiving placebo, 1 patient receiving lorcaserin 10 mg QD, and 1 patient receiving lorcaserin 10 mg BID.

- Placebo: 3 SAEs in 2 patients
    - Ectopic pregnancy and miscarriage in a 35-year-old Black female approximately 4 weeks into the trial
    - Pneumonia (SAE 1) approximately 6 weeks into the trial and nephrolithiasis (SAE 2) approximately 10 weeks into the trial in a 54-year-old White male

- Lorcaserin 10 mg QD: 1 SAE in 1 patient
    - Major depressive disorder in a 38-year-old White female (patient 08-012), with symptoms starting approximately 2 months into the trial. The narrative for this case is presented in Appendix C.

- Lorcaserin 10 mg BID: 1 SAE in 1 patient
    - Seizure in a 35-year-old Black female (patient 15-002) approximately 2 months into the trial. The narrative for this case is presented in Appendix C.

Depression and seizures are discussed further in sections 8.4.3.2 and 8.4.4.2, respectively.

8.2.3 Phase 3

Overall, the incidence of SAEs 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 30).

For unclear reasons, there were proportionately more SAEs in the lorcaserin groups in the BLOSSOM study than in the BLOOM study (BLOOM Year 1: lorcaserin 10 mg BID, 2.4%; placebo, 2.3%; BLOSSOM: lorcaserin 10 mg BID, 3.1%, lorcaserin 10 mg QD, 3.4%; placebo, 2.2%). The imbalance in the BLOSSOM study was primarily driven by events in the cardiac, hepatobiliary, and psychiatric system organ classes (SOCs), and these SAEs are discussed further below.

Table 30. SAEs by SOC, Lorcaserin 10 mg BID Incidence Greater than Placebo, Pooled Phase 3 Trials, Year 1

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
Total	87 (2.7)	27 (3.4)	73 (2.3)
Infections And Infestations	11 (0.3)	1 (0.1)	6 (0.2)
Hepatobiliary Disorders	9 (0.3)	2 (0.2)	5 (0.2)
Cardiac Disorders	9 (0.3)	1 (0.1)	3 (0.1)
Reproductive System And Breast Disorders	8 (0.3)	2 (0.2)	7 (0.2)
Respiratory, Thoracic And Mediastinal Disorders	6 (0.2)	1 (0.1)	4 (0.1)
Psychiatric Disorders	6 (0.2)	0	0
General Disorders And Administration Site Conditions*	4 (0.1)	1 (0.1)	2 (0.1)
Metabolism And Nutrition Disorders	1 (<0.1)	0	0
Vascular Disorders	1 (<0.1)	0	0
* All were SAEs of "chest pain"			

Source: NDA 22529, ISS Table A4

Although comprising relatively few events overall, the imbalance in psychiatric SAEs is particularly notable, with 6 events reported in the lorcaserin 10 mg BID group and none in placebo. The psychiatric SAEs are listed here; the narratives can be found in Appendix C.

Table 31. Psychiatric SAEs, Phase 3 Trials

Study	**ID**	**Age/Sex/Race**	**Baseline Weight Quartile**	**Verbatim Term**	**Preferred Term**	**Severity**	**Hospitalized?**	**Drug Discontinued/ Study Withdrawal**
BLOOM	180-S141	36/F/W	> Q3	Suicide attempt	Suicide attempt	Severe	Yes	Yes
BLOSSOM	2139-S030	57/M/W	> Q3	Alcohol induced psychotic disorder	Alcoholic psychosis	Severe	Yes	Yes
BLOSSOM	2174-S061	53/F/W	Q2 - Q3	Nervous breakdown	Mental disorder	Moderate	Yes	No
BLOSSOM	2182-S037	39/F/W	Q2 - Q3	Suicidal thoughts	Suicidal ideation	Severe	Yes	Yes
BLOSSOM	2255-S030	30/F/Hisp	≤ Q1	Moderate depression	Depression	Moderate	No	Yes
BLOSSOM	2255-S039	58/M/W	Q1 - Q2	Psychiatric crisis	Acute psychosis	Severe	Yes	Yes

Source: Reviewer created from NDA 22529 datasets

Additional SAEs of interest were identified by exploring the MedDRA high level terms (HLT). Cholelithiasis and cholecystitis from the hepatobiliary SOC and ischemic coronary artery disorders from the cardiac disorders SOC occurred at a numerically higher incidence in the lorcaserin groups than in placebo.

Table 32. SAEs of Interest by High Level Term, Phase 3 Trials

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
High Level Term, SAEs			
Cholecystitis and cholelithiasis	9 (0.3)	2 (0.3)	4 (0.1)
Ischemic coronary artery disorders	7 (0.2)	0	0

Source: Reviewer created from NDA 22529 datasets

Gallbladder-related events are addressed in section 8.5.1.2.

The following table lists the specific SAEs within the ischemic coronary events HLT, all within the lorcaserin 10 mg BID group:

Table 33. Ischemic Coronary SAEs, Phase 3 Trials

Study	ID	Age/Sex/Race	Baseline Weight Quartile	Verbatim Term	Preferred Term	Severity	Hospitalized?	Drug Discontinued/ Study Withdrawal
BLOOM	119-S084	62/F/W	≤ Q1	Unstable angina	Angina unstable	Moderate	Yes	No
BLOSSOM	2128-S010	59/M/W	> Q3	Acute MI	Acute myocardial infarction	Severe	Yes	No
BLOSSOM	2137-S083	58/F/W	≤ Q1	Angina	Angina pectoris	Moderate	Yes	Yes
BLOSSOM	2196-S002	49/M/W	Q2 - Q3	Probable acute coronary syndrome	Acute coronary syndrome	Moderate	No	No
BLOSSOM	2203-S058	44/M/W	> Q3	Non Q wave myocardial infarction	Myocardial infarction	Moderate	Yes	No
BLOSSOM	2236-S032	54/F/W	≤ Q1	Myocardial infarction	Myocardial infarction	Severe	Yes	Yes
BLOSSOM	2250-S008	39/M/Hisp	> Q3	Myocardial infarction	Myocardial infarction	Mild	Yes	Yes

Source: Reviewer created from NDA 22529 datasets

Ischemic cardiac events are addressed in section 8.5.3.2.

Table 34 presents the BLOOM Year 2 SAEs by SOC.

In Year 2 of BLOOM, 2 SAEs occurred in more than one patient in the lorcaserin/lorcaserin treatment group: osteoarthritis (2 events) and rectocele (2 events).

Overall, neoplasm SAEs were not greater in the lorcaserin treatment groups than placebo in Year 2 of BLOOM: the 2 neoplasms that occurred in the lorcaserin/lorcaserin group

were uterine leiomyoma and benign pituitary tumor; the 2 that occurred in the lorcaserin/placebo group were colon cancer and prostate cancer. The 5 neoplasms that occurred in the placebo/placebo group were: uterine leiomyoma (3 patients), papillary thyroid cancer, and squamous cell carcinoma.

Patient 145-S044 (lorcaserin/placebo) attempted suicide during Year 2 of BLOOM. This SAE was coded under the 'Injury, Poisoning and Procedural Complications' SOC as an intentional overdose. This event is discussed further in 8.4.3.2.2 and the narrative is in Appendix C.

Table 34. BLOOM Year 2 SAEs, Re-Randomized Patients

	Lorc/Lorc N=573	**Lorc/Pbo N=283**	**Pbo/Pbo N=697**
Total, Year 2 SAEs	15 (2.6)	6 (2.1)	24 (3.4)
Musculoskeletal And Connective Tissue Disorders	3 (0.5)	1 (0.4)	3 (0.4)
Infections And Infestations	3 (0.5)	1 (0.4)	2 (0.3)
Neoplasms Benign, Malignant And Unspecified	2 (0.3)	2 (0.7)	5 (0.7)
Reproductive System And Breast Disorders	2 (0.3)	1 (0.4)	0
Hepatobiliary Disorders	2 (0.3)	0	0
Injury, Poisoning And Procedural Complications	1 (0.2)	1 (0.4)	4 (0.6)
Gastrointestinal Disorders	1 (0.2)	0	3 (0.4)
Immune System Disorders	1 (0.2)	0	0
Investigations	1 (0.2)	0	0
Cardiac Disorders	0	1 (0.4)	3 (0.4)
Respiratory, Thoracic And Mediastinal Disorders	0	1 (0.4)	1 (0.1)
Nervous System Disorders	0	0	2 (0.3)
Renal And Urinary Disorders	0	0	1 (0.1)

Source: NDA 22529, APD356-009 CSR Table 14.3.16

8.3 Adverse Events Associated with Discontinuation

8.3.1 Phase 1

No adverse event (AE) led to withdrawal in any single-dose study in healthy subjects, in single-dose studies evaluating individuals with renal or hepatic impairment, or in the multiple-dose study APD356-002.

In the thorough QT study APD356-007, one subject (lorcaserin 40 mg) experienced an AE of hematemesis and was withdrawn from the study. Although no other subject had 'withdrawal from study' recorded as the action taken for an AE, 4 other subjects assigned to the lorcaserin 40 mg group withdrew; their withdrawals were likely due in part to AEs that included nausea, vomiting, and/or headache.

In the APD356-013 study of abuse potential in experienced recreational drug users, 2 subjects withdrew as a result of adverse events; 1 individual experienced an AE of vomiting following the administration of lorcaserin 60 mg and chose not to participate in subsequent treatment periods, and a second subject experienced an AE of depressed mood following administration of a single dose of lorcaserin 40 mg. Because the

depressed mood did not resolve by the next scheduled dosing period, the subject was withdrawn. This narrative can be found in Appendix C (see: participant 9050). Depression is discussed further in section 8.4.3.2.

Two studies were conducted to assess the DDI of lorcaserin and dextromethorphan (metabolized by CYP2D6). Although no subject had 'withdrawal from study' recorded as the action taken for an adverse event in study APD356-008, 12 subjects (out of 24) withdrew consent on the morning of Day 9 after having received a single dose of dextromethorphan on Day 1 and a single dose of lorcaserin 20 mg on Day 8. One subject received a single dose of dextromethorphan on Days 1 and 10 and a single dose of lorcaserin 20 mg on Days 8, 9, and 10 prior to withdrawing from the study. The following rationale is taken from the study report:

> "The disposition for each of the 13 subjects was listed as "subject decision". The AEs reported by the 13 subjects who chose to discontinue did not differ in type or intensity from AEs observed in previous studies in which APD356 [lorcaserin] was well tolerated, nor were the 13 discontinuations attributed to AEs. However, TEAEs may have contributed to the subjects' group decision to withdraw."

In the second DDI study, APD356-012, one subject discontinued due to a headache during lorcaserin 10 mg BID administration.

8.3.2 Phase 2

Nine of the 352 patients enrolled in the APD356-003 study withdrew due to adverse events; 3 were assigned to lorcaserin 1 mg QD, 2 to lorcaserin 5 mg QD, and 4 to lorcaserin 15 mg QD. One patient (lorcaserin 5 mg) discontinued due to elevated ALT (77 mg/dL) associated with discolored feces and abdominal pain and was lost to follow-up. Another patient (lorcaserin 15 mg) discontinued due to increased electrocardiographic PR interval (390 msec) approximately 3 weeks into the trial; the Day 1 PR interval was 202 msec. Holter monitoring 2 weeks after study drug discontinuation demonstrated several periods of prolonged PR interval. The narrative is presented in Appendix C (see: patient 19-119).

Reviewer comment: Although it appears that this patient may have had an underlying conduction defect, lorcaserin does appear to be associated with prolonged PR and decreased heart rate. This safety issue is discussed further in section 8.5.3.1.

Table 35 enumerates the AEs in this trial that led to discontinuation. The preferred term 'Blood glucose increased' was found in the AE database as an AE leading to study withdrawal; however, this AE was not reported in the NDA integrated summary of safety.

Table 35. AEs Leading to Discontinuation, APD356-003

	Pbo N=86	Lorc 1 QD N=90	Lorc 5 QD N=89	Lorc 15 QD N=87
Total AEs leading to discontinuation	0	3 (3.3)	2 (2.2)	4 (4.6)
Infections and infestations	0	2 (2.2)	1 (1.1)	1 (1.1)
Influenza	0	1 (1.1)	0	1 (1.1)
Pneumonia	0	0	1 (1.1)	0
Tooth abscess	0	1 (1.1)	0	0
Investigations	0	1 (1.1)	1 (1.1)	1 (1.1)
Alanine aminotransferase increased	0	0	1 (1.1)	0
Blood glucose increased	0	1 (1.1)	0	0
Electrocardiogram PR interval	0	0	0	1 (1.1)
Gastrointestinal disorders	0	0	1 (1.1)	1 (1.1)
Abdominal pain	0	0	1 (1.1)	0
Feces discolored	0	0	1 (1.1)	0
Stomatitis	0	0	0	1 (1.1)
Nervous system disorders	0	0	0	1 (1.1)
Headache	0	0	0	1 (1.1)

Source: Reviewer created from NDA 22529 datasets

Seventeen of the 469 patients enrolled in the APD356-004 study withdrew due to adverse events; 2 were assigned to placebo, 1 to lorcaserin 10 mg QD, 9 to lorcaserin 15 mg QD, and 5 to lorcaserin 10 mg BID. The table below demonstrates that the lorcaserin 15 mg QD treatment appears to have been less well-tolerated (i.e., patients experienced more AEs leading to discontinuation) than the lorcaserin 10 mg QD or BID treatments, primarily due to headache, dizziness, and nausea.

Table 36. AEs Leading to Discontinuation, APD356-004

	Pbo N=118	Lorc 10 QD N=117	Lorc 15 QD N=118	Lorc 10 BID N=116
Total AEs leading to discontinuation	2 (1.7)	1 (0.9)	9 (7.6)	5 (4.3)
Nervous system disorders	0	0	7 (5.9)	2 (1.7)
Headache	0	0	5 (4.2)	1 (0.9)
Convulsions NOS	0	0	0	1 (0.9)
Tremor	0	0	0	1 (0.9)
Dizziness	0	0	3 (2.5)	0
Somnolence	0	0	1 (0.8)	0
Cardiac disorders	0	0	0	2 (1.7)
Atrioventricular block complete	0	0	0	1 (0.9)
Palpitations	0	0	0	1 (0.9)
Gastrointestinal disorders	0	0	3 (2.5)	1 (0.9)
Vomiting NOS	0	0	0	1 (0.9)
Nausea	0	0	2 (1.7)	0
Dysgeusia	0	0	1 (0.8)	0
General disorders and administration site conditions	1 (0.8)	0	1 (0.8)	1 (0.9)
Fatigue	1 (0.8)	0	1 (0.8)	1 (0.9)
Investigations	0	1 (0.9)	0	1 (0.9)
Liver function test abnormal	0	0	0	1 (0.9)
Blood pressure increased	0	1 (0.9)	0	0
Reproductive system and breast disorders	0	0	0	1 (0.9)
Metrorrhagia	0	0	0	1 (0.9)
Psychiatric disorders	0	0	2 (1.7)	0
Insomnia	0	0	1 (0.8)	0
Nervousness	0	0	1 (0.8)	0
Eye disorders	0	0	1 (0.8)	0
Vision blurred	0	0	1 (0.8)	0
Musculoskeletal and connective tissue disorders	0	0	1 (0.8)	0
Pain in extremity	0	0	1 (0.8)	0
Renal and urinary disorders	0	0	1 (0.8)	0
Pollakiuria	0	0	1 (0.8)	0
Infections and infestations	1 (0.8)	0	0	0
Upper respiratory tract infection NOS	1 (0.8)	0	0	0

Source: Reviewer created from NDA 22529 datasets

Note the following:

- The AE of convulsion (verbatim term "seizure"; lorcaserin 10 mg BID) is discussed above with the discussion of SAEs (section 8.2).
- Patient 25/007 (lorcaserin 10 mg BID) is a 44-year-old White female who discontinued 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. Serotonin toxicity is discussed further in section 8.4.6.

- An AE of complete atrioventricular (AV) block associated with bradycardia occurred in a 26-year-old Black female patient (lorcaserin 10 mg BID) with no significant medical history, but with an "insignificant" intraventricular conduction delay on the Day 1 ECG. Study drug was stopped approximately 2 months into the study because of this finding. The narrative is presented in Appendix C (see: patient 23-034). Bradycardia, PR interval prolongation, and other AV conduction issues are discussed in section 8.5.3.1.
- A 41-year-old female patient (lorcaserin 10 mg BID) was discontinued on Day 16 due to an AE of 'liver function test abnormalities'; which consisted of an ALT of 55 IU/L (normal range: 6-37 IU/L) and AST 138 IU/L (normal range 10-36 IU/L). Both values subsequently normalized within 2 weeks of discontinuation.

8.3.3 Phase 3

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

In general, AEs leading to withdrawal/study drug discontinuation were similar between lorcaserin and placebo (see Table 37). Neurological and psychiatric AEs led to greater discontinuations and are presented by those preferred terms with numeric imbalances in Table 38. Other imbalances were seen in the general disorders SOC, mostly due to discontinuations because of fatigue, chest pain, malaise, and chills, and the musculoskeletal SOC, mostly due to discontinuations because of pain in a variety of body locations.

Table 37. Discontinuations Due to Adverse Events by SOC, Lorcaserin Greater than Placebo, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
Total	274 (8.6)	60 (7.5)	217 (6.8)
Nervous System Disorders	84 (2.6)	15 (1.9)	49 (1.5)
Psychiatric Disorders	71 (2.2)	13 (1.6)	36 (1.1)
General Disorders And Administration Site Conditions	38 (1.2)	4 (0.5)	19 (0.6)
Gastrointestinal Disorders	37 (1.2)	10 (1.2)	37 (1.2)
Musculoskeletal And Connective Tissue Disorders	19 (0.6)	5 (0.6)	9 (0.3)
Cardiac Disorders	15 (0.5)	3 (0.4)	13 (0.4)
Neoplasms Benign, Malignant And Unspecified	14 (0.4)	4 (0.5)	11 (0.3)
Respiratory, Thoracic And Mediastinal Disorders	12 (0.4)	1 (0.1)	7 (0.2)
Vascular Disorders	11 (0.3)	1 (0.1)	8 (0.3)
Reproductive System And Breast Disorders	9 (0.3)	0	8 (0.3)
Hepatobiliary Disorders	4 (0.1)	0	2 (0.1)
Metabolism And Nutrition Disorders	3 (0.1)	4 (0.5)	3 (0.1)

Source: NDA 22529, ISS Table 40

Table 38. Discontinuations due to Nervous System and Psychiatric Disorders AEs, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
Nervous System Disorders	84 (2.6)	15 (1.9)	49 (1.5)
Headache	41 (1.3)	10 (1.2)	24 (0.8)
Dizziness	23 (0.7)	2 (0.2)	6 (0.2)
Migraine	5 (0.2)	1 (0.1)	1 (<0.1)
Psychiatric Disorders	71 (2.2)	13 (1.6)	36 (1.1)
Depression	29 (0.9)	1 (0.1)	16 (0.5)
Anxiety	12 (0.4)	3 (0.4)	8 (0.3)
Suicidal ideation	7 (0.2)	0	2 (0.1)
Depressed mood	6 (0.2)	1 (0.1)	2 (0.1)
Insomnia	5 (0.2)	2 (0.2)	6 (0.2)
Irritability	4 (0.1)	2 (0.2)	2 (0.1)

Source: NDA 22529, ISS Table 41

Headache and dizziness are adverse events (along with nausea) that appear to define the tolerability profile of lorcaserin.

Although there were similar numbers of patients who had depression adverse events in the Phase 3 trials (see section 8.4.3.2), more patients discontinued due to depression/depressed mood/suicidal ideation in the lorcaserin 10 mg BID group than in the placebo group.

A total of 52 patients discontinued due to adverse events during the second year of the BLOOM trial (Table 39).

Table 39. Discontinuations due to AEs, BLOOM Year 2

	Lorc/Lorc N=573	Lorc/Pbo N=283	Pbo/Pbo N=697
Total Discontinuations Due to AEs, BLOOM Year 2	21 (3.7)	12 (4.2)	19 (2.7)
Psychiatric Disorders	7 (1.2)	3 (1.1)	6 (0.9)
Musculoskeletal And Connective Tissue Disorders	3 (0.5)	1 (0.4)	0
General Disorders And Administration Site Conditions	2 (0.3)	2 (0.7)	0
Nervous System Disorders	2 (0.3)	1 (0.4)	3 (0.4)
Gastrointestinal Disorders	2 (0.3)	0	1 (0.1)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	1 (0.2)	2 (0.7)	1 (0.1)
Infections And Infestations	1 (0.2)	1 (0.4)	0
Cardiac Disorders	1 (0.2)	0	3 (0.4)
Investigations	1 (0.2)	0	1 (0.1)
Hepatobiliary Disorders	1 (0.2)	0	0
Injury, Poisoning And Procedural Complications	0	2 (0.7)	1 (0.1)
Skin And Subcutaneous Tissue Disorders	0	1 (0.4)	1 (0.1)
Renal And Urinary Disorders	0	0	1 (0.1)
Respiratory, Thoracic And Mediastinal Disorders	0	0	1 (0.1)
Vascular Disorders	0	0	1 (0.1)

Source: NDA 22529, APD356-009 CSR Table 14.3.14

Notable AEs leading to discontinuation by preferred term in Year 2 of BLOOM include:

- In the psychiatric SOC, AEs leading to withdrawal in the lorcaserin/lorcaserin group included depression (4 patients), anxiety (2 patients), and adjustment disorder (1 patient).
- An AE of biliary dyskinesia from the hepatobiliary SOC was reported at Week 80 in a 51-year-old White female patient randomized to lorcaserin/lorcaserin.
- From the neurologic disorders SOC, 1 patient discontinued due to headache in the lorcaserin/lorcaserin group.
- One patient in the lorcaserin/lorcaserin group and 1 in the placebo/placebo group discontinued due to mitral valve incompetence in the cardiac disorders SOC.

8.4 Targeted Safety Issues

8.4.1 Heart Valve Assessment

As described in section 2, recent work on the etiology of anorexigen-associated VHD implicates the 5HT2B receptor as the likely target. Activation of this receptor on heart valves is postulated to promote mitogenesis of fibroblasts and smooth muscle cells, causing the characteristic fibrotic changes associated with exposure to 5HT2B agonists.[20]

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 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 and

[20] Bhattacharyya S, et al. Drug-induced fibrotic valvular heart disease. Lancet 2009; 374: 577–85.

therefore the definition employed for clinically significant VHD due to anorexigen use has been defined as mild or greater aortic insufficiency and/or moderate or greater mitral insufficiency (FDA-defined VHD).[9] The primary safety endpoint for the lorcaserin program was the incidence of FDA-defined VHD.

Given the heightened concern regarding risk of 5HT2 receptor agonists and VHD, FDA requested a robust echocardiographic database in order to rule out a relative risk of 1.5 for FDA-defined VHD. The Phase 3 studies were not individually powered to rule out this risk;[21] therefore, the primary endpoint was calculated from Phase 3 pooled data at the 52-week time point.

In assessing the valvular safety of lorcaserin, we have presented here the echocardiographic findings, both for the primary endpoint of FDA-defined VHD at 52 weeks, as well as FDA-defined VHD at other time points, data from individual trials, data for the lorcaserin 10 mg QD dose, data from Phase 2 studies, and data from individual valves, including right-sided valves (tricuspid regurgitation, TR, and pulmonic regurgitation, PR). In addition, some information about individual patients with FDA-defined VHD and adverse events that could be considered potential cardiac valve toxicity signals have been presented.

8.4.1.1 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 2 blinded central readers (primary and secondary). In the BLOOM study, a panel of 19 cardiologists and in the BLOSSOM study, a panel of 23 cardiologists trained on the protocol by Biomedical Systems (BMS) served as blinded central readers for this study.

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)

[21] Smith SR, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 2010; 363: 245-56.

- 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, 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 both BLOOM and BLOSSOM, 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, 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 both BLOOM and BLOSSOM, 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 protocol 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.

8.4.1.2 FDA-Defined Valvular Heart Disease

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. The primary echocardiographic endpoint results are bolded in the table below. The relative risk for FDA-defined VHD in this analysis was 1.07 (95% CI: 0.74, 1.55).

Table 40. FDA-Defined VHD

	BLOOM		BLOSSOM			POOLED	
	Pbo	**Lorc 10 BID**	**Pbo**	**Lorc 10 QD**	**Lorc 10 BID**	**Pbo**	**Lorc 10 BID**
Week 24							
Safety pop N	1089	1213	1103	601	1170	2192	2383
Safety pop n (%)	21 (1.9)	25 (2.1)	20 (1.8)	12 (2.0)	27 (2.3)	41 (1.87)	52 (2.18)
Relative Risk (90% CI)		1.07 (0.66, 1.73)		1.27 (0.79, 2.06)	1.10 (0.61, 2.00)		1.17 (0.83, 1.64)
Relative Risk (95% CI)		1.07 (0.60, 1.90)		1.27 (0.72, 2.26)	1.10 (0.61, 2.00)		1.17 (0.78,1.75)
Completers pop N	709	882	797	447	863	1506	1745
Completers pop n (%)	14 (2.0)	20 (2.3)	17 (2.1)	9 (2.0)	20 (2.3)	31 (2.06)	40 (2.29)
Relative Risk (90% CI)		1.15 (0.65, 2.02)			1.09 (0.64, 1.86)		1.12 (0.76, 1.65)
Relative Risk (95% CI)		1.15 (0.58, 2.26)			1.09 (0.57, 2.06)		1.12 (0.70, 1.77)
Week 52							
Safety pop N	1191	1278	1153	622	1208	**2344**	**2486**
Safety pop n (%)	28 (2.4)	34 (2.7)	23 (2.0)	9 (1.4)	24 (2.0)	**51 (2.18)**	**58 (2.33)**
Relative Risk (90% CI)		1.13 (0.75, 1.71)		0.73 (0.38, 1.38)	1.00 (0.62, 1.60)		**1.07 (0.78, 1.46)**
Relative Risk (95% CI)		1.13 (0.69, 1.85)		0.73 (0.34, 1.56)	1.00 (0.57, 1.75)		**1.07 (0.74, 1.55)**
Completers pop N	698	857	790	448	853	1488	1710
Completers pop n (%)	21 (3.0)	29 (3.4)	19 (2.4)	7 (1.6)	13 (1.5)	40 (2.69)	42 (2.46)
Relative Risk (90% CI)		1.12 (0.71, 1.79)			0.63 (0.35, 1.14)		0.90 (0.63, 1.29)
Relative Risk (95% CI)		1.12 (0.65, 1.95)			0.63 (0.32, 1.27)		0.90 (0.59, 1.38)
Exposed at least 3 months pop N	1028	1167	1059	574	1101	2087	2268
Exposed at least 3 months pop n (%)	26 (2.5)	33 (2.8)	23 (2.2)	9 (1.6)	22 (2.0)	49 (2.35)	55 (2.43)
Relative Risk (90% CI)		1.12 (0.73, 1.71)		0.72 (0.38, 1.37)	0.92 (0.57, 1.49)		1.03 (0.75, 1.41)
Relative Risk (95% CI)		1.12 (0.67, 1.86)		0.72 (0.34, 1.55)	0.92 (0.52, 1.64)		1.03 (0.70, 1.50)

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

The primary safety endpoint of Week 52 FDA-defined VHD in the pooled Phase 3 population was further categorized by valve and degree of regurgitation. There were no cases of moderate or severe aortic regurgitation (AR) or severe mitral regurgitation (MR) that comprised the primary endpoint.

Table 41. Week 52 FDA-Defined VHD, Degree of Regurgitation of Affected Valves

	Lorc 10 BID N=2486	**Pbo N=2344**
Total	58 (2.3)	51 (2.2)
Mild AR	31[a] (1.2)	36 (1.5)
Moderate MR	29[a] (1.2)	15 (0.6)
[a] 2 patients on lorcaserin 10 mg BID had both mild AR and moderate MR		

Source: Reviewer created from NDA 22529 dataset

A greater proportion of lorcaserin-treated patients experienced FDA-defined VHD at Week 24 than placebo-treated patients. This apparent treatment-difference was attenuated at Week 52. Additionally, a greater relative risk for FDA-defined VHD was seen in the ITT population than in the completers population or 3-month exposed population.

The sponsor evaluated whether patients with FDA-defined VHD at Week 24 withdrew from the study at a higher incidence than those without, which could artificially diminish any lorcaserin effect at Week 52. In BLOOM, 5 patients in the lorcaserin BID group and 8 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, 4 patients assigned to lorcaserin BID, 3 assigned to lorcaserin QD and 2 assigned to placebo had FDA-defined 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.

A total of 48 patients (27 lorcaserin 10 mg BID and 21 placebo) who were diagnosed with FDA-defined VHD at Week 24 subsequently "reverted" back to non-FDA-defined VHD at Week 52. Eleven percent of the lorcaserin-treated reverters and 29% of the placebo-treated reverters had discontinued drug prior to the 52 week visit.

The following subgroups of the pooled safety population were evaluated for development of FDA-defined VHD at Week 52: sex, race, baseline weight, and weight responders. Overall, Asian patients and potentially those at the lowest baseline weight and weight responders had a higher incidence of FDA-defined VHD at Week 52, whereas Hispanic patients appeared to have a lower incidence.

Table 42. FDA-Defined VHD by Subgroup

	Lorc 10 BID	Pbo
Female	49 / 2006 (2.4%)	39 / 1874 (2.1%)
Male	9 / 480 (1.9%)	12 / 470 (2.6%)
White	44 / 1767 (2.5%)	40 / 1629 (2.5%)
Black	10 / 429 (2.3%)	7 / 421 (1.7%)
Asian	2 / 18 (11.1%)	1 / 15 (6.7%)
Hispanic	1 / 235 (0.4%)	3 / 249 (1.2%)
Other	1 / 37 (2.7%)	0 / 30 (0)
Q1 (≤ 88.3 kg)	22 / 625 (3.5%)	17 / 595 (2.9%)
Q2 (> 88.3 - 98.7 kg)	12 / 620 (1.9%)	9 / 593 (1.5%)
Q3 (> 98.7 - 110.5 kg)	15 / 629 (2.4%)	13 / 581 (2.2%)
Q4 (> 110.5 kg)	9 / 612 (1.5%)	12 / 575 (2.1%)
Responders	36 / 1349 (2.7%)	19 / 634 (3.0%)
Non-Responders	22 / 1137 (1.9%)	32 / 1710 (1.9%)

Source: NDA 22529, ISS Tables 169 and 170

The pooled data were explored for the relationship between the development of FDA-defined VHD and age and weight change.

Mean age was greater for those who developed FDA-defined VHD at Week 52 than those who did not, but was similar between treatment groups.

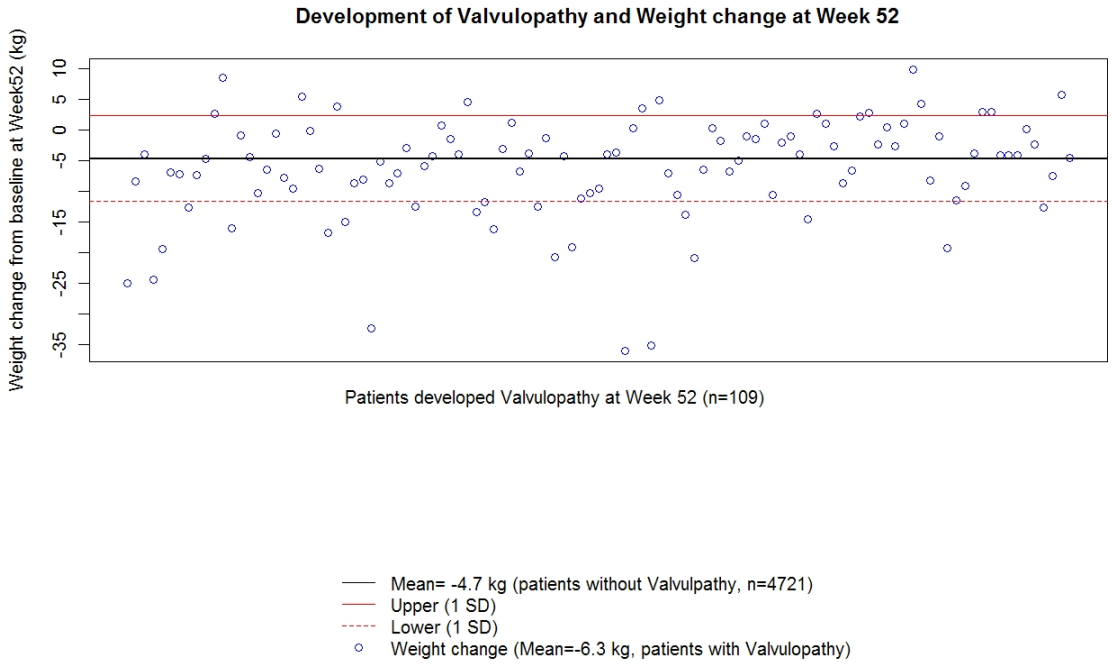
Table 43. Mean (SD) Age of Patients with and without FDA-Defined VHD at Week 52

	Lorc 10 BID	Lorc 10 QD	Pbo
FDA-Defined VHD at Week 52	51.14 (9.47)	54.56 (4.93)	51.76 (10.47)
No FDA-Defined VHD at Week 52	44.94 (11.11)	44.49 (11.33)	45.23 (11.26)

Source: Reviewer created from NDA 22529 datasets

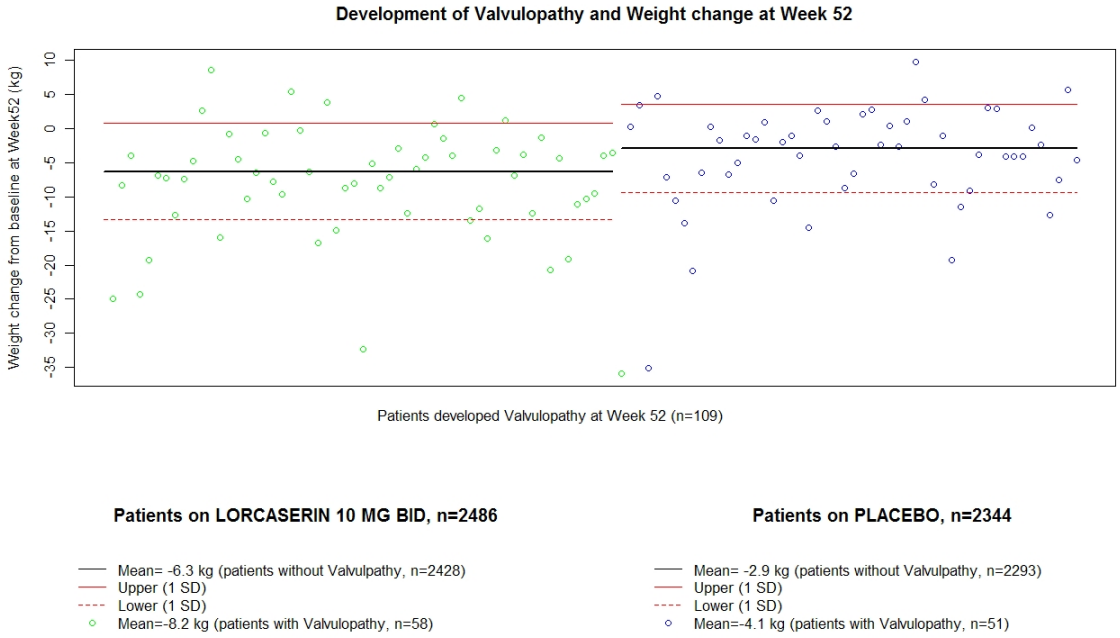
The mean weight loss in patients without FDA-defined VHD was -4.7 kg; the mean weight loss in those patients with FDA-defined VHD at Week 52 was -6.3 kg (Figure 14). However, when 5 FDA-defined VHD outliers are removed, the mean change – and difference between groups – is attenuated (mean weight loss for patients with FDA-defined VHD -5.1 kg).

Figure 14. Development of FDA-Defined VHD and Weight Change at Week 52



Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Figure 15. Development of FDA-Defined VHD and Weight Change by Treatment Group at Week 52



Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Because of the re-randomization, the analysis of FDA-defined VHD in Year 2 of BLOOM is somewhat challenging to interpret; the results are as follows (statistical analysis was not conducted by the sponsor):

Table 44. 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, APD356-009 CSR Table 72

Echocardiograms were also performed in Phase 2 trials APD356-003 and APD356-004 to explore the development of FDA-defined VHD. In the 1-month trial APD356-003, studies were conducted at screening, at Day 29, and at Day 90 (~2 months after cessation of study drug). In the 3-month trial APD356-004, echocardiograms were performed at screening and at Day 85. Both Phase 2 studies excluded patients with pre-existing FDA-defined VHD, and further restricted enrollment as follows:

- APD356-003: > trace MR excluded; > absent AR excluded; > mild TR excluded
- APD356-004: > mild MR excluded; > absent AR excluded (except patients 50 years or older, who had > trace AR excluded); > mild TR excluded

In study APD356-003, 1 patient in the lorcaserin 15 mg QD group developed FDA-defined VHD (moderate MR, from trace) on Day 90.

In study APD356-004, 4 patients met criteria for FDA-defined VHD during the study: 2 patients in the placebo group and 1 patient in the 15 mg QD treatment group increased from mild to moderate MR, and 1 patient in the 15 mg QD treatment group increased from trace to mild AR.

8.4.1.2.1 Inter- and Intra-variability Assessment

Variability with echocardiography reading was assessed in 2 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. Please see Appendix D for a full discussion and the methods and results of this assessment.

Overall, the inter- and intra-reader variability observed using the standard echocardiograms was consistent with variability data reported by other investigators.[22] 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 slightly greater than that of the adjudicated reads.

[22] 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 45. Relative Risk of FDA-Defined VHD by Reader

	BLOOM		BLOSSOM	
	Lorc 10 BID	**Pbo**	**Lorc 10 BID**	**Pbo**
Reader A				
VHD, n (%)	35 (2.7%)	24 (2.0%)	38 (3.2%)	29 (2.5%)
Relative Risk (95% CI)	1.36 (0.81, 2.27)		1.25 (0.78, 2.02)	
Mantel-Haenszel Pooled RR (95% CI)	**1.30 (0.92, 1.84)**			
Reader B				
VHD, n (%)	28 (2.2%)	28 (2.4%)	27 (3.2%)	19 (2.5%)
Relative Risk (95% CI)	0.93 (0.55, 1.56)		1.35 (0.76, 2.42)	
Mantel-Haenszel Pooled RR (95% CI)	**1.10 (0.75, 1.62)**			
Adjudicated Reads (Primary Analysis)				
VHD, n (%)	34 (2.7%)	28 (2.4%)	24 (2.0%)	23 (2.0%)
Relative Risk (95% CI)	1.13 (0.69, 1.85)		1.00 (0.57, 1.75)	
Mantel-Haenszel Pooled RR (95% CI)	**1.07 (0.74, 1.55)**			

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

8.4.1.3 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 exclude those increases.

Table 46. 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	8.17%	7.36%	1.11 (0.91, 1.35)	0.321
Mitral	20.26%	17.67%	1.15 (1.02, 1.29)	0.025
Pulmonic	17.06%	15.23%	1.12 (0.98, 1.28)	0.101
Tricuspid	18.23%	15.64%	1.17 (1.02, 1.32)	0.019
Any Valve	44.81%	40.74%	1.10 (1.03, 1.17)	0.005

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 47. 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	7.68%	7.05%	1.09 (0.89, 1.33)	0.405
Mitral	21.36%	19.57%	1.09 (0.98, 1.22)	0.123
Pulmonic	17.48%	15.32%	1.14 (1.00, 1.30)	0.042
Tricuspid	17.98%	16.30%	1.10 (0.97, 1.25)	0.121
Any Valve	46.94%	42.36%	1.11 (1.04, 1.18)	0.001

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 48. 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	1.39%	1.38%	1.00 (0.62, 1.63)	0.99
Mitral	10.01%	8.03%	1.24 (1.04, 1.50)	0.019
Pulmonic	17.06%	15.23%	1.12 (0.98, 1.28)	0.101
Tricuspid	12.86%	9.64%	1.33 (1.13, 1.57)	0.0006
Any Valve	31.37%	27.67%	1.13 (1.04, 1.24)	0.006

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 49. 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	1.25%	1.54%	0.81 (0.51, 1.30)	0.384
Mitral	9.99%	8.47%	1.18 (0.99, 1.41)	0.066
Pulmonic	17.48%	15.32%	1.14 (1.00, 1.30)	0.042
Tricuspid	12.25%	10.03%	1.22 (1.04, 1.43)	0.014
Any Valve	32.76%	28.42%	1.15 (1.06, 1.25)	0.001

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

The majority of the increases from baseline in mitral valvular regurgitation score were by 1; in either treatment group at Week 52, the maximum increase was 2. The narrative of the patient who increased by 3 grades at Week 24 is presented below.

Table 50. Number (%) of Patients with a Given Change from Baseline in Mitral Regurgitation, Pooled Phase 3 Trials

	Lorc 10 BID	Pbo
Week 24		
N	2448	2241
Increased by 1, n (%)	465 (19.0)	375 (16.7)
Increased by 2, n (%)	30 (1.2)	21 (0.9)
Increased by 3, n (%)	1 (<0.1)	0
Week 52		
N	2552	2396
Increased by 1, n (%)	515 (20.2)	446 (18.6)
Increased by 2, n (%)	30 (1.2)	23 (1.0)

Source: NDA 22529, ISS Statistical Report Tables E41.1 and E41.5

- Patient 2186-S075 in the BLOSSOM study was a 49-year-old White female with a past medical history of pyuria and depression who developed an increase from absent MR at baseline to moderate MR at Week 24. As reported by the investigator, the patient was asymptomatic, but did report an AE of upper respiratory infection several days prior to the echocardiogram being conducted. Subsequent visits did not reveal changes in blood pressure or pulse, nor symptoms suggestive of cardiac disease (mitral

insufficiency in particular) and she was not referred to a cardiologist, nor was she withdrawn from the study. The Week 52 echocardiogram was reported as mild MR.

Of note, there was only 1 patient who developed severe MR during the Phase 3 program. Patient 2115-S070 was a 45-year-old Black female randomized to placebo who had moderate MR at baseline and severe MR at Week 24.

The majority of the increases from baseline in aortic valvular regurgitation score were by 1; in either treatment group at Weeks 24 and 52, the maximum increase was 2.

Table 51. Number (%) of Patients with a Given Change from Baseline in Aortic Regurgitation

	Lorc 10 BID	**Pbo**
Week 24		
N	2448	2241
Increased by 1, n (%)	190 (7.8)	157 (7.0)
Increased by 2, n (%)	10 (0.4)	8 (0.4)
Week 52		
N	2552	2396
Increased by 1, n (%)	184 (7.2)	154 (6.4)
Increased by 2, n (%)	12 (0.5)	15 (0.6)

Source: NDA 22529, ISS Statistical Report Tables E41.0 and E41.4

No patients in the Phase 3 program developed severe AR.

In BLOOM, patients could continue on therapy or be re-randomized from lorcaserin to placebo for a second year. The following table presents increases in mitral or aortic valve regurgitation at the Weeks 76 and 104 visits from the Week 52 visit.

Table 52. Proportion of Patients Who Experienced Any Increase in Mitral or Aortic Valve Regurgitation, Weeks 76 and 104 of BLOOM

	Lorc/Lorc N=573	**Lorc/Pbo N=283**	**Pbo/Pbo N=697**
From Week 52 to Week 76	119 (25.2)	61 (25.5)	162 (27.2)
From Week 52 to Week 104	105 (21.6)	56 (22.7)	148 (24.1)

Source: NDA 22529, APD356-009 CSR Table 14.3.122

In the BLOSSOM trial, patients who had FDA-defined VHD at baseline were permitted to enroll into the trial. These patients did not appear to develop worsening of their valvular disease over the 52-week course of the trial.

Table 53. 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 N=66	**Pbo N=52**
Worsening of MR	7 (10.6)	12 (23.1)
Worsening of AR	1 (1.5)	4 (7.7)

Source: NDA 22529, ISS Statistical Report Tables E42.0 and E42.1

As Table 46 to Table 49 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.[23,24] Specific grade increases of tricuspid valves regurgitation were further assessed.

The majority of the increases from baseline in tricuspid valvular regurgitation score were by 1; in either treatment group at Week 52, the maximum increase was 2. The narrative of the patient treated with lorcaserin 10 mg BID who increased by 3 grades at Week 24 is presented below. A second patient treated with lorcaserin 10 mg QD who increased 3 grades, trace to severe, is presented in Table 55.

Table 54. Number (%) of Patients with a Given Change from Baseline in Tricuspid Regurgitation

	Lorc 10 BID	**Pbo**
Week 24		
N	2419	2219
Increased by 1, n (%)	408 (16.9)	336 (15.1)
Increased by 2, n (%)	32 (1.3)	11 (0.5)
Increased by 3, n (%)	1 (<0.1)	0
Week 52		
N	2526	2371
Increased by 1, n (%)	425 (16.8)	366 (15.4)
Increased by 2, n (%)	28 (1.1)	20 (0.8)
Increased by 3, n (%)	0	0

Source: NDA 22529, ISS Statistical Report Tables E41.3 and E41.7

- Patient 2200-S013 in the BLOSSOM study was a 33-year-old White female with a past medical history of seasonal allergies and asthma who developed an increase from baseline absent TR to moderate TR at Week 24. She was not withdrawn from the study. The Week 52 echocardiogram was reported as mild TR.

[23] 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.
[24] Redfield MM, et al. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. Ann Intern Med July 1992; 117(1): 50-52.

Nine patients developed severe tricuspid regurgitation during the trials, 4 patients treated with lorcaserin 10 mg BID (0.1%), 4 patients treated with lorcaserin 10 mg QD (0.5%), and 1 patient treated with placebo (<0.1%). None had a pulmonary artery systolic pressure (PASP) > 35 mmHg.

Table 55. Patients with Severe Tricuspid Regurgitation, Pooled 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 NDA 22529 datasets

Finally, given that alternative definitions of drug-related VHD have been used, notably in the investigations into dopamine agonist-associated VHD,[25] 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, we found that 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.

8.4.1.4 Adverse Events Related to Heart Valves

No patient 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 AEs 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 AE.

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

[25] 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 56. 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 57. Cardiac-Valve Related AEs, Pooled Phase 3 Trials

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

Source: Reviewer created from NDA 22529 datasets

In Year 2, the following cardiac valve related adverse events were reported:

Table 58. Cardiac Valve-Related AEs, BLOOM Year 2

	Lorc/Lorc N=573	Lorc/Pbo N=283	Pbo/Pbo N=697
Total, Cardiac Valve-Related AEs	4 (0.7)	1 (0.4)	4 (0.6)
Mitral valve incompetence	2 (0.3)	0	2 (0.3)
Echocardiogram abnormal	1 (0.2)	0	1 (0.1)
Tricuspid valve incompetence	1 (0.2)	0	0
Mitral valve prolapse	0	1 (0.4)	0
Aortic valve incompetence	0	0	1 (0.1)

Source: Reviewer created from NDA 22529 datasets

Ten (0.3%) patients on lorcaserin 10 mg BID, 1 (0.1%) patient on lorcaserin 10 mg QD, and 4 (0.1%) patients on placebo were reported to have a cardiac murmur during the Phase 3 trials. The sponsor reviewed the cardiac murmur AEs along with the relevant echocardiographic findings from the most temporally proximate study: 2 patients (1 in the lorcaserin 10 mg QD group and 1 in the lorcaserin 10 mg BID group) likely had murmurs related to aortic stenosis. Two patients from BLOOM (144-S011, 161-S088, both lorcaserin 10 mg BID) and 1 patient (2140-S033, lorcaserin 10 mg BID) from BLOSSOM had increased mitral or aortic valvular regurgitant scores associated with the adverse event of cardiac murmur. On the next echocardiogram, Patient 144-S011 had improvement in MR (to absent) and AR (to absent); patient 161-S088 had improvement in MR (trace) and stable AR (trace) at Week 76. Patient 2140-S033 did not have a subsequent echocardiogram for comparison.

The sponsor evaluated congestive heart failure (CHF)-related terms in patients in the BLOSSOM trial who were enrolled with baseline FDA-defined VHD in the event that even a small increase in regurgitation led to CHF decompensation. Among CHF-related search terms only the adverse event of peripheral edema was reported: 1 in the lorcaserin 10 mg BID group (1.2%) and 1 in the lorcaserin 10 mg QD group (3.2%).

8.4.2 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.[26] 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).[27] It has been estimated that 1 in 1000 or fewer patients who are exposed to such agents ultimately develop PPH.[28]

[26] 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.
[27] 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.
[28] Endocrinologic and Metabolic Drugs Advisory Committee, NDA 20344, Dexfenfluramine hydrochloride, 28 Sept 1995.
Transcript accessed 1 Aug 2010: http://www.fda.gov/ohrms/dockets/ac/redux.htm

Anorexigens associated with PPH are thought to act by increasing serotonin release via the serotonin transporter.[29] Other potential serotonin mediators may include the 5HT1B, 5HT2A, and 5HT2B receptors.[30,31]

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.[32]

PASP positively correlates with age and BMI and is higher in men than women.[33] Higher PASP may in fact be physiological in very obese patients.[32] 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".[34] 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.

The change in PASP from Baseline to Week 52 was negative for both treatment groups in the pooled Phase 3 studies. The least squared mean between treatment difference, lorcaserin 10 mg BID versus placebo, was 0.16 (-0.20, 0.52, p=0.38).

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[29] Rothman RB and Baumann MH. Serotonin releasing agents. Neurochemical, therapeutic and adverse effects. Pharmacol Biochem Behav. 2002 Apr;71(4): 825-36.

[30] Dempsie Y and MacLean MR. Pulmonary hypertension: therapeutic targets within the serotonin system. Br J Pharmacol 2008; 155: 455-62.

[31] Launay, J-M, et al. Function of the serotonin 5-hydroxytryptamine 2B receptor in pulmonary hypertension. Nature Med 2002 Oct; 8(10): 1129-35.

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

[33] 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.

[34] 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.

Table 59. Change from Baseline in PASP (mmHg) at Week 52

	BLOOM		BLOSSOM	
	Lorc 10 BID	**Pbo**	**Lorc 10 BID**	**Pbo**
Screening/Baseline, N	815	820	900	885
Screening/Baseline PASP, Mean (SD)	25.69 (4.994)	25.39 (4.961)	24.77 (5.32)	24.54 (5.16)
Week 52, N	591	547	619	583
PASP Change from Baseline, Mean	-0.92	-0.23	0.04	-0.43

Source: NDA 22529, APD356-009 CSR Table 74 and APD356-011 CSR Table 53

The proportion of patients who experienced changes of ≥ 10 mmHg, ≥ 15 mmHg, ≥ 20 mmHg, or ≥ 25 mmHg from baseline to Week 24 or Week 52 is summarized in the table below.

Table 60. Patients with Increases in PASP from Baseline, Pooled Phase 3 Trials

	Lorc 10 BID	**Pbo**
Week 24	N=1045	N=936
≥ 10 mmHg	39 (3.7)	30 (3.2)
≥ 15 mmHg	10 (1.0)	8 (0.9)
≥ 20 mmHg	2 (0.2)	2 (0.2)
≥ 25 mmHg	0	0
Week 52	N=1210	N=1130
≥ 10 mmHg	32 (2.6)	38 (3.4)
≥ 15 mmHg	13 (1.1)	7 (0.6)
≥ 20 mmHg	4 (0.3)	1 (0.1)
≥ 25 mmHg	1 (0.1)	0

Source: NDA 22529, ISS Table 191

At Week 24, 1 patient assigned to placebo had a PASP value ≥ 45 mmHg. At Week 52, 1 patient assigned to placebo had PASP ≥ 45 mmHg, and 2 patients assigned to lorcaserin had PASP ≥ 45 mmHg (both of which were also ≥ 50 mmHg; these patients are described below).

Table 61. Patients with Selected PASP Values, Pooled Phase 3 Trials

	Lorc 10 BID	**Pbo**
Week 24	N=1495	N=1281
≥ 35 mmHg	33 (2.2)	29 (2.3)
≥ 40 mmHg	3 (0.2)	4 (0.3)
≥ 45 mmHg	0	1 (0.1)
≥ 50 mmHg	0	0
≥ 55 mmHg	0	0
≥ 60 mmHg	0	0
Week 52	N=1838	N=1632
≥ 35 mmHg	35 (1.9)	24 (1.5)
≥ 40 mmHg	5 (0.3)	3 (0.2)
≥ 45 mmHg	2 (0.1)	1 (0.1)
≥ 50 mmHg	2 (0.1)	0
≥ 55 mmHg	0	0
≥ 60 mmHg	0	0

Source: NDA 22529, ISS Table 192

The following patients at Week 52 had a PASP ≥ 50 mmHg as well as an increase from baseline of ≥ 15 mmHg:

- 2145-S080 (lorcaserin 10 mg BID): The patient was a 53-year-old Black female with a 30-year history of cigarette smoking and a remote history of pneumonia. The echocardiograms showed mild MR and absent AR at Baseline, Week 24 and Week 52. PASP was 31.5 mmHg at baseline. At Week 24 PASP was 37.2 mmHg, and at Week 52 PASP was 53.7 mmHg. The patient was evaluated by a cardiologist approximately 3 weeks after the Week 52 echocardiogram. The patient reported exertional dyspnea and symptoms of sleep apnea to the cardiologist. After reviewing the study echocardiograms, the cardiologist performed a treadmill test and a sleep study. The treadmill test was unremarkable. The sleep study revealed mild obstructive sleep apnea, moderate in REM sleep. Sleep apnea and possible pulmonary disease were considered the most likely causes of the elevated PASP. The management recommendations from the cardiologist and sleep physician included weight loss, and possible CPAP, ENT surgery, or oral appliance therapy.

Reviewer comment: The 30-year smoking history and sleep apnea are plausible alternative etiologies for pulmonary hypertension. However, given that the PASP increased over the year in which the patient was treated with lorcaserin, the potential for a contributing effect of the drug cannot be excluded.

- 145-S094 (lorcaserin 10 mg BID): The patient was a 51-year-old White female with noncontributory medical history who experienced an increase in PASP to 54.5 mmHg after withdrawal from the study. She was a non-smoker and consumed 3 alcoholic beverages per week. The screening echocardiogram showed mild MR and absent AR, PASP was 36.3 mm Hg, LVEF was 65%, and chamber dimensions were within normal limits. The patient withdrew from the trial after approximately 6 months because she was unable to make the scheduled appointments. On the early

termination echocardiogram, PASP was 39.7 mm Hg. The patient returned for the intended Week 52 echocardiogram on approximately 6 months after early termination, which showed PASP of 54.4 mm Hg. The BLOOM study report notes that no relevant AEs or concomitant medications were reported. Information about the patient's activities between September 2007 and the January 2008 echocardiogram are not available. The NDA integrated summary of safety states that a cardiologist external to the clinical trial evaluated this patient and performed a diagnostic echocardiogram that showed no evidence of elevated PASP. This information, however, was not included in the BLOOM study report.

During Year 2 of the BLOOM trial, 1 (0.2%) patient treated with placebo and 1 (0.3%) patient treated with lorcaserin 10 mg BID had PASP ≥ 40 mmHg. No patients had PASP ≥ 50 mmHg. At Week 104, 4 (1.5%) patients treated with placebo and 1 (0.4%) patient treated with lorcaserin 10 mg BID had PASP increases of 15 mmHg or greater.

8.4.3 Psychiatric Safety Issues

8.4.3.1 Abuse-Related Adverse Events

Lorcaserin is known to possess activity at the 5HT2A receptor (see section 2). An adverse event profile consistent with 5HT2A activity could include hallucinations, euphoria, and other perceptual or dissociative symptoms.[35] Such adverse events were seen predominantly in the studies in healthy (lower weight) individuals at supratherapeutic doses.

The following tables adapted from the NDA integrated summary of safety describe potential abuse-related terms in the single dose studies in healthy patients, in the thorough QT and abuse liability studies, and in the drug-drug interaction studies, respectively, based on preferred and verbatim term recommendations from the FDA Controlled Substances Staff (CSS). Of note, CSS is conducting a separate review of the abuse liability study. These potential abuse-related adverse events include specific perceptual and dissociative terms, such as hallucinations and euphoric mood as well as non-specific terms such as somnolence and dizziness, which were both seen more frequently in the lorcaserin groups. Dizziness is a common lorcaserin-related adverse event and is reviewed separately in section 8.4.4.4.

Of note, a healthy 48-year-old White female treated with a single dose of lorcaserin 40 mg (participant 025) experienced severe AEs of disorientation and hallucination in the APD356-001a study 30 minutes to 2 hours after receiving the dose. See Appendix C for the full narrative of this case.

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

Table 62. Incidence of Potential Perceptual or Dissociative AEs in Single Dose Studies in Healthy Individuals

	Pbo N=35	**Lorc 0.1 N=20**	**Lorc 1 N=20**	**Lorc 10 N=114**	**Lorc 20 N=12**	**Lorc 40 N=6**
Total	2 (5.7)	1 (5.0)	1 (5.0)	14 (12.3)	1 (8.3)	5 (83.3)
Euphoria-related						
Dizziness	1 (2.9)	1 (5.0)	1 (5.0)	10 (8.8)	1 (8.3)	2 (33.3)
Euphoric mood	0	0	0	2 (1.8)	0	3 (50.0)
Feeling abnormal	0	0	0	1 (0.9)	0	0
Feeling drunk	0	0	0	0	0	1 (16.7)
Inappropriate affect	0	0	0	0	0	1 (16.7)
Mood altered	0	0	0	0	0	1 (16.7)
Depressant-related						
Asthenia	0	0	0	0	0	1 (16.7)
Fatigue	0	0	0	1 (0.9)	0	0
Sluggish	0	0	0	0	0	1 (16.7)
Somnolence	1 (2.9)	0	0	2 (1.8)	0	0
Perceptual disturbances and psychotomimetic-related effects						
Abnormal dreams	0	0	0	1 (0.9)	0	0
Disorientation	0	0	0	0	0	1 (16.7)
Hallucination	0	0	0	0	0	1 (16.7)

Due to the inclusion of crossover studies, individuals may appear more than once across treatment groups.

Source: NDA 22529, Abuse Liability Evaluation Table 13

Table 63. Incidence of Potential Perceptual or Dissociative AEs, APD356-007

	Pbo N=60	**Pbo/Moxi N=60**	**Lorc 15 QD N=60**	**Lorc 40 QD N=64**
Total	3 (5.0)	8 (13.3)	15 (25.0)	39 (60.9)
Euphoria-related				
Dizziness	2 (3.3)	7 (11.7)	10 (16.7)	29 (45.3)
Dizziness postural	0	1 (1.7)	0	2 (3.1)
Euphoric mood	1 (1.7)	0	5 (8.3)	6 (9.4)
Feeling abnormal	0	0	1 (1.7)	0
Mood altered	0	0	1 (1.7)	5 (7.8)
Depressant-related				
Fatigue	0	0	0	2 (3.1)
Somnolence	0	0	0	1 (1.6)
Stimulation and anxiety-related				
Anxiety	0	1 (1.7)	0	0
Excitability	0	0	0	1 (1.6)
Irritability	0	0	0	1 (1.6)
Nervousness	0	0	0	1 (1.6)
Restlessness	1 (1.7)	0	0	0
Perceptual disturbances and psychotomimetic-related effects				
Abnormal dreams	1 (1.7)	0	2 (3.3)	2 (3.1)
Bradyphrenia	0	0	1 (1.7)	0
Disorientation	0	0	0	1 (1.6)
Hypoaesthesia	0	0	1 (1.7)	0
Paraesthesia	0	0	9 (15.0)	12 (18.8)

Source: NDA 22529, Abuse Liability Evaluation Table 14

Table 64. Incidence of Potential Perceptual or Dissociative AEs, APD356-013

	Pbo N=31	Lorc 20 N=33	Lorc 40 N=34	Lorc 60 N=31	Ket 100 N=32	Zol 15 N=32	Zol 30 N=31
Euphoria-related							
Dizziness	0	1 (3.0)	5 (14.7)	6 (19.4)	4 (12.5)	4 (12.5)	5 (16.1)
Elevated mood	0	0	0	0	0	0	1 (3.2)
Euphoric mood	0	2 (6.1)	6 (17.6)	6 (17.6)	16 (50.0)	4 (12.5)	5 (16.1)
Depressant-related							
Asthenia	0	0	1 (2.9)	0	0	0	0
Fatigue	0	3 (9.1)	1 (2.9)	0	2 (6.3)	1 (3.1)	2 (6.5)
Somnolence	7 (22.6)	2 (6.1)	5 (14.7)	2 (6.5)	3 (9.4)	29 (90.6)	28 (90.3)
Stimulation and anxiety-related							
Anxiety	1 (3.2)	2 (6.1)	1 (2.9)	3 (9.7)	0	0	0
Irritability	1 (3.2)	0	2 (5.9)	1 (3.2)	0	1 (3.1)	0
Restlessness	0	0	1 (2.9)	1 (3.2)	0	0	2 (6.5)
Perceptual disturbances and psychotomimetic-related effects							
Abnormal dreams	0	0	0	1 (3.2)	0	0	0
Disorientation	0	0	0	1 (3.2)	0	0	0
Feeling abnormal	1 (3.2)	1 (3.0)	1 (2.9)	0	0	0	0
Hallucination, visual	0	0	0	0	0	0	1 (3.2)
Illusion	0	0	0	0	0	1 (3.1)	0
Paraesthesia	1 (3.2)	1 (3.0)	5 (14.7)	5 (16.1)	0	0	0
Peripheral coldness	0	1 (3.0)	1 (2.9)	1 (3.2)	0	0	0

Ket=ketamine; Zol=zolpidem

Source: NDA 22529, Abuse Liability Evaluation Table 12 and Reviewer created from datasets

Table 65. Incidence of Potential Perceptual or Dissociative AEs, DDI Studies

	APD356-008 Lorc 20 QD N=24	APD356-012 Lorc 10 BID N=24
Total	12 (50.0)	10 (41.7)
Euphoria-related		
Dizziness	9 (37.5)	6 (25.0)
Euphoric mood	1 (4.2)	5 (20.8)
Depressant-related		
Asthenia	3 (12.5)	0
Fatigue	3 (12.5)	0
Somnolence	1 (4.2)	0
Stimulation and anxiety-related		
Anxiety	3 (12.5)	0
Feeling jittery	0	1 (4.2)
Irritability	1 (4.2)	0
Perceptual disturbances and psychotomimetic-related effects		
Hallucination	1 (4.2)	0
Paraesthesia	1 (4.2)	2 (8.3)

Source: NDA 22529, Abuse Liability Evaluation Table 15

In contrast to the studies in healthy populations and with therapeutic doses, trials in obese patients demonstrated lorcaserin-associated abuse-related AEs infrequently.

Table 66. Incidence of Potential Perceptual or Dissociative AEs, Phase 2 Trials

	APD356-003				APD356-004			
	Pbo N=86	**Lorc 1 QD N=90**	**Lorc 5 QD N=89**	**Lorc 15 QD N=87**	**Pbo N=118**	**Lorc 10 QD N=117**	**Lorc 15 QD N=118**	**Lorc 10 BID N=116**
Total	5 (5.8)	4 (4.4)	5 (5.6)	10 (11.5)	7 (5.9)	18 (15.4)	19 (16.1)	21 (18.1)
Euphoria-related								
Dizziness	3 (3.5)	2 (2.2)	1 (1.1)	4 (4.6)	0	7 (6.0)	9 (7.6)	9 (7.8)
Dizziness exertional	0	0	0	0	0	0	0	1 (0.9)
Euphoric mood	0	0	0	0	0	1 (0.9)	0	0
Feeling abnormal*	0	0	0	2 (2.3)	0	0	1 (0.8)	3 (2.6)
Depressant-related								
Asthenia	1 (1.2)	0	0	1 (1.1)	0	1 (0.9)	0	0
Fatigue	0	0	1 (1.1)	1 (1.1)	3 (2.5)	5 (4.3)	7 (5.9)	5 (4.3)
Lethargy	0	0	1 (1.1)	1 (1.1)	0	0	0	1 (0.9)
Sedation	0	1 (1.1)	0	0	0	0	0	0
Somnolence	0	1 (1.1)	0	0	0	1(0.9)	4 (3.4)	3 (2.6)
Stimulation and anxiety-related								
Agitation	0	0	1 (1.1)	0	0	0	0	0
Excitability	0	0	0	0	0	0	1 (0.8)	0
Anxiety	1 (1.2)	0	0	0	2 (1.7)	2 (1.7)	1 (0.8)	1 (0.9)
Energy increased	1 (1.2)	0	0	0	0	0	0	1 (0.9)
Nervousness	0	0	0	0	0	0	1 (0.8)	1 (0.9)
Restlessness	0	0	0	0	0	0	1 (0.8)	1 (0.9)
Perceptual disturbances and psychotomimetic-related effects								
Confusional state	0	0	0	0	0	1 (0.9)	0	0
Hypoaesthesia	1 (1.2)	0	0	1 (1.1)	0	1 (0.9)	1 (0.8)	2 (1.7)
Nightmare	0	0	0	1 (1.1)	1 (0.8)	0	1 (0.8)	0
Paraesthesia	0	0	1 (1.1)	1 (1.1)	1 (0.8)	2 (1.7)	0	0

* Includes such verbatim terms as fuzzy, muzzy, dazed, spacey/spaced out

Source: NDA 22529, Abuse Liability Evaluation Table 16

In the Phase 3 trials, 6 patients assigned to lorcaserin 10 mg BID and 3 assigned to lorcaserin QD reported euphoric mood, as compared to 1 patient assigned to placebo. Euphoric mood tended to occur on Day 1 of dosing, with symptoms generally lasting from 1 day to 1 month. Abnormal dreams occurred at excess frequency in the lorcaserin 10 mg BID group (0.5% of patients) as compared to placebo (0.2%). Dissociation was reported twice during the Phase 3 trials, both events at lorcaserin 10 mg BID. The single hallucination in the pooled studies occurred in a patient taking placebo.

Table 67. Incidence of Potential Perceptual or Dissociative AEs, Phase 3 Trials, Pooled

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
Total Perceptual or Dissociative-Related AEs	659 (20.6)	136 (17.0)	370 (11.6)
Total, Euphoria-related AEs	283 (8.9)	55 (6.9)	127 (4.0)
Dizziness	270 (8.5)	50 (6.2)	122 (3.8)
Feeling abnormal	7 (0.2)	2 (0.2)	3 (0.1)
Euphoric mood	6 (0.2)	3 (0.4)	1 (<0.1)
Dizziness postural	4 (0.1)	0	1 (<0.1)
Feeling drunk	2 (0.1)	0	0
Feeling of relaxation	0	0	1 (<0.1)
Total, Depressant-related AEs	325 (10.2)	68 (8.5)	168 (5.3)
Fatigue	229 (7.2)	53 (6.6)	114 (3.6)
Somnolence	51 (1.6)	6 (0.7)	25 (0.8)
Lethargy	25 (0.8)	3 (0.4)	16 (0.5)
Asthenia	21 (0.7)	5 (0.6)	13 (0.4)
Malaise	14 (0.4)	3 (0.4)	4 (0.1)
Hypersomnia	7 (0.2)	0	3 (0.1)
Sedation	2 (0.1)	0	0
Sluggishness	1 (<0.1)	0	2 (0.1)
Total simulation and anxiety-related AEs	75 (2.3)	19 (2.4)	60 (1.9)
Anxiety	49 (1.5)	15 (1.9)	47 (1.5)
Feeling jittery	12 (0.4)	1 (0.1)	3 (0.1)
Restlessness	7 (0.2)	0	3 (0.1)
Agitation	4 (0.1)	1 (0.1)	4 (0.1)
Psychomotor hyperactivity	3 (0.1)	2 (0.2)	0
Energy increased	2 (0.1)	0	1 (<0.1)
Nervousness	1 (<0.1)	1 (0.1)	3 (0.1)
Hypervigilance	1 (<0.1)	0	0
Anxiety disorder	0	1 (0.1)	0
Total, perceptual disturbances and psychotomimetic-related effects AEs	99 (3.1)	24 (3.0)	52 (1.6)
Paraesthesia	37 (1.2)	12 (1.5)	15 (0.5)
Abnormal dreams	16 (0.5)	2 (0.2)	6 (0.2)
Hypoaesthesia	13 (0.4)	7 (0.9)	19 (0.6)
Confusional state	6 (0.2)	2 (0.2)	1 (<0.1)
Disorientation	4 (0.1)	1 (0.1)	4 (0.1)
Anger	4 (0.1)	0	2 (0.1)
Nightmare	4 (0.1)	0	1 (<0.1)
Hypoaesthesia facial	3 (0.1)	0	1 (<0.1)
Dysaesthesia	3 (0.1)	0	0
Dysarthria	3 (0.1)	0	0
Sensory disturbance	2 (0.1)	2 (0.2)	2 (0.1)
Paraesthesia oral	2 (0.1)	1 (0.1)	0
Hyperaesthesia	2 (0.1)	0	1 (<0.1)
Dissociation	2 (0.1)	0	0
Aggression	1 (<0.1)	0	1 (<0.1)
Speech disorder	1 (<0.1)	0	1 (<0.1)
Acute psychosis	1 (<0.1)	0	0
Hypoaesthesia eye	1 (<0.1)	0	0

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Tachyphrenia	1 (<0.1)	0	0
Hallucination	0	0	1 (<0.1)
Total Substance-related disorders AEs	2 (0.1)	1 (0.1)	0
Drug withdrawal headache	1 (<0.1)	0	0
Drug withdrawal syndrome	1 (<0.1)	0	0
Substance abuse	0	1 (0.1)	0

Source: NDA 22529, ISS Statistical Report Table S10.1

As discussed in section 8.2, 2 patients on lorcaserin reported SAEs that were coded as a psychotic episode (see Appendix C for full narratives):

- Patient 2255-S039 was a 58-year-old White male with no prior psychiatric history, who was hospitalized for mixed depression and anxiety (preferred term: acute psychosis). Extended inpatient and outpatient treatment was provided for the symptoms, which persisted after study drug was discontinued. This case is also discussed in sections 8.2.3 and 8.4.3.2.2.

Reviewer comment: Despite the mapping of the verbatim term 'psychiatric crisis' to the preferred term 'acute psychosis', it is not clear that this patient actually had a psychotic event.

- Patient 2139-S030 was a 58-year-old White male with a past medical history of hypertension, gout, dyspepsia, diverticulosis, osteoarthritis, dream sleep disturbance, chornic venous insufficiency, idiopathic edema, and insomnia, who was hospitalized 9 months into treatment with lorcaserin for poor sleep, abnormal dreaming, and possible hallucinations (preferred term: alcoholic psychosis).

8.4.3.2 Depression and suicidality

8.4.3.2.1 Depression

Major depression, anxiety, or other psychiatric disease requiring treatment with prescription medication (e.g., SSRIs, SNRIs, tricyclics, antipsychotics, lithium) within the past 2 years in the BLOOM trial and within the past 1 year in the BLOSSOM trial were exclusion criteria for the lorcaserin program. At baseline, 8.0% of the pooled lorcaserin 10 mg BID group, 7.4% of the lorcaserin 10 mg QD group, and 7.9% of the placebo group reported a medical history of depression. Baseline frequency was similar between the BLOOM and BLOSSOM trials.

Depression was evaluated in two ways in the lorcaserin program: with standard adverse event reporting, and prospectively with the Beck Depression Inventory-II (BDI-II).[36] The BDI-II is a widely used self-report instrument for determining the severity of depression. The 21 items evaluated by this instrument are as follows:

[36] Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory (BDI-II). 2nd ed. San Antonio, TX: The Psychological Association; 1996.

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
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. 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 specifically on question 9 (Suicidal Thoughts or Wishes) at baseline were excluded from the trials.

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,[37] pharmacotherapy,[37] and bariatric surgery.[38]

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 trial.

BDI-II results were monitored by the investigators throughout the trials; they were provided with the following guidance in the event of a particular BDI-II score: if the

[37] Faulconbridge LF, et al. Changes in symptoms of depression with weight loss: results of a randomized trial. Obesity 2009 May; 17(5): 1009-16.
[38] Hayden MJ, et al. Characterization of the improvement in depressive symptoms following bariatric surgery. Obes Surg. 2010 Jun 18. [Epub ahead of print]

score was 0-19, the investigators were not instructed to take a specific action, in the case of a score 20-28, they were to consider referring to a primary care physician (PCP) for evaluation of possible depression, and for scores ≥ 29, they were to refer to a mental health provider (MHP) or PCP for evaluation of depression.

We looked at the BDI-II total score results by mean and categorical changes, and by visit and highest value.

As Table 68 shows, BDI-II mean total score decreased in both treatment groups and with no statistically significant difference in Week 52 mean change in total BDI-II scores between lorcaserin and placebo. It is noted that the point estimate of the mean change for the lorcaserin group is slightly greater (more negative), but the clinical significance of this change is unclear. Baseline BDI-II scores were lower than what has been previously described in obesity trials.[37,38]

Table 68. Mean Change in BDI-II Score, Week 52 LOCF, Phase 3 Trials, Pooled

Treatment	**N**	**Baseline**	**Week 52**	**Change from Baseline [LS Mean (95% CI)]**	**p-value**
Pbo	2905	4.05 (4.06)	3.22 (4.45)	-0.84 (-0.99, -0.69)	<0.001
Lorc 10 BID	2981	4.09 (4.13)	3.15 (4.47)	-0.92 (-1.07, -0.78)	<0.001
Between Treatment Difference			**Difference in LS Means (95% CI)**		**p-value**
Lorc 10 BID vs. Pbo			-0.08 (-0.29, 0.13)		0.453

Source: NDA 22529, ISS Statistical Report Table S18.3

Categorical assessments of the BDI-II total score were also undertaken, using the definitions for depression severity in the Beck manual.[36] We looked at the categorical results 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 (relative risk=2.44, p=0.12), looking at both studies combined. Nevertheless, a similar trend in the other categories was not noted. The majority of patients scored in the lowest depression category (0-13), with slightly more lorcaserin-treated patients in the lowest category as compared to those treated with placebo.

Table 69. Summary of Categorical BDI-II Total Score at Week 52 (LOCF), Phase 3 Trials

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 70. Incidence of Severe Depression based on BDI-II Total Score at Week 52 (LOCF), Phase 3 Trials

	BLOOM		BLOSSOM	
	Pbo	**Lorc 10 BID**	**Pbo**	**Lorc 10 BID**
Severe Depression	2	4	2	6
Patients with at least 1 post-baseline assessment	1428	1477	1486	1510
Incidence of Severe Depression	0.14%	0.27%	0.13%	0.40%
Relative Risk (95% CI)	1.93 (0.36, 10.54)		2.95 (0.60, 14.60)	
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	**2.44 (0.77, 7.77)**			
P-value for the statistics of Cochran-Mantel-Haenszel	**0.12**			

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Similarly, in a separate analysis of total BDI-II scores in which the highest score for Year 1 was evaluated, a slightly greater proportion of patients were classified as having severe depression.

Table 71. Summary of Categorical Highest BDI-II Total Score after Baseline to Week 52, Phase 3 Trials

	BLOOM		BLOSSOM	
	Pbo	**Lorc 10 BID**	**Pbo**	**Lorc 10 BID**
Patients with at least 1 post-baseline assessment	1428	1477	1486	1510
Severe Depression (score: 29 – 63)	6 (0.4%)	7 (0.5%)	2 (0.1%)	6 (0.4%)

Source: Reviewer created from NDA 22529 datasets

In Year 2 of BLOOM, 2 patients assigned to the lorcaserin/lorcaserin group, 1 patient assigned to the lorcaserin/placebo group, and 2 patients assigned to the placebo/placebo group had BDI-II scores ≥ 29, indicating severe depression.

Five patients had BDI-II total scores ≥ 40 at any time in the Phase 3 trials: 2 in the lorcaserin 10 mg BID group, 2 in the placebo group, and 1 in the lorcaserin/placebo group during Year 2 of BLOOM. Table 72 lists these patients by treatment group, with week of high value, associated depression AE, and whether the BDI-II question 9 (regarding suicidality) was positive. No obvious pattern emerged for these patients with the highest BDI-II scores.

Table 72. Patients with BDI-II Scores Greater than or Equal to 40, Phase 3 Trials

ID Study	Age	Sex	Race	Baseline Value	Week	Exam Value	Depression AE reported?	Question 9 positive?
Lorc 10 BID								
126-S031 BLOOM	36	F	White	0	20	40	Yes, sev: moderate, started at Week 8	Yes
2259-S003 BLOSSOM	39	F	Black	16	4	54	Yes, sev: moderate, started at Week 2	No
Lorc/Pbo								
188-S039 BLOOM	35	F	Black	1	104	48	No	Yes
Pbo								
146-014 BLOOM	24	F	White	0	24	45	Yes, sev: moderate, started at Week 22	No
2130-S040 BLOSSOM	52	F	Black	6	4	43	Yes, sev: severe, started on Day 1	No

sev=severity

Source: Reviewer created from NDA 22529 datasets

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 not seen more frequently in the lorcaserin group.

Table 73. Summary of Categorical BDI-II, Item 18 (Highest Score after Baseline), Phase 3 Trials

	BLOOM		BLOSSOM	
	Pbo	**Lorc 10 BID**	**Pbo**	**Lorc 10 BID**
No appetite at all (score=3A)	5 (0.3%)	3 (0.2%)	2 (0.1%)	6 (0.4%)
Appetite is much less (score=2A)	126 (8.0%)	268 (16.8%)	138 (8.6%)	274 (17.1%)
Appetite is somewhat less (score=1A)	685 (43.2%)	857 (53.8%)	760 (47.5%)	818 (51.1%)
No Appetite change (score=0)	580 (36.6%)	336 (21.1%)	540 (33.7%)	395 (24.7%)
Appetite is somewhat greater (score=1B)	27 (1.7%)	13 (0.1%)	42 (2.6%)	16 (1.0%)
Appetite is much greater (score=2B)	2 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Crave food all the time (score=3B)	4 (0.3%)	0 (0%)	3 (0.2%)	1 (0.1%)
Unknown	155 (9.8%)	115 (7.2%)	115 (7.2%)	91 (5.7%)

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

As an additional assessment of the potential for lorcaserin to cause depression, the sponsor evaluated the AE database for depression-related AEs by using the standardized MedDRA query (SMQ) for depression.[39] The following preferred terms were used in the search; the bolded items were those found in the lorcaserin database:

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

Table 74. 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 Table 75 demonstrates, the incidence of depression as defined by the narrow SMQ is similar between the lorcaserin and placebo groups. When the search is broadened, the imbalance between treatment groups is noted; this appears to be due primarily to lorcaserin-mediated changes in concentration and attention (these and related AEs are discussed further in section 8.4.4.1).

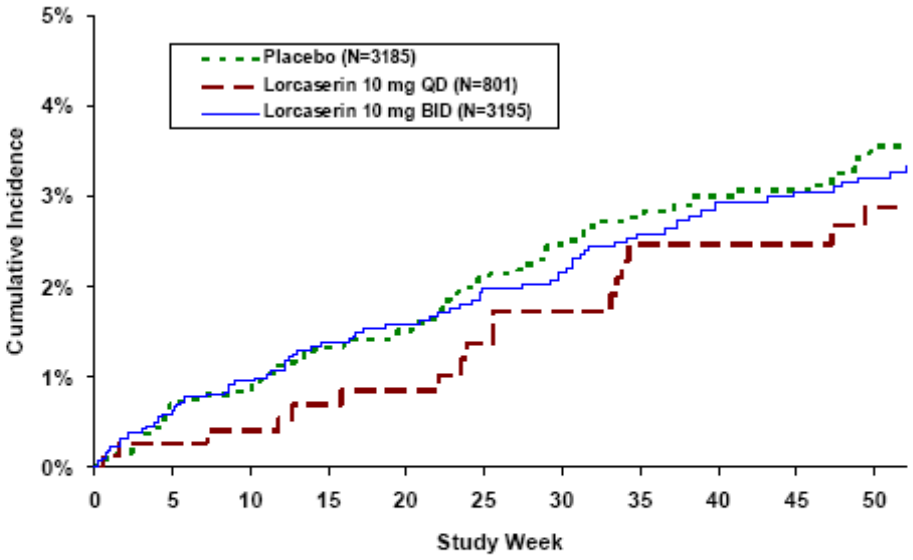
Table 75. Incidence of Depression, Phase 3 Trials, Pooled

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

Source: NDA 22529, ISS Statistical Report Table S09.1 and Response to FDA Questions from 16 July 2010 email Table 2

The sponsor additionally presented the depression SMQ results over time, as seen in Figure 16 and Figure 17.

Figure 16. Depression, Narrow SMQ

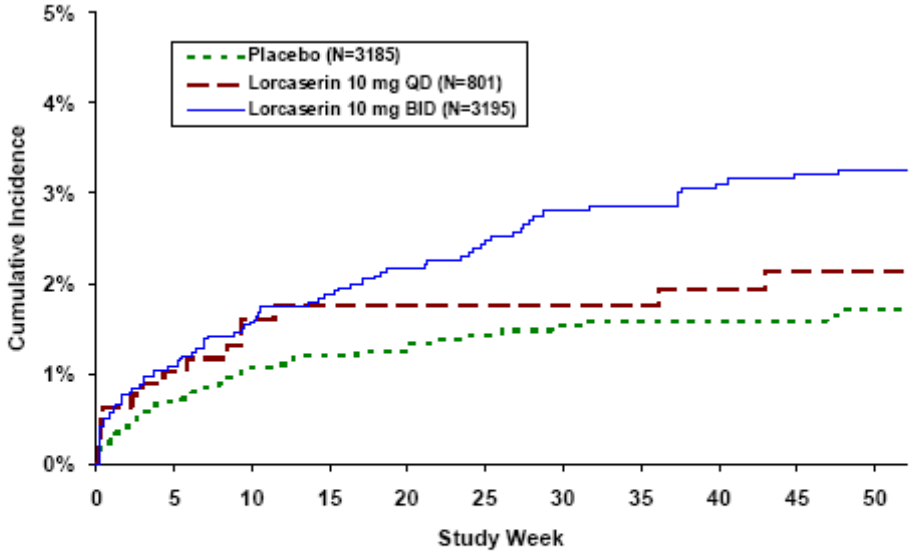


Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52
Placebo	3185	1990	1178
Lorcaserin 10 mg QD	801	574	360
Lorcaserin 10 mg BID	3195	2234	1406

Source: NDA 22529, ISS Statistical Report Figure S01.4

Figure 17. Depression, Broad SMQ



Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52
Placebo	3185	2001	1188
Lorcaserin 10 mg QD	801	572	362
Lorcaserin 10 mg BID	3195	2209	1387

Source: NDA 22529, ISS Statistical Review Figure S01.5

The Year 2 data from BLOOM provide further insight into the incidence of depression in this population when treated for a longer period of time. Table 76 describes the second year results in the re-randomized population. A greater proportion of patients in this population who were treated with lorcaserin experienced depression or depressed mood than placebo-treated patients; a similar incidence was seen in patients switched from lorcaserin to placebo. The trend seen in the broad SMQ was not seen in the second year of BLOOM.

Table 76. Incidence of Depression, BLOOM Year 2

	Lorc/Lorc N=573	**Lorc/Pbo N=283**	**Pbo/Pbo N=697**
Total, Narrow Depression SMQ	16 (2.8)	8 (2.8)	14 (2.0)
Depression	12 (2.1)	4 (1.4)	11 (1.6)
Depressed mood	5 (0.9)	4 (1.4)	3 (0.4)
Total, Broad Depression SMQ	2 (0.3)	2 (0.7)	3 (0.4)
Initial insomnia	1 (0.2)	1 (0.4)	1 (0.1)
Memory impairment	1 (0.2)	0	1 (0.1)
Disturbance in attention	0	1 (0.4)	1 (0.1)
Hypersomnia	0	0	1 (0.1)

Source: Reviewer created from NDA 22529 datasets

Some studies have suggested that patients with obesity are at a higher risk for depression,[40] with a particularly consistent relationship in women.[41,42] (This is supported by the baseline incidence of depression in the Phase 3 database: 8.6% of women and 4.7% of men reported a past medical history of depression.) 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 77), although 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 exposure (see section 5).

In this patient population, depression by narrow SMQ is similar between males and females, as reflected in the placebo groups. However, the relative incidence in the lorcaserin 10 mg BID group is greater than placebo in female patients and lower in male patients.

Table 77. Depression, Narrow SMQ by Weight Quartile and Gender

	Lorc 10 BID	**Lorc 10 QD**	**Pbo**
Q1 (≤ 88.3 kg)	27 (3.4)	2 (0.9)	18 (2.3)
Q2 (> 88.3 – 98.7 kg)	18 (2.3)	6 (2.8)	24 (3.0)
Q3 (> 98.7 – 110.5 kg)	20 (2.5)	3 (1.7)	17 (2.1)
Q4 (> 110.5 kg)	16 (2.0)	6 (3.0)	19 (2.5)
Female	73 (2.8)	16 (2.4)	62 (2.4)
Male	8 (1.4)	1 (0.7)	16 (2.6)

Source: NDA 22529, ISS Table 215 and ISS Statistical Report Tables S20.1 and S20.2

With respect to those AEs within the narrow SMQs that led to discontinuation, as noted in the earlier analysis of discontinuation AEs in section 8.3, patients in the lorcaserin 10 mg BID group were slightly more likely to discontinue due to depression AEs.

Table 78. Discontinuations due to Depression, Narrow SMQ, Phase 3 Trials

	Lorc 10 BID	**Lorc 10 QD**	**Pbo**
BLOOM	19 (1.2)	-	12 (0.8)
BLOSSOM	23 (1.4)	6 (0.7)	12 (0.7)
Pooled	42 (1.3)	6 (0.7)	24 (0.8)

Source: Reviewer created from NDA 22529 datasets

Patients in the lorcaserin 10 mg BID group were not more likely than those in the placebo group to have initiated concomitant medications identified in the sponsor's database as antidepressants:

[40] 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.
[41] 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.
[42] 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.

Table 79. Change in Antidepressant Use (Initiation or Increase), Phase 3 Trials, Pooled

	Lorc 10 BID N=3195	**Pbo N=3185**
Patients who initiated antidepressant from Baseline to Week 52, N (%)	24 (0.8)	34 (1.1)
Patients who increased dose of antidepressant from Baseline to Week 52, N (%)	3 (0.1)	1 (<0.1)

Source: NDA 22529, 2 Apr 2010 Response to 74-day filing request Tables 11 and 12

In the abuse liability study, 5 participants experienced AEs of depressed mood after single supratherapeutic doses of lorcaserin; a similar pattern was not seen in study APD356-001a, the single dose study in healthy individuals at lorcaserin doses up to 40 mg.

Table 80. Participants with Depression-Related AEs, Abuse Liability Study (APD356-013)

ID	**AE Terms**	**Lorcaserin Dose**
9006	Depressed mood and tearfulness	60 mg
9009	Depressed mood and tearfulness	60 mg
9024	Depressed mood	40 mg
9050	Depressed mood and crying	40 mg
9059	Depressed mood	20 mg
	Depressed mood and disturbance in attention	40 mg

Source: NDA 22529, ISS p 177

8.4.3.2.2 Suicidality

Recent FDA reviews of drugs for the treatment of obesity have raised concerns that certain centrally-acting agents may be associated with an increased risk for suicidality.[43,44] 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).[45] 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,[46] and is recommended by FDA for those obesity development programs that have not implemented C-SSRS.

[43] 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.

[44] 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.

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

[46] 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.

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 stated that they used a modified application of C-CASA to retrospectively assess their AE database for suicidal events, but the limitations to the sponsor's approach are discussed below.

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

In BLOOM, investigators were instructed to perform an assessment (often retrospectively) of any patient who responded with 1 or greater to question 9 of the BDI-II, or who volunteered information about potentially self-injurious thoughts or actions. A referral to a mental health professional was advised, and notes from such evaluations were obtained by the study sites. All information was provided in a blinded fashion to the sponsor, where 3 sponsor physicians considered all available information to assign a "suicidality score", using the following rating scale (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

This rating system was implemented after the BLOOM study was underway. Each sponsor physician conducted an independent review of the cases, and once the ratings were compiled, the 3 physicians met to review and discuss the cases. In those cases in which there were discrepancies in scores, some of the raters assigned a score of "5" (passive suicidal ideation), and the other(s) assigned "6" (not enough information), or "0", no suicidal ideation. During the meeting, the reviewers agreed to the following conventions in order to reach consensus:

- If a case was identified due to a positive response on the BDI-II question 9, a rating of "0" (no suicidal ideation) was not appropriate, since the patient had communicated suicidal ideation through the response.

- If a case was identified due to a positive response on the BDI-II question 9, and no additional information could be obtained from the site, and there was no indication of planning or action, passive ideation was assumed and a score of "5" rather than "6" was assigned.

Reviewer comment: This rating system is problematic for the following reasons: 1) the convention devised to ensure agreement did not appear to allow for any other answer aside from "5" (with the exception of the 2 suicide attempts, which were rated as "2"), and 2) the conventions were devised and agreed-upon by the same individuals conducting the case review and after their individual reviews were completed. One advantage of the C-SSRS as a prospective tool is that it decreases the potential for false positives that can be generated from such single item data.[47] The sponsor's modified C-CASA did not appear to have a means for case adjudication.

In BLOSSOM, the investigators (instead of the sponsor) applied the rating scale for any patient who indicated potential suicidal thoughts or actions. According to the sponsor, the ratings assigned by the investigators were accepted as final. There were no cases in which an investigator had difficulty selecting a rating, and no ratings were disputed or debated by the medical monitors or by the sponsor.

In BLOOM, the majority of suicidality ratings were based on the BDI-II question 9 results and the AEs 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 AEs independent of BDI-II administration. The narratives for these 2 patients (145-S044 and 180-S141) are in Appendix C. One AE related to suicidality ('suicidal ideation', patient 189-S044, placebo) was reported without a corresponding BDI-II question 9 score. See the narrative in Appendix C.

In BLOSSOM, all patients with AEs of suicidal ideation or behavior had a positive BDI-II question 9 score. One patient (2182-S037, lorcaserin 10 mg BID) presented to the emergency room with suicidal thoughts and depression and had an AE that was generated independently from the positive BDI-II question 9 scores that she had on 2 occasions (see narrative in Appendix C). All ratings in BLOSSOM were coded by the investigators as "5" (passive ideation).

We evaluated the positive BDI-II question 9 scores at Week 52 and by highest value in Year 1.

[47] Posner K. C-CASA and C-SSRS in CNS Clinical Trials: Development and Implementation. At: http://www.iom.edu/~/media/Files/Activity%20Files/Research/NeuroForum/Suicidality%20meeting/web%20files/Posner.ashx. Accessed 1 July 2010.

Table 81. Summary of Categorical BDI-II, Item 9 at Week 52 (LOCF) by Treatment Group, Phase 3 Trials

	BLOOM		BLOSSOM	
	Placebo	**Lorc 10 BID**	**Placebo**	**Lorc 10 BID**
Suicidal Thoughts (score: 1 ~ 3)	9 (0.6%)	6 (0.4%)	6 (0.4%)	12 (0.8%)
Non Suicidal Thoughts (score: 0)	1420 (89.7%)	1472 (92.4%)	1480 (92.4%)	1500 (93.6%)
Unknown (score: missing)	155 (9.8%)	115 (7.2%)	115 (7.2%)	90 (5.6%)

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 82. Incidence of Suicidal Thoughts based on BDI-II Item 9 at Week 52 (LOCF) by Treatment Group, Phase 3 Trials

	BLOOM		BLOSSOM	
	Placebo	**Lorc 10 BID**	**Placebo**	**Lorc 10 BID**
Suicidal Thoughts	9	6	6	12
Patients with at least 1 post-baseline assessment	1429	1478	1486	1512
Incidence of Suicidal Thoughts	0.63%	0.41%	0.40%	0.79%
Relative Risk (95% CI)	0.65 (0.23, 1.81)		1.97 (0.74, 5.22)	
Mantel-Haenszel 'Pooled' Relative Risk (95% CI)	**1.20 (0.604, 2.370)**			
P-value for the statistics of Cochran-Mantel-Haenszel	**0.65**			

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

When evaluating BDI-II question 9 by highest score at any time in the study, slightly more patients in the lorcaserin 10 mg BID group had positive scores on at least one occasion as compared to the placebo group (Table 83).

Table 83. Summary of Categorical BDI-II, Item 9 (Highest Score after Baseline to Week 52) by Treatment Group, Phase 3 Trials

	BLOOM		BLOSSOM	
	Placebo	**Lorc 10 BID**	**Placebo**	**Lorc 10 BID**
Patients with at least 1 post-baseline assessment	1429	1478	1486	1512
Suicidal Thoughts (score: 1 ~ 3)	16 (1.1%)	17 (1.2%)	12 (0.8%)	17 (1.1%)

Source: Reviewer created from NDA 22529 datasets

In Year 2 of BLOOM, 10 patients reported a post-baseline BDI-II question 9 score > 0 (not including those with a positive screening BDI-II question 9 score), 4 patients randomized to lorcaserin/lorcaserin, 5 patients re-randomized from lorcaserin to placebo (lorcaserin/placebo), and 1 patient randomized to placebo/placebo.

Investigators reported results of the BDI-II inconsistently as AEs. With the exception of 2 suicide attempts and 2 instances in which patients reported a suicidal thought

independent of the BDI-II (see discussion above), all AEs in the Suicide/Self-injury SMQ were derived from the BDI-II question 9 results.

In BLOOM, most investigators did not report positive question 9 responses as AEs, whereas investigators in BLOSSOM were instructed to record positive responses as AEs in order to facilitate application of the modified C-CASA process. Despite this, not all positive BDI-II question 9 responses were reported as AEs.

Reviewer comment: We identified two events from narratives that should have, at a minimum, been adjudicated for possible suicidal ideation; see the narratives for patient 2174-S061 and patient 2255-S039 in Appendix C. These cases underscore the limitations of identifying potential cases using only single item scores and MedDRA preferred terms.

Table 84. Suicide/Self-Injury SMQ AEs, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
Total, suicide/self-injury SMQ	19 (0.6)	6 (0.7)	14 (0.4)
Suicidal ideation	18 (0.6)	5 (0.6)	13 (0.4)
Self-injurious ideation	0	0	1 (<0.1)
Suicide attempt	1 (<0.1)	0	0
Depression suicidal	0	1 (0.1)	0

Source: NDA 22529, ISS Table 64

Table 85. Suicide/Self-Injury SMQ AEs, BLOOM Year 2

	Lorc/Lorc N=573	**Lorc/Pbo N=283**	**Pbo/Pbo N=697**
Total, suicide/self-injury SMQ	1 (0.2)	1 (0.4)	0
Suicidal ideation	1 (0.2)	1 (0.4)	0
Intentional overdose	0	1 (0.4)	0

Source: NDA 22529, ISS Table 64

8.4.4 Neurological Safety Issues

8.4.4.1 Cognitive effects

Centrally-acting obesity drugs of a variety of mechanisms have been found to possess neuropsychiatric effects, including adverse effects on cognition.[48] 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.[35,49]

[48] Nathan PJ, et al. Neuropsychiatric adverse effects of centrally acting obesity drugs. CNS Neurosci Ther 2010 Jul 7. [Epub ahead of print]

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

In APD356-001a, a single-dose study in healthy subjects, the following cognitive tests were conducted pre-dose and at 2, 4, and 8 hours post-dose: Four-Choice Reaction Time Task, Memory Scanning, and Trail Making Test. No obvious impairment was reported.

In study APD356-002, a multiple-dose study in healthy subjects, cognitive function was assessed using a battery of tasks from the Cognitive Drug Research (CDR) computerized assessment system. The following tests were conducted: Immediate Word Recall, Picture Presentation, Simple Reaction Time, Digit Vigilance, Choice Reaction Time, Spatial Working Memory, Numeric Working Memory, Delayed Word Recall, Word Recognition, and Picture Recognition.

The sponsor maintained that there was no clear support for a clinically relevant pattern of dose-dependent impairment to cognition following multiple doses of 3, 10, or 20 mg lorcaserin over 14 days. 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.[49]

Cognitive AEs from the single dose (healthy individuals) and Phase 2 trials, respectively, are as follows:

Table 86. Cognitive AEs from Pooled Single Dose Studies, Healthy Individuals

	Pbo N=35	**Lorc 0.1 N=20**	**Lorc 1 N=20**	**Lorc 10 N=114**	**Lorc 20 N=12**	**Lorc 40 N=6**
Total	0	0	0	1 (1.0)	1 (8.3)	0
Disturbance in attention	0	0	0	0	1 (8.3)	0
Cognitive disorder	0	0	0	1 (1.0)	0	0

Source: NDA 22529, ISS Table 252

Table 87. Cognitive AEs from Phase 2 Trials

	APD356-003				**APD356-004**			
	Pbo N=86	**Lorc 1 QD N=90**	**Lorc 5 QD N=89**	**Lorc 15 QD N=87**	**Pbo N=118**	**Lorc 10 QD N=117**	**Lorc 15 QD N=118**	**Lorc 10 BID N=116**
Total	1 (1.2)	0	0	0	0	2 (1.7)	0	0
Amnesia	0	0	0	0	0	1 (0.9)	0	0
Depressed level of consciousness	1 (1.2)	0	0	0	0	0	0	0
Mental status change	0	0	0	0	0	1 (0.9)	0	0

Source: NDA 22529, ISS Table 255

We conducted an exploratory analysis of cognitive impairment in the Phase 3 trials using the MedDRA Dementia SMQ. 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:

Table 88. 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 89 demonstrates that patients in the lorcaserin 10 mg BID treatment group reported these cognitive AEs approximately 3 times more frequently than those in the lorcaserin 10 mg QD or placebo groups.

Table 89. Cognitive-Related AEs, Pooled Phase 3 Trials

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

Source: Reviewer created from NDA 22529 datasets

Adverse events in Table 90 were reported as SAEs. The available narratives can be found in Appendix C. Patient 180-S108, in particular, had a compelling event of dysphasia/aphasia (word finding impairment) shortly after starting lorcaserin that was alleviated with drug discontinuation.

Table 90. Cognitive-Related SAEs, Pooled Phase 3 Trials

Study	ID	Treatment	Verbatim Term	MedDRA Preferred Term
BLOOM	180-S108	Lorcaserin 10 mg BID	DYSPHASIA	Dysphasia
BLOOM	189-S070	Lorcaserin 10 mg BID	SHORT TERM MEMORY LOSS	Amnesia

Source: Reviewer created from NDA 22529 datasets

In Year 2 of BLOOM, there were 4 additional events in the modified dementia SMQ: 2 (0.3%) in the lorcaserin/lorcaserin group (PTs: 'confusional state' and 'memory impairment') and 2 (0.3%) in the placebo/placebo group (PTs: 'memory impairment' and 'aphasia'). The lorcaserin-treated patients were not discontinued from the trial due to these AEs.

8.4.4.2 Seizures

Seizures were reported in the animal studies, but at high clinical exposure multiples. Seizures occurred at single doses of lorcaserin 100 and 300 mg/kg in the mouse. A dose of 250 mg/kg/day produced exposure multiples of 25 and 27 times (males and females) the exposure achieved in humans at a dose of lorcaserin 10 mg BID. One male cynomolgous monkey given 100 mg/kg/day (human exposure multiple: 74) in a 28-day study experienced a seizure.

Three AEs of seizure/convulsion occurred in the lorcaserin development program; 2 randomized to lorcaserin and one patient still blinded in the BLOOM-DM trial. In

addition, there was one AE of opisthotonus after 1 day of dosing in a patient randomized to lorcaserin who ultimately was diagnosed with partial seizures (this case was not captured as a seizure AE, but was found in the narratives of patients with possible serotonin-related AEs). There was also one AE in a placebo-treated patient reported as syncopal episode as per a hospital discharge summary, although it was somewhat unclear if this patient had experienced seizure-like activity.

Two of the 3 seizure AEs were new-onset, 1 in a patient randomized to lorcaserin 10 mg BID (study APD356-004) and 1 in a patient still blinded to treatment (BLOOM-DM). The latter patient had 2 seizure events.

In the APD356-004 trial, a 12-week, placebo-controlled trial of lorcaserin in obese adults, 1 seizure was reported in a patient treated with lorcaserin 10 mg BID (patient 15-002). This event was discussed in section 8.2.2 (SAEs) and the narrative is presented in Appendix C.

No seizures were reported in the 2 year BLOOM trial. One event that was ultimately coded as a syncopal episode was initially reported as seizure versus vasovagal faint in a patient treated with placebo:

- A SAE was reported for patient 154-S027 assigned to placebo. This was a 55-year-old White female with a history of hypertension (treated with lisinopril), previous history of syncopal episodes and heavy alcohol use, who felt unwell, had nausea in the evening of presentation and passed out while having a bowel movement. She returned to the living room, felt faint, and then reportedly lost consciousness again. Her friend reported that her body became stiff and she was making "funny faces". She was treated in the ER for low sodium and potassium, had a negative head CT, and was kept in the hospital overnight for observation. The discharge summary diagnosis was syncopal episode.

No seizures were reported as SAEs in the BLOSSOM trial. One AE of "seizure like activity" (verbatim term) was reported as an adverse event in a patient treated with lorcaserin 10 mg BID:

- Patient 2211-S023 was a 20-year-old Hispanic female with a history of back pain, no tobacco or alcohol use, and on no concomitant medications. Three months into the study, an AE of "seizure like activity" during phlebotomy was reported, moderate in intensity, unlikely related to study drug, and resolved on the same day. She reported a history of several similar events that had occurred since childhood. The patient was withdrawn from the study in response to the adverse event, and chose not to pursue neurological work-up.

One AE of opisthotonus in a patient treated with lorcaserin 10 mg BID and subsequently diagnosed with partial seizures was reported:

- Patient 2118-S028 was a 29-year-old Black female who was randomized to lorcaserin 10 mg BID. The patient experienced an AE of opisthotonus (verbatim term: dystonic reaction) on Study Day 1. She presented for randomization with symptoms of an upper respiratory infection (URI). Following the study visit (during which she received her first dose of study drug), the patient presented to an emergency department for evaluation of the URI. She was diagnosed with acute asthma, and was given prednisone; shortly after receiving the prednisone, a dystonic reaction occurred, which was treated with diphenhydramine and benztropine mesylate. She discontinued from the study due to the adverse event. The patient subsequently underwent evaluation by a neurologist, who diagnosed partial seizures and initiated treatment with an unknown medication. The AE of opisthotonus was considered by the investigator to be moderate in intensity, and was initially considered probably related to study drug. Emergency department personnel attributed the reaction to the prednisone administration.

Reviewer comment: The dystonic reaction appears unlikely related to lorcaserin given the temporal relationship to prednisone. The basis for the seizure diagnosis is unclear from the narrative.

Two seizures were reported in the BLOOM-DM trial in a single patient; these were reported as SAEs. This report is still blinded, and the narrative is presented in Appendix C.

8.4.4.3 Paraesthesia

Paraesthesia was seen more frequently in lorcaserin-treated groups than in those treated with placebo, although there was not a clear dose-relationship. The following table is a compilation of paraesthesia events (MedDRA preferred terms: ‘paraesthesia’, ‘paraesthesia oral’) from the lorcaserin clinical studies:

Table 91. Paraesthesia AEs

	Treatment	n (%) with Paraesthesia
Single Dose Studies, Healthy Participants		
Pooled	Pbo	0
	Lorc 0.1	0
	Lorc 1	0
	Lorc 10	1 (0.9)
	Lorc 20	1 (8.3)
	Lorc 40	0
Multiple Dose, Healthy Participants		
APD356-002	Pbo	0
	Lorc 3	0
	Lorc 10	0
	Lorc 20	0
APD356-007	Pbo	0
	Lorc 15 QD	9 (15.0)
	Lorc 40 QD	12 (18.8)
DDI Studies		
APD356-008	Pbo/Dex	0
	Lorc 20 QD	1 (4.0)
APD356-012	Pbo/Dex	0
	Lorc 10 BID	2 (8.3)
Specific Populations		
APD356-016	Lorc 10	0
APD356-017	Lorc 10	0
APD356-013	Pbo	1 (3.2)
	Lorc 20	1 (3.0)
	Lorc 40	5 (14.7)
	Lorc 60	5 (16.1)
Phase 2		
APD356-003	Pbo	0
	Lorc 1 QD	0
	Lorc 5 QD	1 (1.1)
	Lorc 15 QD	1 (1.1)
APD356-004	Pbo	1 (0.8)
	Lorc 10 QD	2 (1.7)
	Lorc 15 QD	0
	Lorc 10 BID	0
Phase 3		
Pooled, Year 1	Pbo	15 (0.5)
	Lorc 10 QD	12 (1.5)
	Lorc 10 BID	38 (1.2)
BLOOM, Year 2	Lorc/Lorc	4 (0.7)
	Lorc/Pbo	2 (0.7)
	Pbo/Pbo	1 (0.1)

Source: NDA 22529, ISS Table 72 and APD356-009 CSR Table 14.3.8

8.4.4.4 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. As discussed in section 8.3, discontinuations due to dizziness in the Phase 3 trials were more frequently seen in the lorcaserin 10 mg BID group (0.7%) than in the lorcaserin 10 mg QD (0.2%) or placebo (0.2%) groups.

Table 92. Dizziness AEs

	Treatment	n (%) with Dizziness
Single Dose Studies, Healthy Participants		
Pooled	Pbo	0
	Lorc 0.1	0
	Lorc 1	1 (5.0)
	Lorc 10	9 (7.9)
	Lorc 20	3 (25.0)
	Lorc 40	3 (50.0)
Multiple Dose, Healthy Participants		
APD356-002	Pbo	1 (11.1)
	Lorc 3	0
	Lorc 10	0
	Lorc 20	1 (16.7)
APD356-007	Pbo	3 (3.3)
	Lorc 15 QD	14 (16.7)
	Lorc 40 QD	50 (45.3)
DDI Studies		
APD356-008	Pbo/Dex	0
	Lorc 20 QD	9 (37.5)
APD356-012	Pbo/Dex	4 (16.7)
	Lorc 10 BID	6 (25.0)
Specific Populations		
APD356-016	Lorc 10	2 (5.0)
APD356-017	Lorc 10	1 (4.2)
APD356-013	Pbo	0
	Lorc 20	1 (3.0)
	Lorc 40	5 (14.7)
	Lorc 60	6 (19.4)
Phase 2		
APD356-003	Pbo	3 (3.5)
	Lorc 1 QD	2 (2.2)
	Lorc 5 QD	1 (1.1)
	Lorc 15 QD	4 (4.6)
APD356-004	Pbo	0
	Lorc 10 QD	7 (6.0)
	Lorc 15 QD	9 (7.6)
	Lorc 10 BID	9 (7.8)
Phase 3		
Pooled, Year 1	Pbo	123 (3.9)
	Lorc 10 QD	50 (6.2)
	Lorc 10 BID	273 (8.5)
BLOOM, Year 2	Lorc/Lorc	11 (1.9)
	Lorc/Pbo	8 (2.8)
	Pbo/Pbo	17 (2.4)

Source: NDA 22529, ISS Table 74 and APD356-009 CSR Table 14.3.8

The following tables suggest that lower weight patients and women are more susceptible to lorcaserin-related dizziness:

Table 93. Dizziness by Baseline Body Weight, Pooled Phase 3 Trials

	Lorc 10 BID	Lorc 10 QD	Pbo
Q1 (≤ 88.3 kg)	89 (11.3)	22 (10.3)	23 (2.9)
Q2 (> 88.3 - 98.7 kg)	74 (9.4)	13 (6.0)	36 (4.5)
Q3 (> 98.7 - 110.5 kg)	67 (8.3)	6 (3.4)	31 (3.8)
Q4 (> 110.5 kg)	43 (5.3)	9 (4.5)	33 (4.3)

Source: NDA 22529, ISS Table 215

Table 94. Dizziness by Sex, Pooled Phase 3 Trials

	Women		Men	
	Lorc 10 BID N=2610	**Placebo N=2580**	**Lorc 10 BID N=585**	**Placebo N=605**
Total	243 (9.3)	94 (3.6)	30 (5.1)	29 (4.8)
Dizziness	241 (9.2)	93 (3.6)	29 (5.0)	29 (4.8)
Dizziness postural	3 (0.1)	1 (<0.1)	1 (0.2)	0

Source: NDA 22529, ISS Statistical Report Tables S20.1 and S20.2

8.4.4.5 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. As discussed in section 8.3, discontinuations due to headache in the Phase 3 trials were seen only somewhat more frequently in the lorcaserin 10 mg BID (1.3%) and the lorcaserin 10 mg QD (1.2%) groups than the placebo (0.8%) group.

Table 95. Headache AEs

	Treatment	n (%) with Headache
Single Dose Studies, Healthy Participants		
Pooled	Pbo	6 (17.1)
	Lorc 0.1	3 (15.0)
	Lorc 1	0
	Lorc 10	37 (32.5)
	Lorc 20	7 (58.3)
	Lorc 40	5 (83.3)
Multiple Dose, Healthy Participants		
APD356-002	Pbo	1 (11.1)
	Lorc 3	0
	Lorc 10	3 (50.0)
	Lorc 20	5 (83.3)
APD356-007	Pbo	12 (11.7)
	Lorc 15 QD	53 (58.3)
	Lorc 40 QD	63 (82.8)
DDI Studies		
APD356-008	Pbo/Dex	1 (4.2)
	Lorc 20 QD	17 (70.8)
APD356-012	Pbo/Dex	3 (12.5)
	Lorc 10 BID	13 (54.2)
Specific Populations		
APD356-016	Lorc 10	4 (10.0)
APD356-017	Lorc 10	1 (4.2)
APD356-013	Pbo	8 (25.8)
	Lorc 20	20 (60.6)
	Lorc 40	29 (85.3)
	Lorc 60	26 (83.9)
Phase 2		
APD356-003	Pbo	12 (14.0)
	Lorc 1 QD	14 (15.6)
	Lorc 5 QD	7 (7.9)
	Lorc 15 QD	18 (20.7)
APD356-004	Pbo	21 (17.8)
	Lorc 10 QD	35 (29.9)
	Lorc 15 QD	38 (32.2)
	Lorc 10 BID	31 (26.7)
Phase 3		
Pooled, Year 1	Pbo	321 (10.1)
	Lorc 10 QD	125 (15.6)
	Lorc 10 BID	537 (16.8)
BLOOM, Year 2	Lorc/Lorc	41 (7.2)
	Lorc/Pbo	18 (6.4)
	Pbo/Pbo	30 (4.3)

Dex=dextromethorphan

Source: NDA 22529, ISS Tables 18, 21, 29, 31, 33, and 35, and APD356-009 CSR Table 67

Headaches were seen more frequently in the Phase 3 program in women than in men, but the impact of lorcaserin on headaches was similar between the groups.

Table 96. Headache AEs by Sex, Pooled Phase 3 Trials

	Women		Men	
	Lorc 10 BID N=2610	**Placebo N=2580**	**Lorc 10 BID N=585**	**Placebo N=605**
Total	484 (18.5)	286 (11.1)	84 (14.4)	51 (8.4)
Headache	458 (17.5)	271 (10.5)	79 (13.5)	50 (8.3)
Tension headache	29 (1.1)	19 (0.7)	5 (0.9)	1 (0.2)
Drug withdrawal headache	1 (<0.1)	0	0	0

Source: NDA 22529, ISS Table 23

8.4.5 Malignancies

In 2-year carcinogenicity studies in rats, lorcaserin caused mammary gland tumors in both genders 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 and therefore clinical relevance is uncertain. Please see Dr. Fred Alavi's review for details of the animal findings.

Overall, malignancies were seen infrequently in the Phase 3 program. No formal cancer screening was conducted.

Table 97. Neoplasms (MedDRA Malignant or unspecified tumours SMQ), Pooled Phase 3 Trials

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Total	24 (0.8)	4 (0.5)	31 (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 (0.2)
Prostate cancer	2 (0.1)	1 (0.1)	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)	0	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	0
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)

Source: Reviewer created from NDA 22529 datasets

Table 98. 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 NDA 22529 datasets

8.4.5.1 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 malignant breast cells *in vitro*.[50] However, mechanistic studies conducted in animals do not conclusively support attribution of lorcaserin-induced increases in mammary tumors to prolactin. The relationship of prolactin to human breast carcinogenesis is unknown. Because lorcaserin increased prolactin concentrations after single doses in study APD356-001a (see section 5.2), the sponsor was asked to conduct an evaluation of chronic prolactin release in the Phase 3 program.

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.[51] 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.[52]

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.[53] 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.[52] With the exception of oral contraceptives, a relationship between these medications and breast cancer has not been definitely demonstrated to date.[53] However, studies have generally been limited by short duration and low risk populations.

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 a dedicated substudy evaluating effects on prolactin concentrations with chronic administration.

Over the 2 years of the Phase 3 trials, 7 women randomized to lorcaserin 10 mg BID (0.3% of women), 1 woman randomized to lorcaserin 10 mg QD (0.2%), and 5 women randomized to placebo (0.2%) were diagnosed with a breast neoplasm, as shown in Table 99. On average, women with breast cancer exposed to lorcaserin were slightly younger (50 vs. 52 years) and were diagnosed later in the trial (205 vs. 125 days).

[50] 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.
[51] Freeman ME, et al. Prolactin: structure, function, and regulation of secretion. Physiol Rev 2000; 80: 1523-631.
[52] Haddad PM and Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. Drugs 2004; 64(20): 2291-314.
[53] Tworoger SS and Hankinson SE. Prolactin and breast cancer etiology: an epidemiologic perspective. J Mammary Gland Biol Neoplasia 2008 Mar; 13(1): 41-53.

Table 99. 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

As would be expected, transient increases in plasma prolactin were observed after single-dose lorcaserin administration in study APD356-001a. 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.

In order to assess the effects of lorcaserin on prolactin concentrations over chronic dosing, a substudy within the BLOSSOM Phase 3 trial was conducted.

Blood samples for prolactin measurement were collected from all patients at selected sites (n=20 sites, 1504 patients), constituting approximately 38% of randomized patients. Samples were obtained in the morning prior to administration of study medication and 2 ± 0.5 hours after study drug administration on Day 1 and at Weeks 4, 12, 24 and 52/exit. 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 (gender, menopausal status) and treatment group.

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 100. Baseline Prolactin Concentrations (Mean and Range), BLOSSOM Substudy

	Lorc 10 BID	**Lorc 10 QD**	**Pbo**
Mean (SD), ng/mL	9.17 (7.58)	9.45 (6.88)	9.75 (11.13)
Range, ng/mL	1.4-87.6	0.5-36.6	2.5-141

Source: NDA 22529, APD356-011 Supplemental Report Table 2

At baseline, prolactin concentrations in quartiles were as follows:

Table 101. Baseline Prolactin Concentrations (Quartiles, ng/mL), BLOSSOM Substudy

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
Pre/perimenopausal Pbo	≤ 6.25	> 6.25-8.50	> 8.50-11.75	> 11.75
Pre/perimenopausal Lorc 10 QD	≤ 6.50	> 6.50-8.60	> 8.60-12.00	> 12.00
Pre/perimenopausal Lorc 10 BID	≤ 6.20	> 6.20-8.20	> 8.20-11.90	> 11.90
Postmenopausal Pbo	≤ 5.00	> 5.00-6.50	> 6.50-8.70	> 8.70
Postmenopausal Lorc 10 QD	≤ 5.00	> 5.00-6.00	> 6.00-10.40	> 10.40
Postmenopausal Lorc 10 BID	≤ 4.60	> 4.60-5.70	> 5.70-8.15	> 8.15
Men Pbo	≤ 5.30	> 5.30-6.90	> 6.90-9.40	> 9.40
Men Lorc 10 QD	≤ 5.15	> 5.15-6.60	> 6.60-8.80	> 8.80
Men Lorc 10 BID	≤ 5.15	> 5.15-6.50	> 6.50-8.65	> 8.65
Total Pbo	≤ 5.50	> 5.50-7.50	> 7.50-10.90	> 10.90
Total Lorc 10 QD	≤ 5.60	> 5.60-7.75	> 7.75-11.60	> 11.60
Total Lorc 10 BID	≤ 5.30	> 5.30-7.50	> 7.50-10.90	> 10.90

Source: NDA 22529, APD356-011 Supplemental 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 102). It is unclear if the lower prolactin concentrations in the BLOSSOM trial reflect a true prolactin difference in the obese population, if it reflects that the patients in the BLOSSOM trial had a lower baseline breast cancer risk than the general population, or if the difference was assay-related. Based on a National Cancer

Institute (NCI) Breast Cancer Risk Assessment Tool (BCRT) survey[54] 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.

Table 102. 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 55 and 56

Lorcaserin was associated with increases from pre-dose to post-dose at all time points, and the proportion of patients who increased in prolactin quartile from pre- to post-dose increased at all time points (Table 103).

Lorcaserin was also associated with small increases in mean pre-dose prolactin from baseline to post-baseline visits. However, lorcaserin was not associated with an increase in the proportion of patients with an increase in prolactin quartile (Table 103) or pre-dose prolactin above the upper limit of normal.

[54] http://www.cancer.gov/bcrisktool Accessed 10 July 2010.
[55] 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.
[56] Tworoger SS, et al. Plasma prolactin concentrations and risk of postmenopausal breast cancer. Cancer Res 2004 Sept; 64: 6814.

Table 103. Percent of Patients with Increase in Prolactin Quartile, BLOSSOM Substudy

		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	30.2	28.4	5.8	-	-	-
	Postmenopausal	25.0	22.8	10.4	-	-	-
	Men	18.6	15.9	11.4	-	-	-
	Total	25.5	18.9	6.0	-	-	-
Week 4	Pre/perimenopausal	27.1	28.4	21.1	25.6	29.9	25.4
	Postmenopausal	23.4	19.6	16.5	24.6	23.4	26.0
	Men	12.9	19.2	14.3	22.8	30.0	19.1
	Total	24.3	19.3	15.8	23.6	25.5	23.7
Week 12	Pre/perimenopausal	37.0	33.3	15.1	25.4	24.1	21.6
	Postmenopausal	26.5	22.0	16.3	25.3	26.2	24.3
	Men	23.1	31.8	26.7	27.0	26.1	21.5
	Total	28.5	22.7	15.8	27.1	28.7	25.6
Week 24	Pre/perimenopausal	38.7	37.5	23.0	24.7	18.4	31.6
	Postmenopausal	28.6	16.7	12.5	30.8	13.9	26.8
	Men	14.9	11.8	18.4	28.3	31.6	32.1
	Total	27.4	23.8	20.0	28.0	20.9	28.8
Week 52	Pre/perimenopausal	29.3	26.8	19.6	34.1	18.2	29.2
	Postmenopausal	33.8	23.3	8.7	35.4	21.2	23.6
	Men	27.0	21.4	18.2	28.6	21.4	29.2
	Total	30.9	25.3	17.5	33.1	24.5	29.5

Source: NDA 22529, APD356-011 Supplemental Report Tables 5 and 7

Reviewer comment: This reviewer would agree with the sponsor's interpretation that lorcaserin increases prolactin concentrations transiently after dosing, but is not associated with persistent increases in prolactin with chronic dosing. Although there were no patients found to have significant prolactin elevations in the substudy, the data collection was limited. These data cannot rule out significant lorcaserin-related increases in prolactin that may occur rarely.

Relevant prolactin data were not acquired at the time of diagnosis for any of the patients diagnosed with breast cancer during the study (Table 99). Two of these patients had prolactin concentrations collected during the BLOSSOM substudy (2203-S032 and 2141-S039); all values were within normal limits.

8.4.6 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.[57,58] Recent

[57] Boyer EW and Shannon M. The serotonin syndrome. N Engl J Med 2005; 352 (11): 1112-20.
[58] Wappler F, et al. Pathological role of serotonin system in malignant hyperthermia. Br J Anaesth 2001; 87: 794-8.

work in this area suggests that agonism at the 5HT2A receptor contributes to serotonin syndrome.[57,59]

There were 2 cases within the lorcaserin development program that the investigators considered to fall within the spectrum of serotonin toxicity:

- Phase 2 patient 25/007 from study APD356-004 (lorcaserin 10 mg BID) was mentioned in section 8.3.

- There was one adverse event with a preferred term of 'serotonin syndrome' in the Phase 3 trials. The narrative of this case in a patient (2109-S025) randomized to lorcaserin 10 mg BID concomitantly taking guiafenisen with dextromethorphan for upper respiratory symptoms can be found in Appendix C.

Reviewer comment: Although the sponsor dismissed this case as not meeting strict serotonin syndrome criteria, Boyer and Shannon note that manifestations of the syndrome can range from barely perceptible to lethal.[57] Supratherapeutic doses of dextromethorphan have been described as pro-serotonergic in combination with a SSRI.[60] This case was notable for a dextromethorphan positive re-challenge and de-challenge.

The time-to-event plot in Figure 18 is based on the incidence of a combination of preferred terms in the Phase 3 program: these preferred terms were derived from the major diagnostic criteria for serotonin syndrome by the sponsor. Bolded preferred terms are those that occurred in the lorcaserin Phase 3 database.

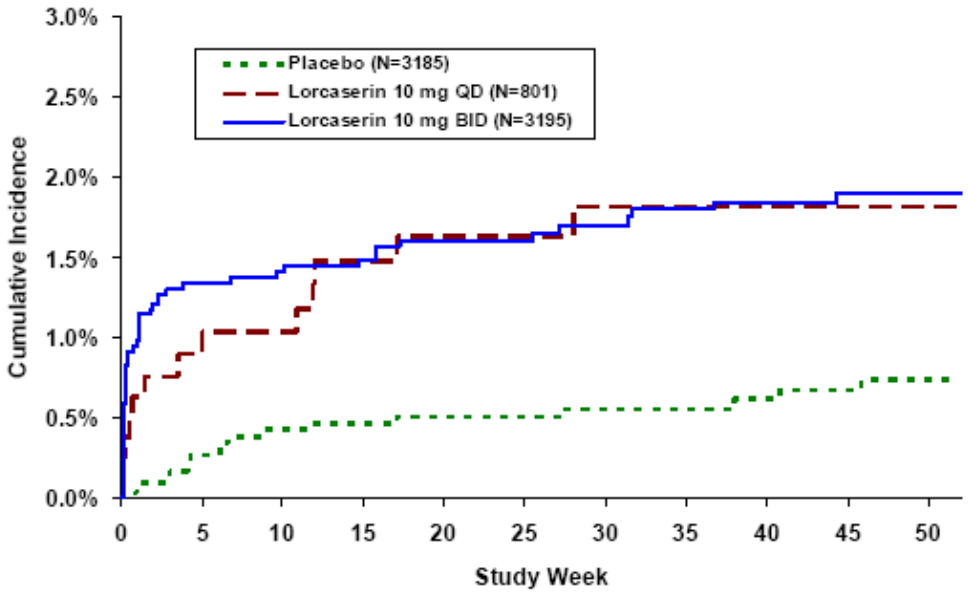
[59] Isbister GK and Whyte IM. Serotonin toxicity and malignant hyperthermia: role of 5HT2 receptors. Br J Anaesth 2002; 88(4): 603.
[60] Schwartz AR, et al. Dextromethorphan-induced serotonin syndrome. Clin Toxicol 2008 Sep; 46(8): 771-3.

Table 104. MedDRA Preferred Terms Potentially Related to Serotonin Toxicity

Serotonin Toxicity Preferred Terms
Confusional state
Disorientation
Delirium
Coma (or any PT that contained "coma")
Hyperthermia
Hyperhidrosis
Sweating fever
Clonus
Myoclonus
Hypertonia
Opsoclonus myoclonus
Tremor
Intention tremor
Essential tremor
Chills
Hyperreflex

Source: NDA 22529, ISS p 199

Figure 18. Time to First Event of Potentially Serotonin-Related Adverse Events During 52 Weeks of Study



Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52
Placebo	3185	2014	1198
Lorcaserin 10 mg QD	801	572	366
Lorcaserin 10 mg BID	3195	2227	1408

Source: NDA 22529, ISS Statistical Review Figure S01.3

'Chills', 'tremor', and 'confusional state' primarily drive the imbalance seen in the lorcaserin-treated groups. No severe manifestations of serotonin syndrome, such as hyperthermia or neuromuscular rigidity were reported.

Table 105. Incidence of AEs Potentially Related to Serotonin Toxicity, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
Serotonin Syndrome/Toxicity	55 (1.7)	13 (1.6)	18 (0.6)
Chills	32 (1.0)	6 (0.7)	6 (0.2)
Tremor	10 (0.3)	3 (0.4)	3 (0.1)
Confusional state	6 (0.2)	2 (0.2)	1 (<0.1)
Disorientation	4 (0.1)	1 (0.1)	4 (0.1)
Hyperhidrosis	2 (0.1)	1 (0.1)	6 (0.2)
Intention tremor	1 (<0.1)	0	0

Source: NDA 22529, ISS Table 80

8.5 Other Adverse Events and Related Laboratory Findings

8.5.1 Hepatobiliary Events and Related Laboratory Data

8.5.1.1 Hepatic events

One subject treated with lorcaserin 10 mg BID in the BLOOM trial (patient 111-S002) 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 and was withdrawn from study on Study Day 1 after dosing. 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. Laboratory data for this patient are presented below.

Table 106. Laboratory Data, BLOOM Patient 111-S002

	Screen	**Random**	**Wk 2 (Unscheduled)**	**Wk 4**	**Wk 12 (Last visit)**
Alkaline phosphatase (U/L)	140	516	568	206	176
ALT (U/L)	18	140	236	110	70
AST (U/L)	16	45	133	48	43
Total bilirubin (mg/dL)	0.1	0.2	0.3	0.3	0.3

Source: Reviewer created from NDA 22529 datasets

Two other liver-related adverse events from the hepatobiliary SOC occurred in 2 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: 1 patient was treated with lorcaserin 10 mg BID in the first year and re-randomized to

placebo in the second year (AE occurred on Study Day 602) and 1 patient was treated with placebo throughout the 2-year trial (AE occurred on Study Day 496).

The FDA Guidance for evaluating premarketing drug-induced liver injury[61] 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 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: > upper limit of normal (ULN), > 3x ULN, > 5x ULN, and > 20x ULN. There were 5 (0.2%) lorcaserin 10 mg BID, 1 (0.1%) lorcaserin 10 mg QD, and 4 (0.1%) placebo patients meeting the > 5x ULN category (Table 107). No patients in the lorcaserin treatment groups and 1 (< 0.1%) patient in the placebo group met the > 20x ULN criteria.

Table 107. Number (%) Patients with ALT Values Exceeding Selected Cutoffs, Pooled Phase 3 Trials

	Lorc 10 BID N=2991	**Lorc 10 QD N=754**	**Pbo N=2918**
> ULN	317 (10.6)	95 (12.6)	375 (12.9)
> 3x ULN	11 (0.4)	4 (0.5)	13 (0.4)
> 5x ULN	5 (0.2)	1 (0.1)	4 (0.1)
> 20x ULN	0	0	1 (<0.1)

Source: NDA 22529, ISS Statistical Report Table S14

Lorcaserin-treated patients with ALT > 5x ULN are described as follows:

- Patient 111-S002 is discussed above.

- In patient 2119-S048, the ALT of 300 U/L occurred approximately three months after study drug start. Previous ALT levels were within the normal range. Follow-up ALT values were 52 U/L followed by 25 U/L. All subsequent ALT values remained in the normal range. The AST was also elevated (171 U/L) at the same time as the ALT of 300 U/L. Subsequent AST values were in the normal range. Total bilirubin values remained in the normal range throughout the study. Adverse events of moderate, 'elevated ALT' and 'elevated AST' were reported on Study Day 92. A mild AE of elevated alkaline phosphatase (ALP) was also reported. The patient also had adverse events of 'stomach cramps' and 'diarrhea' during this time period. Study drug was stopped and restarted. The patient completed the study without recurrence of liver function test abnormalities.

[61] 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.

- In patient 2131-S093, the ALT of 547 U/L occurred approximately 1 year after study drug start. Previous ALT values were within the normal range. The follow-up ALT was 176 U/L with subsequent value of 41 U/L. The AST was also elevated and subsequently declined at the same time points with values of 286, 86, and 43 U/L. Total bilirubin values remained in the normal range throughout the study. Study drug was not interrupted, and the patient completed the study. An adverse event of moderate 'elevated liver function tests' was reported on Study Day 365.

- In patient 2211-S022, ALT was elevated at baseline with a value of 57 U/L. Subsequent values were 255, 492, and 255 U/L; no further ALT values are available. AST values were also elevated for this patient with a maximum value of 160 U/L. The last available AST value was 115 U/L. Total bilirubin values remained in the normal range throughout the study. The patient was discontinued from study on Study Day 62 in response to adverse events of moderate 'elevated ALT' and 'elevated AST'.

- In patient 2233-S065, the ALT of 316 U/L occurred approximately 3 weeks after study drug start. Subsequent ALT values were 51 U/L followed by 106 U/L. No further ALT values are available. The AST was elevated with a value of 141 U/L on the same day as the ALT of 316 U/L. Subsequent AST values were within the normal range. Total bilirubin values remained in the normal range throughout the study. An adverse event of mild 'elevated aminotransferase' was reported. Concurrent adverse events of 'abdominal left lower quadrant and center pain' and 'fullness in anterior neck' were reported. Study drug was stopped and restarted 7 days later. The patient withdrew from the study ~3 months later for unrelated reasons.

- In patient 2014-S050, the ALT was initially elevated approximately 6 months after study drug start with a value of 259 U/L. Follow-up ALT values were 712 U/L and 60 U/L. Subsequent ALT values remained in the normal range throughout the remainder of the study. AST values followed a similar pattern with an initial elevation of 62 U/L and subsequent value of 512 U/L. All subsequent AST values were within the normal range. Total bilirubin was mildly elevated at baseline with a value of 1.2 mg/dL. All total bilirubin values were within the normal range after study drug start. Adverse events of severe 'elevated ALT' and 'elevated AST' were reported on Study Day 167. Study drug was stopped and restarted without recurrence of laboratory abnormalities. The patient completed the study.

In Year 2 of BLOOM, 3 patients experienced ALT elevations > 3x ULN; 2 assigned to lorcaserin/lorcaserin and 1 assigned to lorcaserin/placebo. Only one patient (109-S025, lorcaserin/lorcaserin) had a value > 5x ULN. On Week 64, she had an AE reported of 'Hepatic enzyme elevated'; study drug was stopped and restarted. Laboratory data for this patient are presented below:

Table 108. Laboratory Data, BLOOM Patient 109-S025

Study Week	Alk Phos (U/L)	ALT (U/L)	AST (U/L)	Total bilirubin (mg/dL)
0	80	14	18	0.5
4	73	17	15	0.3
12	74	16	15	0.4
24	70	17	19	0.4
36	67	12	13	0.5
52	76	13	15	0.6
64	148	383	163	0.7
68	73	17	18	0.5
76	72	28	25	0.3
88	66	14	16	0.3
104	82	16	17	0.2

Source: Reviewer created from NDA 22529 datasets

8.5.1.2 Gallbladder events

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.[62]

As discussed in section 8.2, patients randomized to lorcaserin had more SAEs 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.

Table 109. Gallbladder-Related Adverse Events, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Total Gallbladder-Related AEs	26 (0.8)	5 (0.6)	16 (0.5)
Cholelithiasis	11 (0.3)	2 (0.2)	10 (0.3)
Cholecystitis	8 (0.3)	2 (0.2)	5 (0.2)
Biliary dyskinesia	3 (0.1)	0	1 (<0.1)
Gallbladder disorder	2 (0.1)	1 (0.1)	1 (<0.1)
Cholecystitis acute	2 (0.1)	0	2 (0.1)
Cholecystitis chronic	2 (0.1)	0	0
Biliary colic	1 (<0.1)	0	0
Gallbladder non-functioning	1 (<0.1)	0	0
Gallbladder pain	1 (<0.1)	0	0

Source: NDA 22529, ISS Table 76 and Reviewer created from datasets

A similar pattern was seen in Year 2 of BLOOM.

[62] Stinton LM, et al. Epidemiology of gallstones. Gastroenterol Clin North Am 2010 Jun; 39(2): 157-69, vii.

Table 110. Gallbladder-Related Adverse Events, BLOOM Year 2

	Lorc/Lorc N=573	**Lorc/Pbo N=283**	**Pbo/Pbo N=697**
Total Gallbladder-Related AEs	5 (0.9)	1 (0.4)	4 (0.6)
Cholelithiasis	3 (0.5)	1 (0.4)	2 (0.3)
Cholecystitis	1 (0.2)	0	1 (0.1)
Biliary dyskinesia	1 (0.2)	0	0
Cholecystitis chronic	0	0	1 (0.1)
Gallbladder disorder	0	0	1 (0.1)

Source: Reviewer created from NDA 22529 datasets

8.5.2 Gastrointestinal Adverse Events

Nausea and vomiting were among the most frequent adverse events seen in the clinical program. 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 4 hours). In the Phase 3 trials, 8% of patients with nausea AEs and 5% of patients with vomiting AEs discontinued the study due to these events. By the second year of BLOOM, there was no excess in the reports of nausea or vomiting in the lorcaserin-treated patients.

Table 111. Nausea and Vomiting AEs

	Treatment	n (%) with Nausea	n (%) with Vomiting
Single Dose Studies, Healthy Participants			
Pooled	Pbo	1 (2.9)	0
	Lorc 0.1	0	0
	Lorc 1	0	0
	Lorc 10	10 (8.8)	5 (4.4)
	Lorc 20	4 (33.3)	0
	Lorc 40	2 (33.3)	2 (33.3)
Multiple Dose, Healthy Participants			
APD356-002	Pbo	0	0
	Lorc 3	0	1 (16.7)
	Lorc 10	0	0
	Lorc 20	3 (50.0)	2 (33.3)
APD356-007	Pbo	4 (6.7)	0
	Lorc 15 QD	13 (16.7)	4 (6.7)
	Lorc 40 QD	53 (54.7)	13 (17.2)
DDI Studies			
APD356-008	Pbo/Dex	0	0
	Lorc 20 QD	8 (33.3)	3 (12.5)
APD356-012	Pbo/Dex	3 (12.5)	1 (4.2)
	Lorc 10 BID	1 (4.2)	1 (4.2)
Specific Populations			
APD356-016	Lorc 10	1 (2.5)	0
APD356-017	Lorc 10	1 (4.2)	0
APD356-013	Pbo	0	0
	Lorc 20	7 (21.2)	1 (3.0)
	Lorc 40	17 (50.0)	1 (2.9)
	Lorc 60	14 (45.2)	2 (6.5)
Phase 2			
APD356-003	Pbo	3 (3.5)	2 (2.3)
	Lorc 1 QD	5 (5.6)	3 (3.3)
	Lorc 5 QD	5 (5.6)	2 (2.2)
	Lorc 15 QD	8 (9.2)	3 (3.4)
APD356-004	Pbo	4 (3.4)	1 (0.8)
	Lorc 10 QD	10 (8.5)	2 (1.7)
	Lorc 15 QD	11 (9.3)	2 (1.7)
	Lorc 10 BID	13 (11.2)	6 (5.2)
Phase 3			
Pooled, Year 1	Pbo	17 (5.3)	83 (2.6)
	Lorc 10 QD	61 (7.6)	32 (4.0)
	Lorc 10 BID	264 (8.3)	122 (3.8)
BLOOM, Year 2	Lorc/Lorc	20 (3.5)	12 (2.1)
	Lorc/Pbo	9 (3.2)	8 (2.8)
	Pbo/Pbo	29 (4.2)	14 (2.0)

Source: NDA 22529, ISS Table 75 and APD356-009 CSR Table 14.3.8

8.5.3 Cardiac Events and Electrocardiograms

8.5.3.1 Electrocardiograms and related adverse events

Study APD356-007 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. The study was reviewed by the FDA Interdisciplinary Review Team for QT studies (IRT). Findings included:

- 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.

Table 112. ECG Parameters, Study APD356-007

	Pbo N=60	**Mox 400 N=60**	**Lorc 15 N=60**	**Lorc 40 N=59**
Mean changes				
HR (bpm)	0.9	2.7	-0.6	-1.6
PR (msec)	1.5	0.2	3.6	4.0
QRS (msec)	-0.4	-0.8	-0.2	-0.5
QT (msec)	-4.2	-2.5	-4.5	-6.7
QTcF (msec)	-2.6	2.8	-5.7	-9.9
QTcB (msec)	-1.7	5.6	-6.3	-11.5
Time averaged QTcI results				
QTcI (msec)	-2.8	2.9	-5.0	-9.6
QTcI Max Mean Change	13.0	18.8	13.2	8.7
QTcI new > 500 msec: N (%)	0	0	0	0
QTcI new > 480 msec: N (%)	0	0	0	0
QTcI 30-60 msec increase: N (%)	2 (3%)	6 (10%)	3 (5%)	1 (2%)
QTcI > 60 msec increase: N (%)	0	0	0	0

Source: NDA 22529, APD356-007 CSR Table 14

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 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 113. Summary of Subjects who Experienced an Increase from Baseline in PR Interval (msec), Phase 2 Trials

Study APD356-003				
	Pbo N=85	**Lorc 1 QD N=89**	**Lorc 5 QD N=88**	**Lorc 15 QD N=87**
PR > 200 msec*	1 (1.2%)	1 (1.1%)	4 (4.5%)	1 (1.1%)
ΔPR > 15 msec	14 (16.5%)	10 (11.2%)	15 (17.0%)	27 (31.0%)
Study APD356-004				
	Pbo N=118	**Lorc 10 QD N=117**	**Lorc 15 QD N=117**	**Lorc 10 BID N=116**
PR > 200 msec*	0	3 (2.6%)	2 (1.7%)	5 (4.3%)
ΔPR > 15 msec	17 (14.4%)	22 (18.8%)	23 (19.7%)	34 (29.3%)
*in subjects with PR interval ≤ 200 msec at baseline				

Source: NDA 22529, ISS Tables 135 and 136

Table 114. Selected ECG Findings, Pooled Phase 3 Trials

	Lorc 10 BID	**Lorc 10 QD**	**Pbo**
Mean (SE) Change in HR from Baseline at Week 52	-1.94 (0.191)	-0.31 (0.366)	-0.29 (0.208)
Mean (SE) Change in RR Interval from Baseline at Week 52	29.89 (2.772)	6.41 (5.104)	4.13 (2.940)
Mean (SE) Change in PR Interval from Baseline at Week 52	2.98 (0.290)	1.87 (0.530)	2.08 (0.300)
Number (%) of Patients with PR Change:			
> 20 msec	270 (10.2%)	46 (7.7%)	211 (8.3%)
> 40 msec	16 (0.6%)	1 (0.2%)	22 (0.9%)
Number (%) of Patients with PR:			
> 200 msec and baseline ≤ 200 msec	104 (3.9%)	14 (2.3%)	77 (3.0%)
> 200 msec and baseline > 200 msec	84 (3.2%)	7 (1.2%)	60 (2.4%)

Source: NDA 22529, ISS Tables 138, 139, 141, and 142

A search of the lorcaserin Phase 2 and 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.

In the Phase 2 trials, 1 subject (lorcaserin 15 mg QD, study APD356-003) had an AE of 'Electrocardiogram PR interval increased'; 1 subject (lorcaserin 1 mg QD, study APD356-003) had an AE of 'Atrioventricular block first degree', and 1 subject (lorcaserin 10 mg BID, study APD356-004) had an AE of 'Atrioventricular block complete'.

As Table 115 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. One event (preferred term: 'electrocardiogram PR prolongation' in a placebo-treated patient) led to study discontinuation, and 1 event (preferred term: 'sick sinus syndrome' in a lorcaserin 10 mg QD treated patient) was classified as a SAE. This patient (2186-S053) was a 65-year-old White male who developed two events of tachycardia-

bradycardia syndrome in association with atrial fibrillation; the first occasion while being temporarily off of drug for lumbar spine surgery.

Table 115. Bradyarrhythmia Adverse Events, Pooled Phase 3 Trials

	Lorc 10 BID	Lorc 10 QD	Pbo
Total, Bradyarrhythmia AEs	14 (0.4)	2 (0.2)	6 (0.2)
Sinus bradycardia	5 (0.2)	0	2 (0.1)
Bradycardia	4 (0.1)	1 (0.1)	1 (<0.1)
Atrioventricular block first degree	3 (0.1)	0	1 (<0.1)
Electrocardiogram PR prolongation	1 (<0.1)	0	2 (0.1)
Heart rate decreased	1 (<0.1)	0	0
Sick sinus syndrome	0	1 (0.1)	0

Source: Reviewer created from NDA 22529 datasets

Heart rate (HR) findings in the pooled Phase 3 trials support these findings: 5.7% of lorcaserin 10 mg BID versus 3.3% of placebo-treated patients had a HR less than 60 beats per minute (BPM) and 1.2% lorcaserin 10 mg BID versus 0.8% placebo-treated patients had a HR less than 45 BPM during 52 weeks of treatment.

8.5.3.2 Ischemic cardiac adverse events

Lorcaserin does not appear to share the sympathetic nervous system activation that has been described with sibutramine and phentermine: mean heart rate and blood pressure are decreased 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.[63] Any potential relevance of these 5HT2A cardiovascular effects to lorcaserin is unknown.

An exploratory analysis of ischemic cardiac adverse events was conducted. The background rate of cardiovascular disease in the Phase 3 program was very low at 0.3-1.1%, as described in section 6.5.

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.

[63] 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 116. 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 Phase 3 trials. The placebo incidence was primarily driven by the relatively nonspecific preferred term 'blood creatine phosphokinase increased'. As shown in Table 32 and Table 33 of section 8.2 (serious adverse events), ischemic coronary artery disorder SAEs occurred only in the lorcaserin 10 mg BID group.

Note, however, 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.

Table 117. Ischemic Heart Disease AEs, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
Total, MedDRA Ischaemic heart disease SMQ	15 (0.5)	1 (0.1)	6 (0.2)
Myocardial infarction	4 (0.1)	0	0
Angina pectoris	2 (0.1)	1 (0.1)	0
Electrocardiogram T wave abnormal	2 (0.1)	0	0
Coronary artery disease	1 (<0.1)	0	2 (0.1)
Angina unstable	1 (<0.1)	0	1 (<0.1)
Troponin increased	1 (<0.1)	0	1 (<0.1)
Acute coronary syndrome	1 (<0.1)	0	0
Acute myocardial infarction	1 (<0.1)	0	0
Cardiac stress test abnormal	1 (<0.1)	0	0
Electrocardiogram ST segment abnormal	1 (<0.1)	0	0
Electrocardiogram ST-T change	1 (<0.1)	0	0
Myocardial ischaemia	1 (<0.1)	0	0
Blood creatine phosphokinase increased	0	0	3 (0.1)

Source: Reviewer created from NDA 22529 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; all in patients treated with lorcaserin 10 mg BID. There was one death due to cardiorespiratory arrest in a placebo patient, but this has been attributed to an asthma exacerbation (section 8.1).

Table 118. MACE (Exploratory/Unadjudicated), Pooled Phase 3 Trials

	Lorc 10 BID N=3195	**Lorc 10 QD N=801**	**Pbo N=3185**
Total, MACE	6 (0.2)	0	0
Myocardial infarction	4 (0.1)	0	0
Acute myocardial infarction	1 (<0.1)	0	0
Cerebrovascular accident	1 (<0.1)	0	0

Source: Reviewer created from NDA 22529 datasets

Cardiac ischemia events were not seen in the lorcaserin-treated group in BLOOM Year 2 (Table 119). Furthermore, there were no events of stroke or cardiovascular death in Year 2.

Table 119. Ischemic Heart Disease AEs, BLOOM Year 2

	Lorc/Lorc N=573	Lorc/Pbo N=283	Pbo/Pbo N=697
Total, MedDRA Ischaemic heart disease SMQ	0	2 (0.7)	2 (0.3)
Arteriosclerosis coronary artery	0	1 (0.4)	0
Coronary artery occlusion	0	1 (0.4)	1 (0.1)
Myocardial infarction	0	0	1 (0.1)

Source: Reviewer created from NDA 22529 datasets

8.5.4 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 120). Bolded terms were those found in the lorcaserin Phase 3 program. Within the pooled Phase 3 trials, 0 patients assigned to placebo and 1 (< 0.1%) assigned to lorcaserin 10 mg BID had adverse events within the acute renal failure narrow SMQ. When the broad SMQ was applied, 12 (0.4%) placebo patients and 17 (0.5%) lorcaserin 10 mg BID patients experienced adverse events.

Table 120. 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 22529, 2 Apr 2010 Response to 74-day filing letter requests Table 7

Table 121. Renal Failure SMQ, Phase 3 Trials Pooled

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Total, MedDRA Renal Failure Narrow SMQ	1 (<0.1)	1 (0.1)	0
Renal failure	0	1 (0.1)	0
Renal failure acute	1 (<0.1)	0	0
Total, MedDRA Renal Failure Broad SMQ	17 (0.5)	5 (0.6)	12 (0.4)
Protein urine present	7 (0.2)	3 (0.4)	1 (<0.1)
Proteinuria	8 (0.3)	2 (0.2)	9 (0.3)
Blood creatinine increased	2 (0.1)	0	1 (<0.1)
Blood urea increased	2 (0.1)	0	1 (<0.1)
Urine output decreased	0	0	1 (<0.1)

Source: NDA 22529, 2 Apr 2010 Response to 74-day filing letter requests Table S09.1.0

Brief narratives for patients with AEs of renal failure are presented:

- Patient 2102-S039 (lorcaserin 10 mg BID) was a 38-year-old Black female with a history of heartburn, gastroesophageal reflux disease, and stress headaches who presented to the emergency room with the complaint of chest pain, and was found to have mild acute renal failure, thought likely due to dehydration. Serum creatinine on admission was 1.30 mg/dL and 0.90 mg/dL on discharge. After work-up, she was diagnosed with atypical chest pain, most likely musculoskeletal.

- Patient 2196-S004 (lorcaserin 10 mg QD) was a 55-year-old White female with a history of hypertension and dyslipidemia and baseline serum creatinine of 1.2 mg/dL. She was diagnosed with mild renal insufficiency on Study Day 110 (serum creatinine: 1.4 mg/dL). Lisinopril was temporarily discontinued on Study Day 116. Serum creatinine was 1.3, 1.4, and 1.0 mg/dL on Weeks 24, 36, and 52, respectively.

Table 122. Renal Failure SMQ, BLOOM Year 2

	Lorc/Lorc N=573	Lorc/Pla N=283	Pla/Pla N=697
Total, Renal Failure SMQ	0	2 (0.7)	1 (0.1)
Blood creatinine increased	0	0	1 (0.1)
Blood urea increased	0	0	1 (0.1)
Proteinuria	0	0	1 (0.1)
Protein urine present	0	1 (0.4)	0

Source: Reviewer created from NDA 22529 datasets

Reviewer comment: Despite the animal findings, the renal adverse events in the Phase 3 program do not suggest an increased risk with lorcaserin. Renal events in populations that could be more vulnerable to renal toxicity, such as those with diabetes or the elderly, have not been studied, however.

Evaluations of categorical laboratory data for creatinine, calculated creatinine clearance, and blood urea nitrogen (BUN) do not suggest a significant drug effect (Table 123).

Table 123. Categorical Laboratory Data, Kidney Parameters, Pooled Phase 3 Trials

	Lorc 10 BID	Lorc 10 QD	Pbo
Creatinine			
> Baseline or > ULN	53.1%	57.2%	53.9%
> 1.5x Baseline or > 1.5x ULN	0.5%	0.7%	0.5%
> 3x Baseline or > 3x ULN	<0.1%	0	<0.1%
> 6x ULN	0	0	<0.1%
Creatinine Clearance			
< 60-30 mL/min	0.6%	0.4%	0.3%
< 30-15 mL/min	0	0	<0.1%
< 15 mL/min	0	0	<0.1%
Creatinine Clearance (IBW)			
< 60-30 mL/min	15.6%	15.3%	16.0%
< 30-15 mL/min	0.1%	0	0
< 15 mL/min	0	0	0.1%
BUN			
23-26 mg/dL	4.5%	4.4%	5.5%
27-31 mg/dL	1.1%	1.3%	1.3%
> 31 mg/dL	0.2%	0.3%	0.3%

Source: NDA 22529, 2 Apr 2010 Response to 74-day filing letter requests Table S14.1.1

8.5.5 Priapism

Serotonin activation at the 5HT2C receptor has been implicated in priapism seen in animals.[64] 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 125 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.

[64] 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 124. 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 22529, 7 Mar 2010 Response to 74-day filing letter requests Table 8

Table 125. Priapism AEs, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Priapism	0	1 (0.1)	2 (0.1)
Spontaneous penile erection	0	1 (0.1)	1 (<0.1)
Erection increased	0	0	1 (<0.1)

Source: NDA 22529, 2 Apr 2010 Response to 74-day filing letter requests Table S09.1.0

Reviewer comment: 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.

8.5.6 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 was seen. In the Phase 3 program, slightly more patients treated with lorcaserin had decreases in hematocrit, and 0.9% of patients treated with loraserin 10 mg BID as compared to 0.7% of patients treated with placebo had hemoglobin values less than 10 g/dL. Only 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.

Table 126. RBC-Related AEs, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Total, RBC-Related AEs	31 (1.0)	6 (0.7)	22 (0.7)
Anaemia	22 (0.7)	5 (0.6)	17 (0.5)
Haemoglobin decreased	9 (0.3)	1 (0.1)	5 (0.2)
Haematocrit decreased	6 (0.2)	1 (0.1)	2 (0.1)
Red blood cell count decreased	2 (0.1)	0	0

Source: Reviewer created from NDA 22529 datasets

Dose-related decreases in white blood cells (WBC), neutrophils, and lymphocytes were noted (Table 127). Adverse events related to decreases in WBCs were infrequent, but greater in lorcaserin-treated patients than those who were placebo-treated (Table 128).

Table 127. Percent of Patients with Neutrophil Counts below Pre-Defined Cut-Offs, Pooled Phase 3 Trials

	Lorc 10 BID	Lorc 10 QD	Pbo
< Lower limit of normal (LLN)	5.8%	5.7%	4.5%
< 1.5 x 10^9/L	2.8%	2.7%	2.2%
< 1 x 10^9/L	0.6%	0.4%	0.3%
< 0.5 x 10^9/L	<0.1%	0.1%	0

Source: NDA 22529, 2 Apr 2010 Response to 74-day filing letter requests Table S14.2.1

Table 128. WBC-Related AEs, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Total, WBC-Related AEs	10 (0.3)	5 (0.6)	3 (0.1)
White blood cell count decreased	6 (0.2)	1 (0.1)	2 (0.1)
Neutrophil count decreased	3 (0.1)	2 (0.2)	0
Neutropenia	2 (0.1)	3 (0.4)	2 (0.1)
Leukopenia	2 (0.1)	1 (0.1)	0
Lymphocyte count decreased	1 (<0.1)	0	0
Lymphopenia	1 (<0.1)	0	0

Source: Reviewer created from NDA 22529 datasets

All adverse events of neutropenia were considered mild and non-serious. No patient discontinued due to a neutropenia AE.

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 x 10^9/L. No patients treated with lorcaserin 10 mg BID had platelet counts less than 50 x 10^9/L in the Year 1 Phase 3 pooled trials. One patient had an adverse event of 'thrombocytopenia' (mild) and 2 patients had adverse events of 'platelet count decreased' (1 mild, 1 moderate). No patient discontinued the trial due to these adverse events.

APPENDICES

Appendix A. Inclusion and Exclusion Criteria, Phase 3 Trials

BLOOM

Inclusion Criteria

1. Males or females aged between 18 and 65 years (inclusive)
2. Able to give signed informed consent
3. Ambulatory and able to perform exercise program (Arena Healthy Lifestyle Program)
4.
    a. Eligible female patients will be:
        - non-pregnant, evidenced by a negative serum hCG pregnancy test at Screening and a urine dipstick pregnancy test on Day 1 prior to dosing
        - non-lactating
        - surgically sterile or postmenopausal, or agree to continue to use an accepted method of birth control during and for at least 3 months after last study medication administration
            – Acceptable methods of birth control are: hormonal contraceptives; single barrier method; intrauterine device; surgical sterility for at least 3 months prior to screening for tubal ligation performed laparoscopically; surgical sterility for at least 6 months prior to screening for hysterectomy and/or bilateral oophorectomy; and/or postmenopausal status (defined as at least 2 years without menses). Abstinence is not considered an acceptable method of birth control for this study.
    b. Eligible male subjects will be:
        - surgically sterile (i.e., vasectomy) for at least 3 months prior to screening or agree to use a condom when sexually active
5. Body Mass Index (BMI) is 30 to 45 kg/m^2 (obese) with or without co-morbid conditions or 27 to 29.9 kg/m^2 (overweight) with at least one treated or untreated comorbid condition (hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea). For untreated co-morbid conditions the condition must be considered by the Investigator to be clinically stable.
6. Considered to be in stable health in the opinion of the Investigator, as determined by:
        - A pre-study physical examination
        - A medical history indicating either no clinically significant abnormalities or stable co-morbid condition(s)
        - Vital signs within normal ranges or if outside of the normal range are not deemed clinically significant in the opinion of the Investigator
        - Pre-study clinical laboratory findings within normal range, or if outside of the normal range, not deemed clinically significant in the opinion of the Investigator
        - A 12-lead ECG showing no active ischemia

Exclusion Criteria

1. Prior participation in any study of lorcaserin. Patients who signed an informed consent for a prior lorcaserin study may be eligible provided they were not randomized in the prior study, and there were no clinically significant findings from the previous study echocardiogram that would exclude them from this study.
2. Clinically significant new illness in the 1 month before screening
3. Not suitable to participate in the study in the opinion of the Investigator including an existing physical or mental condition that prevents compliance with the protocol
4. Diabetes mellitus (type I, II or other). A remote history of gestational diabetes that has resolved is not exclusionary.
5. Recent history (within 2 years before entering the study) of major depression, anxiety, or other psychiatric disease requiring treatment with prescription medication (e.g., SSRI's, SNRI's [including buproprion], tricyclics, antipsychotics, lithium). Use of SSRI's and SNRI's (including buproprion) for reasons other than active psychiatric indications (e.g., migraine, weight loss, smoking cessation) must meet a 3-month washout.
6. Total score on the Beck Depression Inventory-II (BDI-II) $\geq$ 20 or a score > 0 specifically on question 9 (Suicidal Thoughts or Wishes)
7. History of a binge eating disorder as suggested by a score > 17 on the Binge Eating Scale
8. History of epilepsy or other seizure disorder
9. Surgical procedure for the treatment of obesity (i.e., gastric bypass, gastric banding)
10. Anticipation of surgery during the study period that may interfere with completion or compliance with the protocol
11. Uncontrolled hypertension, defined as systolic blood pressure $\geq$140 or diastolic blood pressure $\geq$ 90 on 2 separate readings which should be done on 2 separate days. Patients who have uncontrolled hypertension at screening may be re-screened > 1 month following initiation or adjustment of antihypertensive therapy.
12. History of valve replacement surgery or CABG or other invasive cardiovascular surgical procedure including PCI. A diagnostic cardiac catheterization does not exclude the patient if no stent placement, angioplasty, or plaque removal occurred during the procedure.
13. Myocardial infarction (diagnosed by cardiac enzyme[s] and/or diagnostic ECG), CVA, TIA or RIND within 6 months, cardiac arrhythmia requiring medical or surgical treatment within 6 months of screening
14. Major surgical procedure (intrathoracic, intracranial, intraperitoneal, liposuction) within 6 months of screening
15. Unstable angina
16. History of congestive heart failure caused by insufficiency or stenosis of any heart valve
17. History of pulmonary artery hypertension
18. Symptomatic untreated congestive heart failure of any etiology (stably treated class I or II CHF of ischemic or hypertensive etiology is acceptable)
19. History of organ transplantation

20. Abnormal TSH lab value > 1.5x ULN. Patients with slightly higher TSH (~2x ULN) will be considered on an individual basis if T4 is in the mid-to high portion of the normal range or free T4 is normal. If initiation or adjustment of L-thyroxine is anticipated, patients should not be enrolled
21. Hyperthyroidism, including abnormal screening lab values with T4 > ULN and TSH < LLN, and patients taking methimazole or PTU and/or beta-blockers for hyperthyroidism.
22. Fasting triglycerides > 499 mg/dL on 2 days (i.e., if elevated at Screening, but not on a subsequent re-check, patient will be eligible; if elevated on re-check, patient is not eligible). Patients with fasting triglycerides >499 and LDL-cholesterol <130 may be eligible for the study if they have no history of pancreatitis, CVA, TIA, RIND, or myocardial infarction, but must be approved through the ICON Medical Monitor prior to randomization. Patients with elevated triglycerides at screening may be re-screened > 3 months after initiation or adjustment of lipid lowering treatment, if study enrollment has not been closed.
23. LDL-cholesterol ≥ 190 mg/dL. Patients with elevated LDL-cholesterol at screening may be re-screened > 3 months after initiation or adjustment of lipid lowering treatment, if study enrollment has not been closed.
24. HbA1c greater than ULN (i.e., > 6.5%)
25. Fasting glucose > 126 mg/dL on 2 days (i.e., if elevated at Screening, but not on a subsequent re-check, patient will be eligible; if elevated on re-check, patient is not eligible)
26. Clinically significant abnormal hepatic (e.g., AST or ALT > 2.5x ULN, or total bilirubin > 1.5x ULN) or renal function lab tests (e.g., creatinine > 1.25x ULN) suggestive of hepatic or renal impairment
27. Positive result of HIV, hepatitis B or hepatitis C screens
28. Malignancy within 5 years of the screening visit (except basal cell or squamous cell carcinoma with clean surgical margins)
29. Initiation of a new prescription medication within 1 month prior to screening with the following exceptions:
    - Patients being treated for dyslipidemia (e.g., statins) must be on a stable dose of prescription medication or OTC niacin for at least 3 months prior to screening
    - Patients being treated for hypothyroidism must be adequately replaced on a stable dose of medication (e.g., levothyroxine) for at least 3 months prior to screening
    - Patients receiving a short course (≤ 10 days) of prescription antibiotic, antifungal, or antiviral partially or entirely within the 1 month preceding the screening visit for the following conditions:
        - Dental work
        - Sinusitis
        - Pharyngitis
        - Bronchitis (acute)
        - Otitis media
        - Minor superficial skin infections (e.g., impetigo, carbuncle)

- Uncomplicated urinary tract infection (cystitis, urethritis)
- Vulvovaginal candidiasis
- Occasional antiviral use for recurrent genital herpes simplex

30. Medication history that includes use of one or more of the following:
    - Any use of fenfluramine or related derivatives (i.e., dexfenfluramine, norfenfluramine)
    - Use within 5 years of the Screening Visit agents that have documented correlation with increased incidence of valvulopathy and/or primary pulmonary hypertension (e.g., Cyproheptadine, Trazodone, Nefazodone, Amoxapine, tricyclic antidepressants, mirtazapine, pergolide, ergotamine, methysergide)
31. Recent treatment (i.e., within 1 month of the screening visit) with over-the-counter weight loss products or appetite suppressants (including herbal weight loss agents) or St. John's Wort, or within 3 months with a prescription anti-obesity drug (e.g., phentermine, sibutramine, orlistat) or lipid dissolving injections (e.g., Lipodissolve)
32. Recent treatment (i.e., within 3 months of the screening visit) with oral or parenteral corticosteroids, metformin, or topiramate
33. Recent history (within 2 years prior to the screening visit) of alcohol or drug/solvent abuse or a positive screen for drugs of abuse at screening. In some cases, patients with a positive drug screen may be eligible for the study with approval from the Medical Monitor if the patient has a documented medical history (e.g., osteoarthritis) requiring the need for chronic pain treatment and a documented concomitant medication resulting in a positive drug screen and provided the patient is considered by the Investigator to be reliable to participate in the study.
34. Significant change in smoking habits within 3 months prior to screening
35. Smoke more than ½ pack of cigarettes per day, more than 2 cigars/day, or use 3 or more pinches of smokeless tobacco per day
36. Participated in any clinical study with an investigational drug, biologic, or device within 1 month prior to the first day of dosing
37. Significant change in diet or level of physical activity within 1 month prior to dosing.
38. Change in weight of > 5 kg within 3 months
39. Use of very-low calorie (< 1,000/day) liquid weight loss diet within 6 months
40. Unwilling, or whose partner is unwilling, to use an adequate means of contraception during and for 3 months following completion/withdrawal of the study
41. Documented sensitivity to gelatin (lorcaserin will be contained in gelatin capsules).
42. Any of the following findings on screening echocardiography:
    - Aortic regurgitation mild or greater
    - Mitral regurgitation moderate or greater
    - Mitral or aortic valve stenosis greater than mild (i.e., AS: jet > 3.0 m/s, mean gradient > 25 mmHg, and AVA < 1.5 cm2; MS: mean gradient > 5 mmHg and MVA < 1.5 cm^2)
    - Pulmonary artery pressure (PASP) > 40 mm Hg (and/or tricuspid regurgitation jet velocity > 2.9 m/s)
    - In cases where an actual PASP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at

the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤ 100 msecs will be excluded, suggesting an elevated mean pulmonary artery pressure; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size

- Left ventricular ejection fraction < 45%
- Intracardiac mass, tumor or thrombus
- Evidence of congenital heart disease
- Clinically significant pericardial effusion (e.g., moderate or larger or with hemodynamic compromise)

BLOSSOM

Inclusion Criteria

1. Males or females aged between 18 and 65 years (inclusive)
2. Able to give signed informed consent
3. Ambulatory and able to perform exercise program (Arena Healthy Lifestyle Program)
4. Eligible male and female patients must agree not to participate in a conception process (i.e., active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization)
5. Female patients will be:
    a. non-pregnant, evidenced by a negative serum hCG pregnancy test at Screening and a urine dipstick pregnancy test on Day 1 prior to dosing
    b. non-lactating
    c. surgically sterile or postmenopausal, or agree to continue to use an accepted method of birth control during and for at least 3 months after last study medication administration
        - Acceptable methods of birth control are: hormonal contraceptives; single barrier method; intrauterine device; surgical sterility for at least 3 months prior to screening for tubal ligation performed laparoscopically; surgical sterility for at least 6 months prior to screening for hysterectomy and/or bilateral oophorectomy; and/or postmenopausal status (defined as at least 2 years without menses). ***Intended abstinence is not considered an acceptable method of birth control for this study; patients who are currently abstinent must agree to use an acceptable method of birth control should they become sexually active during the study.***
6. Male patients will be:
    a. surgically sterile (i.e. vasectomy), for at least 3 months prior to screening
    b. agree to use a condom when sexually active with a female partner who is not using an acceptable method of birth control
7. Body Mass Index (BMI) is 30 to 45 kg/m^2 with or without a comorbid condition (e.g., hypertension, dyslipidemia, CV disease, glucose intolerance, sleep apnea), or 27 to 29.9 kg/m^2 with at least one comorbid condition
8. Considered to be in stable health in the opinion of the Investigator, as determined by:

a. A pre-study physical examination
b. A medical history indicating either no clinically significant abnormalities; stable co-morbid condition(s)
c. Vital signs within normal ranges (except as described in Exclusion Criteria) or if outside of the normal range are not deemed clinically significant in the opinion of the Investigator
d. Pre-study clinical laboratory findings within normal range, or if outside of the normal range, not deemed clinically significant in the opinion of the Investigator
e. A 12-lead ECG showing no active ischemia. Either the QTcB or the QTcF must be equal to or below 450 msec.

Exclusion Criteria

1. Prior participation in any study of lorcaserin. Patients who may have signed an informed consent for a prior lorcaserin study may be eligible provided they were not randomized in the prior study and there were no clinically significant findings from the previous study echocardiogram that would exclude them from this study
2. Clinically significant new illness in the **1 month** before screening and any time prior to randomization.
3. Not suitable to participate in the study in the opinion of the Investigator including an existing physical or mental condition that prevents compliance with the protocol
4. Recent history (within **1 year** before entering the study) of major depression, anxiety, or other psychiatric disease requiring treatment with prescription medication (e.g., SSRI's, SNRI's, tricyclics, antipsychotics, lithium, Wellbutrin®). Use of SSRI's and SNRI's (including buproprion) for reasons other than active psychiatric indications (e.g., migraine, weight loss, smoking cessation) must meet a **3-month** washout prior to randomization
5. Patients must not have taken St. John's Wort within **1 month** prior to the screening visit and for the duration of the study. St. John's Wort has been associated with serotonin syndrome when used with another serotonergic drug
6. Evidence of significant depression that impairs daily functioning, as suggested by a score of the Beck Depression Inventory-II (BDI-II) ≥ 20, or a score > 0 on Question No.9 (pertaining to suicidal thoughts)
7. History of a binge eating disorder (a score > 17 on the Binge Eating Scale)
8. History of epilepsy or other seizure disorder, or use of medications for a seizure disorder, within **2 years** of screening
9. Surgical procedure for the treatment of obesity (i.e., gastric bypass, gastric banding), even if reversed prior to screening
10. Planned surgery during the study period that may interfere with completion or compliance with the protocol
11. Uncontrolled hypertension, defined as systolic blood pressure ≥ 150 or diastolic blood pressure ≥ 95 on 2 readings taken on different days. Patients who have uncontrolled hypertension at screening may be re-screened > 1 month following initiation or adjustment of antihypertensive therapy
12. History of any of the following cardiovascular conditions:

a. Valve replacement surgery
b. Myocardial infarction (diagnosed by cardiac enzyme[s] and/or diagnostic ECG), CVA, TIA or RIND within **3 months** of screening; cardiac arrhythmia requiring medical or surgical treatment within **3 months** of screening
c. Unstable angina
d. History of congestive heart failure caused by insufficiency, damage, or stenosis of any heart valve
e. History of pulmonary artery hypertension

13. History of organ transplantation
14. Abnormal TSH lab value > 1.5x ULN.
15. Hyperthyroidism, including abnormal screening lab values with T4 > ULN and TSH < LLN, and patients taking methimazole or PTU and/or beta-blockers for hyperthyroidism
16. AST or ALT > 2.5x ULN, or total bilirubin > 1.5x ULN
17. Serum creatinine > 1.5x ULN
18. Fasting triglycerides > 499 mg/dL on 2 days (i.e., if elevated at Screening, but not on a subsequent re-check, patient will be eligible; if elevated on re-check, patient is not eligible). Patients with fasting triglycerides > 499 mg/dL and LDL-cholesterol < 100 mg/dL may be eligible for the study if they have no history of pancreatitis, CVA, TIA, RIND, or myocardial infarction, but must be approved through the Medical Monitor prior to randomization. Patients with elevated triglycerides at screening may be re-screened > 3 months after initiation or adjustment of lipid lowering treatment, if study enrollment has not been closed
19. Positive result of HIV, hepatitis B or hepatitis C screens
20. Malignancy within **5 years** of the screening visit (except basal cell or squamous cell carcinoma with clean surgical margins)
21. Initiation of a new prescription medication within **1 month** prior to screening with the following exceptions:
    a. No new agents for treatment of dyslipidemia or changes in dose of agents already in use within **3 months** prior to screening (includes niacin obtained without prescription)
    b. Patients being treated for hypothyroidism must be adequately replaced on a stable dose of medication (e.g., levothyroxine) for at least **3 months** prior to screening
    c. The use of a brief (≤ 10 days) course of oral or topical antibiotic for minor URI, UTI, dental work, or skin infection is allowed within **the screening period**, but ***must be completed before first dose of study medication***
22. Medication history that includes use of one or more of the following:
    a. fenfluramine or related derivatives (i.e., dexfenfluramine, norfenfluramine)
    b. 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)
23. Recent treatment (i.e., within **1 month** of the screening visit and any time prior to randomization) with over-the-counter weight loss products or appetite suppressants (including herbal weight loss agents), or within 3 months and any time prior to

randomization with a prescription weight loss drug (e.g., phentermine, sibutramine, orlistat) or lipid dissolving injections (e.g., Lipodissolve)

24. Recent history (within **2 years** prior to the screening visit) of alcohol or drug/solvent abuse or a positive screen for drugs of abuse at screening; patients who have a positive urine drug screen that is likely caused by prescribed use of pain medication may be allowed to enroll at the discretion of the Medical Monitor
25. Significant change in smoking habits within **3 months** prior to screening
26. Participated in any clinical study with an investigational drug, biologic, or device within **1 month** prior to screening
27. Significant change in diet or level of physical activity within **1 month** prior to dosing.
28. Change in weight of > 5 kg within **3 months** of screening
29. Use of very-low calorie (< 1,000/day) liquid weight loss diet within **6 months** prior to screening and any time prior to randomization
30. Unwilling, or whose partner is unwilling, to use an adequate means of contraception during and for **3 months** following completion/withdrawal of the study
31. Major surgical procedure (intrathoracic, intracranial, intraperitoneal, liposuction) within **6 months** of screening and any time prior to randomization
32. Arthroscopic or laparoscopic surgery within **3 months** of screening and any time prior to randomization
33. Diabetes mellitus (type I, II or other). A past history of gestational diabetes that has resolved is permissible
34. Confirmed fasting glucose > 126 mg/dL at screening or HgbA1c greater than ULN (6.5% at Central Laboratory)
35. Recent treatment (within **1 month** of the screening visit and any time prior to randomization) with topiramate

Appendix B. Study Designs, Phase 3 Trials

BLOOM

Primary Objectives:

- Year 1: To assess the weight loss effect of lorcaserin at the end of Year 1 (Week 52)
- Year 2: To assess the ability of lorcaserin to maintain body weight loss achieved during Year 1, as assessed at the end of Year 2 (Week 104)

Secondary Objectives:

- To assess the ongoing safety of lorcaserin
- To assess specifically any changes in heart valve regurgitation or pulmonary artery pressure associated with the use of lorcaserin
- To assess potential further weight loss during the second year of treatment
- To assess any changes in CV risk factors associated with obesity (i.e., dyslipidemia, insulin sensitivity, hypertension, central fat distribution, biomarkers of CV risk)
- To assess any changes in mood
- To assess any changes in Quality of Life measures

Design:

This was a randomized, double-blind, placebo-controlled, parallel-group assessment of the effects of lorcaserin during 104 weeks of administration. Each patient was to have completed screening procedures within 4 weeks of dosing on Day 1. Eligible patients were randomized to receive study drug for an initial 52 weeks, with periodic follow-up visits to assess efficacy and safety parameters. Patients who completed the initial 52 weeks of treatment were eligible to continue in the study for Year 2.

Patients participated in the Arena Healthy Lifestyle Program, designed by the Behavioral Health Solutions (BHS) division of Johnson & Johnson Health Care Systems, Inc. The objectives of the program were to: develop a moderate-intensity weight management program for all APD356 study participants, standardize the weight management program across all study sites, maximize patient recruitment and retention, and maintain counselor motivation. The program included one-on-one counseling (following a program of selected topics on weight management and motivation), a prescribed diet that was approximately 600 fewer calories per day than the patient's estimated energy requirement, and food and activity logs kept by the patients between visits to assess compliance. Thirty minutes of moderate exercise per day was encouraged.

Table 129. Schedule of Events and Procedures, Year 1

Evaluation	**Screening**[1]	**Randomization**	**Dosing Period (Study Week)**													
	-28 to -1	**Day 1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/Exit**[2]
Informed Consent	X															
Medical History	X															
Physical/Neurological Exam	X			X												X
Beck Depression Inventory-II	X			X		X										X
Binge Eating Scale	X							X								
Echocardiogram	X[3]							X			X					X
12-Lead ECG	X			X												X
Clinical Labs	X	X		X		X		X								X
Drugs of Abuse Screen	X							X								
Thyroid Function Tests (i.e., T4, TSH)	X							X			X					X
Hemoglobin A1c	X															X
CV Risk Markers (i.e., CRP, fibrinogen)		X						X	X							X
Markers of Glucose Intolerance (i.e., fasting glucose and insulin)		X				X		X								X
Pharmacokinetic Sample[4]						X[4]		X			X					
Plasma Sample for Banking[5]		X														X
Pregnancy Test[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Virology Screen (HIV, Hep C, and HBsAg)	X							X								
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Measures:																
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist and Hip Circumference	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment (i.e., Impact of Weight Questionnaire – Lite)		X				X										X
Diet and Exercise Counseling		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Study Drug and Perform Drug Accountability and Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Assessments (including antihypertensives and lipid agents)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Evaluation	Screening[1]	Randomization	Dosing Period (Study Week)													
	-28 to -1	Day 1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/Exit[2]
IVRS Call[8]	X	X				X										X
Drug Administration[9]		←	←	←	←	←	←	←	←	←	←	←	←	→		
Adverse Event Monitoring		←	←	←	←	←	←	X	←	←	X	←	←	X		

1 All screening activities are to be completed within 28 days, or sooner, prior to dosing on Day 1.

2 At the completion of Year 1 or upon early termination from the study, all procedures should be performed as indicated. For patients who prematurely discontinue during Year 1, an exit visit will be performed upon exit from the study and a follow-up phone call will be performed approximately 2 weeks 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. Refer to Section 5.5.1 for guidance regarding the Exit echocardiogram for patients who discontinue the study during Year 1.

3 The screening echocardiogram should be performed for patients that have been deemed eligible for the study by meeting all other entry criteria.

4 PK sampling will be performed only at a subset of study sites at the Week 12 Visit (pre-dose and 2 hours (±15 mins) after dose.

5 A plasma sample will be collected from each patient at Day 1 (baseline), Week 24, and Week 52 or upon Early Termination. Patients will have the ability during the informed consent process to opt out of having these samples collected. These plasma samples will not be used for genetic testing.

6 Serum hCG pregnancy test required at Screening and Week 52/Exit for all female subjects. Urine dipstick pregnancy test will be done at other study visits as indicated for all female subjects.

7 Vital sign measurements (blood pressure, heart rate, respirations, and body temperature taken in supine position after 5-minute rest); Day 1 measurements will be taken before first dose

8 Sites will call the IVRS as indicated starting at the Screening Visit. The IVRS will be used to track screening and randomization and each patient's progress through the study to ensure that adequate drug supply is at the site. On Day 1 and at Week 52, the site will be requested to enter the patient's body weight, which will be used to stratify each patient for re-randomization at Year 2.

9 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 22529, APD356-009 Appendix 16.1.1 Protocol Table 7

Table 130. Schedule of Events and Procedures, Year 2

Evaluation	**Dosing Period (Study Week)**													
	56	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104/Exit**	**106**
Physical/Neurological Exam													X	
Beck Depression Inventory-II			X										X	
Echocardiogram													X	
12-Lead ECG													X	
Clinical Labs			X	X									X	
Thyroid Function Tests (i.e., T4, TSH)				X			X						X	
Hemoglobin A1c				X									X	
CV Risk Markers (i.e., CRP, fibrinogen)				X									X	
Markers of Glucose Intolerance (i.e., fasting glucose and insulin)				X			X						X	
Pregnancy Test[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy Measures:														
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Waist and Hip Circumference	X	X	X	X	X	X	X	X	X	X	X	X	X	
Quality of Life Assessment (i.e., Impact of Weight Questionnaire – Lite)			X										X	
Collect Study Drug and Perform Drug Accountability and Compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication Assessments (including antihypertensives and lipid agents)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diet and Exercise Counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	
IVRS Call[8]			X										X	
Drug Administration[9]	◄												►	
Adverse Event Monitoring	◄													►
Telephone Follow-up														X

1 At the completion of Year 2 or upon early termination from the study, all exit procedures will be performed. There will be a phone follow-up 2 weeks after the final dose of study medication, during which any AEs will be collected. For patients who prematurely discontinue during Year 2, an exit visit will be performed and a follow-up phone call will be performed ~ 2 weeks after last dose. D/C patients will be asked to return at the Week 104 visit, even if interim visits have been missed, for a follow-up body weight.

2 A serum hCG pregnancy test will be done at the Week 104/Exit visit for all female subjects. A urine dipstick pregnancy test will be done at all other visits as indicated.

Source: NDA 22529, APD356-009 Appendix 16.1.1 Protocol Table 8

Patient Population:

Patients were males and females aged 18-65 years with a BMI of 30 to 45 kg/m^2, or with a BMI of 27 to 29.9 kg/m^2 with at least one cardiovascular comorbid condition (hypertension, dyslipidemia, CV disease, glucose intolerance, or sleep apnea). A total of 3182 obese patients and overweight patients with comorbidities were randomized in Year 1. Patients who completed the initial 52 weeks of treatment (N=1599) were eligible to continue in the study. See Appendix A for inclusion and exclusion criteria.

Treatment Groups:

In Year 1, patients were randomized 1:1 to placebo or lorcaserin 10 mg BID.

Upon enrollment to Year 2 of the study, patients were stratified as "responders" (≥ 5% body weight loss from Baseline to Week 52) or "non-responders" (< 5% body weight loss during the same time period). Patients who received placebo during Year 1 remained on placebo for Year 2. Patients who received placebo during Year 1 remained on placebo for Year 2. Patients who received lorcaserin during Year 1 were re-randomized within each of these two strata in a 2:1 ratio to either remain on lorcaserin 10 mg BID or switch to placebo, respectively, for Year 2 as follows:

Table 131. BLOOM Treatment Assignments

Group	**Year 1**	**Year 2**	**Abbreviation**
A (Responders)	Placebo	Placebo	Pbo/Pbo
B (Non-responders)	Placebo	Placebo	Pbo/Pbo
C (Responders)	Lorcaserin	Placebo	Lorc/Pbo
D (Responders)	Lorcaserin	Lorcaserin	Lorc/Lorc
E (Non-responders)	Lorcaserin	Placebo	Lorc/Pbo
F (Non-reponders)	Lorcaserin	Lorcaserin	Lorc/Lorc

Source: NDA 22529, APD356-009 CSR p 23

At the time of Year 2 randomization, 14 patients were stratified to incorrect responder status ('responder', 'non-responder') because an incorrect body weight was entered in the IVRS system. The correct weights were entered at a later time, and the responder status were corrected and updated in the IVRS system and the database.

Primary endpoints:

The original primary efficacy endpoint for Year 1 of the study was the proportion of patients achieving ≥ 5% reduction in body weight after 52 weeks of treatment when compared to baseline. To accommodate the 10% categorical weight loss criterion of the European Medicines Agency (EMEA), the protocol was subsequently amended to provide for three hierarchically ordered Week 52 endpoints: the proportion of patients achieving ≥ 5% reduction in body weight from baseline, absolute weight change from baseline, and the proportion of patients achieving ≥ 10% reduction in body weight from baseline. The primary efficacy objective for Year 2 of the study was to assess the ability

of lorcaserin to maintain patients' weight loss achieved by the end of Year 1 through the end of the second year.

Secondary endpoints:

- Change in BMI (kg/m^2)
- Change in waist circumference (cm)
- Change in total cholesterol (%)
- Change in LDL cholesterol (%)
- Change in HDL cholesterol (%)
- Change in triglycerides (%)
- Change in fasting glucose (mg/dL)
- Change in fasting insulin (μIU/mL)
- Change in HOMA-IR
- Change in CRP (mg/L)
- Change in systolic blood pressure (mmHg)
- Change in fibrinogen (mg/dL)
- Change in diastolic blood pressure (mmHg)
- Change in IWQOL-LITE score

Statistical Considerations:

The analysis populations were defined as follows:

- MITT population: Patients were analyzed in the treatment group to which they were initially randomized, Year 1 (for MITT1) and Year 2 (for MITT2), regardless of the treatment received during the course of the trial.
- W52 population: All randomized patients who had a post-baseline body weight recorded between Days 350 to 395. This includes patients who withdrew from the study prior to Week 52 and returned for a body weight measurement between Days 350 to 395 for their intended Week 52 visit.
- PP population: Patients not meeting a set of pre-defined deviations that were considered to be important (major) deviations. During Year 1, these deviations included the following:
  - No body weight recorded within 2 weeks (Days 357-371) of the scheduled 52-Week Visit.
  - Stopped tobacco use at Week 52 of the study if a tobacco user at Baseline.
  - Study drug intake compliance calculated over 52 weeks of the study was < 80% or > 120%.
  - Body weights provided for fewer than 10 of the 14 scheduled visits during Year 1.
  - No Baseline body weight measurement recorded.

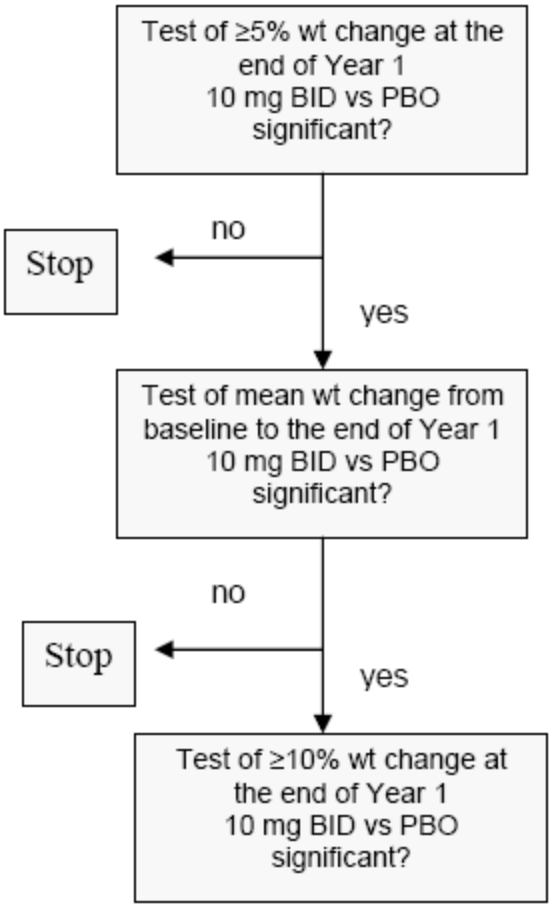
  Deviations that were considered to be important during Year 2 included the following:
  - No body weight recorded within 2 weeks (Days 721-735) of the scheduled 104-week Visit.

- Stopped tobacco use at Week 104 of the study if a tobacco user at Baseline.
- Study drug intake compliance calculated over 104 weeks of the study was < 80% or > 120%.
- Provided body weights for fewer than 10 of the 13 scheduled visits during Year 2.
- No Baseline body weight, or no Week 52 body weight measurement recorded within 2 weeks (Days 357-371) of the scheduled Week 52 Visit.

All statistical summaries and analyses of efficacy endpoints were provided for the MITT1 and MITT2 populations. Analyses of the primary endpoint for Year 1 and change in body weight from Baseline to Week 52 were provided for the W52 and PP1 populations.

Analyses of the primary endpoint for Year 2 and for change in body weight (from Week 52 to Week 104; from Baseline to Week 104) were provided for the PP2 population.

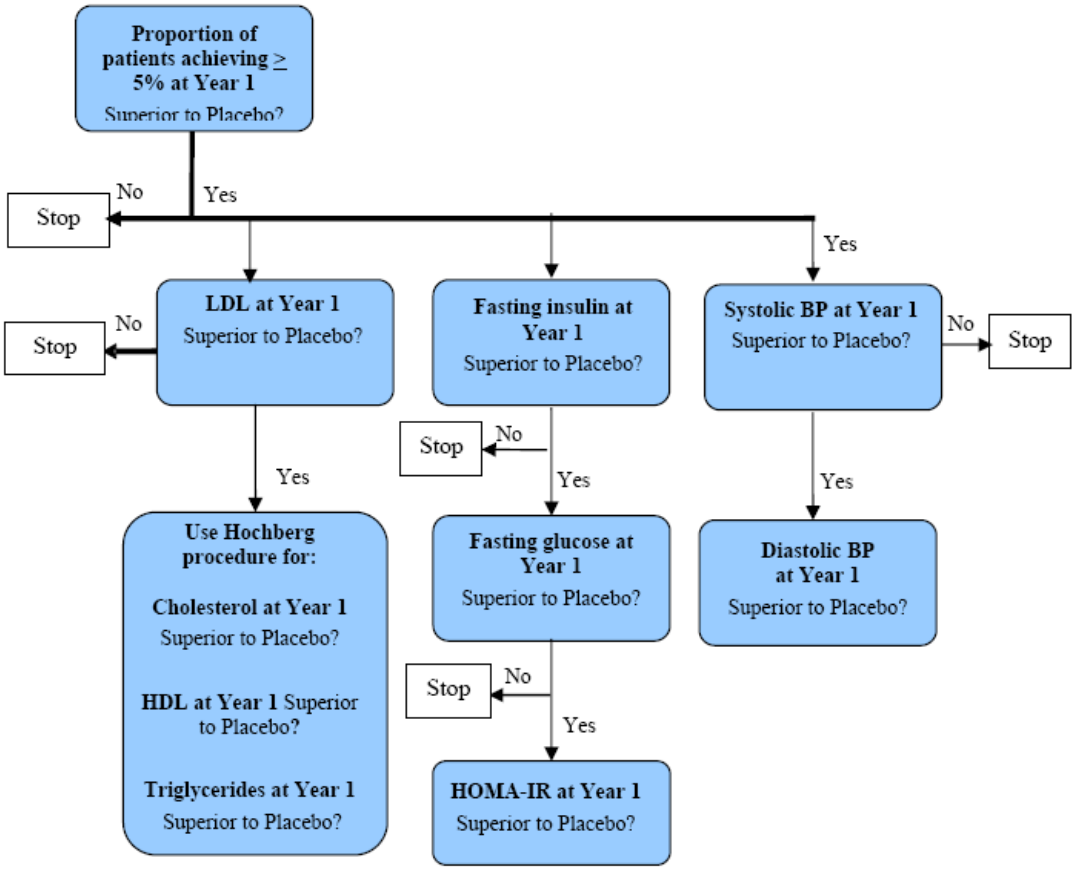
Figure 19. Testing Procedure for the Primary Efficacy Endpoints



Source: NDA 22529, APD356-009 Appendix 16.1.9 SAP Figure 2

The overall testing procedure for the key secondary efficacy endpoints and their relationship to testing of the primary efficacy endpoint is described below. All statistical analyses were completed using two-sided tests at the 0.05 level of significance ($\alpha = 0.05$).

Figure 20. Testing Procedure for the Key Secondary Efficacy Endpoints



Source: NDA 22529, APD356-009 Appendix 16.1.9 SAP Figure 3

Protocol Amendments and Changes to the Planned Analyses:

Table 132. Protocol Amendments

Amendment	Date	Description
1	30 October 2006	Changed screening period from 21 to 28 days prior to randomization
		Revised exclusion criterion #6 to include patients who scored > 0 on BDI-II question 9
		Added collection of plasma sample on Day 1, Week 24, and Week 52 or early termination for banking on a voluntary basis for all patients
		Added exclusion criterion #30 to exclude patients with prior history of fenfluramine or related derivative (dexfenfluramine, norfenfluramine) usage (patients enrolled prior to Amendment 1 were allowed to continue in the study with documentation of prior fenfluramine use)
2	16 April 2008	Revised exit echocardiogram procedures
3	10 September 2008	Updated primary efficacy endpoints to accommodate inclusion of 10% responders in overall analyses
		Added new section to describe procedures for efficacy assessments with regards to multiplicity and testing of the efficacy hypothesis

Source: NDA 22529, APD356-009 CSR p 45

BLOSSOM

Primary Objective:

- To assess the weight loss effect of lorcaserin during 1 year of treatment

Secondary Objectives:

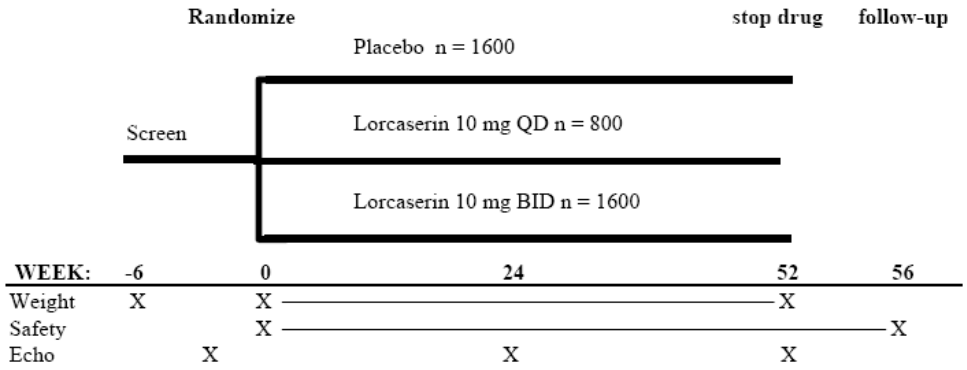
- To assess the safety of lorcaserin
- To assess changes in cardiovascular risk factors associated with obesity (i.e., dyslipidemia, hypertension) between Baseline and Week 52
- To assess changes in mood between Baseline and Week 52
- To assess echocardiographically-determined heart valve and pulmonary artery pressure changes associated with weight reduction and/or lorcaserin use during 1 year of lorcaserin treatment
- To assess changes in Quality of Life measures during 1 year of lorcaserin treatment
- To assess population pharmacokinetics of lorcaserin

Design:

This was a randomized, double-blind, placebo-controlled, parallel-group assessment of the effects of lorcaserin during 52 weeks of administration.

Patients were randomized 2:1:2 to placebo, lorcaserin 10 mg QD, or lorcaserin 10 mg BID. Each patient was to have completed screening procedures within 6 weeks of dosing on Day 1. Study design schematic is presented below:

Figure 21. BLOSSOM Study Design



Source: NDA 22529, APD356-011 CSR Figure 1

As in BLOOM, patients participated in the Arena Healthy Lifestyle Program.

Table 133. Schedule of Events and Procedures

Evaluation	Screening[1]	Randomization	Dosing Period (Study Week)															F/U
	-42 to -1	Day 1	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/Exit[2]	56
Informed Consent	X																	
Medical History	X	X[3]																
Physical Exam	X	X[3]			X													
Beck Depression Inventory-II	X				X													
Binge Eating Scale	X								X									
Echocardiogram	X[4]								X									
12-Lead ECG	X														X			
Clinical Labs	X	X			X		X		X	X			X		X	X	X	
Drugs of Abuse Screen	X															X		
Thyroid Function Tests (T4, TSH) and HbA1c	X																	
Pregnancy Test[5]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Virology Screen (HIV, Hep C, and HBsAg)	X														X			
Vital signs[6]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy Measures: Body Weight Waist and Hip Circumference[7]	X	 X X		X	X	X	X	X	X	 X X	X	X	X	X	X	X	 X X	
DEXA[8]		X																
PK Blood Collection[9]							X											
Prolactin[10]		X			X		X		X									
Apolipoprotein A1[11]		X							X						X			
Apolipoprotein B[11]		X							X						X			
Quality of Life Assessment		X													X			
IVRS Call[12]	X	X					X			X			X		X	X	X	
Concomitant Medications Assessments		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diet and Exercise Counseling		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect Study Medication and Perform Drug Accountability and Compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Evaluation	Screening[1]	Randomization	Dosing Period (Study Week)														F/U
	-42 to -1	Day 1	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/Exit[2]	56
Drug Administration[13]		◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	
Adverse Event Monitoring		◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►

1 All screening activities are to be completed within 42 days, or sooner, prior to dosing on Day 1.

2 At the completion 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.

3 Partial examination to update findings from the examination performed at screening.

4 Baseline echocardiogram must be acquired before randomization; randomization may occur as soon as echo core lab determines that the study technical quality is acceptable; interpretation need **not** be completed prior to randomization.

5 Serum hCG pregnancy test required at Screening and Week 52/Exit. Urine dipstick pregnancy test will be done at other study visits as indicated for all female subjects regardless of childbearing potential.

6 Vital sign measurements (blood pressure, heart rate, and body temperature taken in supine position after 5-minute rest); Day 1 measurements will be taken before first dose and approximately 2 hrs after the first dose. Height will be measured at screening only.

7 Hip and waist circumference to be measured in triplicate. Final result will be the average of the 3 measurements.

8 DEXA scan to be performed Day 1/Randomization (+ 2 weeks), Week 24 (± 2 weeks), and Week 52/Exit; (± 2 weeks) in a subset of randomized patients at selected "Radiant" sites.

9 PK samples will be collected from approximately 1/3 of randomized patients.

10 Blood samples for prolactin measurement will be collected prior to and after administration of study medication from approximately 1/3 of randomized patients. For females, reproductive status and the start date of last menstrual period will be documented at each visit for prolactin measurement.

11 Blood samples and laboratory tests for Apolipoprotein A1 and Apolipoprotein B will be collected prior to administration of study medication from approximately 1/3 of randomized patients.

12 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 screening, study completion or early termination.

13 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 22529, APD356-011 Appendix 16.1.1 Protocol Table 2

Patient Population:

A total of 4008 obese patients and overweight patients with comorbidities were randomized. See Appendix A for inclusion and exclusion criteria.

Treatment Groups:

Patients were randomized 2:1:2 to placebo, lorcaserin 10 mg QD, or lorcaserin 10 mg BID.

Primary endpoints:

- Percent of patients achieving ≥ 5% weight loss
- Change from baseline in body weight
- Percent of patients achieving ≥ 10% weight loss

Secondary endpoints:

- Change in waist circumference from Baseline to the Week 52 visit
- Change in blood pressure (systolic and diastolic) from Baseline to Week 52
- Change in lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Change in Body Fat from Baseline to Week 52
- Change in Quality of Life measures from Baseline to Week 52

Statistical Considerations:

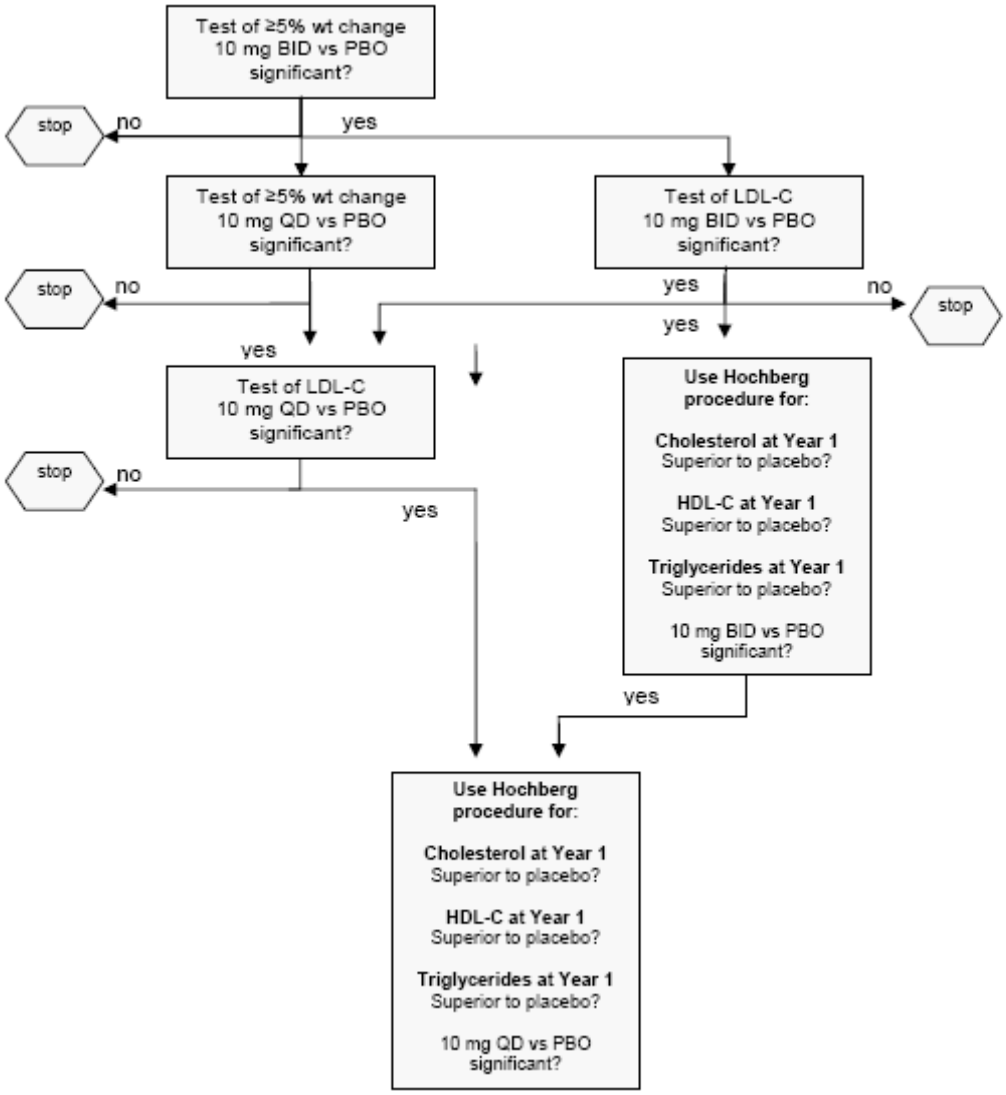
The endpoints in the secondary hypotheses were grouped into 4 families: lipids, blood pressure, body composition, and Quality of Life. Once the test of the primary hypothesis on the 5% responders was significant, the secondary hypotheses were tested simultaneously at 0.05 level in a conditional manner prioritized in the following order:

- Lipids: LDL-C, and using Hochberg procedure for total cholesterol, HDL-C, triglycerides;
- Blood pressure: systolic blood pressure, diastolic blood pressure;
- Body composition: total body fat;

Quality of Life: total score

Figure 22 describes the overall testing procedure for the secondary hypotheses (example: lipid family) and their relationship to testing of the primary hypothesis as described above.

Figure 22. Flowchart for Secondary Efficacy Analyses for Lipid Family



Source: NDA 22529, APD356-011 Appendix 16.1.9 SAP Figure 3

Protocol Amendments and Changes to the Planned Analyses:

Amendment 1: Echocardiogram exclusion criteria removed and screening echocardiogram was removed (based on findings of EDSMB); added Week 4 prolactin

Amendment 2: Increased sample size to 4000

Amendment 3: Revised hypothesis, efficacy assessments, and data analysis sections to accommodate inclusion of 10% weight reduction group in overall analyses. Added "Change in Body Fat from Baseline to Week 52" as a secondary efficacy assessment.

Appendix C. Selected Patient Narratives

APD356-001a

Lorcaserin 40 mg

Participant 025 was a 48-year-old healthy White female who received a single dose of study drug. She reported mild nausea approximately 30 min after dosing and soon after the subject was giggling and shortly after laughing without any reason. A few minutes later she felt intoxicated (like after a few alcoholic drinks) and felt she was not in control of herself. She became disorientated (first only to time, but later to place and person). Between approximately 1 hour and 2 hours after dosing she was disorientated, restless, intermittently unresponsive to verbal commands, crying at times, nauseous, and hallucinating ('Where are my arms? My arms have gone?'). Vital signs were stable at the time, pulse approximately 100 beats per minute. Approximately 3 hours after dosing she was no longer disoriented. Remaining symptoms of nausea, tremor of the right hand and stomachache were improved but not resolved at the time of report writing.

APD356-003

Lorcaserin 15 mg QD

Patient 19-119, a 27-year-old Black female, was randomized and received her first dose of study drug on 18 February 2005. Her medical history was significant for occasional heartburn and headaches. She presented on Day 22 (14 March 2005) with a prolonged PR interval of 390 msec. The PR interval on Day 1 was 202 msec. Study drug was discontinued, and the ECG was repeated the next day (15 March 2005). This repeat ECG showed a PR interval of 208 msec. A second ECG, performed 4 minutes later, indicated a possible conduction defect, manifested by a varying PR interval (186-440 msec). According to the central cardiologist over-reader, the first 3 beats recorded had a PR interval of 198 to 208 msec, but the last 5 beats had a marked prolongation of the PR interval that varied from approximately 360 to 400 msec. Holter monitoring performed on 28 March 2005 and 29 March 2005, 2 weeks after discontinuing study drug, demonstrated several periods of prolonged PR interval in the same range as previously observed. The patient did not complete the treatment or follow-up visits based on patient decision, and the date of her last visit was 28 March 2005.

APD356-004

Lorcaserin 10 mg QD

Patient 08-012 was a 38-year-old White female who was randomized and received her first dose of study drug on 08 August 2005. Her medical history was significant for migraine headaches, pinched nerve, insomnia, a mood disorder with reported pain and rage, asthma, hyperlipidemia, and allergies to sulfa drugs, hydrocodone/acetaminophen, morphine, clove oil, povidone-iodine, ragweed, and mold.

During the course of the study, the patient reported AEs of somnolence (09-10 August 2005), anxiety (16 November 2005 on), and depressive symptoms (18 October-16 November 2005). On 16 November 2005 at her exit visit, physical examination revealed that the patient had a slight tremor in her hands, was pacing, and unable to sit still. On the same day, the patient had a psychological evaluation, following observations by the study site staff that she had appeared to be in considerable distress reporting high levels of anxiety, tearfulness, and difficulty sleeping for several weeks. The psychological assessment indicated that the patient met the criteria for major depression based on the following symptoms: loss of pleasure in almost all activities, decreased appetite, insomnia, psychomotor agitation, irritability, fatigue, and decreased concentration. These symptoms were noted to be present on most days for more than 2 weeks. She also reported high levels of anxiety daily and panic attacks, which had been occurring over the last month and coincided with her participation in this study as well as significant life stressors. Concomitant medications included oral zolpidem 5 mg once daily, oral diphenhydramine 25 mg as needed, and oral alprazolam 0.5 mg as needed. A review of the Bond & Lader VAS and SSQ dating from the Day 1 to Day 85 visits correlated with the patient's reported complaints of feeling sad, withdrawn, lethargic, discontented, troubled, and tense, especially between the Day 57 and Day 85 visits. The patient was seen by a clinical social worker for counseling and was advised to be evaluated by a psychiatrist. In November, the patient's gynecologist started her on oral escitalopram oxalate 10 mg once daily and she reported that it was helping her symptoms. Her last dose of study drug was on 01 November 2005 and her last visit was on 16 November 2005. She subsequently refused to return to the study site for a follow-up visit and was considered lost to follow-up. The event was considered to be resolved with sequelae. The patient did not complete the follow-up period. The investigator considered the event of major depressive disorder 'serious' because it was an important medical event.

Lorcaserin 10 mg BID

Patient 15-002 was a 35-year-old Black female who was randomized and received her first dose of study drug on 01 July 2005. Her medical history was significant for lower back pain and seasonal allergies. On the night of 10 September 2005, the patient experienced "blacking out," and was taken to the emergency room and subsequently admitted to the hospital. A neurology consultation on 11 September 2005 led to a diagnosis of new onset seizure. The neurologist noted that the seizure occurred after days of stress and decreased oral intake. A magnetic resonance imaging scan showed scattered foci of abnormally increased signal intensity in the hemispheric white matter, consistent with vasculitis, including migraine syndrome. A magnetic resonance angiography scan of the head was normal, an antinuclear antibody test was negative, and an electroencephalogram showed spike/slow wave pattern. During the hospitalization, the patient was not treated with any seizure medications and had no further seizures. She had mild hypokalemia that was believed to be due to gastrointestinal losses and was treated with potassium. The event was considered to be resolved on 13 September 2005, and the patient was discharged the same day. The patient was discontinued from the study on 30 August 2005 due to this event. The patient's last study visit, and therefore her last

documented dose of study drug, was on 30 August 2005; however, the SAE report indicated that the patient's last dose of study drug was 09 September 2005. The patient did not complete that treatment period or the follow-up period and was lost to follow-up.

Patient 23-034, a 26-year-old Black female, was randomized and received her first dose of study drug on 26 July 2005. She had no significant medical history. On 20 September 2005, the patient was reported to have AEs of complete AV block and bradycardia. An ECG performed on this date revealed clinically insignificant sinus bradycardia. Previous ECG results included an insignificant intraventricular conduction delay on 26 July 2005; sinus bradycardia, sinus arrhythmia, and first degree AV block on 09 August 2005; and sinus bradycardia with marked arrhythmia on 25 August 2005. A Holter monitor was placed on 21 September 2005 and showed intermittent bradycardia and approximately 20 episodes of complete heart block, each with 1 skipped ventricular beat. Study drug was stopped by investigator decision on 23 September 2005 when the Holter report was received. Two follow-up Holter examinations off study drug showed 2 pauses each. A consulting cardiologist considered the Holter findings not clinically significant. On 20 October 2005, the patient reported to an emergency department complaining of nausea, left-sided facial numbness, and left arm numbness. Assessments revealed clinically insignificant sinus bradycardia with sinus arrhythmia on ECG, and left-sided numbness and progressive bradycardia on physical examination. The AEs resolved spontaneously during the emergency department visit, and a head CT scan was normal. The patient did not complete the follow-up period.

APD356-009 (BLOOM) – Year 1

<u>Lorcaserin 10 mg BID</u>

Patient 180-S108 is a 43-year-old White female who began study drug on 02 January 2007. The patient does not have relevant medical history. On Study Day 32, the patient experienced an SAE of dysphasia. The AE was described as "hard to find a word". The patient stated she had never experienced this type of word confusion prior to study participation. Study drug was discontinued and the patient was withdrawn from the study. The event resolved 6 days after cessation of lorcaserin.

Patient 180-S141 is a 36-year-old White female who began treatment on 22 January 2007. Relevant medical history includes migraines. On Study Day 106, the patient experienced an SAE of attempted suicide by ingesting metformin, Lipitor, and antihypertensive medications, which resulted in hospitalization. Treatment for the event included trazodone and fluoxetine. Study drug was discontinued and the patient was withdrawn from the study. The patient had no reported history of neuropsychiatric disease; however, the patient's husband reported that she had been recently fired from her job due to embezzlement of company funds. The husband reported that this was totally out of character for her. BDI scores were 0, 3, and 1 on 23 Dec 2006, 19 Feb 2007, and 16 Apr 2007, respectively. The event was reported as severe in intensity and was considered resolved on Study Day 113.

Patient 189-S070 is a 28-year-old White male who began study drug on 23 January 2007. Relevant medical history includes migraines, headaches, and resting tremor. On Study Day 25, the patient experienced an SAE of nervous system disorder (neurological dysfunction) consisting of nausea and vomiting, slurred speech, blurred vision, and short term memory loss. He also complained of concomitant chest pain, and declined to seek medical care at that time. At a follow-up study visit, his symptoms, with the exception of some morning nausea, had resolved. Consultation with a neurologist revealed no abnormality and the electroencephalogram (EEG) was normal. No imaging study was performed. Study drug was discontinued immediately at the time of the event. The patient refused additional medical care and elected to withdraw from the study. The event was reported as moderate in intensity, possibly related to study drug, and was considered resolved on Study Day 29.

Placebo

Patient 189-S044 is a 54-year-old White female, who began treatment on 13 December 2006. On Study Day 22, she experienced an AE of suicidal thoughts which she reported as mild in severity. The event was considered not related to study drug and no action was taken with regards to study drug. Results of the patient's BDI-II completed at the Screening visit include a Total Score of "1" and a Question 9 Score of "0". Upon reporting the AE, the patient's Suicidality Rating was assessed as a "5". On Study Day 41, study drug was discontinued and the patient elected to withdraw from the study citing personal issues and lack of efficacy as reason for withdrawal. The outcome of the AE is unknown.

APD356-009 (BLOOM) – Year 2

Lorcaserin/Placebo

Patient 145-S044 is a 48-year-old White female who began treatment with lorcaserin 10 mg BID on 22 November 2006 and was re-randomized to placebo on 28 November 2007. The patient had no history of depression or other mental health problems. An AE of depression was reported on Study Day 491. On Study Day 495, the patient experienced an SAE of intentional overdose by ingesting ibuprofen, levothyroxine, cyclobenzaprine, and alcohol with the intent of committing suicide following an upsetting conversation. The patient was hospitalized and treated with venlafaxine. Study drug was discontinued, and the patient was withdrawn from the study. The event was reported as severe and was considered resolved on Study Day 495.

APD356-010 (BLOOM-DM)

Blinded

Patient 1130-S015 is a 54-year-old Hispanic male, with a medical history significant for hypertension, hypercholesterolemia, and type 2 diabetes mellitus, and a negative history for seizure, stroke or TIA. The patient denied alcohol or recreational drug use. On Study

Day 119 the patient experienced a witnessed SAE of seizure with estimated duration 2-3 minutes. The seizure resolved prior to presentation at an emergency department. Post-ictal glucose measured at the hospital was 178 mg/dL (normal 70-99 mg/dL), a toxicology screen was negative, and no metabolic abnormalities were noted. Fasting glucose values measured around the time of the event were 90 mg/dL on Study Day 14, 101 mg/dL on Study Day 165, and 70 mg/dL on Study Day 239; HbA1C declined from 8.7 at randomization to 6.7 on Study Day 83 and 6.5 on Study Day 165. No IVRS calls for suspected hypoglycemia were made. Treatment included fosphenytoin and levetiracetam. MRI of the brain indicated mild generalized intracranial atrophy and no significant acute intracranial process. EEG was normal at rest, with hyperventilation and with photic stimulation. The event was reported as mild in intensity and resolved on Study Day 119. Although the investigator reported the event as possibly related to study, the treating neurologist considered a relationship to study drug unlikely. The investigator did not withdraw the patient from the study.

On Study Day 217 the patient was diagnosed with an AE of transient ischemic attack after reporting a 30-minute episode of right-sided numbness and chest pain. An echocardiographic study and carotid Doppler showed only bilateral carotid plaque with 1-39% stenosis. Acetylsalicylic acid and simvastatin were prescribed.

On Study Day 234, the patient reported a second apparent seizure. The SAE of seizure was not witnessed; he lost neither bladder nor bowel function, and no precipitating factors were reported. No pre-seizure blood glucose is available; post-ictal glucose was 196 mg/dL. A CT scan of the head without contrast was negative for acute lesions, infarcts, or hemorrhage. A neurological exam was benign. The levetiracetam concentration was reportedly low, and the dose was increased; phenytoin had been discontinued several weeks prior to this event. The event was reported as mild in intensity, possibly related to study drug, and resolved on Study Day 234. Study drug was permanently discontinued.

Reviewer comment: We await unblinding of this trial to make an assessment of this case. It is somewhat concerning that no alternative cause was found and a second seizure occurred on study drug (although it is noted that an antiseizure medication concentration was reported as low).

APD356-011 (BLOSSOM)

Lorcaserin 10 mg BID

Patient 2109-S025 is 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 Mucinex DM (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 5 hours, but re-appeared with her evening dose of study drug and again taking Mucinex DM. The next morning, the symptoms were resolved. She did not take the study drug that morning. She took her last dose of clarithromycin 3 days later, and started amoxicillin 2 days after cessation of clarithromycin (Study Day 62).

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 Mucinex DM, and re-start study drug approximately 1 week after the initial symptoms. The re-challenge was uneventful, with no re-appearance of symptoms.

Patient 2139-S030 was a 58-year-old White male with a past medical history of hypertension, gout, dyspepsia, diverticulosis, osteoarthritis, dream sleep disturbance, chronic venous insufficiency, idiopathic edema, and insomnia, who was hospitalized 9 months into treatment with lorcaserin for poor sleep, abnormal dreaming, and possible hallucinations (preferred term: alcoholic psychosis). The patient had a history of consuming 3-4 alcoholic drinks per day, with 1-2 month periods of no alcohol consumption. Concomitant medications included amlodipine, colchicine, and CoQ10. The first dose of therapy was 3 April 2008 and the patient's last dose of therapy prior to event onset was 3 January 2009.

On 3 January 2009, the patient presented to the emergency room with complaints of very poor sleep for the past 4 months, as well as auditory and visual hallucinations for approximately 1 year, as well as disordered thoughts. He admitted past heavy drinking but reported no alcohol intake for over 2 weeks. A geropsychiatry evaluation reportedly determined the patient was possibly experiencing delirium tremens [provided notes did not discuss this possibility]. An alcohol concentration was negative, and a urine drug screen was positive for acetaminophen. The patient was given intravenous fluids containing folate, magnesium, vitamins, and thiamine, and admitted to the hospital. The same day he signed out of the hospital against medical advice and immediately returned to the emergency room for further evaluation. He appeared "somewhat delusional" and was treated with lorazepam for jitteriness. On 4 January 2009, the patient was admitted to an inpatient psychiatric center under a temporary detention order and diagnosed with alcohol-induced psychotic disorder. Laboratory tests of admission were clinically unremarkable. The patient was treated with supportive therapy and psychotropic medications and received alcohol education while hospitalized. The patient was discharged 9 January 2009. The patient was withdrawn from the study due to the event.

Reviewer comment: It is notable that the diagnosis of alcohol-induced *psychotic disorder was made without knowledge that the patient was in a drug trial.*

Patient 2174-S061 is a 53-year-old White female who began study drug on 17 May 2008. The patient reported a history of migraines and a twenty-year history of intermittent depression. The past couple of years had been stressful as she had been

angry, irritable, and had difficulties controlling her behavior because she was impulsive and explosive. The patient had no previous admissions to psychiatric hospital; however, she had prior treatment as an outpatient. On Study Day 272, the patient experienced a SAE of nervous breakdown (preferred term, mental disorder), characterized by anger and a desire to harm her supervisor due to work-related stress. The patient had received a note from her job supervisor questioning the patient's lack of respect for persons supervising her work. The patient was experiencing a migraine at the time and also reported a 2-year history of harassment by her supervisor. After reacting very angrily to the supervisor's accusation, the patient went to the psychiatry office in the medical facility where she worked and stated she was having a nervous breakdown as she was having suicidal thoughts and wanted to do bodily harm to her supervisor.

Treatment included hospitalization at a mental health facility and therapy for anger management. Treatment medications included fluoxetine, which the patient did not take after discharge. No action was taken with regard to study drug. The patient was placed on disability leave from her job after her supervisor obtained a restraining order against her.

The patient reported the event of nervous breakdown to the site during a regularly scheduled study visit on 28 March 2009. She did not appear depressed or suicidal to the investigator at that time, and was allowed to remain in the study under supervision. The event was reported as moderate in intensity and was considered resolved on Study Day 275.

Reviewer comment: The reported suicidal ideation at the time of the event was not adjudicated. The patient documentation notes that she had made a significant mistake in transcribing at work, which was not described further. It is unknown if this is a problem she has had in past (prior to lorcaserin treatment), but given that lorcaserin can be associated with difficulties in concentration and attention, it is conceivable that completing some tasks at work may be impaired.

Patient 2182-S037 is a 40-year-old White female who began study drug on 19 March 2008. Relevant medical history is significant for depression and postpartum depression. On Study Day 220, the patient presented to the ER with suicidal thoughts and depression and was admitted to the hospital for the SAE of suicidal thoughts. The patient had previously reported suicidal ideation during her Week 4 visit (Study Day 30; from BDI-II), and was referred to her primary care physician. Treatment medications included bupropion and trazodone. Study drug was discontinued and the patient was withdrawn from the study. The event was reported as severe in intensity and was considered resolved with sequelae on Study Day 226.

Patient 2255-S030 is a 30-year-old Hispanic female who began study drug on 01 April 2008. The patient has no relevant medical history. On Study Day 63, the patient contacted the study site to inform them that she had stopped study drug because of depressive symptoms that included negative thoughts, loss of enjoyment, increased irritability, increased sleeping, increased tearfulness, and loss of enjoyment. The patient

reported that her family and spouse had become very concerned about the dramatic change in her affect. With 10 days to 2 weeks of discontinuing study drug she felt a big change in mood, resolution of symptoms, and a return to her former demeanor. She did not seek medical care and declined evaluation by a mental health practitioner. No treatment was given. Study drug was discontinued and the patient was withdrawn from the study. BDI-II total scores were 3 and 4 at Screening and Week 4. The investigator considered the event to be medically important, and reported an SAE of moderate depression. The event was reported as moderate in intensity and was considered resolved on Study Day 84.

Reviewer comment: The investigator attributed the relationship to study drug as 'possible' for the following reasons: the patient wad a well-educated, well-informed nurse historian who has been socially well-adjusted and demonstrated that she could tolerate high levels of distress while under challenging concurrent circumstances. She did not demonstrate any medical symptoms of depression at screening and had a negative history of depression and psychiatric illness. This reviewer also notes that the patient had a positive dechallenge.

Patient 2255-S039 is a 58-year-old White male who began study drug on 24 April 2008. Relevant medical history is significant for insomnia (for which he took diphenhydramine), increased fatigue, and morning lethargy, but negative for depression or anxiety. On Study Day 15, the patient reported an AE of depression (rated severe in intensity, but with no action taken). On Study Day 31, the patient stopped study drug due to worsening symptoms of depression and his personal physician prescribed alprazolam and escitalopram on Study Day 34 for "acute anxiety attack". On Study Day 35, the patient presented to an ER with symptoms of mixed anxiety and depression that were unrelieved by the alprazolam, a SAE term of psychiatric crisis (preferred term, acute psychosis) was reported by the investigator. Treatment included intravenous diazepam and inpatient treatment at a psychiatric hospital. During hospitalization, the patient denied any active suicidal ideation; however, the patient's wife reported that the patient stated that he was "giving up" and was "not going to live like this"; he refused to be left alone. BDI-II total scores were 8 and 12 at Screening and Week 4, respectively. Study drug was discontinued and the patient was withdrawn from the study. The event was reported as severe in intensity. The patient's wife reported to the site that he was enrolled in a psychiatric day program; he was subsequently lost to follow-up and his outcome is unknown.

Reviewer comment: It is notable that the patient had no prior history of depression or anxiety and that, by report, he had no known life or health changes that could have brought about this event. His wife's report of the patient's statements could be construed as suicidal ideation, but unfortunately, this was not explored further (at a minimum should have gone through the adjudication process). Because the symptoms of depression and anxiety did not abate once study drug was discontinued (and in fact, the hospitalization occurred 4 days after study drug was discontinued), the potential relationship to lorcaserin is unclear.

APD356-013

Lorcaserin 40 mg

Participant 9050 was a 29-year-old White female who weighed 67 kg and had a BMI of 22.1 kg/m^2 and withdrew from the trial after receiving the lorcaserin 40 mg dose during the first dosing period. She reported AEs of nausea, vomiting, dyspepsia, paresthesia, tremor, hot/cold flashes, facial itchiness, and anorexia within ~3 hours of dosing. AEs of crying (moderate intensity) and depressed feeling (mild intensity) were notable; the AE of crying resolved within 3.5 hours, but the depressed feeling persisted for 19 days, prompting study discontinuation. The subject had no reported history of depression or mood disorder.

Appendix D. Echocardiogram Inter- and Intravariability Analyses

Screening/Baseline Analyses of Concordance

In BLOOM, echocardiographic images were obtained at screening from all potential patients deemed eligible for the study by meeting all other entry criteria. Echocardiograms were obtained from 4117 patients. Biomedical Systems (BMS), Inc. (St. Louis, MO) provided standardized training for all echocardiographers, and implemented centralized procedures for collecting, analyzing, and reporting echocardiographic data.

A panel of 19 cardiologists trained on the protocol by BMS served as blinded central readers for this study. Echocardiograms were read by both a primary and a secondary blinded central reader. Any discrepant readings between the primary and secondary readers were adjudicated by a third reader at BMS. When the 2 readings matched according to the criteria described above, 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.

Of the 4117 screening echocardiograms performed, 1680 (40.8%) were adjudicated by a third reader. Complete data interpretations for 3876 echocardiograms for MR and 3858 echocardiograms for AR are available from both Reader A and Reader B. Reader A and Reader B had the same interpretation for 61.1% of the MR readings and 84.0% of the AR readings.

The largest absolute difference observed between readers was either a 3-category increase or a 3-category decrease in regurgitation. The kappa result for AR was 0.43 and for MR 0.46 (Table 134), which would indicate a “moderate” strength of agreement (Table 135).

In BLOSSOM, echocardiographic images were obtained at baseline. Echocardiograms were obtained from 4588 patients.

A panel of 23 cardiologists trained on the protocol by BMS served as blinded central readers for this study. Echocardiograms were read by both a primary and a secondary blinded central reader. 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 criteria described above, 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.

Of the 4588 baseline echocardiograms performed, 1701 (37.1%) were adjudicated by a third reader. Complete data interpretations for 4587 echocardiograms for MR and 4588 echocardiograms for AR are available from both Reader A and Reader B. Reader A and Reader B had the same interpretation for 54.5% of the MR readings and 86.9% of the AR readings.

The largest absolute difference observed was either a 3-category increase or a 2-category decrease in regurgitation. The kappa result for AR was 0.26 (Table 134), which would indicate a "fair" strength of agreement (Table 135), and the kappa result for MR was 0.41 (Table 134), which would indicate a "moderate" strength of agreement (Table 135).

Table 134. Summary Statistics for Difference between the Interpretations of Reader A and Reader B

	N	Mean	SD	Minimum	Median	Maximum	Kappa (95% CI)
BLOOM							
MR	3876	-0.11	0.65	-3.0	0.0	3.0	0.46 (0.44, 0.48)
AR	3858	-0.04	0.41	-3.0	0.0	2.0	0.43 (0.40, 0.47)
BLOSSOM							
MR	4587	-0.11	0.71	-2.0	0.0	2.0	0.26 (0.24, 0.28)
AR	4588	-0.03	0.39	-2.0	0.0	3.0	0.41 (0.37, 0.44)

Source: NDA 22529, APD356-009 Appendix 16.1.9 Echo Screening Variability Report Table 3 and APD356-011 Appendix 16.1.9 Echo Baseline Variability Report Table 3

Table 135. Agreement Measures for Categorical Data

Kappa Statistic	Strength of Agreement
< 0.00	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost Perfect

Source: Reference 65

Standard Set

In both BLOOM and BLOSSOM, a standard set of 14 echocardiograms that encompass a range of AR and MR was randomly interspersed periodically among study echocardiograms for each reader at screening, and 6-month readings. The nominal "correct" interpretation was established by a single experienced cardiologist. This testing procedure was designed to identify and remediate any reader inconsistencies prior to the Month 12 echocardiogram reads. These standard echocardiograms were selected from archival studies performed at the echocardiography core laboratory as representative of normal studies or selected valvular abnormalities. All were coded to appear to the readers as if they were patients in the BLOOM or BLOSSOM study, respectively; the readers did not know which echocardiograms belonged to study patients and which were "dummy" standard echocardiograms.

[65] Landis JR and Koch GG. The measurement of observer agreement. Biometrics 1977; 33: 159-74.

The 14 echocardiograms were compiled from the pool of echocardiograms available from the APD356-003 and APD356-004 studies, in which a similar echocardiography protocol was utilized. The test set of echocardiograms was blinded by means of mock site and subject identification and randomly interspersed among study echocardiograms on a periodic basis for each of the blinded cardiologists. The administration of the test set was such that each cardiologist read each of the test echocardiograms two times, once during the reading of screening echocardiograms ("Read 1") and again during the reading of the 6-month echocardiograms ("Read 2").

The following comparisons were performed to evaluate the intra- and inter-reader variability for MR (or AR):

- Read 1 versus Target MR (AR)
- Read 2 versus Target MR (AR)
- Reads 1 and 2 combined versus Target MR (AR)
- Read 1 versus Read 2
- Read 1 versus Mode Reading for MR (AR)
- Read 2 versus Mode Reading for MR (AR)
- Reads 1 and 2 combined versus Mode Reading for MR (AR)
- All possible pairs of Readers at Read 1 and Read 2

For each of the above comparisons, the number and percentage of test echocardiograms interpreted correctly/identically were determined.

The differences in regurgitation categories (Read 2 – Read 1) were summarized using basic summary statistics (mean, standard deviation, minimum, maximum). The possible difference in regurgitation categories ranges from -4 to 4, where a difference of +2 indicates a two category increase from Read 1 to Read 2 and a difference of -2 indicates a two-category decrease from Read 1 to Read 2.

The sponsor utilized the same kappa statistic as with the baseline/screening echocardiogram inter-reader variability analysis.

In the BLOOM study, 19 cardiologists were assigned to read the echocardiograms. During the initial reads (Read 1), 17 of the 19 cardiologists provided interpretations for all the MR echocardiograms, and 14 provided interpretations for all the AR echocardiograms. Following the Read 1 period, one reader withdrew participation and provided no interpretations for the Read 2 period. Read 2 interpretations were provided for all MR echocardiograms by 17 of the cardiologists, and for all AR echocardiograms by 18 of the cardiologists.

The overall number and percentages of the identically/correctly interpreted echocardiograms for the MR and AR comparisons are given below.

Table 136. Number and Percentage for Identical Readings, BLOOM

Comparisons	Number (%) of Identical Readings	Kappa (95% CI)
Mitral Valve		
Read 1 versus Target MR	98 / 150 (65%)	
Read 2 versus Target MR	86 / 143 (60%)	
Read 1 versus Read 2	111 / 141 (79%)	0.69 (0.59, 0.79)
Read 1 and Read 2 versus Mode MR	211 / 296 (71%)	
Aortic Valve		
Read 1 versus Target AR	94 / 146 (64%)	
Read 2 versus Target AR	87 / 144 (60%)	
Read 1 versus Read 2	103 / 136 (76%)	0.66 (0.57, 0.76)
Read 1 and Read 2 versus Mode AR	217 / 296 (73%)	

Source: NDA 22529, APD356-009 Appendix 16.1.9 Echo Standard Set Variability Analysis Tables 2, 3, and 6

In the BLOSSOM study, 23 cardiologists were assigned to read the echocardiograms, and all readers read all test echocardiograms.

The overall number and percentages of the identically/correctly interpreted echocardiograms for the MR and AR comparisons are given below.

Table 137. Number and Percentage for Identical Readings, BLOSSOM

Comparisons	Number (%) of Identical Readings	Kappa (95% CI)
Mitral Valve		
Read 1 versus Target MR	108 / 184 (59%)	
Read 2 versus Target MR	103 / 184 (56%)	
Read 1 versus Read 2	134 / 184 (73%)	0.62 (0.52, 0.71)
Read 1 and Read 2 versus Mode MR	219 / 368 (60%)	
Aortic Valve		
Read 1 versus Target AR	123 / 184 (67%)	
Read 2 versus Target AR	119 / 184 (65%)	
Read 1 versus Read 2	160 / 184 (87%)	0.81 (0.74, 0.88)
Read 1 and Read 2 versus Mode AR	285 / 368 (77%)	

Source: NDA 22529, APD356-011 Appendix 16.1.9 Echo Standard Set Variability Analysis Tables 2, 3, and 6

The echocardiogram laboratory (BMS) was given a list of cardiologists with ratings for remedial action and additional training if appropriate in the BLOOM study; this remedial action was not described for the BLOSSOM study. The actions taken on part of BMS were not described.