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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name	Julie Golden
Review Completion Date	19 June 2012

Established Name	Lorcaserin hydrochloride
Proposed Trade Name	Belviq
Therapeutic Class	Obesity
Applicant	Arena Pharmaceuticals

Formulation	Tablet
Dosing Regimen	10 mg twice daily
Indication	Weight loss
Intended Populations	BMI ≥ 30 kg/m ²
	BMI ≥ 27 kg/m ² with ≥ 1 weight-related co-morbidity

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this application because: 1) despite modest mean placebo-subtracted weight loss, a clinically and statistically significantly greater proportion of patients achieved five percent weight loss on lorcaserin versus placebo, and 2) serious risks are, for the most part, theoretical and can be managed with labeling. My recommendation is heavily influenced by the 18 votes in favor of (versus four votes against) approval by the May 10, 2012 advisory committee, and the lack of treatment options available for the obese patient population.

I do have concerns that lorcaserin will be used by a large number of patients at higher doses and in unstudied drug combinations. In addition, there may be as-of-yet unidentified patient populations that are particularly vulnerable to clinically significant off-target effects, such as neuropsychiatric effects and valvulopathy. Based on current data, however, I believe that labeling can adequately address risk management and that more data obtained in the post-marketing setting will continue to inform risk benefit and safe use of the drug (see section 1.4).

1.2 Risk Benefit Assessment

Obesity is a notoriously difficult condition to treat, and often requires a multi-disciplinary and multi-treatment approach. The options for pharmacological management are extremely limited, due modest weight loss efficacy and a series of high-profile safety issues that have led to market withdrawals in the U.S. and Europe (e.g., fenfluramine and derivatives, phenylpropanolamine, rimonabant, and sibutramine).

The goal of treating obesity with drugs is to improve health and prevent weight-related diseases. Nevertheless, we have very limited information on drugs' ability to impact health outcomes. As noted in FDA's weight management guidance, a weight loss of five percent was selected to tie the measurable effect of a drug to expected cardiovascular and metabolic benefits.

Lorcaserin meets one of the two efficacy criteria FDA has recommended for obesity drugs. Based on the results of three Phase 3 trials at one year, lorcaserin's treatment effect for weight loss is within the 3.0-3.7% range, which falls below the five percent mean benchmark for mean placebo-subtracted weight loss. Nevertheless, a meaningfully greater proportion of patients achieved five percent weight loss with lorcaserin plus diet and exercise than those on placebo plus diet and exercise. Importantly, lorcaserin appeared to uniquely benefit the type 2 diabetes patient population, with a placebo-subtracted decrease in HbA1c of 0.5% at one year.

Presumably, if sustained, this would translate into prevention of diabetes-related morbidity.

Despite study limitations such as a large number of drop-outs, I believe that the fact that lorcaserin's treatment effect was highly consistent using a variety of sensitivity analyses indicates a good understanding of the weight loss benefit in the studied patient populations. I also believe that the large Phase 3 program allowed for adequate characterization of drug-related adverse effects for marketing. However, I acknowledge that there remains some uncertainty surrounding theoretical risks that require further monitoring and assessment post-marketing:

- Valvular heart disease: It is difficult to know for sure whether the imbalance in FDA-defined VHD noted in the clinical trials is drug-related or a result of ascertainment or other bias, but I believe that lorcaserin's 5HT₂ receptor selectivity and activation data are reassuring. Further study should be directed toward whether lorcaserin leads to hemodynamically consequential valvular regurgitation (i.e., add-on echocardiography to the required long-term trial in high-risk patients). This has not been observed in the clinical trials to-date. Because of some data that suggest that heart tissue in patients with cardiomyopathy may over-express 5HT_{2B} receptors¹, I recommend warning about use of lorcaserin in patients with hemodynamically significant valvular disease or congestive heart failure.
- Ischemic or thrombotic cardiovascular risk: As articulated by the March 2012 advisory committee, obesity drugs, even those without a clear cardiovascular (CV) signal, should be evaluated for CV risk given: 1) that a major reason for treatment of obesity is to prevent adverse CV events, 2) diabetes drugs have to undergo a CV risk analysis prior to approval and there is much overlap between these drug classes and patient populations, and 3) historically, obesity drugs have had a poor track record for CV safety. In the non-diabetes population, lorcaserin decreased blood pressure and heart rate, and lipid changes were generally favorable. In the diabetes population, statistically significant changes were not seen for blood pressure. There were slightly more patients with an adverse event of hypertension in the lorcaserin treatment group than the placebo-treated group in the diabetes trial only. It is difficult to know what to make of the isolated hypertension finding, since in total, the CV biomarker data look favorable or neutral. A number of analyses were conducted utilizing the adverse CV event reporting terms in the Phase 3 trials. The results are neither especially worrisome nor reassuring (point estimates range from 0.78 to 1.11 and upper bounds of the 95% confidence interval range from 1.54 to 2.84). I agree with the majority of the May 10, 2010 advisory committee members that a post-marketing CV outcomes trial (versus further pre-marketing assessment) would appropriately assess the risk of a drug that does not have an obvious CV signal, and

¹ Jaffré F, et al. Serotonin and angiotensin receptors in cardiac fibroblasts coregulate adrenergic-dependent cardiac hypertrophy. *Circ Res*. 2009;104:113-23.

furthermore that lorcaserin was “caught in the middle” of an as-of-yet unformulated new FDA policy decision.

- Psychiatric effects such as dissociation and mood disorders: It is worth noting that lorcaserin has the same mechanism-of-action as a number of psychedelic drugs. Its predicted potency at 5HT2A receptors at clinical exposure should mean that most patients should not develop adverse psychotic or hallucinogenic reactions, but as such findings were seen at doses that patients could reasonably achieve with lorcaserin abuse (four times clinical exposure) suggests that such reactions may be seen post-marketing. Furthermore, there may be patients who are vulnerable or clinical situations that may predispose patients to such reactions. In addition, I am not convinced that lorcaserin has been completely exonerated of the risk of mood disorders, particularly depression and suicidality. There were some imbalances for serious adverse events of depression and slightly more patients on lorcaserin experienced suicidal ideation in the clinical trials. Ongoing clinical trials should continue to assess for these events and labeling should warn of the risk of abuse potential and overdose.
- Cognitive dysfunction: Centrally-acting obesity drugs of a variety of mechanisms have been found to possess adverse effects on cognitive function. The 5HT2A receptor is thought to play a role in cognition and memory. Cognitive adverse events were identified in the Phase 3 database, in which impairments in attention and memory were seen three to four times as frequently in the lorcaserin 10 mg BID treated group as compared to placebo. Cognitive dysfunction should be an adverse event of interest in both the CV outcomes trial, in which patients will be older and with more co-morbidities than in the Phase 3 database, as well as in the pediatric population where the long-term impact of such effects is unknown. Somnolence and sedation adverse events were also seen twice as frequently in the lorcaserin group as compared to placebo. Labeling should warn of the risk of operating heavy machinery until the effects are known in an individual patient.
- Serotonin syndrome: Serotonin toxicity is a constellation of neuromuscular, psychiatric, and autonomic nervous system symptoms and signs that result from an excess of serotonin.^{2,3} Some researchers suggest that agonism at the 5HT2A receptor contributes to serotonin syndrome.^{2,4} There were two cases within the lorcaserin development program that the investigators considered to fall within the spectrum of serotonin toxicity, including one adverse event of ‘serotonin syndrome’ in a patient concomitantly taking dextromethorphan. Serotonin syndrome is a potentially lethal adverse event that may be plausibly related to the use of lorcaserin.

² Boyer EW and Shannon M. The serotonin syndrome. N Engl J Med 2005; 352 (11): 1112-20.

³ Wappler F, et al. Pathological role of serotonin system in malignant hyperthermia. Br J Anaesth 2001; 87: 794-8.

⁴ Isbister GK and Whyte IM. Serotonin toxicity and malignant hyperthermia: role of 5HT2 receptors. Br J Anaesth 2002; 88(4): 603.

Labeling should warn about concomitant use with serotonergic agents and that clinical suspicion should be raised in the setting of certain characteristic signs and symptoms.

- **Breast neoplasms and other malignancies:** A large part of the review of the original NDA submission and discussion at the two lorcaserin advisory committee meetings was related to the rat carcinogenicity study findings. In the original submission, lorcaserin caused mammary gland tumors in both sexes at clinically relevant exposures, with no safety margin identified for female rats. Mammary adenocarcinoma and fibroadenoma were not easily distinguished. A prolactin-mediated mechanism of tumorigenesis was raised by the sponsor. 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. Astrocytoma was particularly concerning, given that lorcaserin targets the central nervous system. As part of the NDA resubmission, an independent blinded pathology working group readjudicated the mammary tumors; their findings mitigated the diagnostic uncertainty and provided an adequate safety margin for adenocarcinoma. Mammary fibroadenoma was still noted at all doses. The relationship of fibroadenoma to circulating prolactin remains uncertain. Prolactin is only modestly elevated in animals (and humans) with lorcaserin. Finally, drug concentrations in the cerebrospinal fluid (CSF) of human volunteers also provided an adequate safety margin for the astrocytoma finding. Despite these reassuring findings, I think cancer surveillance should be considered as part of the CV outcomes trial. Lorcaserin has been characterized as a carcinogen in rats, and I am not convinced that we fully understand its effects with respect to tumor promotion in humans.

In summary, I would consider the risk benefit profile for lorcaserin currently favorable, with an admittedly modest benefit but also a manageable and monitorable safety profile. This risk benefit assessment may change as additional information becomes available after marketing.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The company should be required to conduct the following studies post-marketing:

- A cardiovascular outcomes trial in a high-risk patient population that additionally includes echocardiograms, cancer surveillance including breast cancer screening, and monitoring for adverse events of special interest, including

hallucinations/psychosis, mood disorders (utilizing standard questionnaires), cognitive dysfunction, prolactin-related adverse events, and prospective monitoring for priapism. A certain proportion of patients treated with serotonergic drugs, such as SSRIs and SNRIs, should be enrolled.

- A number of nonclinical and clinical studies should be conducted to fulfill the pediatric requirements, including a juvenile animal study, staged single-dose PK trials, and one-year safety and efficacy trials in high-risk children ages 12-16 and 7-11, with echocardiograms, cognitive assessments, DEXA assessments, anthropometry (including linear growth), and Tanner staging.

If feasible, I recommend the following additional post-marketing trial be conducted, given the likelihood for co-administration of lorcaserin and phentermine:

- A one-year factorial safety and efficacy trial that would include the following arms: lorcaserin alone, phentermine alone, lorcaserin-phentermine, and placebo.

2 Introduction and Regulatory Background

2.1 Product Information

Lorcaserin hydrochloride (proposed tradename: Belviq) is a new molecular entity (NME) developed for weight management. It is a first-in-class 5-hydroxytryptamine 2C (5HT_{2C}) receptor agonist; the 5HT_{2C} receptor resides in appetite centers in the brain and regulates energy intake.

The proposed indication is as follows:

BELVIQ is indicated as an adjunct to diet and exercise for weight management, including weight loss and maintenance, in obese patients with an initial body mass index greater than or equal to 30 kg/m², or overweight patients with a body mass index greater than or equal to 27 kg/m² in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea, type 2 diabetes).

The proposed dose for marketing is 10 mg twice-a-day (BID).

2.2 Tables of Currently Available Treatments for Proposed Indications

The only currently approved drug with a weight management indication for the same patient population (BMI \geq 30 kg/m² or \geq 27 kg/m² with at least one weight-related comorbid condition) is orlistat (Xenical).

2.3 Availability of Proposed Active Ingredient in the United States

Lorcaserin hydrochloride is not available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Fenfluramine and dexfenfluramine, nonspecific 5HT₂ agonists, were FDA-approved for the treatment of obesity in 1973 and 1996, respectively. The drugs' association with primary pulmonary hypertension (PPH) had been identified prior to the U.S. approval of dexfenfluramine; however, by 1997 both drugs had been removed from the U.S. market due to the not previously described association with left-sided VHD.^{5,6}

Sibutramine and orlistat were approved for chronic obesity treatment shortly after the withdrawal of fenfluramine and dexfenfluramine. The publication of SCOUT^{7,8} in 2010 demonstrated that sibutramine treatment in patients at high risk for cardiovascular disease resulted in 11.4% of patients developing a major adverse cardiovascular event as compared to 10% of placebo-treated patients. Sibutramine was recently removed from the U.S. market due to these findings. Orlistat, the only currently FDA-approved obesity drug, has four-year weight loss data (45% of orlistat-treated patients lost 5% or more of body weight as compared to 28% of placebo-treated patients). Additionally, orlistat was shown to delay the onset of type 2 diabetes in obese patients with impaired glucose tolerance over this four-year trial period. Nevertheless, orlistat is now used most often in its lower dose in a nonprescription setting, a setting in which long-term benefit has not been evaluated. Additionally, orlistat has been associated with rare events of serious liver toxicity.

Despite meeting the efficacy requirements for chronic weight loss established in the newly published FDA draft guidance for weight management products, the development program for rimonabant, the first in a wave of cannabinoid-1 receptor antagonists for obesity, was dismantled after suicidality concerns emerged.

Finally, the fixed dose combination of phentermine and topiramate, currently under review for the treatment of obesity, has a number of safety issues identified during review, including teratogenicity, increases in heart rate, (b) (4)

⁵ Connolly HM, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med. 1997 Aug 28;337(9): 581-8.

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

⁷ James WPT, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010; 363:905-17.

⁸ FDA Early Communication about an Ongoing Safety Review of Meridia (sibutramine hydrochloride). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm191650.htm> Accessed 19 July 2010.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Please refer to the original clinical review, dated October 21, 2010, for a summary of presubmission regulatory activity leading up to the original NDA submission and September 2010 advisory committee discussion. A complete response letter was issued October 22, 2010, based on the following non-clinical and clinical deficiencies:

Nonclinical

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

Clinical

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

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

2.6 Other Relevant Background Information

The 5HT₂ receptor is a member of the G-protein-coupled family of serotonin receptors, and is the target for a variety of centrally-acting drugs, including those to treat depression, migraine, and obesity. The three sub-classes, 5HT_{2A}, 5HT_{2B}, and 5HT_{2C} have widely differing tissue distributions. Differences in receptor affinity and activity may predict a 5HT₂ receptor agonist's desired action as well as its toxicity. Dr. Todd Bourcier's briefing document for the May 10, 2012 advisory committee meeting describes binding profile and functional activity of lorcaserin at the 5HT_{2A}, 5HT_{2B}, and 5HT_{2C} receptors.

In brief, the 5HT_{2A} 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.⁹ The 5HT_{2A} receptor is

⁹ Hoyer D, et al. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). *Pharmacol Rev* 1994 Jun; 46(2): 157-203.

thought to be the target for hallucinogens such as d-lysergic acid diethylamide (LSD).¹⁰ The 5HT_{2B} receptor is distributed in the brain in low concentrations, and at higher concentrations in the lung, kidney, heart, intestine, and stomach.⁹ 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.¹¹ The 5HT_{2C} 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.¹⁰ The 5HT_{2C} receptor has high homology to the 5HT_{2A} receptor, and therefore has similar pharmacological binding profiles.¹² The agonism of the 5HT_{2C} receptor is thought to induce hypophagia, hyperthermia, penile erections, and anxiety, and decrease locomotor activity in rats.^{13,14,15}

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Comments from the original NDA review regarding the original NDA submission are unchanged.

The sponsor was asked during this review cycle to clarify a number of adverse events, and they responded in a timely fashion.

3.2 Compliance with Good Clinical Practices

The sponsor attested that clinical trials (BLOOM-DM, TULIP, and APD356-022) were conducted in compliance with the Declaration of Helsinki on biomedical research involving human volunteers and regulatory guidance, and that clinical investigators obtained and documented volunteer informed consent for each patient screened for each study.

¹⁰ Roth BL, et al. 5-Hydroxytryptamine₂-family receptors (5-Hydroxytryptamine_{2A}, 5-Hydroxytryptamine_{2B}, 5-Hydroxytryptamine_{2C}): where structure meets function. *Pharmacol Ther* 1998; 79(3): 231-57.

¹¹ 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.

¹² Giorgetti M and Tecott LH. Contributions of 5HT_{2C} receptors to multiple actions of central serotonin systems. *Eur J Pharmacol* 2004; 488: 1-9.

¹³ Kimura Y, et al. Pharmacological profile of YM348, a novel, potent and orally active 5-HT_{2C} receptor agonist. *Eur J Pharmacol* 1 Jan 2004; 483(1): 37-43.

¹⁴ 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.

¹⁵ Kimura A, et al. Overexpression of 5-HT_{2C} receptors in forebrain leads to elevated anxiety and hypoactivity. *Eur J Neurosci* 2009; 30: 299-306.

Four clinical sites closed during the conduct of BLOOM-DM, which impacted 12 patients (discontinued due to site closure): four placebo and eight lorcaserin 10 mg BID patients.

- Site 1102 (Keith Klatt, M.D.): Principal Investigator left Covance site, opened a competing CRO
- Site 1186 (Timothy Fagan, M.D.): Site closed due to financial circumstances
- Site 1199 (Thomas Knutson, M.D.): Site was sold to a company that opted to end all clinical trials
- Site 1211 (Lori Wynstock, M.D.): Principal Investigator left site, site closed

Dr. Dan Streja's investigative site in the BLOOM-DM trial was audited and received a No Action Indicated (NAI) letter. At this site, 153 patients were screened, 51 patients enrolled, and 34 patients completed the study.

Dr. Stephen Aronoff's investigative site in the BLOOM-DM trial was audited and received a Voluntary Action Indicated (VAI) letter. At this site, 58 patients were screened, 30 patients enrolled, and 23 patients completed the study. Specific findings were as follows:

1. Failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60]. Specifically,
 - The study protocol required that an echocardiogram be conducted at Baseline, Week 24, and Week 52/Early Termination. Echocardiograms were not always performed as required by the protocol. The following subjects did not have protocol-required echocardiograms performed: Subject 029, Week 52; Subject 032, Early Termination Visit; Subject 012, Week 24; Subject 016, Early Termination Visit; and Subject 014, Week 24.
 - The study protocol required waist and hip circumference measurements to be recorded at different time points including at the time of randomization. Hip circumference measurements were not done for 4 subjects (Subjects 005, 012, 014, and 016) at the time of randomization.
 - The study protocol required the verification that the informed consent document was signed prior to the subject undergoing any study related procedures. Subject 024's informed consent was signed on April 9, 2008 after the patient had the Baseline echocardiogram, which occurred on March 19, 2008.
 - The study protocol required that serious adverse events (SAEs) be reported for any subject required hospitalization. Subject 027 was taken to the hospital and had surgery the next day for a broken left wrist and left for arm. An SAE was not reported for this hospitalization.
 - Subject 049 was assigned one drug kit but received another.

2. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation [21CFR312.64].

Specifically,

- Not all IVRS fax sheets were retained. As a result it was difficult to verify the correct kit assignment for some of the subjects.
- Drug Accountability (Exposure) Logs were not completed and maintained.

DSI had the following assessment and recommendation: *The final classification of Clinical Investigator inspection of Dr. Dan A. Streja is No Action Indicated (NAI). The preliminary classification of the Clinical Investigator inspection of Dr. Stephen Aronoff is Voluntary Action Indicated (VAI). Although regulatory violations were noted at Dr. Stephen Aronoff's site, the violations reported on the Form FDA 483 appear isolated and the nature of the findings appears unlikely to significantly impact reliability of the data.*

I do have concerns regarding the five patients (2 lorcaserin 10 mg BID, 2 lorcaserin 10 mg QD, and 1 placebo) who did not have echocardiography at isolated time points; however, in a trial of over 600 patients, the omissions are unlikely to impact the overall results.

3.3 Financial Disclosures

The sponsor has certified that no investigator from the Phase 3 pivotal trials has entered into a financial agreement with the sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no chemistry issues that impact the efficacy or safety assessment of lorcaserin.

4.2 Clinical Microbiology

Not applicable. Lorcaserin is not an injectable.

4.3 Preclinical Pharmacology/Toxicology

Regarding receptor selectivity, the following summarizes Dr. Todd Bourcier's briefing document from the May 2012 advisory committee:

- Additional studies to clarify discrepancies in the receptor potency data reported in the original NDA were provided.
- The new studies show that lorcaserin is at least 3- to 5-fold less potent than originally reported at all three 5HT2 receptor subtypes. Based on the new estimates of receptor potency, maximal concentrations of lorcaserin (free fraction) observed in human plasma and anticipated in human brain tissue is notably lower than the EC50 for activation of 5HT2A and 2B, while remaining above the EC50 for activation of 5HT2C *in vitro*. Plasma concentrations of lorcaserin at the therapeutic dose are thus expected to remain within the selective range for activation of 5HT2C.
- Lorcaserin grouped with low-potency 5HT2B agonists that are not known to be associated with clinical valvulopathy in *in vitro* functional assays. Compounds known to cause clinical valvulopathy showed substantially higher 5HT2B receptor potency in these assays.
- The 2011 receptor potency data provides supportive evidence that off-target activation of the 5HT2A or 2B receptors is unlikely at the proposed clinical dose of lorcaserin.

Regarding carcinogenicity, the following summarizes Dr. Fred Alavi's briefing document from the May 2012 advisory committee:

- Lorcaserin was identified as a non-genotoxic carcinogen in Sprague-Dawley rats: mammary neoplasms in males and females, and neoplasms of the brain, peripheral nerves, skin, subcutis, and liver and thyroid gland of males
- The occurrence of mammary and brain neoplasms were of most concern regarding human risk assessment because no safety margin was identified for the former, and the safety margin was uncertain for the latter
- A pathology working group (PWG) readjudicated all mammary and lung masses from female rats, and found that mammary adenocarcinoma has a safety margin of 24-fold to the clinical dose, and that there was no safety margin (≤ 7 -fold) to the clinical dose for benign fibroadenoma
- Lorcaserin minimally affected plasma and tissue prolactin
- Clinical data (cerebrospinal fluid (CSF) concentrations in humans) indicated that partitioning of lorcaserin to the CNS in human subjects is substantially lower than predicted by nonclinical studies in rats and non-human primates
- A safety margin of 70-fold for astrocytoma in rats, based on estimated brain levels of lorcaserin, presents a negligible clinical risk

See section 4.4.3 for the human CSF study results.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

This section is unchanged from the original clinical review.

4.4.2 Pharmacodynamics

This section is unchanged from the original clinical review.

4.4.3 Pharmacokinetics

Drug Concentrations in Blood

As stated in Dr. Immo Zadezensky's clinical pharmacology review:

A longitudinal PK/PD model in non-diabetic patients predicted 4% (\pm 6%) for the placebo, 7% (\pm 6%) for lorcaserin 10 mg QD, and 9% (\pm 6%) for lorcaserin 10 mg BID. For diabetic patients, model-predicted values were 3% (\pm 4%) for the placebo, 6% (\pm 5%) for lorcaserin 10 mg QD and 6% (\pm 6%) for lorcaserin 10 mg BID. As noted in section 6, a dose-response for efficacy was not seen in the BLOOM-DM trial.

Dr. Zadezensky pooled the population PK data from BLOOM-DM with those of the BLOOM and BLOSSOM trials and concluded that the exposure-response (weight loss) relationship supports the proposed lorcaserin dose of 10 mg BID.

Drug Concentrations in Cerebrospinal Fluid

Study APD356-022 was an open-label Phase 1 study to assess the pharmacokinetic properties of lorcaserin at steady state in the CSF of healthy volunteers. This study was a single-site, open-label study of healthy overweight or obese adult male or female subjects ages 18-65 years with a BMI 27-35 kg/m².

A total of 10 subjects were planned for enrollment. Eleven subjects were randomized into the study, received at least one dose of lorcaserin and were included in the safety analysis, and nine subjects completed the study and were included in the pharmacokinetic analysis.

Lorcaserin was administered at a dose of 10 mg BID for six days, and then once in the morning on the seventh day to reach steady state.

The following conclusions are based on the results of pharmacokinetic analyses:

- Plasma steady-state was achieved by Day 4. All subjects were at steady-state on Day 7, when CSF was sampled.
- The plasma $C_{\max,ss}$ geometric mean was 61.7 ng/mL at 2 h.
- The CSF $C_{\max,ss}$ geometric mean was 0.87 ng/mL at 6 h.
- At steady state, the geometric mean ratio of CSF to plasma exposure was (GMR [90% CI]):
 - AUC_{0-t} : 0.017 (0.015, 0.018)
 - $C_{\max,ss}$: 0.014 (0.012, 0.016)
 - $C_{\min,ss}$: 0.016 (0.013, 0.018)

Non-clinical brain:CSF ratios were used to project human brain exposure, and brain exposure ratios were calculated. At the 10 mg/kg/day (no astrocytoma seen) and 30 mg/kg/day (astrocytoma seen) doses used in the two-year male rat carcinogenicity study, brain exposure margins relative to human brain at the maximum recommended dose were greater than or equal to 70 and 360, respectively. In the female rat, where astrocytoma was not increased even at the 100 mg/kg/day dose, the exposure margin was calculated to be greater than 1000.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

See the original clinical review for a table of clinical trials reviewed in the first submission. The following is a table of the three clinical trials submitted with the resubmission.

Table 1. Clinical Trial Reports Submitted with Complete Response

Type of Study	Study Identifier	Primary Objective	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	N	Healthy or Diagnosis	Duration
Safety and Efficacy	APD356-010 (BLOOM-DM)	Assess the weight loss effect of lorcaserin at the end of 52 weeks and in overweight and obese patients with type 2 diabetes mellitus managed with oral hypoglycemic agent(s)	Randomized, double-blind, placebo-controlled, parallel group study	Lorcaserin 10 mg and matching placebo, QD and BID/52 weeks, oral	604	Obese and overweight patients with type 2 diabetes mellitus	52 weeks
Energy Expenditure / Metabolism	APD356-014 (TULIP)	To assess the effect of lorcaserin on 24h energy metabolism after 56 days of treatment	Double-blind, randomized, placebo-controlled, parallel group study	Lorcaserin 10 mg and matching placebo, BID/56 days, oral	57	Overweight and obese patients	56 days
PK	APD356-022	Assess the PK properties of lorcaserin dosed to steady state in the cerebrospinal fluid of healthy subjects	Open-label, multiple-dose PK study	Lorcaserin 10 mg BID (days 1-6), 10 mg QD (day 7), oral	11	Healthy subjects	7 days

Source: NDA 022529 (resubmission), Tabular Listing of All Clinical Studies

5.2 Review Strategy

I am the primary reviewer for the clinical review and am responsible for its content. I referred to Dr. Janice Derr's statistical efficacy review and Dr. Xiao Ding's statistical safety review for those respective sections. In addition, Dr. Eugenio Andraca-Carrera conducted additional analyses of cardiovascular risk and valvular heart disease. I refer to other disciplines' reviews where indicated.

5.3 Discussion of Individual Studies/Clinical Trials

Arena Pharmaceuticals originally submitted New Drug Application (NDA) 022529 to FDA in December of 2009. Data from NDA 022529 were presented at the Endocrine and Metabolic Drugs Advisory Committee (EMDAC) on September 16, 2010 and reviewed in the original clinical review, dated October 21, 2010. The original Phase 3 clinical program included two pivotal trials, with similar patient populations and endpoints.

- Study APD356-009 (Behavioral modification and Lorcaserin for Overweight and Obesity Management; BLOOM) was a placebo-controlled two-year trial to assess the effect of lorcaserin on weight. A total of 3182 male and female patients ages 18-65 years with a BMI 30-45 kg/m² with or without a co-morbid condition or 27-29.9 kg/m² with at least one co-morbid condition, were randomized 1:1 to lorcaserin 10 mg BID or placebo. After one year of treatment, the lorcaserin group was re-randomized 2:1 to lorcaserin 10 mg BID or placebo, stratified by 5% weight loss responder status. The placebo group remained on placebo for the second year.
- Study APD356-011 (Behavioral modification and Lorcaserin Second Study for Obesity Management; BLOSSOM) was a placebo-controlled one-year trial to assess the effect of lorcaserin on weight. A total of 4008 male and female patients ages 18-65 years with a BMI 30-45 kg/m² with or without a co-morbid condition or 27-29.9 kg/m² with at least one co-morbid condition were randomized 2:1:2 to lorcaserin 10 mg BID, lorcaserin 10 mg QD, or placebo.

This NDA resubmission includes the following new clinical data:

- Study APD356-022 was a single-site, seven-day, open-label study of healthy overweight or obese individuals ages 18-65 years in order to evaluate the pharmacokinetic properties of lorcaserin dosed to steady state in the cerebrospinal fluid (CSF). A total of 10 subjects were planned for enrollment, 11 subjects were randomized into the study, received at least one dose of lorcaserin and were included in the safety analysis, and nine subjects completed the study and were included in the pharmacokinetic analysis.
- Study APD356-014 (TULIP) was a double-blind, randomized, placebo-controlled, parallel-group study to assess the effects of lorcaserin on energy metabolism, energy intake, and body composition during 56 days of administration to overweight and obese male and female individuals, aged 18 to 65 years. Fifty-seven patients were randomized in a 1:1 ratio to lorcaserin 10 mg BID or placebo.
- Study APD356-010 (BLOOM-DM) was a 52-week, double-blind, randomized, placebo-controlled, parallel-group trial to assess the safety and efficacy of lorcaserin versus placebo in overweight and obese patients with type 2 diabetes mellitus managed with oral hypoglycemic agents. All patients were instructed to maintain a standardized 600 kcal deficient diet and exercise program. Approximately 750 patients were originally planned for enrollment into the study (lorcaserin 10 mg BID: lorcaserin 10 mg QD: placebo; 1:1:1) but due to slow enrollment this number was reduced to 600 in Amendment 3 (lorcaserin 10 mg BID: placebo; 1:1). Patients randomized into the lorcaserin 10 mg QD group prior to the implementation of Amendment 3 remained enrolled in the trial to complete all planned study procedures. A total of 604 patients were randomized and 603 were analyzed for

safety. The efficacy analyses included three populations: Modified Intent-to-Treat (MITT, N=593), Completers (CP, N=401), and Intended Week 52 (IW52, N=417). See Appendix 9.4 for a description of the study design.

6 Review of Efficacy

Efficacy Summary

The original submission included two pivotal Phase 3 placebo-controlled safety and efficacy trials that evaluated more than 7000 patients with body mass index (BMI) ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related co-morbidity (hypertension, dyslipidemia, glucose intolerance, cardiovascular disease, and/or sleep apnea):

- BLOOM: a 104-week trial that evaluated lorcaserin 10 mg BID versus placebo in a 1:1 randomization; in the second year, the lorcaserin-treated patients were re-randomized 2:1 to lorcaserin or placebo
- BLOSSOM: a one-year trial that evaluated two lorcaserin doses, 10 mg once daily (QD) and 10 mg BID versus placebo

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

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

- At Week 52, mean placebo-subtracted weight loss from baseline for lorcaserin 10 mg BID was 3.1%
- At Week 52, 37.5% of patients on lorcaserin 10 mg BID and 16.1% of patients on placebo lost at least 5% of baseline body weight
- At Week 52, mean placebo-subtracted change in HbA1c for lorcaserin 10 mg BID was 0.49%
- At Week 52, more patients on lorcaserin 10 mg BID than placebo achieved HbA1c < 7% (50.4% vs. 26.3%), HbA1c < 6.5% (23.9% vs. 8.6%), fasting plasma glucose < 126 mg/dL (42.2% vs. 29.1%), and fasting plasma glucose < 100 mg/dL (14.1% vs. 5.7%)

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

6.1 Indication

6.1.1 Methods

The efficacy review focuses on the BLOOM-DM trial, comparing it to the Phase 3 trials reviewed in the original NDA submission, BLOOM and BLOSSOM, where appropriate. The newly-submitted Phase 2 trial TULIP was primarily a mechanistic study; efficacy results from this trial are summarized.

6.1.2 Demographics

The following table enumerates the demographics and baseline weight and comorbidity data for the three Phase 3 trials. The majority of the patients were female and white, although there was a somewhat larger proportion of males and minorities in the BLOOM-DM trial than in BLOOM and BLOSSOM. Patients in the BLOOM-DM trial were also slightly older than patients in the non-diabetes trials. Mean BMI was 36 kg/m² and mean weight was 100 kg in the BLOOM and BLOSSOM trials; baseline weight was slightly higher in the BLOOM-DM trial, likely because of a relatively higher proportion of men in the trial. The majority of diagnosed comorbidities at baseline were hypertension and dyslipidemia in the non-diabetes trials. Patients with diabetes also had increased incidences of other comorbidities. Treatment groups were generally well-matched; BLOOM-DM demographic and baseline data shown in Table 3.

Table 2. Patient Demographics and Baseline Co-morbidities by Trial, Safety Population

	BLOOM N=3177	BLOSSOM N=4004	BLOOM-DM N=603
Age, years mean +/- SD	44.1 +/- 11.2	43.8 +/- 11.8	52.7 +/- 8.7
Sex, % female	83.5	79.8	54.2
Race/Ethnicity			
White, %	66.9	67.0	60.5
Black, %	18.8	19.6	20.9
Hispanic, %	12.4	11.0	13.8
BMI, kg/m ² mean +/- SD	36.2 (4.3)	35.9 (4.2)	36.0 (4.5)
Weight, kg mean +/- SD	100.1 (15.6)	100.2 (16.0)	103.6 (17.8)
Comorbidity			
Hypertension, %	21.3	23.6	61.0
Dyslipidemia, %	33.3	27.7	53.0
CVD/CAD*, %	0.3	1.1	7.1
Diabetes mellitus, %	0.0	0.0	100.0
Sleep apnea, %	4.0	4.3	13.7
* reported as cardiovascular disease (CVD) in BLOOM and BLOSSOM and coronary artery disease (CAD) in BLOOM-DM			

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

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

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

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

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

6.1.3 Subject Disposition

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

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

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

Table 4. Patient Populations, BLOOM-DM

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

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

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

Table 5. Reasons for Discontinuation, Phase 3 Trials

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

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

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

6.1.4 Analysis of Primary Endpoints

5% Weight Loss Responder Analysis

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

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

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

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

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

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

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

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

In the BLOOM-DM completers and intended Week 52 populations, a greater proportion of patients in all treatment groups achieved 5% weight loss (CP: lorcaserin 10 mg BID 44.6% vs. placebo 17.9%, $p < 0.001$; IW52: lorcaserin 10 mg BID 42.9% vs. placebo 19.4%, $p < 0.001$). The greater proportion of patients in the IW52 patient population who achieved 5% weight loss reflects the fact that this is a population of completers in addition to a self-selected group of patients (N=16) willing to return to be weighed at Week 52. (In fact, the intent of this sensitivity analysis is to bring 100%, or very close to 100%, of patients who prematurely discontinued back for follow-up weight at Week 52.¹⁶)

To understand the differences in dose response seen in the two trials that evaluated a lorcaserin 10 mg QD dose, the weight results of the BLOSSOM trial, including the lorcaserin 10 mg QD dose are presented in contrast to the BLOOM-DM results, in those patients randomized prior to Amendment 3 (at which point randomization in the lorcaserin 10 mg QD arm ended). As noted above, whereas a dose response was seen in the BLOSSOM trial, such a finding was not seen in the BLOOM-DM trial (Table 8 and Table 9).

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

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

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

Source: NDA 022529, BLOSSOM CSR, Table 9

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

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

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

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

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

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

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

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

Randomization for BLOOM-DM was stratified by baseline HbA1c ($\geq 9\%$ and $< 9\%$) and anti-hyperglycemic medication (use of sulfonylurea and metformin). As might be expected, patients with a higher HbA1c at baseline as well as those using sulfonylureas at baseline were less likely to achieve 5% weight loss in either the lorcaserin or placebo treatment groups.

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

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

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

Mean Weight Change

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

weight compared to 1.5% lost by patients receiving placebo at Week 52; a between treatment mean difference of 3.1%.

Table 12. Percent Weight Change from Baseline to Week 52, BLOOM and BLOSSOM (MITT/LOCF)

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

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

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

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

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

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

In the 5% responder analysis, weight loss was evaluated by HbA1c subgroups using a 9% cut-off (which was a stratification cut-point). However, patients with an HbA1c value of 9% or greater comprised approximately 18% of the study population. Therefore, FDA conducted an analysis of weight loss as a continuous variable using a cut-off close to the mean HbA1c value: 8%. This analysis (Table 14) suggests that patients with HbA1c less than 8% had a better weight loss response to lorcaserin than those with HbA1c 8% or greater (interaction p value = 0.021).

Table 14. Percent Weight Change from Baseline to Week 52 by Screening HbA1c, BLOOM-DM (MITT/LOCF)

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

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

10% Weight Loss Responder Analysis

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

Table 15. 10% Weight Loss Responders at Week 52, BLOOM and BLOSSOM (MITT/LOCF)

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

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

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

Table 16. 10% Weight Loss Responders at Week 52, BLOOM-DM (MITT/LOCF)

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

Source: NDA 022529 BLOOM-DM CSR, Table 11

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

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

Table 17. 10% Weight Loss Responders at Week 52, BLOSSOM (MITT/LOCF)

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

Source: NDA 022529 BLOSSOM CSR, Table 12

Table 18. 10% Weight Loss Responders at Week 52, BLOOM-DM Subgroup Enrolled Prior to Amendment 3 (MITT/LOCF)

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

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

6.1.5 Analysis of Secondary Endpoints

Glycemia-Related Endpoints

Changes in Laboratory Values

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

In BLOOM-DM, lorcaserin 10 mg BID improved glycemic control in patients with type 2 diabetes mellitus, as shown by significant decreases in HbA1c (Table 19) and fasting plasma glucose (Table 20). Results were very similar in the completers population (data not shown). Fasting insulin decreased slightly from baseline in all groups, with no statistically significant difference between lorcaserin and placebo groups (Table 21). Lorcaserin 10 mg QD results were not significantly different from BID results for any of the parameters tested.

Table 19. Analysis of Change from Baseline in HbA1c (%) at Week 52, BLOOM-DM (MITT/LOCF)

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

Source: NDA 022529 BLOOM-DM CSR, Table 11.21

Table 20. Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dL) at Week 52, BLOOM-DM (MITT/LOCF)

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

Source: NDA 022529 BLOOM-DM CSR, Table 11.25

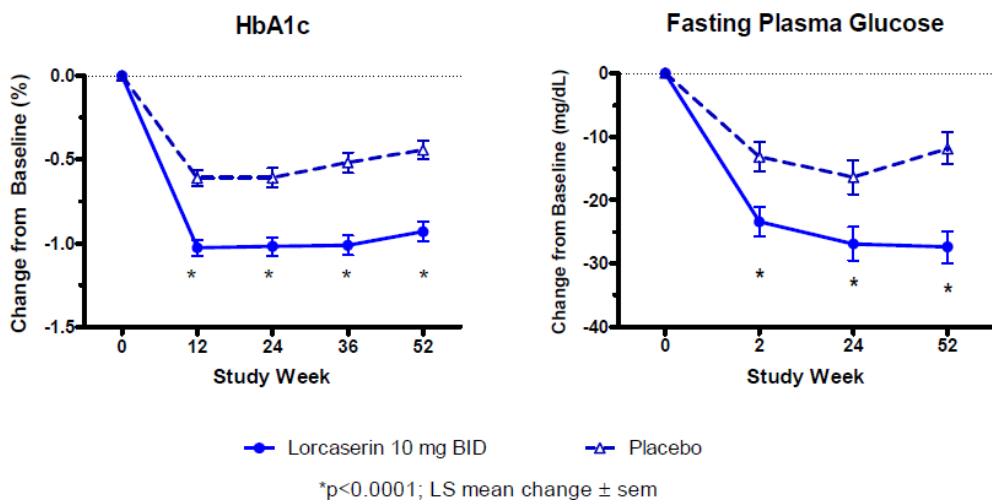
Table 21. Analysis of Change from Baseline in Fasting Insulin ($\mu\text{IU/mL}$) at Week 52, BLOOM-DM (MITT/LOCF)

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

Source: NDA 022529 BLOOM-DM CSR, Table 11.22

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

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



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

Various subgroup analyses were conducted: fasting plasma glucose using a cut-off of 126 mg/dL, and HbA1c using a cut-off of 9% as assessed by the sponsor (unadjusted), and HbA1c using a cut-off of 8% as assessed by FDA (reported as LSMeans). Lorcaserin was associated with greater improvement in HbA1c and fasting glucose than placebo in each of the glycemic control subgroups. For the 9% HbA1c cut-off, the interaction p-value for the difference between treatment groups was not statistically significant ($p = 0.865$). When using the 8% cut-off, there is a trend toward a greater HbA1c treatment effect in the patients with higher HbA1c at baseline, interaction p-value = 0.060 (Table 23).

Table 22. Change in Glycemic Parameters from Baseline at Week 52 by Fasting Plasma Glucose and HbA1c Subgroups, BLOOM-DM (MITT/LOCF)

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

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

Table 23. Change in HbA1c from Baseline at Week 52 by HbA1c < 8% and ≥ 8%, BLOOM-DM (MITT/LOCF)

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

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

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

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

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

Table 24. Summary of Change from Baseline in Glycemic Parameters at Week 52 by Responders Groups, BLOOM-DM (MITT)

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

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

The homeostatic model assessment is a model used to estimate insulin resistance (HOMA-IR) and beta-cell function (HOMA-B) from fasting plasma glucose and insulin. These values correlate with the euglycemic and hyperglycemic clamp (HOMA-IR) and the intravenous glucose tolerance test and hyperglycemic clamp (HOMA-B).¹⁷ At Week 52 in the BLOOM-DM trial, HOMA-IR decreased (between treatment difference -3.1, 95% CI: -0.57, -0.05) and HOMA-B values increased (between treatment difference +6.5, 95% CI: -1.65, 14.60) in patients treated with lorcaserin 10 mg BID at Week 52 as compared to placebo (beneficial directions of change). According to the prespecified conditional testing paradigm, formal statistical analyses were not conducted since change in insulin did not differ significantly between placebo and lorcaserin.

Diabetes Medication Changes

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

¹⁷ Matthews DR, et al. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28:412-9.

clinical judgment. Table 25 demonstrates changes in diabetes drugs during the course of the trial. Although the randomization scheme was different for the lorcaserin 10 mg QD arm, it is included in the table for descriptive purposes.

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

Table 25. Changes in Use of Drugs to Treat Type 2 Diabetes Mellitus, BLOOM-DM (MITT/LOCF)

	Lorc 10 BID N=251	Lorc 10 QD N=94	Pbo N=248
Patients with Change in Daily Dose, n (%)^a			
Decrease	43 (17.1)	22 (23.4)	29 (11.7)
No Change	172 (68.5)	58 (61.7)	161 (64.9)
Increase	34 (13.5)	11 (11.7)	55 (22.2)
Patients who Discontinued All Diabetes Medications, n (%)			
	3 (1.2)	0	1 (0.4)
Mean (SD) % Daily Dose Change^b			
Metformin	-0.8 (35.9)	3.0 (36.6)	6.6 (40.1)
SFU	-16.0 (63.0)	-24.6 (58.0)	6.5 (98.9)
Glitazone	-16.4 (40.3)	-21.3 (57.9)	3.3 (89.0)
Gliptin	-4.3 (20.9)	-16.7 (38.9)	-6.9 (34.1)
Patients who Started New Diabetes Medication by Class, n (%)^{c,d}			
Metformin	3 (1.2)	1 (1.1)	3 (1.2)
SFU	9 (3.5)	3 (3.2)	10 (4.0)
Glitazone	3 (1.2)	1 (1.1)	9 (3.6)
Gliptin	10 (3.9)	3 (3.2)	13 (5.1)
Patients who Stopped Diabetes Medication by Class, n (%)^{c,d}			
Metformin	10 (3.9)	2 (2.1)	0 (0.0)
SFU	21 (8.2)	13 (13.7)	8 (3.2)
Glitazone	8 (3.1)	8 (8.4)	4 (1.6)
Gliptin	1 (0.4)	2 (2.1)	3 (1.2)
a Total daily dose of all anti-hyperglycemic agents			
b For medications with missing dose, data are omitted			
c Refers to initiation of new drug between randomization and final visit			
d Denominator=safety population			

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

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

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

Table 26. Number (%) of Patients who Changed the Total Daily Dose of or Initiated Anti-Diabetes Medication from Baseline to Week 52, BLOOM and BLOSSOM (Safety Population)

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

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

Anthropometric Measures

Waist Circumference and BMI

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

Table 27. Change from Baseline in Waist Circumference (cm) at Week 52, BLOOM and BLOSSOM (MITT/LOCF)

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

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

Table 28. Change from Baseline in Waist Circumference (cm) at Week 52, BLOOM-DM (MITT/LOCF)

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

Source: NDA 022529 BLOOM-DM CSR, Table 11.13

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

Table 29. Change from Baseline in Body Mass Index (kg/m²) at Week 52, BLOOM and BLOSSOM (MITT/LOCF)

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

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

Table 30. Change from Baseline in Body Mass Index (kg/m²) at Week 52, BLOOM-DM (MITT/LOCF)

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

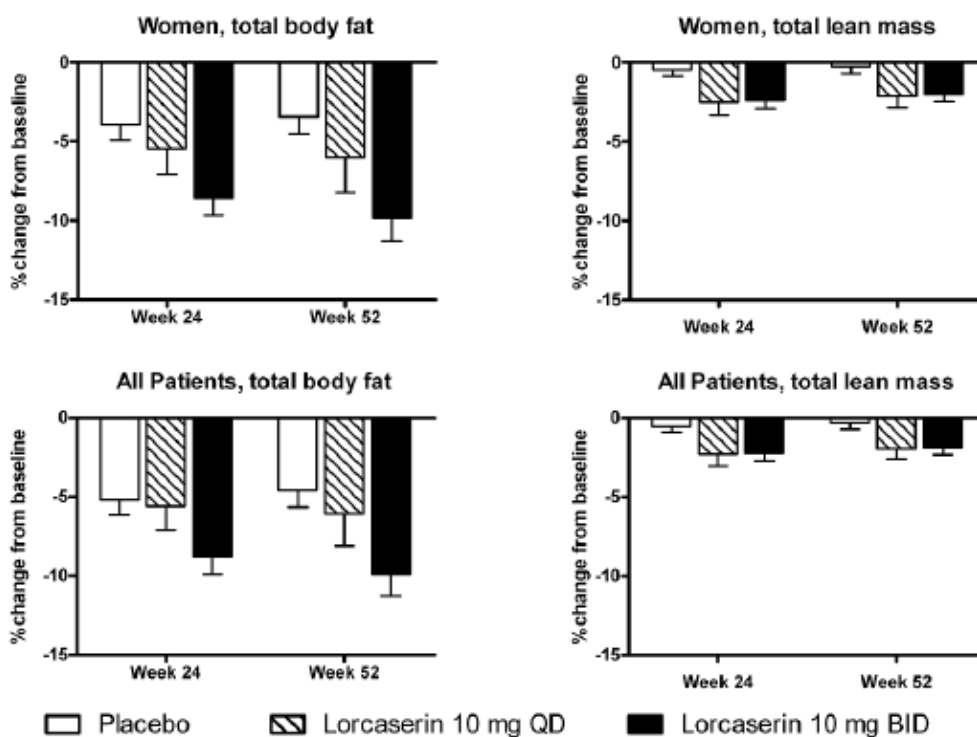
Source: NDA 022529 BLOOM-DM CSR, Table 11.5

DEXA

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

patients treated with placebo (Week 52 lorcaserin 10 BID vs. placebo difference in mean lean body mass -0.66, $p=0.024$).

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



Source: NDA 022529 ISE, Figure 12

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

In the Phase 2 trial TULIP, results of which were included in this resubmission, the decrease from baseline to Day 57 in fat mass measured by DEXA did not differ between the lorcaserin and placebo groups. Patients treated with lorcaserin lost significantly more lean body mass as compared to placebo ($p < 0.01$). See the TULIP summary in section 6.1.10 for more details.

6.1.6 Other Endpoints

Cardiovascular-Related

Blood Pressure

In the individual Phase 3 trials the mean decrease in systolic blood pressure (SBP) with lorcaserin 10 mg BID was greater than with placebo (see Table 31); the difference was statistically significant in the BLOOM trial. By contrast, in the BLOOM-DM trial, there was no significant difference in mean SBP in the lorcaserin 10 mg BID group as compared to placebo, and although both groups had mean decreases, the placebo group had a slightly greater decrease (see Table 32). See section 7.4.3 in the safety review for a discussion of blood pressure outliers and adverse events.

Table 31. Change in Baseline in Systolic Blood Pressure at Week 52, BLOOM and BLOSSOM (MITT/LOCF)

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

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

Table 32. Change in Baseline in Systolic Blood Pressure at Week 52, BLOOM-DM (MITT/LOCF)

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

Source: NDA 022529 BLOOM-DM CSR, Table 11.16

For diastolic blood pressure (DBP), a statistically significant decrease was seen in the lorcaserin group as compared to the placebo group in the pooled non-diabetes trials (see Table 33), but not in the BLOOM-DM trial (see Table 34).

Table 33. Change in Baseline in Diastolic Blood Pressure at Week 52, BLOOM and BLOSSOM (MITT/LOCF)

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

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

Table 34. Change in Baseline in Diastolic Blood Pressure at Week 52, BLOOM-DM (MITT/LOCF)

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

Source: NDA 022529 BLOOM-DM CSR, Table 11.17

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

Table 35. Change in Blood Pressure at Week 52 by Responder Groups, BLOOM and BLOSSOM (MITT/LOCF)

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

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

The following table from the original briefing document suggests that slightly fewer patients treated with lorcaserin 10 mg BID than placebo or lorcaserin 10 mg QD

required initiation or an increase in dose of antihypertensive medication in the pooled non-diabetes trials. This could account for any unfavorable blood pressure differences noted between treatment groups.

Table 36. Number (%) of Patients who Changed the Total Daily Dose of or Initiated Antihypertensive Medications from Baseline to Week 52, BLOOM and BLOSSOM (Safety Population)

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

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

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

Table 37. Number (%) of Patients Receiving Antihypertensive Concomitant Medications at Any Time in the Trial, BLOOM-DM (Safety Population)

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

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

Lipids

In the non-diabetes Phase 3 trials, treatment with lorcaserin was associated with decreases in triglycerides (TG). HDL cholesterol initially decreased from baseline in lorcaserin and placebo treatment groups before returning to baseline values and increasing in the lorcaserin group. These changes are consistent with HDL-C changes that occur with active weight loss and weight maintenance.^{18,19} The lowest mean LDL cholesterol and total cholesterol values were observed after four weeks of treatment with lorcaserin 10 mg BID, and values increased from baseline during the remaining study period in both the lorcaserin- and placebo-treated groups. For all lipid

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.

parameters, the responders had more favorable changes than non-responders. As compared to placebo, the beneficial effect of lorcaserin on TG was seen in the responder group, but not in the non-responder group. Conversely, HDL-C appeared to increase to a greater extent in the placebo responders as compared to the lorcaserin responders. Fewer patients treated with lorcaserin 10 mg BID than placebo required initiation or an increase in dose of lipid-altering medications.

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

Table 38. Percent Change in Lipids at Week 52, BLOOM-DM (MITT/LOCF)

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

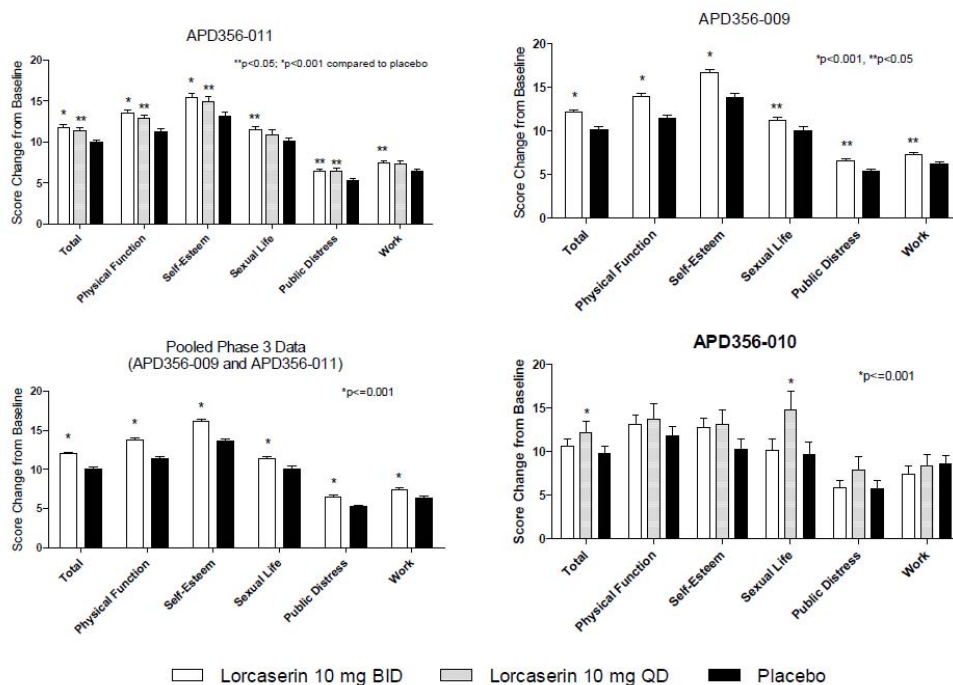
Source: NDA 022529 BLOOM-DM CSR, Tables 11.6, 11.7, 11.8, and 11.10

Quality of Life

Quality of life was evaluated using the Impact of Weight on Quality of Life (IWQOL) - Lite questionnaire, a 31-item self-report measure of obesity-specific quality of life. The IWQOL-Lite provides an overall total score as well as scores on five domains: (1) physical function, (2) self esteem, (3) sexual life, (4) public distress, and (5) work. Scores range from 0 to 100, with 100 representing the best and 0 the most impaired quality of life.²⁰ The assessments were given at baseline, Week 24, and Week 52. In all Phase 3 studies, mean increase (improvement) in IWQOL-Lite score was numerically greater in lorcaserin groups than in the placebo group. Figure 3 describes the results; lorcaserin groups as compared to placebo in BLOOM-DM generally did not reach statistical significance, which may have been due to smaller sample size than the non-diabetes trials. The clinical significance of the degree of changes observed is unknown.

²⁰ Duval K, et al. An overview of obesity-specific quality of life questionnaires. Obesity Reviews. 2006; 7:347-60.

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



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

6.1.7 Subpopulations

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

Table 39. 5% Weight Loss Responders at Week 52, BLOOM-DM (MITT) by Demographic and Baseline Characteristics

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

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

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

To contrast the dose-related mean percent weight change for the lorcaserin 10 mg QD dose in the non-diabetes versus the diabetes populations, Table 40 and Table 41 present the results for BLOSSOM (non-DM) and BLOOM-DM pre-Amendment 3.

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

Table 40. Percent Weight Change from Baseline to Week 52, BLOSSOM (MITT/LOCF)

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

Source: NDA 022529 BLOSSOM CSR, Table 11.4

Table 41. Percent Weight Change from Baseline to Week 52, BLOOM-DM Subgroup Enrolled Prior to Amendment 3 (MITT/LOCF)

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

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

As noted in the original review, 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.

Given the entirety of clinical dosing information, in addition to the quirk in the study design for BLOOM-DM (stopped randomizing into the lorcaserin 10 mg QD arm half-

way through enrollment), I believe that there is enough evidence to support approval of the lorcaserin 10 mg BID dose over the lorcaserin 10 mg QD dose.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Unchanged from the original NDA review.

6.1.10 Additional Efficacy Issues/Analyses

TULIP

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

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

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

The primary efficacy analysis was change in 24-hr energy expenditure (EE) (kcal/day) from baseline to the Day 56 visit, as measured in a metabolic chamber. A tendency for reduced 24-hr EE was seen in patients treated with lorcaserin versus placebo (-162 ± 20 kcal/24 hr vs. -103 ± 21 kcal/24 hr, $p = 0.05$). Similarly, mean resting metabolic rate (RMR) as measured by a hood calorimeter decreased more in the lorcaserin as compared to the placebo group on Day 56 (-84 ± 21 kcal/24 hr vs. -0.71 ± 22 kcal/24 hr, $p = 0.008$). The between-treatment results were not significantly different after adjusting for body composition, implying no prevention of metabolic adaptation with lorcaserin. In summary, lorcaserin neither increased EE nor prevented the metabolic adaptation (i.e., the typical decrease of EE) associated with weight loss.

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

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

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

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

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

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

Source: NDA 022529 TULIP CSR, Table 14.2.3.2

7 Review of Safety

Safety Summary

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

- Valvular heart disease: In the original submission, the selectivity of lorcaserin at the clinical dose for the 5HT_{2C} receptor versus the 5HT_{2B} receptor, which is implicated in fenfluramine-associated valvulopathy, was uncertain. Additional data have been provided with this resubmission to address the receptor selectivity and potency of lorcaserin, and as noted by Dr. Todd Bourcier notes in the briefing document for the May 2012 advisory committee meeting, plasma concentrations of lorcaserin at the therapeutic dose are expected to remain within the selective range for activation of 5HT_{2C}. Nevertheless, in the pooled analysis of the Phase 3 echocardiographic data, the relative risk for FDA-defined valvular heart disease (VHD), defined as mitral regurgitation greater than mild or aortic regurgitation greater than trace was 1.16, with a 95% confidence interval (CI) of 0.81 to 1.67. This upper bound exceeds the 1.5 upper bound requested by FDA to rule out an excess risk of VHD. The point estimate and upper bound were similar in a number of sensitivity analyses conducted by the sponsor and FDA statistician. Furthermore, individual valve regurgitation was fairly consistently increased in the lorcaserin treatment group. Whether these findings can be explained by ascertainment or other bias (due to greater weight loss in the lorcaserin group) is unknown.
- Neuropsychiatric effects: Lorcaserin had poor tolerability in early phase trials in which doses of at least 40 mg were administered, particularly to lower-weight females. Hallucinatory effects were seen in a female subject treated with 40 mg at a C_{max} of 176.90 ng/mL (Phase 3 lorcaserin C_{max} range: 1-156 ng/mL). Six adverse events of euphoria were seen in the Phase 3 trials in the lorcaserin 10 mg BID group and one in the placebo group. No euphoria was seen in BLOOM-DM. Depression adverse events overall (based on a narrow selection of adverse event terms) were not more frequent in the non-diabetes Phase 3 trials in lorcaserin versus placebo groups, although they were slightly more frequent in lorcaserin group in the BLOOM-DM trial. The BLOOM-DM trial supported the findings from the non-diabetes trials that there was a small imbalance in serious adverse events of depression, discontinuations due to adverse events of depression, and suicidality scores (based on a single questionnaire item) in the lorcaserin-treated patients as compared to placebo-treated patients. The BLOOM-DM trial also supported the finding that cognitive impairment was seen more frequently in the lorcaserin-treated patients as compared to the placebo-treated patients. Other neuropsychiatric adverse events that are dose-related and were more frequently seen in lorcaserin-treated patients include headaches, dizziness, and paresthesias.
- Prolactin increases: Prolactin was monitored in a subset of patients in BLOSSOM and in the BLOOM-DM trial due to the proposed association between prolactin increases in animals and mammary tumorigenesis. No definitive comments can be made regarding breast cancer in women from the Phase 3 trials. Lorcaserin does appear to induce a mild prolactin increase in some patients, although the proportion of patients in any treatment group with prolactin values greater than the upper limit of normal was small. At Week 52 there was a slightly increased proportion of

patients treated with lorcaserin with prolactin values greater than the upper limit of normal (ULN), greater than two times (2x) ULN, and visit pre-dose > 2x baseline pre-dose values. No lorcaserin-treated patient was found to have prolactin values > 10x ULN. Similarly, adverse events related to measured increases in prolactin or that could be considered potentially related to prolactin increases (e.g., galactorrhea, gynecomastia, sexual dysfunction, or menstrual abnormalities) were infrequent.

- **Cardiovascular:** The lorcaserin trials were not powered or designed to rule out a prespecified degree of ischemic cardiovascular risk. In general, risk factors for cardiovascular disease, such as changes in blood pressure, lipids, and glycemia were improved with weight loss. BLOOM-DM was aberrant in that there was actually an increase in the proportion of patients treated with lorcaserin with adverse events of hypertension; this finding was not seen in the non-diabetes trials. In an unadjudicated pooled analysis, 20 (0.6%) lorcaserin 10 mg BID and 13 (0.4%) placebo patients had adverse events related to ischemic heart disease. In a separate exploratory analysis, six (0.2%) lorcaserin 10 mg BID and two (0.1%) placebo patients had adverse events of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Because of the exploratory nature of these analyses, formal statistical testing was not conducted. Of note, the sponsor contracted with physicians from the Brigham and Women's Hospital (Boston, Massachusetts) for a blinded post-hoc adjudication of death, cardiovascular ischemic events, and cerebrovascular events from the BLOOM and BLOSSOM trials. In these two trials, the lorcaserin 10 mg BID group had five such events, lorcaserin 10 mg QD had no events, and placebo had six events. There was one event in the second year of the BLOOM trial in a patient re-randomized from lorcaserin 10 mg BID to placebo. BLOOM-DM did not have its cardiovascular events adjudicated in this post-hoc process.
- **Hypoglycemia:** As would be expected due to the improved glycemic control seen in patients with type 2 diabetes in the BLOOM-DM trial, adverse events of hypoglycemia were seen more frequently in lorcaserin-treated patients as compared to placebo-treated patients. Importantly, none of the adverse events was reported as serious, none led to study withdrawal or study drug discontinuation, and none required treatment by emergency personnel or with parenteral agents. No action was taken for the majority of events in all treatment groups, and all events resolved.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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

7.1.2 Categorization of Adverse Events

Adverse event coding for the resubmitted data utilized MedDRA Dictionary Version 12.0 to be consistent with the original NDA. The MedDRA browser on my computer is Version 3.0.1b (used for SMQ searches). I had no major concerns with the categorization of adverse events from the newly-submitted data. Comments from the original NDA review are unchanged.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Non-diabetes trials BLOOM and BLOSSOM were pooled for the original safety review, given their similar patient populations. For much of this review, BLOOM-DM adverse events are presented alongside the BLOOM and BLOSSOM pool, given the differences in co-morbidities, age, and percent female in the BLOOM-DM trial. See Table 2 for the contrasting patient populations. Certain Phase 3 safety data were pooled together, however, in order to increase power, such as echocardiographic and prolactin data.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

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

Table 43. Summary of Patients Randomized in Lorcaserin Phase 2 and Phase 3 Trials

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

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

7.2.2 Explorations for Dose Response

Dose response in the Phase 3 trials was evaluated in the BLOSSOM trial, which included a lorcaserin 10 mg QD arm. In addition, limited information is available from the lorcaserin QD arm in the BLOOM-DM trial.

7.2.3 Special Animal and/or In Vitro Testing

The limitations in the animal studies noted in the original review were addressed to a large extent by new data submitted with the complete response. Refer to the nonclinical reviews for more information.

7.2.4 Routine Clinical Testing

Issues noted in the original review are unchanged. In addition, the limitations to the database with respect to the ability to confidently rule out an increase in cardiovascular harm were discussed at the May 2012 advisory committee meeting. See section 7.3.5 for more details.

7.2.5 Metabolic, Clearance, and Interaction Workup

This section is unchanged from the original clinical review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This section is unchanged from the original clinical review.

7.3 Major Safety Results

7.3.1 Deaths

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

7.3.2 Nonfatal Serious Adverse Events

Phase 1 and Phase 2

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

Phase 3

In the BLOOM and BLOSSOM trials, the incidence of serious adverse events from Year 1 of the pooled dataset was 2.7% in the lorcaserin 10 mg BID group, 3.4% in the lorcaserin 10 mg QD group, and 2.3% in the placebo group (Table 44).

In the BLOOM-DM trial, 41 (6.8%) patients experienced 50 serious adverse events. Of these, 16 (6.3%) were in the lorcaserin 10 mg BID treatment group, eight (8.4%) were in the lorcaserin 10 mg QD treatment group, and 17 (6.7%) were in the placebo treatment group. A higher proportion of patients randomized prior to Amendment 3 experienced serious adverse events as compared to those randomized after, perhaps because there were more completers in those randomized prior to Amendment 3.

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

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

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

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

Table 45. Psychiatric Serious Adverse Events, Phase 3 Trials Year 1

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

Source: Reviewer created from datasets

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

7.3.3 Dropouts and/or Discontinuations

Phase 1 and Phase 2

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

Phase 3

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

Adverse events leading to withdrawal/study drug discontinuation were similar between lorcaserin and placebo in the original NDA (see Table 46). In the BLOOM-DM trial, lorcaserin treatment was associated with higher discontinuation incidence due to adverse events than placebo treatment.

Table 46. Discontinuations Due to Adverse Events by SOC, Phase 3 Trials

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

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

In the original NDA, neurological and psychiatric adverse events led to greater discontinuations (Table 47). In the BLOOM-DM trial, preferred terms of 'dizziness', 'cerebrovascular accident', and 'depression' led to more than one patient treated with lorcaserin to discontinue from study drug.

Table 47. Discontinuations due to Nervous System and Psychiatric Disorders Adverse Events, Phase 3 Trials

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

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

7.3.4 Significant Adverse Events

Significant adverse events are addressed in other sections of this review. An analysis of adverse event intensity (severity) is summarized in the following table.

Table 48. Summary of Adverse Event Reports by Maximum Severity in Pooled Non-Diabetes Trials and BLOOM-DM, Safety Population

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Any Adverse Event ^a						
Mild	888 (27.8)	232 (29.0)	815 (25.6)	93 (36.3)	23 (24.2)	79 (31.3)
Moderate	1406 (44.0)	333 (41.6)	1305 (41.0)	118 (46.1)	52 (54.7)	102 (40.5)
Severe	348 (10.9)	88 (11.0)	285 (8.9)	25 (9.8)	13 (13.7)	32 (12.7)
Total	2642 (82.7)	653 (81.5)	2405 (75.5)	236 (92.2)	88 (92.6)	213 (84.5)
Headache ^b						
Mild	294 (9.2)	80 (10.0)	198 (6.2)	24 (9.4)	10 (10.5)	13 (5.2)
Moderate	190 (5.9)	40 (5.0)	104 (3.3)	11 (4.3)	4 (4.2)	3 (1.2)
Severe	53 (1.7)	5 (0.6)	19 (0.6)	2 (0.8)	2 (2.1)	2 (0.8)
Total	537 (16.8)	125 (15.6)	321 (10.1)	37 (14.5)	16 (16.8)	18 (7.1)
Nausea ^b						
Mild	177 (5.5)	38 (4.7)	107 (3.4)	18 (7.0)	7 (7.4)	11 (4.4)
Moderate	77 (2.4)	21 (2.6)	58 (1.8)	6 (2.3)	1 (1.1)	7 (2.8)
Severe	10 (0.3)	2 (0.2)	5 (0.2)	0	0	2 (0.8)
Total	264 (8.3)	61 (7.6)	170 (5.3)	24 (9.4)	8 (8.4)	20 (7.9)
Dizziness ^b						
Mild	204 (6.4)	37 (4.6)	102 (3.2)	13 (5.1)	8 (8.4)	13 (5.2)
Moderate	51 (1.6)	11 (1.4)	20 (0.6)	4 (1.6)	2 (2.1)	3 (1.2)
Severe	14 (0.4)	2 (0.2)	0	1 (0.4)	0	0
Total	269 (8.4)	50 (6.2)	122 (3.8)	18 (7.0)	10 (10.5)	16 (6.3)
Hypoglycemia ^b						
Mild	2 (0.1)	0	0	59 (23.0)	23 (24.2)	42 (16.7)
Moderate	0	0	0	11 (4.3)	6 (6.3)	10 (4.0)
Severe	0	0	0	4 (1.6)	2 (2.1)	1 (0.4)
Total	2 (0.1)	0	0	74 (28.9)	31 (32.6)	53 (21.0)

a Patients reporting one or more adverse events are counted once at the maximum intensity of all adverse events

b Patients reporting the same adverse event at more than one intensity are counted at the maximum intensity

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 16

7.3.5 Submission Specific Primary Safety Concerns

Heart Valve Assessment

As noted in the original review for the EMDAC meeting in September 2010, drugs that release serotonin or target 5HT receptors are under scrutiny due to the observation that certain of these drugs have been associated with an unusual cardiac valvular disease, characterized by fibrotic, regurgitant valves.^{5,21,22} In the years since fenfluramine and dexfenfluramine have been removed from the U.S. market, researchers have identified activation of the 5HT2B receptor as the likely mechanism of this adverse event.^{11,23}

²¹ Redfield MM, et al. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. Ann Intern Med July 1992; 117(1): 50-52.

²² 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.

²³ Setola V, et al. Molecular determinants for the interaction of the valvulopathic anorexigen neorfenfluramine with the 5-HT2B receptor. Mol Pharmacol 2005; 68(1): 20-33.

Despite its relative 5HT_{2C} specificity as compared to 5HT_{2B}, lorcaserin is a novel 5HT₂ agonist, and therefore a comprehensive program of echocardiographic screening and monitoring was undertaken in the development program.

The original series of VHD associated with fenfluramine and dexfenfluramine use was characterized by valvular lesions on both sides of the heart, with a left-sided (mitral or aortic) valve affected in all cases.⁶ Mild or less mitral regurgitation (MR), and trace or less aortic regurgitation (AR), are relatively common conditions in the general population; therefore the definition employed for clinically significant VHD due to anorexigen use was defined as mild or greater AR and/or moderate or greater MR (termed FDA-defined VHD), for use in observational studies.⁶ The original reports suggested as many as one in three exposed patients were affected with this degree of VHD.⁶ More recently, two published meta-analyses evaluated the literature on fenfluramine- and dexfenfluramine-associated VHD and have provided refined (and considerably lower) estimates:

- Sachdev, et al.²⁴ evaluated nine articles, with a total of 3769 patients exposed to fenfluramine or dexfenfluramine and 5009 patients unexposed. These authors found a pooled prevalence of FDA-defined VHD among patients treated for greater than 90 days of 12.0% compared with 5.9% for the unexposed group (prevalence odds ratio 2.2, 95% CI 1.7-2.7). This increase was primarily the result of mild or greater aortic regurgitation (exposed 9.6%, unexposed 4.5%, prevalence odds ratio 2.5, 95% CI 1.9-3.3). The combined analyses also identified a small but statistically significant increase in MR (exposed 3.5%, unexposed 1.8%, prevalence odds ratio 1.6, 95% CI 1.05-2.3). Among patients exposed for less than or equal to 90 days, a trend toward more regurgitation was not statistically significant by either FDA criteria (exposed 6.8%, unexposed 5.8%, prevalence odds ratio 1.4, 95% CI 0.8-2.4) or by individual valve.
- Loke, et al.²⁵ found that of the 1279 patients evaluated in seven uncontrolled cohort studies, 236 (18%) and 60 (5%) were found to have AR and MR, respectively. Pooled data from six controlled cohort studies (exposed N=3035, unexposed N = 1781) yielded for AR a relative risk ratio of 2.32 (95% CI 1.79 to 3.01). Pooled data from six controlled cohort studies (exposed = 3273, unexposed = 2017) yielded for MR a relative risk ratio of 1.55 (95% CI 1.06 to 2.25). These authors also noted that only one case of VHD was detected in 57 randomized controlled trials of appetite suppressants; notably these randomized controlled trials did not employ echocardiographic monitoring.

²⁴ Sachdev M, et al. Effect of fenfluramine-derivative diet pills on cardiac valves: A meta-analysis of observational studies. *Am Heart J* 2002; 144:1065-73.

²⁵ Loke YK, et al. Appetite suppressants and valvular heart disease – a systematic review. *BMC Clin Pharmacol* 2002 Aug 23;2:6.

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

FDA-Defined Valvular Heart Disease

Primary Composite Endpoint

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

Table 49. Incidence of FDA-Defined VHD at Week 52 by Treatment Group, Patients with Baseline VHD Excluded (Safety Population, LOCF)

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Individual Valves Comprising Primary Endpoint

The primary safety endpoint of Week 52 FDA-defined VHD in the Phase 3 population was further categorized by valve. As noted above in the Sachdev and Loke metaanalyses, fenfluramine-associated VHD was driven by increases in aortic regurgitation.^{24,25} Interestingly, the association between lower BMI and VHD cited by the sponsor as a potential source of ascertainment or other bias is primarily driven by mitral (or tricuspid) regurgitation; this particular relationship was not noted with aortic regurgitation.²⁶ FDA's analyses demonstrate that the imbalance in FDA-defined VHD

²⁶ Singh JP, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol. 1999 Mar 15; 83(6): 897-902.

appears to be driven by an increase in MR (Table 50 and Table 51). See below for a discussion of FDA-defined VHD and weight loss.

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

		Total Patients*	Number of Events	Incidence	RR (95% CI)	Pooled RR** (95% CI)
BLOOM	Lorc BID	1278	18	1.41%	0.96	0.89 (0.56, 1.42)
	Pbo	1191	18	1.51%	(0.69, 1.34)	
BLOOM-DM	Lorc BID	210	4	1.90%	2.51	
	Pbo	209	1	0.48%	(0.43, 14.54)	
BLOSSOM	Lorc BID	1208	13	1.08%	0.84	
	Pbo	1153	18	1.56%	(0.62, 1.13)	
Total		5249	72	1.37%		
Number without missing, excluding baseline valvulopathy						
** Stratified Mantel-Haenszel approach						

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 51. Incidence of Moderate or Greater Mitral Regurgitation at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

		Total Patients*	Number of Events	Incidence	RR (95% CI)	Pooled RR** (95% CI)
BLOOM	Lorc BID	1278	17	1.33%	1.31	1.95 (1.05, 3.59)
	Pbo	1191	10	0.84%	(0.80, 2.14)	
BLOOM-DM	Lorc BID	210	2	0.95%	-	
	Pbo	209	0	0%	-	
BLOSSOM	Lorc BID	1208	12	0.99%	1.67	
	Pbo	1153	5	0.43%	(0.80, 3.48)	
Total		5249	46	0.88%		
Number without missing, excluding baseline valvulopathy						
** Stratified Mantel-Haenszel approach						

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

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

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

	Patient ID	Age/Race/Sex	Screening	Week 24	Week 52
Lorc 10 BID	1146-S007	64/black/M	Trace AR	Trace AR	Mild AR
	1146-S018	48/white/M	Mild MR	Moderate MR	Moderate MR
	1161-S061	60/white/M	Trace MR	Trace MR	Moderate MR
	1174-S111	59/white/M	Trace AR	Mild MR	Mild MR
	1217-S020	47/black/M	Trace AR	Mild AR	Mild AR
	1226-S012	57/white/F	Trace AR	Absent AR	Mild AR
Lorc 10 QD	1161-S052*	60/black/M	Trace AR	Mild AR	-
	1174-S027	59/black/M	Absent AR	Absent AR	Mild AR
Placebo	1119-S004*	57/white/F	Trace AR	Mild AR†	-
Bold indicates FDA-defined VHD * Patient discontinued prematurely from trial; last available echo data were carried forward for Week 52 analysis of primary echocardiographic endpoint † Unscheduled echo					

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

FDA-Defined VHD at Additional Time Points

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

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

If the lorcaserin “reverters” from Week 24 to Week 52 improved VHD scores because they prematurely discontinued the trial and then improved off of drug, the Week 52 LOCF analysis could underestimate a drug effect. However, as shown in the Table 53, the pooled Week 24 analysis of FDA-defined VHD was very similar to the Week 52 analysis. In addition, a greater relative risk (point estimate) for FDA-defined VHD was seen in the ITT population than in the completers population (Table 54).

Table 53. Incidence of FDA-Defined VHD at Week 24 by Treatment Group, Patients with Baseline VHD Excluded (Safety Population, LOCF)

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

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

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

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

Table 55. Incidence of FDA-Defined VHD at Either Week 24 or Week 52 by Treatment Group, Patients with Baseline VHD Excluded (Safety Population)

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

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

Table 56. Proportion of Patients Who Developed FDA-Defined VHD from Screening at Weeks 76 and 104, BLOOM Year 2

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

Source: NDA 22529, BLOOM CSR Table 72

Because the primary efficacy analysis for FDA-defined valvular heart disease (VHD) was under-powered to rule out a relative risk of more than 1.5 times placebo, the sponsor conducted additional post-hoc analyses that utilized all echocardiographic data through Week 104 and included enough events of FDA-defined VHD to provide at least 80% power for risk ratio assessments. These analyses are included in the table below, with models that adjust for treatment only, as well as analyses that are additionally adjusted by treatment x year (Cox Proportional Hazards) and study (Piecewise Exponential Model and Generalized Estimating Equations).

Table 57. Summary of Echocardiographic Analyses for Proportion of Patients with FDA-Defined VHD: Pooled Phase 3 Trials, Lorcaserin 10 mg BID versus Placebo

Method	Model	Parameter	Estimate	95% CI
Cox Proportional Hazards stratified by study	Treatment, Treatment x Year	Hazards Ratio	1.13	(0.84, 1.51)
Cox Proportional Hazards stratified by study	Treatment	Hazards Ratio	1.09	(0.83, 1.44)
Piecewise Exponential Model	Full model, adjusting for Study	Hazards Ratio	1.10	(0.82, 1.48)
Piecewise Exponential Model	Adjusting for TRT only. Not for Study	Hazards Ratio	1.09	(0.82, 1.43)
Generalized Estimating Equations	Full model, adjusting for Study	Rate Ratio	1.12	(0.84, 1.499)
Generalized Estimating Equations	Adjusting for TRT only. Not for Study	Rate Ratio	1.08	(0.81, 1.44)

Note: These supplementary analyses use data for Years 1 and 2

Source: by Dr. Eugenio Andraca-Carrera, FDA, Office of Biostatistics, DB7

FDA-Defined VHD by Subgroup

The following subgroups of the pooled safety population were explored for development of FDA-defined VHD at Week 52: sex, race/ethnicity, age, baseline weight quartile, and weight loss responders (Table 58, Table 59, Table 60, Table 61, and Table 62, respectively).

Table 58. FDA-Defined VHD by Subgroup, Sex

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 59. FDA-Defined VHD by Subgroup, Race/Ethnicity

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 60. FDA-Defined VHD by Subgroup, Age

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 61. FDA-Defined VHD by Subgroup, Phase 3 Trials Pooled, Baseline Weight Quartile

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

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

Table 62. FDA-Defined VHD by Subgroup, Phase 3 Trials Pooled, 5% Weight-Loss Responder Status

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

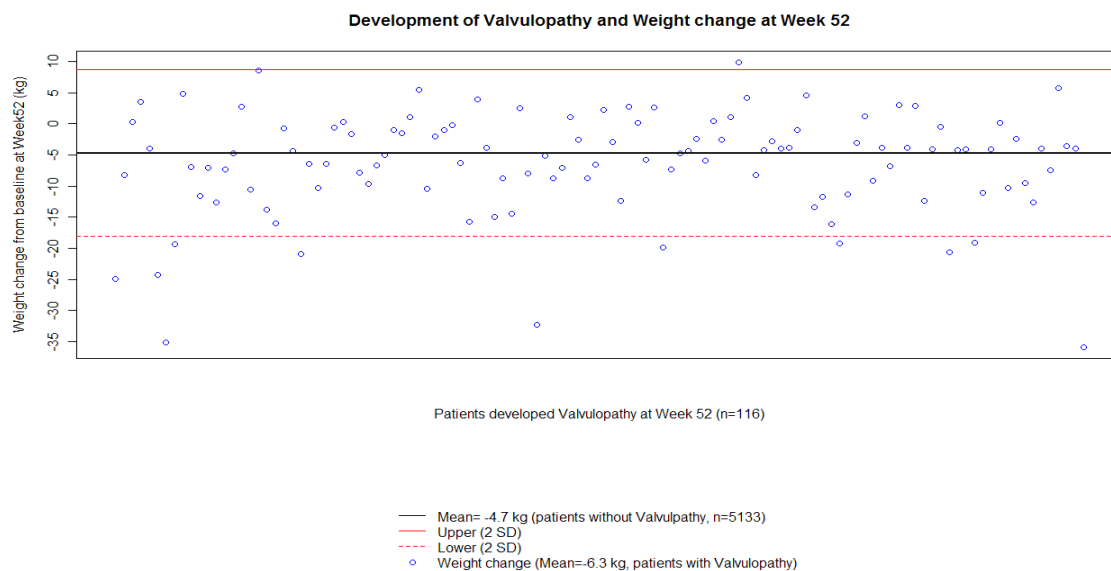
Source: NDA 022529 CR Appendix 2, Tables Pool3 E25.4.a and E25.4.b

FDA-Defined VHD and Weight Loss

To explore how weight loss is related to a Week 52 VHD diagnosis, plots were generated illustrating the weight loss of patients with FDA-defined VHD overlaying a representation of the mean weight loss +/- two standard deviations (2 SD) of those without VHD. Figure 4 and Figure 5 represent the weight loss of individual patients with VHD, depicted as individual circles, superimposed on the mean and 2 SD of the population without VHD, represented by the lines. As seen in Figure 4, mean weight loss in patients without FDA-defined VHD was 4.7 kg, mean weight loss in patients with FDA-defined VHD at Week 52 was 6.3 kg. However, when three FDA-defined VHD outliers are removed, the mean change – and difference between groups – is attenuated (mean weight loss in patients with FDA-defined VHD is 5.2 kg). This may

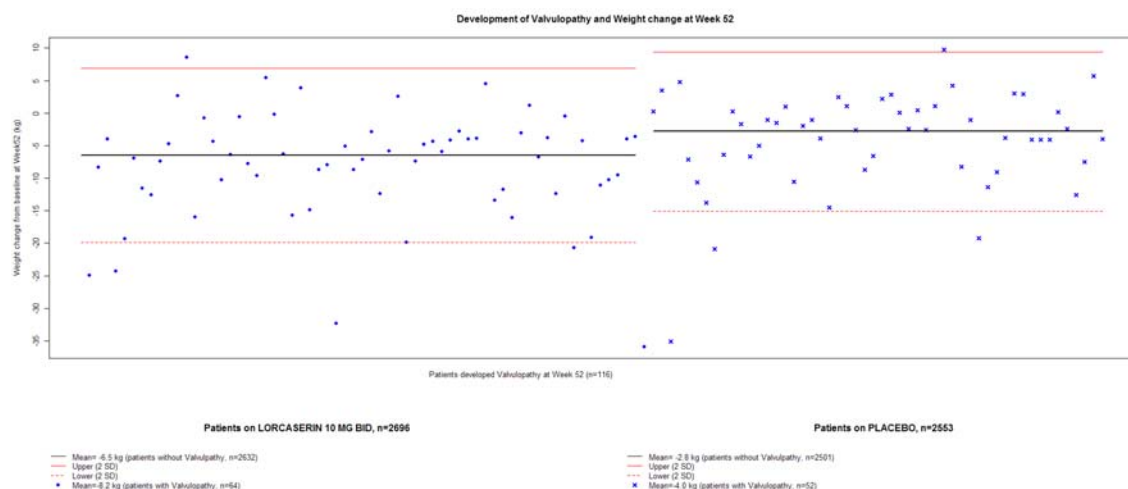
suggest that weight loss per se does not fully explain the difference in VHD between groups.

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



Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

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



Best Possible
Copy

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

To further assess whether there is a relationship between weight loss and development of FDA-defined VHD, FDA statistician Dr. Eugenio Andraca-Carrera conducted the following analyses:

Table 63 shows cases of VHD by treatment group and four strata of percent weight loss. A possible association between % weight loss at week 52 and increased risk of VHD is suggested.

Table 63. Proportion of Patients with Week 52 FDA-Defined VHD by % Weight Loss Strata at Week 52

Weight loss from baseline (wk 52)	Lorc 10 BID		Pbo	
	events / N	%	events / N	%
< 0	7 / 395	1.77%	18 / 831	2.17%
0 - 5%	18 / 866	2.08%	15 / 1049	1.43%
5 - 10%	15 / 726	2.07%	10 / 409	2.44%
10+ %	24 / 709	3.39%	9 / 264	3.41%

Source: Dr. Eugenio Andraca-Carrera, Statistical Reviewer FDA DB7

In order to formally test whether this association is statistically significant, a model for the risk ratio is fit and the results are shown in Table 63.

Three log models are fit to explore the association between percent weight loss at Week 52 and VHD. All models control for age, baseline weight and study. Model 3 also controls for treatment:

- Model 1 is fit among subjects on placebo only.
- Model 2 is fit among subjects on lorcaserin BID only.
- Model 3 is fit among all subjects (except lorcaserin QD).

Dr. Andraca-Carrera comments that all three models suggest a small and non-statistically significant increase in the risk of VHD associated with weight loss (RR ~ 1.03 for each additional 1% loss of weight).

Table 64. Models to Test for the Association between Percent Weight Loss and VHD

Model 1. Placebo only	Estimate		p-value	Risk Ratio	(95% CI)
Age	0.0565	0.0145	0.0001	1.06	(1.03, 1.09)
Baseline weight	0.0009	0.0086	0.9194	1.00	(0.98, 1.02)
% weight loss at week 52	0.0215	0.0207	0.2993	1.02	(0.98, 1.06)
Model 2. Lorc BID only	Estimate		p-value	Risk Ratio	(95% CI)
Age	0.0491	0.0137	0.0003	1.05	(1.02, 1.08)
Baseline weight	-0.0102	0.0082	0.2167	0.99	(0.97, 1.01)
% weight loss at week 52	0.0281	0.0171	0.1003	1.03	(0.99, 1.06)
Model 3. Placebo and Lorc BID	Estimate		p-value	Risk Ratio	(95% CI)
Lorcaserin	0.0566	0.1934	0.7698	1.06	(0.72, 1.55)
Age	0.0529	0.01	<0.0001	1.05	(1.03, 1.08)
Baseline weight	-0.0048	0.0059	0.4235	1.00	(0.98, 1.01)
% weight loss at week 52	0.0256	0.0131	0.0513	1.03	(1.00, 1.05)

Source: Dr. Eugenio Andraca-Carrera, Statistical Reviewer FDA DB7

Inter- and Intra-variability Assessment

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

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

Methods and results of this assessment were presented in the original NDA and were discussed at the last EMDAC meeting. A speaker for the sponsor cited about 25 to 30 percent test-retest variability in the obese patient population.²⁷ Overall, the inter- and intra-reader variability observed using the standard echocardiograms was consistent with variability data reported by other investigators.²⁸ By contrast, inter-reader variability of the pool of cardiologists chosen to read the echocardiograms as assessed using the baseline echocardiograms was greater than that of the standard echocardiogram assessment.

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

Table 65. Relative Risk of FDA-Defined VHD by Reader, Patients with Baseline VHD Excluded (Safety Population, LOCF)

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Secondary Endpoints

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

²⁷ Weisman N, EMDAC 16 September 2010

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

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 67. Proportion of Patients Who Experienced Any Increase from Baseline in Valvular Regurgitation at Week 24, Pooled Phase 3 Trials

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 68. Proportion of Patients Who Experienced Any Increase from Baseline in Valvular Regurgitation at Week 52 LOCF (excluding Absent to Trace), Pooled Phase 3 Trials

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 69. Proportion of Patients Who Experienced Any Increase from Baseline in Valvular Regurgitation at Week 24 (excluding Absent to Trace), Pooled Phase 3 Trials

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

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

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

Table 70. Number (%) of Patients with a Given Change from Baseline in Mitral Regurgitation, Patients Without FDA-VHD at Baseline (LOCF/Safety Population)

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

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

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

Table 71. Number (%) of Patients with a Given Change from Baseline in Aortic Regurgitation, Patients Without FDA-VHD at Baseline (LOCF/Safety Population)

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

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

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

Table 72. Number (%) of Patients with FDA-Defined VHD at Baseline who Experienced an Increase in Mitral or Aortic Valvular Regurgitation at Week 52

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

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

As Table 66 to Table 69 above demonstrate, some suggestion of increased tricuspid and pulmonic valve regurgitation with lorcaserin treatment was seen. Although the FDA definition of anorexigen-related VHD includes the left-sided valves only, the original reports of these cases noted that pathology could affect any valve.^{5,6} Carcinoid- and ergot-related VHD have also been described as involving the tricuspid valve.^{29,30} Specific grade increases of tricuspid valves regurgitation were further assessed. The majority of the increases from baseline in tricuspid valvular regurgitation score were by one.

Table 73. Number (%) of Patients with a Given Change from Baseline in Tricuspid Regurgitation, Patients Without FDA-VHD at Baseline (LOCF/Safety Population)

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

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

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

²⁹ 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.

³⁰ Redfield MM, et al. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. *Ann Intern Med* July 1992; 117(1): 50-52.

Table 74. Patients with Severe Tricuspid Regurgitation, Phase 3 Trials

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

Source: Reviewer created from datasets

Alternative definitions of drug-related VHD have been used, notably in the investigations into dopamine agonist-associated VHD;³¹ therefore, in the original review of the non-diabetes Phase 3 trials, an exploratory analysis of the proportion of patients who developed moderate or severe mitral, aortic, and/or tricuspid regurgitation at Week 52 (LOCF) was assessed. Excluding patients with this degree of regurgitation at baseline, 52/2554 (2.0%) of patients on lorcaserin 10 mg BID and 40/2398 (1.7%) of patients on placebo developed moderate or severe valvular regurgitation at Week 52. In an evaluation of the BLOOM-DM trial, excluding patients with moderate regurgitation at baseline, 4/210 (1.9%) patients on lorcaserin 10 mg BID and 2/209 (1.0%) patients on placebo developed moderate regurgitation at Week 52 (LOCF). No patients in BLOOM-DM developed severe regurgitation at any valve.

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

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

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

³¹ 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.

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

Table 75. 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 76. Cardiac-Valve Related Adverse Events, Phase 3 Trials

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

Source: Reviewer created from datasets

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

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

- Aortic regurgitation (AR) rated moderate or greater
 - Pulmonary artery pressure greater than 50 mm Hg with at least 10 mm Hg increase from baseline
 - LVEF \leq 35
- Withdrawal of study medication and referral to a cardiologist for the following findings:
 - Severe MR
 - Severe AR
 - Pulmonary artery pressure \geq 60 mmHg

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

- Patient 1206-S010 was a 60-year-old female randomized to lorcaserin 10 mg BID, with mild AR at baseline, moderate AR at Week 24 (leading to the alert), and mild AR again at Week 52. The patient had no signs or symptoms referable to AR. She was referred to her primary care physician who did not refer her to a cardiologist.
- Patient 1161-S061 was a 61-year-old male randomized to lorcaserin 10 mg BID, who had an alert of moderate MR plus an increase of two categories from baseline. He was found to have trace MR at baseline, trace MR at Week 24, and moderate MR at Week 52. No signs or symptoms referable to MR were reported. According to the investigator, the patient was doing very well, running six miles daily. The patient was not referred to cardiology, as the investigator believed the change in echocardiogram did not have clinical significance.
- Patient 1274-S004 was a 60-year-old male randomized to lorcaserin 10 mg BID, with mild AR at baseline, trace AR at Week 24, and moderate AR at Week 52 (cause of the alert). No signs or symptoms referable to AR were reported. The patient's cardiologist noted the increase in aortic valve disease in his notes and planned to repeat the echocardiogram in the next six months. The patient returned two weeks later for a pharmacologic stress test, which showed no ischemia but moderate to severe inferoapical defects suggestive of a previous infarct versus a diaphragmatic attenuation artifact.

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

In those patients who were enrolled in the BLOSSOM and BLOOM-DM trials with baseline FDA-defined VHD, adverse events were evaluated for potential congestive

heart failure (CHF)-related terms in the event that even a small increase in regurgitation could lead to CHF decompensation. Among CHF-related search terms only the adverse event of peripheral edema was reported: one patient in the lorcaserin 10 mg BID group and one in the lorcaserin 10 mg QD group in the BLOSSOM trial, and one patient in the placebo group in the BLOOM-DM trial.

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.³² 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).³³ Anorexigens associated with PPH are thought to act by increasing serotonin release via the serotonin transporter.³⁴ Other potential serotonin mediators may include the 5HT1B, 5HT2A, and 5HT2B receptors.^{35,36} It has been estimated that one in 1000 or fewer patients who are exposed to such agents ultimately develop PPH.³⁷

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.³⁸

PASP positively correlates with age and BMI and is higher in men than women.³⁹ Higher PASP may in fact be physiological in very obese patients.³⁸ There are no universally agreed-upon echocardiographic variables used to diagnose PPH, although

³² 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.

³³ Abenham L, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med*. 1996 Aug 29; 335(9): 609-16.

³⁴ Rothman RB and Baumann MH. Serotonin releasing agents. *Neurochemical, therapeutic and adverse effects*. *Pharmacol Biochem Behav*. 2002 Apr;71(4): 825-36.

³⁵ Dempsey Y and MacLean MR. Pulmonary hypertension: therapeutic targets within the serotonin system. *Br J Pharmacol* 2008; 155: 455-62.

³⁶ Launay, J-M, et al. Function of the serotonin 5-hydroxytryptamine 2B receptor in pulmonary hypertension. *Nature Med* 2002 Oct; 8(10): 1129-35.

³⁷ Rich S. EMDAC (NDA 20344, Dexfenfluramine hydrochloride), 28 September 1995. Transcript accessed 5 April 2012: <http://www.fda.gov/ohrms/dockets/ac/95/3107t1b.pdf>

³⁸ Milan A, et al. Echocardiographic indexes for the non-invasive evaluation of pulmonary hemodynamics. *J Am Soc Echocardiogr* 2010; 23: 225-39.

³⁹ 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.

the European Task Force suggest (in their words, arbitrary) cutoffs of PASP > 50 mmHg as “likely” and PASP 37-50 mmHg as “possible”.⁴⁰ 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 least squared mean between treatment difference in PASP in the lorcaserin 10 mg BID versus the placebo group was 0.16 mmHg (95% CI -0.20, 0.52, p=0.38) in the pooled non-diabetes trials and -0.47 mmHg (95% CI -2.64, 1.70, p=0.67) in BLOOM-DM. The following table pools the three trials for mean change in PASP by treatment group:

Table 77. Change from Baseline in PASP (mmHg) at Week 52, Pooled BLOOM, BLOSSOM, and BLOOM-DM (LOCF)

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

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

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

⁴⁰ 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 78. Patients with Increases in PASP from Baseline, Phase 3 Trials

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

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

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

Table 79. Patients with Selected PASP Values, Pooled Phase 3 Trials

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

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

Patient 1158-S019 (lorcaserin 10 mg QD) was a 66-year-old black female whose PASP in BLOOM-DM was noted to have increased from 25.1 mmHg at baseline to 61.7 mmHg at Week 24 and 76.2 mmHg at Week 52. She had a medical history of diabetes, diabetic neuropathy, hypertension, hyperlipidemia, shortness of breath, breast cancer status post radiation, stable angina, COPD (according to the medical records but apparently not recorded in the study database), chronic gastritis, myocardial infarction (not confirmed by the cardiologist who evaluated her), and endoscopic colonic polyp removal with GI bleed and anemia. Her social history was notable for an approximately 1.5 cigarette pack per day smoking history of unknown duration, and that she stopped working in 2007 due to weakness and fatigue. Concomitant medications included metformin, pioglitazone, glimepiride, aspirin, metoprolol, enalapril, hydrochlorothiazide, atorvastatin, ranitidine, albuterol, calcium, iron, capsaicin cream, naproxen, and nitroglycerin, which was added during study (details are not available). During the trial, the patient experienced adverse events of vertigo (day 76) and anemia related to GI

bleed (SAE; day 90). During the hospitalization for the bleed, the patient had a chest X-ray, which demonstrated cardiomegaly and “probable chronic interstitial disease” in part acute due to “pneumonitis versus interstitial edema of the pulmonary artery hypertension”. She completed BLOOM-DM. She was referred to a cardiologist after the Week 24 and 52 echocardiogram result was received; these evaluations confirmed the elevated PASP. The consulting cardiologist offered no specific diagnosis or etiology for the elevated PASP and did not recommend any changes to management (other than presumably adding NTG). Of note, after the patient completed the study, she underwent cardiac stress testing, which was positive. Subsequent cardiac catheterization demonstrated coronary artery disease and a pulmonary artery pressure of 60 mmHg. Several months later, the patient underwent coronary artery bypass surgery. She was found in bed deceased a short time thereafter.

Hypoglycemia

Weight loss is associated with improved glycemic control in patients with diabetes mellitus, and drug-related weight loss can contribute to hypoglycemia in patients on medical treatment for diabetes.⁴¹

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

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

- self-monitored glucose during the event is ≤ 65 mg/dL; or
- no glucose value is available or self-monitored glucose > 65 mg/dL, AND assistance of another person was required to administer treatment (food, beverage, glucose, glucagon) that leads to resolution of symptoms; or
- any event for which intravenous glucose or parenteral glucagon was administered.

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

⁴¹ Xenical (orlistat) Prescribing Information

- Mild/moderate hypoglycemia: capillary glucose < 65 mg/dL that the patient is able to treat himself/herself; or, if glucose is not measured, symptoms of hypoglycemia that resolve within 15 minutes with administration of oral carbohydrates
- Severe hypoglycemia: capillary glucose < 50 mg/dL associated with confusion, loss of consciousness, or seizures; or, in the absence of a glucose determination, confusion, loss of consciousness, or seizures that resolve with the administration of oral carbohydrate, glucagon, or intravenous glucose by another person
- Catastrophic hypoglycemia: severe hypoglycemia that resulted in life-threatening injury to the patient or another person, hospitalization, and/or death; reported as a serious adverse event

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

Table 80. Summary of Patients with IVRS-Reported Suspected Hypoglycemic Events by Protocol-Defined Severity Category

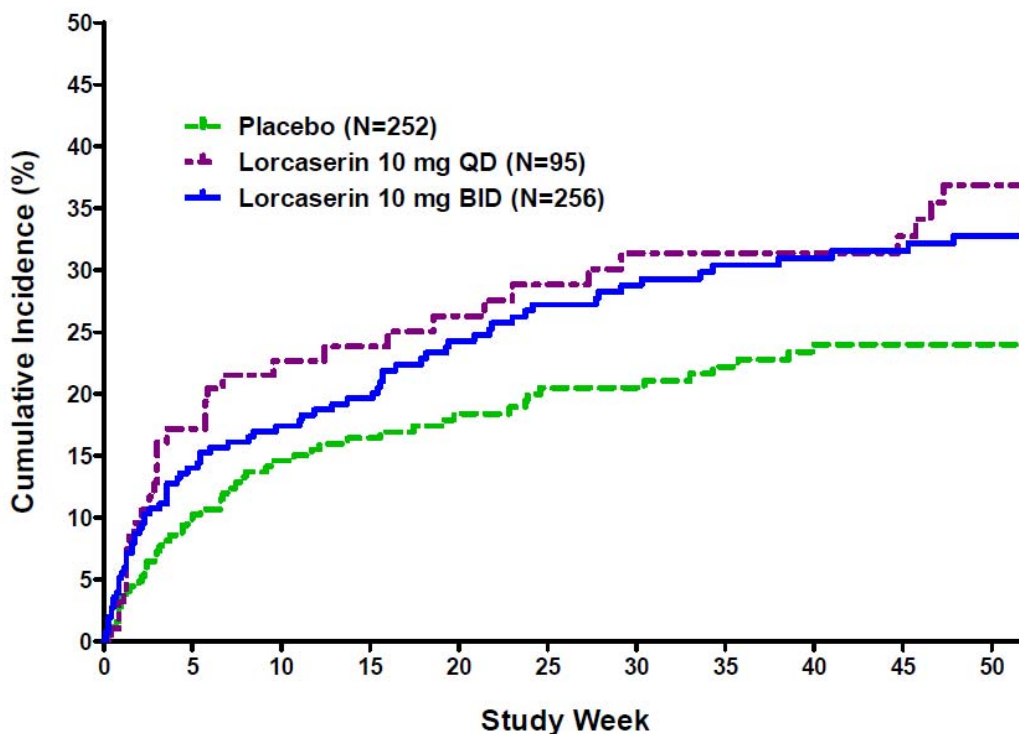
	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
n (%) Patients ^{a,b}	54 (21.1)	27 (28.4)	32 (12.7)
Severe	3 (5.6)	2 (7.4)	1 (3.1)
Mild/Moderate	36 (66.7)	21 (77.8)	25 (78.1)
Neither severity category ^c	15 (27.8)	4 (14.8)	6 (18.8)
Documented symptomatic	40 (74.1)	23 (85.2)	26 (81.3)
Probable symptomatic	13 (24.1)	4 (14.8)	8 (25.0)
Relative	12 (22.2)	10 (37.0)	11 (34.4)
Subgroup analysis by baseline anti-diabetic agent			
Metformin	14/125 (11.2%)	8/48 (16.7%)	5/123 (4.1%)
SFU (+/- metformin)	40/126 (31.7%)	19/46 (41.3%)	27/125 (21.6%)
a Patients reporting one or more events are counted once in the maximum category across all such events.			
b patients reporting one or more events are counted once for each category, and may therefore be counted in multiple categories. As a result, the number of patients in each category may sum to more than the number of patients reporting events.			
c Patients in "neither" had reported blood glucose > 65 mg/dL.			

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

With respect to adverse events of hypoglycemia, the figure below demonstrates the time course of first hypoglycemia events. Hypoglycemia was reported with greater

frequency by patients in both lorcaserin groups as compared to the placebo group. The time to event analysis showed a significant difference between placebo and lorcaserin 10 mg BID ($p=0.041$).

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



Number of patients at risk:

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

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

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

Table 81. Summary of All Adverse Event Terms of ‘Hypoglycaemia’ and ‘Blood Glucose Decreased’

	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
No. (%) patients with PT ‘hypoglycaemia’ ^a	75 (29.3)	32 (33.7)	53 (21.0)
No. of events with PT ‘hypoglycaemia’	523	254	323
Action taken ^b			
None	464 (88.7)	193 (76.0)	233 (72.1)
Took food or beverage	52 (9.9)	60 (23.6)	88 (27.2)
Took concomitant medications	4 (0.8)	0 (0.0)	1 (0.3)
Decreased or stopped diabetic medications	3 (0.6)	1 (0.4)	1 (0.3)
Outcome ^b			
Resolved	523 (100.0)	254 (100.0)	323 (100.0)
Total patients with PT ‘blood glucose decreased’ ^a	1 (0.4)	3 (3.2)	2 (0.8)
Total events with PT ‘blood glucose decreased’	2	59	2
Severity ^{a,c}			
Mild	59 (23.0)	23 (24.2)	42 (16.7)
Moderate	11 (4.3)	6 (6.3)	10 (4.0)
Severe	4 (1.6)	2 (2.1)	1 (0.4)
a denominator = total number of patients			
b denominator = total number of events			
c patients reporting one or more adverse events are counted once at the maximum intensity of all adverse events			

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

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

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

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

Table 82. Incidence of Low Fasting Plasma Glucose Values During 52 Weeks of Study, BLOOM-DM (Safety Population)

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

Source: NDA 022529 BLOOM-DM CSR, Table 14.3.145

Psychiatric Safety Issues

Perceptual or Dissociative Adverse Events

Lorcaserin is known to possess activity at the 5HT_{2A} receptor. An adverse event profile consistent with 5HT_{2A} activity could include hallucinations, euphoria, and other perceptual or dissociative symptoms.⁴² Such adverse events were seen predominantly in the studies in healthy (lower weight) individuals at supratherapeutic doses and were discussed at the original EMDAC meeting.

In contrast to the studies in healthy populations and with therapeutic doses, trials in obese patients demonstrated lorcaserin-associated dissociative adverse events infrequently. The BLOOM-DM trial had a similar overall imbalance between groups as the non-diabetes trials, although some of the imbalance was due to non-specific lorcaserin-associated adverse events, such as paraesthesia and dizziness (Table 83).

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

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

In BLOOM-DM, no patients had an adverse event related to psychosis. There was one patient on lorcaserin 10 mg BID and one patient on placebo with an adverse event of

⁴² Nichols DE. Hallucinogens. *Pharmacol Ther* 2004 Feb; 101(2): 131-81.

'abnormal dreams'. There were no adverse events of 'dissociation' or 'hallucination'. One patient on placebo had an adverse event of 'paranoia'. There was one serious adverse event of 'conversion disorder' in the lorcaserin 10 mg BID group. The patient's narrative is as follows:

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

Table 83. Incidence of Potential Perceptual or Dissociative Adverse Events, Phase 3 Trials (Safety Population)

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

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

Depression and Suicidality

Depression

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

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

- Beck Depression Inventory-II

Depression in the Phase 3 program was evaluated with standard adverse event reporting, and prospectively with the Beck Depression Inventory-II (BDI-II).⁴³ The BDI-II is a widely used self-report instrument for determining the severity of depression. Numerous published studies have shown that weight loss in obese patients is associated with mean improvements in the BDI total score, in patients treated with diet and exercise,⁴⁴ pharmacotherapy,⁴⁴ and bariatric surgery.⁴⁵

The 21 items evaluated by this instrument are as follows:

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

⁴³ Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory (BDI-II). 2nd ed. San Antonio, TX: The Psychological Association; 1996.

⁴⁴ Faulconbridge LF, et al. Changes in symptoms of depression with weight loss: results of a randomized trial. *Obesity* 2009 May; 17(5): 1009-16.

⁴⁵ Hayden MJ, et al. Characterization of the improvement in depressive symptoms following bariatric surgery. *Obes Surg*. 2011 Mar;21(3):328-35.

- 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.⁴³ Special attention was paid to question 9 (Suicidal Thoughts or Wishes), and the results of this analysis are presented separately.

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

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

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

As Table 84 shows, BDI-II mean total score decreased in both treatment groups and with no statistically significant difference between lorcaserin and placebo. Baseline BDI-II scores were lower than what has been previously described in obesity trials.^{44,45}

Table 84. Mean Change in BDI-II Score, Week 52 LOCF, Phase 3 Trials

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

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

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

Table 85. Summary of Categorical BDI-II Total Score at Week 52 (LOCF), Phase 3 Trials

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

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

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

Table 86. Summary of Categorical BDI-II, Item 18 (Highest Score after Baseline), Phase 3 Trials

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

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

- Adverse Events

As an additional assessment of the potential for lorcaserin to cause depression, the sponsor evaluated the adverse event database for depression-related adverse events by using the standardized MedDRA query (SMQ) for depression.⁴⁶ The following preferred terms were used in the search; the bolded items were those found in the lorcaserin database:

⁴⁶ Medical Dictionary for Regulatory Activities (MedDRA), version 13.0

Table 87. Standardized MedDRA Queries (Narrow and Broad) for Depression

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

Source: MedDRA 13.0 Browser version 3.0.1

As seen in Table 88, there was a slightly higher percentage of narrow depression terms in the lorcaserin groups versus placebo in BLOOM-DM trial as compared to the non-diabetes population, in which the incidence of narrow depression was similar between groups. The broadened terms that could be related to depression, such as sleep disturbance and psychomotor changes, led to an imbalance in the lorcaserin 10 mg BID group as compared to placebo in all Phase 3 trials. There were fewer of these events overall in BLOOM-DM.

Table 88. Incidence of Depression, Phase 3 Trials (Safety Population)

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

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

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

- Patient 1147-S040 (lorcaserin 10 mg QD) was a 57-year-old Asian female with a history of diabetes, headaches, short term memory loss, and depression. On Study Day 132, the patient was admitted to the hospital with complaints of a near-syncopal event. During the hospitalization, the evaluation focused on the long-standing memory loss and depression that appeared to underlie the patient's other complaints. On Study Day 134, the event of depression resolved and the patient was discharged from the hospital with the diagnosis of pseudodementia secondary to severe depression. According to the MedWatch form: "The primary investigator felt the syncopal episode was due to the depression which caused an autonomic imbalance making the patient prone to vasovagal attacks.... The neurologist felt the

memory loss was secondary to depression ... He did not feel there was any significant underlying dementia.” The patient was prescribed venlafaxine for depression and withdrew from the study due to the event of depression.

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

- Depression in Subgroups

Some studies have suggested that patients with obesity are at a higher risk for depression,⁴⁷ with a particularly consistent relationship in women.^{48,49} (This is supported by the baseline incidence of depression in the Phase 3 database: 8.6% of women and 4.7% of men in the pooled Phase 3 trials, and 7.3% of women and 4.0% of men in BLOOM-DM, reported a past medical history of depression.) When evaluating the results from the pooled non-diabetes trials and BLOOM-DM together, there is a suggestion of an excess in depression-related adverse events with lorcaserin treatment in females only. The opposite was seen for males (Table 89).

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 89). The results do suggest that the incidence of depression in the lorcaserin 10 mg BID group may be greater than placebo at the lowest body weight, possibly reflecting greater drug exposure.

⁴⁷ 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.

⁴⁸ 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.

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

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

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

Suicidality

Centrally-acting drugs used to treat obesity may be associated with an increased risk for suicidality.^{50,51} 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).⁵² 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,⁵³ and is recommended by FDA for those obesity development programs that have not implemented C-SSRS.

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

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

- 0 I don't have any thoughts of killing myself
- 1 I have thoughts of killing myself, but I would not carry them out
- 2 I would like to kill myself

⁵⁰ FDA EMDAC Briefing Document, NDA 21888 (rimonabant for obesity), 2007.
<http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-background.pdf> Accessed 12 Aug 2010.

⁵¹ FDA EMDAC Briefing Document, NDA 22580 (Qnexa for obesity), 2010.
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicalMetabolicDrugsAdvisoryCommittee/UCM218824.pdf> Accessed 12 Aug 2010.

⁵² Developed by K. Posner, et al.

⁵³ 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.

3 I would kill myself if I had the chance

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

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

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

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

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

Table 90. Summary of Suicidal Scores (BDI-II) and Adverse Events, Phase 3 Trials

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

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

Neurological Safety Issues

Cognitive Effects

Centrally-acting obesity drugs of a variety of mechanisms have been found to possess neuropsychiatric effects, including adverse effects on cognition.⁵⁴ The 5HT_{2A} receptor is thought to play a role in cognition and memory, and alterations in 5HT_{2A} receptor signaling are implicated in the cognitive dysfunction seen in disorders such as schizophrenia and depression.^{42,55} Cognitive tests conducted in the early phase trials were generally unrevealing. In a 14-day study with doses of lorcaserin up to 20 mg, some evidence for impairment to Numeric Working Memory – Speed was seen with the 20 mg dose. However, there was not a clear dose effect, nor was there supportive evidence for effects on Numeric Working Memory – Sensitivity Index, Spatial Working Memory, or other reaction time measures. The clinical relevance of this finding is unclear, although impairment in working memory is consistent with 5HT_{2A} activation.⁵⁵

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

⁵⁴ Nathan PJ, et al. Neuropsychiatric adverse effects of centrally acting obesity drugs. CNS Neurosci Ther 2011 Oct; 17(5): 490-505.

⁵⁵ Williams GV, et al. The physiological role of 5-HT_{2A} receptors in working memory. J Neurosci 1 Apr 2002; 22: 2843-2854.

Table 91. MedDRA Preferred Terms of Interest Related to Cognitive Function

Modified Dementia SMQ	Additional Cognitive Preferred Terms of Interest
Activities of daily living impaired Agnosia Amnesia Amnesic 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	Disturbance in attention Dysphasia Psychomotor retardation

Source: Reviewer generated from MedDRA 13.0 Browser version 3.0.1

Table 92 demonstrates that patients in the lorcaserin 10 mg BID treatment group reported these cognitive adverse events more frequently than those in the lorcaserin 10 mg QD or placebo groups; this table has been updated with the new data from BLOOM-DM, which, although having fewer events, is consistent with the original NDA's finding.

Table 92. Cognitive-Related Adverse Events, Phase 3 Trials

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

Source: Reviewer created from datasets

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

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

In addition, more patients treated with lorcaserin (1.7%) experienced adverse events of somnolence or sedation as compared with placebo (0.8%) in the non-diabetes trials; a similar finding was seen in BLOOM-DM (1.2% vs. 0.8%).

Adverse events of somnolence or sedation were also twice as frequently in the lorcaserin 10 mg BID group (n=53 (1.7%)) as compared to the placebo group (n=25 (0.8%)) in the non-diabetes trials. In the diabetes trial, the incidence of somnolence was 1.2% in the lorcaserin 10 mg BID group and 0.8% in the placebo group.

Paresthesia

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

1.6% of patients treated with lorcaserin 10 mg BID and 0.8% of patients treated with placebo had adverse events of paresthesia.

Dizziness

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

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

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

Headache

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

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

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

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.^{56,57}

⁵⁶ Boyer EW and Shannon M. The serotonin syndrome. N Engl J Med 2005; 352 (11): 1112-20.

⁵⁷ Wappler F, et al. Pathological role of serotonin system in malignant hyperthermia. Br J Anaesth 2001; 87: 794-8.

Recent work in this area suggests that agonism at the 5HT_{2A} receptor contributes to serotonin syndrome.^{56,58}

There were no adverse events of serotonin syndrome in the BLOOM-DM trial. There were two cases within the lorcaserin development program (first submission, presented the the original briefing document) that the investigators considered to fall within the spectrum of serotonin toxicity:

- Patient 25/007 from Phase 2 study APD356-004 (lorcaserin 10 mg BID) was a 44-year-old white female who discontinued the trial after experiencing a constellation of symptoms that included tremor, palpitations, headache, and vomiting on Study Days 1 and 5. The sponsor considered it possible that these symptoms could have represented a mild form of serotonin toxicity.
- There was one adverse event with a preferred term of 'serotonin syndrome' in the BLOSSOM trial. Patient 2109-S025 (lorcaserin 10 mg BID) was a 29-year-old white female with a history of asthma and celiac sprue. On Study Day 57, she developed symptoms of an upper respiratory syndrome and started a course of clarithromycin the next day (Study Day 53). Four days later, she took her morning dose of the study drug and then took over-the-counter guaifenesin with dextromethorphan. Approximately 30 minutes later, she developed vertigo, nausea, vomiting, diarrhea with some minor blood spots in stools, and a blood pressure increase to 135/105 per patient's home reading (in clinic, her BP was 100-122/75-80 on previous visits). The symptoms resolved after approximately five hours, but re-appeared with her evening dose of study drug and again taking guaifenesin with dextromethorphan. The next morning, the symptoms were resolved. She did not take the study drug that morning. She took her last dose of clarithromycin three days later, and started amoxicillin two days after cessation of clarithromycin (Study Day 62).

At the Week 8 clinic visit (Study Day 62), her BP was 110/80 and she was asymptomatic. The investigator diagnosed serotonin syndrome of moderate severity, probably related to study drug's interaction with dextromethorphan. She was directed by the investigator to withhold study drug, discontinue dextromethorphan, and restart study drug approximately one week after the initial symptoms. The rechallenge was uneventful, with no reappearance of symptoms.

The sponsor conducted a search of preferred terms that might be suggestive of serotonin toxicity (Arena search terms, Table 93, below). In the original NDA, nonspecific preferred terms of chills, tremor, and confusional state drove the imbalance between lorcaserin and placebo. These preferred terms were infrequent in the BLOOM-

⁵⁸ Isbister GK and Whyte IM. Serotonin toxicity and malignant hyperthermia: role of 5HT₂ receptors. Br J Anaesth 2002; 88(4): 603.

DM trial. Additional MedDRA SMQs were searched as shown below; a clear imbalance between treatment groups was not evident.

Table 93. Serotonin Toxicity Terms, Pooled Phase 3 Trials and BLOOM-DM (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Arena Search Terms	56 (1.8)	13 (1.6)	18 (0.6)	4 (1.6)	1 (1.1)	4 (1.6)
Chills	32 (1.0)	6 (0.7)	6 (0.2)	1 (0.4)	1 (1.1)	0
Tremor	10 (0.3)	3 (0.4)	3 (0.1)	1 (0.4)	0	3 (1.2)
Confusional state	6 (0.2)	2 (0.2)	1 (<0.1)	1 (0.4)	0	0
Disorientation	4 (0.1)	1 (0.1)	4 (0.1)	1 (0.4)	0	0
Hyperhidrosis	2 (0.1)	1 (0.1)	6 (0.2)	1 (0.4)	0	1 (0.4)
Intention tremor	1 (<0.1)	0	0	0	0	0
Serotonin syndrome	1 (<0.1)	0	0	0	0	0
Neuroleptic Malignant Syndrome, Narrow SMQ	1 (<0.1)	0	0	0	0	0
Neuroleptic Malignant Syndrome, Broad SMQ	194 (6.1)	47 (5.9)	174 (5.5)	26 (10.2)	10 (10.5)	23 (9.1)
Dystonia, Narrow SMQ	1 (<0.1)	0	0	0	0	0
Dystonia, Broad SMQ	67 (2.1)	16 (2.0)	70 (2.2)	12 (4.7)	3 (3.2)	11 (4.4)

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 22

Cardiovascular Risk Assessment

Background

FDA convened an advisory committee March 28-29, 2012, to discuss the cardiovascular (CV) safety requirements for obesity drug approval. This meeting was designed to be similar to the FDA advisory committee held in July 2008 to discuss the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

The guidance for developing new drugs or biologics for the treatment of type 2 diabetes⁵⁹, issued subsequent to the 2008 meeting, recommends that pharmaceutical companies show that their therapies do not result in an unacceptable increase in cardiovascular risk. This recommendation applies to products that do not have a signal of cardiovascular harm in non-clinical or clinical studies.

⁵⁹ Guidance for industry: Diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. In: Guidances (drugs). United States Food and Drug Administration. 2008. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>. Accessed 13 Jan 2012.

The March 2012 advisory committee recommended that sponsors of obesity drugs without a theoretical risk or signal for CV harm should be required to rule out a certain degree of excess CV risk prior to approval.

Lorcaserin was developed prior to the discussions regarding obesity drug CV risk assessments. Therefore, trials were not designed to capture and evaluate CV events; the background risk of CV events was relatively low and there was no procedure set up for prospective adjudication.

However, in light of the recent advisory committee meeting discussion, FDA has conducted several analyses of the unadjudicated CV adverse events collected in the phase 3 trials. In addition, FDA has calculated the relative risk with 95% CI of the sponsor's post-hoc blinded adjudication (by an independent committee) of major adverse cardiovascular events (MACE) from the BLOOM and BLOSSOM trials (Table 100).

Methods

FDA CV Event Search

Because the adverse events were not prospectively adjudicated, nor was there a procedure for internal post-hoc adjudication, we felt that utilizing a listing of prespecified preferred terms within a particular topic of interest with Standardized MedDRA⁶⁰ Queries (SMQs) for assessment of CV risk would be a reasonable approach. Table 94 demonstrates the SMQs that were considered for these analyses. More narrow SMQs are subsumed by broader SMQs as one moves to the left in the table.

Table 94. Standardized MedDRA Queries Considered for CV Risk Analyses

Cerebrovascular Disorders SMQ	Central nervous system haemorrhages and cerebrovascular conditions SMQ	Conditions associated with central nervous system haemorrhages and cerebrovascular accidents SMQ (includes terms such as dysarthria and paralysis)
		Haemorrhagic cerebrovascular conditions SMQ
		Ischaemic cerebrovascular conditions SMQ (includes cerebrovascular accident (stroke) and transient ischemic attack)
	Cerebrovascular disorders, not specified as haemorrhagic or ischaemic SMQ (includes vasculitis and sinus thrombosis)	
Ischaemic heart disease SMQ	Myocardial infarction SMQ	
	Other ischaemic heart disease SMQ (includes angina, arteriosclerosis, angioplasty)	
MedDRA version 14.1		

⁶⁰ MedDRA - the Medical Dictionary for Regulatory Activities - is a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products. <http://www.meddrasso.com> Accessed 23 April 2012.

We chose a “broad” group of terms to encompass a spectrum of possible ischemic cardiac and cerebrovascular events, and a “narrow” group of terms that parallels a stricter MACE definition (see Table 95). We also evaluated the following SMQs separately (please see the Appendix): Cerebrovascular Disorders SMQ (in the lorcaserin database, these terms were equivalent to those in the Central nervous system haemorrhages and cerebrovascular conditions SMQ); Ischaemic cerebrovascular conditions SMQ; Ischaemic heart disease SMQ; and Myocardial infarction SMQ.

Although there were some terms/cases that were not likely associated with a CV event (e.g., intracranial hemorrhage due to trauma), no attempt was made by FDA to alter the SMQ by adding or subtracting terms or cases, since we were not adjudicating all cases.

Table 95. Broad and Narrow Grouping of SMQs

BROAD	NARROW
Haemorrhagic cerebrovascular conditions SMQ	Ischaemic cerebrovascular conditions SMQ
Ischaemic cerebrovascular conditions SMQ	Myocardial infarction SMQ
Ischaemic heart disease SMQ	

Sponsor’s Post-hoc CV Event Adjudication

As described in the FDA clinical briefing document, cardiovascular events from BLOOM and BLOSSOM were independently adjudicated in a post-hoc fashion. BLOOM-DM events were not included.

The adjudication process was conducted by an independent committee (the Cardiovascular Clinical Events Committee (CCEC)) consisting of physicians from the Brigham and Women’s Hospital (Boston, Massachusetts).

The goal of the CCEC was to define and adjudicate the following potential endpoints from BLOOM and BLOSSOM in a consistent and unbiased manner (in essence, MACE-plus):

- Cardiovascular Death
- Cardiovascular Ischemic Events including myocardial infarction and hospitalization for unstable angina
- Cerebrovascular Events including stroke and transient ischemic attack

The sponsor was responsible for identifying potential events from BLOOM and BLOSSOM for review. Potential events were triggered by either (1) death of a subject, (2) report of a serious adverse event (SAE) with a preferred term of chest pain or chest discomfort, or (3) a SAE meeting any of the specific terms in the Ischaemic heart

disease SMQ (including the Myocardial infarction SMQ, Other ischaemic heart disease SMQ), Ischaemic cerebrovascular conditions SMQ, and Conditions associated with central nervous system haemorrhages and cerebrovascular accidents SMQ.

The two physician reviewers were to independently review the cases assigned to them, document and provide supporting information for each event's adjudication directly on the endpoint form, and were responsible for bringing their assigned cases with them to a scheduled review session. At this session, the two physicians that were assigned to each case reviewed the event together and compare adjudications. If the two adjudications agreed on all data fields, the event was considered complete and a single form was signed by both reviewers. If there was initial disagreement and if after discussion, consensus between the two reviewers was reached on a final adjudication, a single form was signed by both reviewers and represented the final adjudication. If after discussion, no consensus was reached, the case would be presented to a third reviewer for final adjudication and a single form would be submitted with all three signatures indicating a final adjudication. See Appendix x for a description of endpoint definitions.

Results

FDA CV Event Search

This section provides the results of the exploratory searches in tabular form, assessing both broad and narrow searches; all adverse events and those considered serious only; comparisons of placebo vs. all lorcaserin patients and vs. lorcaserin 10 mg BID only.

Table 96. Broad Search, All Adverse Events

	Adverse Events in Broad ³ CV Search							
	Treatment	Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	8	5.05	1.37 (0.55, 3.41)	1.37 (0.55, 3.41)	1.08 (0.61, 1.91)	1.09 (0.64, 1.88)
	Lorc 10 BID	1593	11	6.91				
BLOOM-DM	Pbo	252	8	31.75	0.61 (0.20, 1.88)	0.89 (0.35, 2.30)		
	Lorc 10 BID	256	5	19.53				
	Lorc 10 QD	95	5	52.63				
BLOSSOM	Pbo	1601	7	4.37	1.29 (0.48, 3.46)	1.05 (0.41, 2.71)		
	Lorc 10 BID	1602	9	5.62				
	Lorc 10 QD	801	2	2.50				
¹ Lorcaserin 10mg BID vs. placebo								
² All lorcaserin vs. placebo								
³ Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ, and Ischaemic heart disease SMQ								

Source: Dr. Eugenio Andraca-Carrera, Statistical Reviewer FDA DB7

Table 97. Broad Search, Serious Adverse Events Only

	Serious Adverse Events in Broad ³ CV Search							
	Treatment	Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	3	1.89	0.99 (0.20, 4.93)	0.99 (0.20, 4.93)	1.11 (0.45, 2.73)	1.26 (0.55, 2.90)
	Lorc 10 BID	1593	3	1.88				
BLOOM-DM	Pbo	252	2	7.94	0.49 (0.04, 5.44)	1.81 (0.35, 9.39)		
	Lorc 10 BID	256	1	3.91				
	Lorc 10 QD	95	4	42.11				
BLOSSOM	Pbo	1601	4	2.50	1.50 (0.42, 5.33)	1.17 (0.34, 3.99)		
	Lorc 10 BID	1602	6	3.75				
	Lorc 10 QD	801	1	1.25				

¹Lorcaserin 10mg BID vs. placebo.
²All lorcaserin vs. placebo
³Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ and Ischaemic heart disease SMQ

Source: Dr. Eugenio Andraca-Carrera, Statistical Reviewer FDA DB7

Table 98. Narrow Search, All Adverse Events

	Adverse Events in Narrow ³ CV Search							
		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	7	4.42	0.57 (0.17, 1.94)	0.57 (0.17, 1.94)	0.78 (0.40, 1.54)	0.77 (0.40, 1.46)
	Lorc 10 BID	1593	4	2.51				
BLOOM-DM	Pbo	252	7	27.78	0.70 (0.22, 2.23)	0.82 (0.29, 2.28)		
	Lorc 10 BID	256	5	19.53				
	Lorc 10 QD	95	3	31.58				
BLOSSOM	Pbo	1601	5	3.12	1.20 (0.37, 3.94)	0.93 (0.30, 2.94)		
	Lorc 10 BID	1602	6	3.75				
	Lorc 10 QD	801	1	1.25				

¹Lorcaserin 10mg BID vs. placebo
²All lorcaserin vs. placebo
³Narrow Search includes: Ischaemic cerebrovascular conditions SMQ, Myocardial infarction SMQ

Source: Dr. Eugenio Andraca-Carrera, Statistical Reviewer FDA DB7

Table 99. Narrow Search, Serious Adverse Events Only

	Serious Adverse Events in Narrow ³ CV Search							
		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	3	1.89	0.33 (0.03, 3.19)	0.33 (0.03, 3.19)	0.99 (0.35, 2.84)	1.07 (0.40, 2.87)
	Lorc 10 BID	1593	1	0.63				
BLOOM-DM	Pbo	252	2	7.94	0.49 (0.04, 5.44)	1.08 (0.18, 6.50)		
	Lorc 10 BID	256	1	3.91				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	2	1.25	2.50 (0.48, 12.93)	2.00 (0.40, 9.93)		
	Lorc 10 BID	1602	5	3.12				
	Lorc 10 QD	801	1	1.25				

¹Lorcaserin 10mg BID vs. placebo
²All lorcaserin vs. placebo
³Narrow Search includes: Ischaemic cerebrovascular conditions SMQ, Myocardial infarction SMQ

¹Lorcaserin 10mg BID vs. placebo

²All lorcaserin vs. placebo

³Narrow Search includes: Ischaemic cerebrovascular conditions SMQ, Myocardial infarction SMQ

Source: Dr. Eugenio Andraca-Carrera, Statistical Reviewer FDA DB7

Sponsor's Post-hoc CV Event Adjudication

The CCEC received a total of 25 cases blind to treatment assignment for adjudication including 19 potential ischemic events, four potential cerebrovascular events, and two deaths. The two physician reviewers reportedly found the documents provided adequate to adjudicate all cases and reached consensus on all cases.

Overall, 19 potential ischemic event cases yielded five myocardial infarctions, four hospitalizations for unstable angina, and 10 events that did not formally meet either of these criteria. Of the four potential cerebrovascular events, the reviewers coded one stroke, two transient ischemic attacks, and one event that did not formally meet either of these definitions. Both deaths were felt to be non-cardiovascular in nature, with one coded as pulmonary cause, and the other as accident/trauma.

The sponsor unblinded the adjudications, with the results as follows: five lorcaserin 10 mg BID, zero lorcaserin 10 mg QD, six placebo, and one lorc/pbo (Year 2).

The following table exhibits FDA's statistical analysis of the adjudicated CV events in Year 1.

Table 100. Post-Hoc Adjudication of MACE-Plus in BLOOM and BLOSSOM, Year 1

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	3 ^a	1.89	0.33 (0.03, 3.19)	0.63 (0.19, 2.12)	0.85 (0.25, 2.73)
	Lorc 10 BID	1593	1 ^b	0.63			
BLOSSOM	Pbo	1601	3 ^a	1.87	0.89 (0.20, 3.97)		
	Lorc 10 BID	1602	4 ^b	2.50			
	Lorc 10 QD	801	0	0.00			
1 All lorcaserin vs. placebo 2 Lorcaserin 10mg BID vs. placebo a Placebo events consisted of: 2 unstable angina, 1 MI-silent, 1 stroke, ischemic, and 2 TIA b Lorcaserin 10 mg BID events consisted of 1 unstable angina and 4 MI-spontaneous							

Source: Dr. Eugenio Andraca-Carrera, Statistical Reviewer FDA DB7

Priapism

Serotonin activation at the 5HT_{2C} receptor has been implicated in priapism seen in animals.⁶¹ 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 102 shows that priapism was not reported in the lorcaserin 10 mg BID group in Year 1. In Year 2 of BLOOM, no events were reported in the lorcaserin/lorcaserin-treated group.

Although no adverse events of priapism were reported, a definitive conclusion regarding lorcaserin and priapism is limited given that the investigators did not actively question patients about this event.

⁶¹ Millan MJ, et al. 5-HT_{2C} receptors mediate penile erections in rats: actions of novel and selective agonists and antagonists. Eur J Pharmacol 1997; 325: 9–12.

Table 101. MedDRA Search Terms for Priapism

LLT	PT	HLT	SOC
Priapism	Priapism	Erection and ejaculation disorders	Reproductive system and breast disorders
Priapism aggravated			
Clitoral engorgement	Clitoral engorgement	Vulvovaginal signs and symptoms	
Clitorimegaly	Enlarged clitoris	Female gonadal function disorders	Endocrine disorders
Clitoris engorgement			
Clitoris enlarged			
Hypertrophy of clitoris			
Vulvodynia	Vulvovaginal pain		
Erection increased	Erection increased	Sexual arousal disorders	Psychiatric disorders
Penile edema	Penile oedema	Penile disorders NEC	
Penile vascular disorder	Penile vascular disorder		
Penile pain	Penile pain		
Spontaneous penile erection	Spontaneous penile erection		
LLT=lower level term			

Source: NDA 022529 7 Mar 2010 Response to 74-day filing letter requests, Table 8

Table 102. Priapism Adverse Events, Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Priapism	0	1 (0.1)	2 (0.1)	0	0	0
Spontaneous penile erection	0	1 (0.1)	1 (<0.1)	0	0	0
Erection increased	0	0	1 (<0.1)	0	0	0

Source: NDA 022529 2 Apr 2010 Response to 74-day filing letter requests, Table S09.1.0; Summary of Clinical Safety (resubmission), Table 43

Ophthalmological Adverse Events

As noted in the original NDA clinical review, an imbalance was seen in adverse events in the Eye Disorders SOC (4.5% vs. 3.0%) in the non-diabetes trials, with adverse events in lorcaserin-treated patients of 'Vision blurred', 'Dry eye', and 'Visual impairment' occurring at an incidence greater than that of placebo. Similar findings were noted in the BLOOM-DM trial (Table 103). There was not a consistently seen preferred term that drove the imbalance.

Table 103. Eye Disorders with at Least Two Patients in a MedDRA High Level Term, BLOOM-DM (Safety Population)

	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Eye Disorders SOC	16 (6.3)	2 (2.1)	4 (1.6)
Visual disorders NEC	4 (1.6)	0	0
Conjunctival infections, irritations and inflammations	3 (1.2)	1 (1.1)	0
Ocular sensation disorders	2 (0.8)	1 (1.1)	0
Cataract conditions	2 (0.8)	0	0

Source: Reviewer created from datasets

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events that were common in all trials with lorcaserin included headache, dizziness, nausea, and fatigue. Headache and dizziness are discussed in section 7.3.5. Nausea was dose- and exposure-related, seen primarily in patients with the lowest baseline body weight, and seen early after dosing (typically within the first four hours). As would be expected, hypoglycemia was not frequently seen in the trials of patients without diabetes, but as the preferred term 'hypoglycaemia' was the most common adverse event in the BLOOM-DM trial, it is included in Table 104. Hypoglycemia is discussed further in section 7.3.5.

Table 104. Preferred Terms Reported by ≥ 3% of Lorcaserin-treated Patients and More Commonly than with Placebo in the Pooled Non-Diabetes Phase 3 Trials and BLOOM-DM

	BLOOM + BLOSSOM		BLOOM-DM	
	Lorc 10 BID N = 3195	Placebo N = 3185	Lorc 10 BID N = 256	Placebo N = 252
Hypoglycaemia	2 (0.1)	1 (<0.1)	75 (29.3)	53 (21.0)
Headache	537 (16.8)	321 (10.1)	37 (14.5)	18 (7.1)
Nasopharyngitis	414 (13.0)	381 (12.0)	29 (11.3)	25 (9.9)
Dizziness	270 (8.5)	122 (3.8)	18 (7.0)	16 (6.3)
Nausea	264 (8.3)	170 (5.3)	24 (9.4)	20 (7.9)
Fatigue	229 (7.2)	114 (3.6)	19 (7.4)	10 (4.0)
Urinary tract infection	207 (6.5)	171 (5.4)	23 (9.0)	15 (6.0)
Back pain	201 (6.3)	178 (5.6)	30 (11.7)	20 (7.9)
Dry mouth	169 (5.3)	74 (2.3)	4 (1.6)	3 (1.2)
Influenza	138 (4.3)	134 (4.2)	15 (5.9)	13 (5.2)
Gastroenteritis viral	137 (4.3)	101 (3.2)	18 (7.0)	11 (4.4)
Cough	136 (4.3)	109 (3.4)	21 (8.2)	11 (4.4)
Muscle strain	98 (3.1)	74 (2.3)	10 (3.9)	9 (3.6)

Source: Reviewer created from datasets and Summary of Clinical Safety (resubmission), Table 14

7.4.2 Laboratory Findings

This section includes laboratory findings and related adverse events, with the exception of prolactin, which is discussed in section 7.6.1.

Hepatobiliary Events and Related Laboratory Data

Hepatic Events

Hepatic events were infrequent in the lorcaserin development program. As discussed in the briefing document for the first EMDAC meeting:

- Patient 111-S002 (lorcaserin 10 mg BID; BLOOM trial) experienced adverse events of 'hepatomegaly' and 'elevated liver function tests' and discontinued drug prior to the Week 8 visit due to these adverse events. This patient had an elevated alanine aminotransferase (ALT) at randomization with a value of 140 U/L. The ALT value of 236 was recorded at a follow-up visit on Study Day 15. Both ALT and aspartate aminotransferase (AST) declined on subsequent visits. Total bilirubin was not elevated at any time point.
- Two other liver-related adverse events from the hepatobiliary SOC occurred in two patients randomized to placebo in the Year 1 pooled dataset: 'hepatic cyst' and 'hepatomegaly'.
- Two adverse events of 'hepatic steatosis' occurred in the second year of BLOOM: one patient was treated with lorcaserin 10 mg BID in the first year and re-randomized to placebo in the second year (adverse event occurred on Study Day 602) and one patient was treated with placebo throughout the two-year trial (adverse event occurred on Study Day 496).

Adverse events in BLOOM-DM that are liver- or liver laboratory test-related were infrequent (see Table 105). Two adverse events leading to discontinuation in the lorcaserin 10 mg BID group are discussed below.

Table 105. Liver-Related Adverse Events, Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Total, liver-related adverse events	25 (0.8)	15 (1.9)	30 (0.9)	4 (1.6)	1 (1.1)	1 (0.4)
Aspartate aminotransferase increased	11 (0.3)	9 (1.1)	14 (0.4)	1 (0.4)	0	1 (0.4)
Alanine aminotransferase increased	11 (0.3)	8 (1.0)	12 (0.4)	2 (0.8)	0	0
Liver function test abnormal	6 (0.2)	3 (0.4)	5 (0.2)	0	0	0
Hepatic enzyme increased	4 (0.1)	1 (0.1)	4 (0.1)	1 (0.4)	1 (1.1)	0
Blood alkaline phosphatase increased	3 (0.1)	0	1 (<0.1)	0	0	0
Blood bilirubin increased	2 (0.1)	0	3 (0.1)	0	0	0
Hepatomegaly	1 (<0.1)	0	1 (<0.1)	0	0	0
Hepatic enzyme abnormal	0	0	1 (<0.1)	0	0	0
Hepatitis	0	0	0	1 (0.4)	0	0

Source: Reviewer created from datasets

In BLOOM-DM, there was one adverse event of 'hepatitis' (led to discontinuation):

- Patient 1195-S013 (lorcaserin 10 mg BID) was a 55-year-old Hispanic female with a history of diabetes, cholelithiasis status post cholecystectomy, chronic diarrhea, urinary incontinence status post bladder suspension, hypercholesterolemia, hypertension, hyperthyroidism status post partial thyroidectomy, sleep apnea, and seasonal allergies. Concomitant medications at study start were metformin, sitagliptin, olmesartan, l-thyroxine, Caudex, montelukast, aspirin, multivitamin, calcium, and ibuprofen. The patient was also taking a variety of herbal agents and supplements, including cinnamon, Nopal Ultra, aloe vera, cranberry, and Mega Greens. Social history is relevant for absence of drug abuse and for infrequent alcohol use (2-3 glasses of wine per year). Transfusion, sexual, and travel histories were unavailable. The diagnosis of hepatitis was made on the basis of elevated liver function tests (see below). At screening, HBsAg and HCV screens were negative, as was the HIV screen. No follow-up virology screen was documented. The patient was withdrawn from the trial as a result of the adverse event. It was reported as mild intensity, possibly related, and reported as ongoing at study exit.

Table 106. Liver-Related Laboratories, Patient 1195-S013

	Screening	Day 1	Week 4	Week 12	Week 24	Unscheduled	Exit
Study Day	-28	1	27	82	168	179	217
ALT (U/L)	89	110	117	109	223	217†	143
AST (U/L)	54	77	63	68	156	155	77
Total bilirubin (mg/dL)	0.3	0.2	0.3	0.2	0.2	0.3	0.3
Alkaline phosphatase (U/L)	156	148	162	149	169	156†	136
† Denoted "clinically significant" by investigator Normal ranges: Alkaline phosphatase 40-135 U/L, ALT 0-47 U/L, AST 0-37 U/L, Total bilirubin 0.2-1.3 mg/dL							

Source: NDA 022529 Response to Information Request 7 February 2012, Table 1

There was also one patient who withdrew from the trial due to an adverse event of 'hepatic enzyme increased':

- Patient 1121-S024 (lorcaserin 10 mg BID) was a 52-year-old Hispanic female with a history of diabetes, hypertension and hyperlipidemia. Concomitant medications at study start were metformin, estradiol patch, losartan, simvastatin, citalopram, and sitagliptin. She had no reported history of alcohol use or substance abuse. The patient was discontinued early at Week 24 due to an adverse event of 'hepatic enzyme increased'. See table below for the patient's laboratory values; transaminases decreased after discontinuing medication, then increased again approximately two weeks later.

Table 107. Liver-Related Laboratories, Patient 1121-S024

	Screening	Day 1	Week 4	Week 12	Week 24	Unscheduled	Week 52
Study Day	-30	1	26	83	169	211	223
ALT (U/L)	69	94	74	133	196	130	219
AST (U/L)	48	63	51	80	107	89	152
Total bilirubin (mg/dL)	0.2	0.5	0.4	0.4	0.3	0.4	0.4
Alkaline phosphatase (U/L)	80	95	78	88	94	85	85
† Denoted "clinically significant" by investigator							
Normal ranges: Alkaline phosphatase 40-135 U/L, ALT 0-47 U/L, AST 0-37 U/L, Total bilirubin 0.2-1.3 mg/dL							

Source: Reviewer created from datasets

The FDA Guidance for evaluating premarketing drug-induced liver injury⁶² 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: greater than the upper limit of normal (ULN), > 3x ULN, > 5x ULN, and > 20x ULN. In Year 1, there were five (0.2%) lorcaserin 10 mg BID, one (0.1%) lorcaserin 10 mg QD, and four (0.1%) placebo patients meeting the > 5x ULN category in the pooled Phase 3 (non-diabetes) trials; none in the BLOOM-DM trial met this criterion (Table 108). No patients in the lorcaserin treatment groups and one patient in the placebo group in any of the trials met the > 20x ULN criterion.

In Year 2 of BLOOM, three patients experienced ALT elevations > 3x ULN; two assigned to lorcaserin/lorcaserin and one assigned to lorcaserin/placebo. One patient (109-S025, lorcaserin/lorcaserin) had a value > 5x ULN. On Week 64, she had an

⁶² FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf> Accessed 28 July 2010.

adverse event reported of 'hepatic enzyme elevated'; study drug was stopped and restarted.

Table 108. Number (%) Patients with ALT Values Exceeding Selected Cutoffs, Pooled Phase 3 Trials (Non-Diabetes, Year 1) and BLOOM-DM

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=2991	Lorc 10 QD N=754	Pbo N=2918	Lorc 10 BID N=250	Lorc 10 QD N=93	Pbo N=244
ALT						
> ULN	317 (10.6)	95 (12.6)	375 (12.9)	45 (18.0)	21 (22.6)	58 (23.8)
> 3x ULN	11 (0.4)	4 (0.5)	13 (0.4)	2 (0.8)	1 (1.1)	0
> 5x ULN	5 (0.2)	1 (0.1)	4 (0.1)	0	0	0
> 20x ULN	0	0	1 (<0.1)	0	0	0
AST						
> ULN	231 (7.7)	74 (9.8)	284 (9.7)	40 (16.0)	18 (19.4)	46 (18.9)
> 3x ULN	13 (0.4)	3 (0.4)	12 (0.4)	2 (0.8)	1 (1.1)	1 (0.4)
> 5x ULN	2 (<0.1)	1 (0.1)	5 (0.2)	0	1 (1.1)	1 (0.4)
> 20x ULN	0	0	1 (<0.1)	0	0	0
Alk Phos						
> ULN	68 (2.3)	14 (1.9)	71 (2.4)	8 (3.2)	1 (1.1)	4 (1.6)
> 1.5x ULN	3 (0.1)	1 (0.1)	6 (0.2)	0	0	0
> 2.5x ULN	2 (<0.1)	0	2 (<0.1)	0	0	0
> 5x ULN	0	0	0	0	0	0
T. bili						
> ULN	86 (2.9)	27 (3.6)	111 (3.8)	6 (2.4)	4 (4.3)	9 (3.7)
> 1.5x ULN	16 (0.5)	4 (0.5)	27 (0.9)	2 (0.8)	0	0
> 2x ULN	2 (<0.1)	0	7 (0.2)	0	0	0
> 3x ULN	0	0	0	0	0	0
ALT/AST + T. bili						
ALT > 3x ULN + T. bili > 1.5x ULN	0	0	0	0	0	0
AST > 3x ULN + T. bili > 1.5x ULN	0	0	0	0	0	0

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 65; ISS CR Appendix 2, Table S14.1.1; BLOOM-DM CSR, Table 14.3.145

Gallbladder Events

In the Phase 3 program, the remainder of adverse events in the hepatobiliary SOC consisted of cholelithiasis, biliary dyskinesia, and cholecystitis events. Obesity and rapid weight loss are associated with an increased risk for gallstone formation.⁶³

In the non-diabetes trials, patients randomized to lorcaserin had more serious adverse events of cholelithiasis and cholecystitis than those randomized to placebo. Overall, gallbladder-related adverse events were infrequent and only slightly more commonly seen in patients treated with lorcaserin. A similar pattern was seen in Year 2 of BLOOM (data not shown).

⁶³ Stinton LM, et al. Epidemiology of gallstones. Gastroenterol Clin North Am 2010 Jun; 39(2): 157-69, vii.

In BLOOM-DM, one patient randomized to lorcaserin 10 mg BID had a serious adverse event of cholecystitis and was withdrawn from the trial.

Table 109. Gallbladder-Related Adverse Events, Pooled Phase 3 Trials (Non-Diabetes, Year 1) and BLOOM-DM (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Total Gallbladder-Related AEs	26 (0.8)	5 (0.6)	16 (0.5)	2 (0.8)	0	1 (0.4)
Cholelithiasis	11 (0.3)	2 (0.2)	10 (0.3)	1 (0.4)	0	0
Cholecystitis	8 (0.3)	2 (0.2)	5 (0.2)	1 (0.4)	0	1 (0.4)
Biliary dyskinesia	3 (0.1)	0	1 (<0.1)	0	0	0
Gallbladder disorder	2 (0.1)	1 (0.1)	1 (<0.1)	0	0	0
Cholecystitis acute	2 (0.1)	0	2 (0.1)	0	0	0
Cholecystitis chronic	2 (0.1)	0	0	0	0	0
Biliary colic	1 (<0.1)	0	0	0	0	0
Gallbladder non-functioning	1 (<0.1)	0	0	0	0	0
Gallbladder pain	1 (<0.1)	0	0	0	0	0

Source: NDA 022529 ISS, Table 76; reviewer created from datasets

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 110). Bolded terms were those found in the lorcaserin Phase 3 program.

Within the pooled (non-diabetes) Phase 3 trials, one (< 0.1%) patient assigned to lorcaserin 10 mg BID and no patients assigned to placebo had adverse events within the acute renal failure narrow SMQ. When the broad SMQ was applied to the non-diabetes population, 17 (0.5%) lorcaserin 10 mg BID patients and 12 (0.4%) placebo patients experienced adverse events. As discussed in the original review, no patients treated with lorcaserin in the second year of BLOOM had an adverse event in the narrow or broad acute renal failure SMQ.

Patients with diabetes may be prone to kidney injury. Reassuringly, the BLOOM-DM trial did not reveal any increase in acute renal failure adverse events in the lorcaserin-treated patients.

Table 110. Acute Renal Failure SMQ Preferred Terms

Narrow PTs	Broad PTs
Acute prerenal failure Anuria Azotaemia Continuous hemodiafiltration Dialysis Haemodialysis Neonatal anuria Nephropathy toxic Oliguria Peritoneal dialysis Renal failure Renal failure acute Renal failure neonatal Renal impairment Renal impairment neonatal	Albuminuria Blood creatinine abnormal Blood creatinine increased Blood urea abnormal Blood urea increased Blood urea nitrogen/creatinine ratio increased Creatinine renal clearance abnormal Creatinine renal clearance decreased Glomerular filtration rate abnormal Glomerular filtration rate decreased Hypercreatininaemia Nephritis Oedema due to renal disease Protein urine present Proteinuria Renal function test abnormal Renal transplant Renal tubular disorder Renal tubular necrosis Tubulointerstitial nephritis Urea renal clearance decreased Urine output decreased

Source: NDA 022529 2 Apr 2010 Response to 74-day filing letter requests, Table 7

Table 111. Renal Failure SMQ, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Total, MedDRA Renal Failure Narrow SMQ	1 (<0.1)	1 (0.1)	0	1 (0.4)	0	2 (0.8)
Renal failure	0	1 (0.1)	0	0	0	1 (0.4)
Renal failure acute	1 (<0.1)	0	0	0	0	0
Renal impairment	1	0	0	1 (0.4)	0	0
Acute prerenal failure	0	0	0	0	0	1 (0.4)
Total, MedDRA Renal Failure Broad SMQ	17 (0.5)	5 (0.6)	12 (0.4)	2 (0.8)	0	2 (0.8)
Protein urine present	7 (0.2)	3 (0.4)	1 (<0.1)	0	0	0
Proteinuria	8 (0.3)	2 (0.2)	9 (0.3)	1 (0.4)	0	2 (0.8)
Blood creatinine increased	2 (0.1)	0	1 (<0.1)	0	0	0
Blood urea increased	2 (0.1)	0	1 (<0.1)	0	0	0
Urine output decreased	0	0	1 (<0.1)	1 (0.4)	0	0

Source: NDA 022529 2 Apr 2010 Response to 74-day filing letter requests, Table S09.1.0; reviewer created from datasets

Evaluations of categorical laboratory data for creatinine, calculated creatinine clearance, and blood urea nitrogen (BUN) do not suggest a significant drug effect.

Table 112. Categorical Laboratory Data, Kidney Parameters, Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID	Lorc 10 QD	Pbo	Lorc 10 BID	Lorc 10 QD	Pbo
Creatinine						
> Baseline or > ULN	53.1%	57.2%	53.9%	60.0%	62.4%	61.5%
> 1.5x Baseline or > 1.5x ULN	0.5%	0.7%	0.5%	1.2%	0	1.6%
> 3x Baseline or > 3x ULN	<0.1%	0	<0.1%	0	0	0
> 6x ULN	0	0	<0.1%	0	0	0
Creatinine Clearance						
< 60-30 mL/min	0.6%	0.4%	0.3%	2.0%	0	1.7%
< 30-15 mL/min	0	0	<0.1%	0	0	0
< 15 mL/min	0	0	<0.1%	0	0	0
Creatinine Clearance (IBW)						
< 60-30 mL/min	15.6%	15.3%	16.0%	18.4%	12.9%	17.2%
< 30-15 mL/min	0.1%	0	0	0.4%	0	1.2%
< 15 mL/min	0	0	0.1%	0	0	0
BUN						
23-26 mg/dL	4.5%	4.4%	5.5%	15.2%	17.2%	12.7%
27-31 mg/dL	1.1%	1.3%	1.3%	5.6%	6.5%	4.9%
> 31 mg/dL	0.2%	0.3%	0.3%	1.2%	4.3%	1.6%

Source: NDA 022529 2 Apr 2010 Response to 74-day filing letter requests, Table S14.1.1; BLOOM-DM CSR, Table 14.3.145

Hematology Events and Related Laboratory Data

In the mouse, at exposure multiples of 25 and 27 times (males and females) clinical exposure, decreases in red blood cell (RBC) mass were seen. In the non-diabetes Phase 3 trials, 0.9% of patients treated with lorcaserin 10 mg BID as compared to 0.7% of patients treated with placebo had hemoglobin values less than 10 g/dL. In the BLOOM-DM trial, the proportion was 2.0% for lorcaserin 10 mg BID and 3.3% for placebo. In the non-diabetes trials, slightly more patients in the lorcaserin 10 mg BID treated group had adverse events related to anemia or related red blood cell count decreases in the Phase 3 trials; this trend was reversed in the BLOOM-DM trial.

Table 113. Low RBC-Related Adverse Events, Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Total, Low RBC-Related AEs	31 (1.0)	6 (0.7)	22 (0.7)	2 (0.8)	2 (2.1)	7 (2.8)
Anaemia	22 (0.7)	5 (0.6)	17 (0.5)	2 (0.8)	1 (1.1)	3 (1.2)
Haemoglobin decreased	9 (0.3)	1 (0.1)	5 (0.2)	0	1 (1.1)	2 (0.8)
Haematocrit decreased	6 (0.2)	1 (0.1)	2 (0.1)	0	0	3 (1.2)
Red blood cell count decreased	2 (0.1)	0	0	0	0	0

Source: Reviewer created from datasets

Dose-related decreases in white blood cells (WBC), neutrophils, and lymphocytes were noted (Table 114). Adverse events related to decreases in WBCs were infrequent, but greater in lorcaserin-treated patients than those who were placebo-treated (Table 115).

Table 114. Percent of Patients with Neutrophil Counts below Pre-Defined Cut-Offs, Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID	Lorc 10 QD	Pbo	Lorc 10 BID	Lorc 10 QD	Pbo
< Lower limit of normal (LLN)	5.8%	5.7%	4.5%	2.8%	4.3%	1.2%
< $1.5 \times 10^9/L$	2.8%	2.7%	2.2%	0.8%	2.2%	0
< $1 \times 10^9/L$	0.6%	0.4%	0.3%	0.4%	0	0
< $0.5 \times 10^9/L$	<0.1%	0.1%	0	0	0	0

Source: NDA 022529 2 Apr 2010 Response to 74-day filing letter requests, Table S14.2.1; BLOOM-DM CSR, Table 14.3.145

Table 115. Low WBC-Related Adverse Events, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Total, Low WBC-Related AEs	10 (0.3)	5 (0.6)	3 (0.1)	1 (0.4)	0	0
White blood cell count decreased	6 (0.2)	1 (0.1)	2 (0.1)	0	0	0
Neutrophil count decreased	3 (0.1)	2 (0.2)	0	0	0	0
Neutropenia	2 (0.1)	3 (0.4)	2 (0.1)	1 (0.4)	0	0
Leukopenia	2 (0.1)	1 (0.1)	0	0	0	0
Lymphocyte count decreased	1 (<0.1)	0	0	0	0	0
Lymphopenia	1 (<0.1)	0	0	0	0	0

Source: Reviewer created from datasets

All adverse events of neutropenia were considered mild and non-serious. No patient discontinued due to a neutropenia adverse event.

In the Phase 3 trials, a mean decrease in platelets was only seen in the lorcaserin 10 mg BID group, although a similar proportion of patients in the treatment groups had platelet counts less than LLN and $75 \times 10^9/L$. One patient in the non-diabetes trials and one patient in BLOOM-DM had adverse events of 'thrombocytopenia' (mild), both in the lorcaserin 10 mg BID group, and two patients in the non-diabetes trials had adverse events of 'platelet count decreased' (one mild, one moderate), both in the lorcaserin 10 mg BID group. No patient discontinued the trial due to these adverse events.

7.4.3 Vital Signs

See section 7.4.4 below for findings, adverse events, and ECGs related to heart rate.

Blood Pressure and Related Adverse Events

In the pooled non-diabetes trials, 23% of patients in the lorcaserin 10 mg BID and 23% of patients in the placebo-treated group had a history of hypertension. In the BLOOM-DM trial, 61% of lorcaserin 10 mg BID patients and 61% of placebo-treated patients had a history of hypertension.

Increases in blood pressure may portend adverse cardiovascular outcomes with weight loss medications⁶⁴ and therefore, despite the generally favorable effects of lorcaserin on mean blood pressure (see section 6.1.6), outlier blood pressure analyses and related adverse events were explored to ensure there was no concerning signal.

Table 116. Categorical Blood Pressure Values at Any Time During Phase 3 Trials (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3095	Lorc 10 QD N=771	Pbo N=3038	Lorc 10 BID N=251	Lorc 10 QD N=94	Pbo N=248
Systolic BP - High						
120-139	2517 (81.3)	660 (85.6)	2540 (83.6)	235 (93.6)	90 (95.7)	225 (90.7)
140-159	650 (21.0)	215 (27.9)	701 (23.1)	120 (47.8)	44 (46.8)	122 (49.2)
≥ 160	53 (1.7)	16 (2.1)	74 (2.4)	20 (8.0)	7 (7.4)	20 (8.1)
Systolic BP - Low						
85-89	56 (1.8)	12 (1.6)	42 (1.4)	1 (0.4)	1 (1.1)	2 (0.8)
80-84	17 (0.5)	4 (0.5)	15 (0.5)	1 (0.4)	0	0
< 80	14 (0.5)	5 (0.6)	9 (0.3)	0	0	0
Diastolic BP - High						
80-89	2211 (71.4)	601 (78.0)	2284 (75.2)	204 (81.3)	79 (84.0)	207 (83.5)
90-99	624 (20.2)	205 (26.6)	708 (23.3)	74 (29.5)	30 (31.9)	79 (31.9)
≥ 100	69 (2.2)	26 (3.4)	68 (2.2)	8 (3.2)	4 (4.3)	8 (3.2)
Diastolic BP - Low						
< 60	393 (12.7)	78 (10.1)	292 (9.6)	30 (12.0)	11 (11.7)	24 (9.7)

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 75

The hypertension SMQ includes preferred terms such as 'hypertension' and 'blood pressure increased'. The following is an analysis of the pooled (non-diabetes) and BLOOM-DM databases using a modified hypertension SMQ (i.e., removing the preferred term 'metabolic syndrome'). In the review of BLOOM-DM, it was noted that there was an excess of lorcaserin-treated patients with a hypertension-related adverse event. The significance of this finding is unknown as such a finding was not seen in the pooled non-diabetes trials and no significant increase in blood pressure in any trial with lorcaserin.

⁶⁴ James WP, et al. Effect of sibutramine of cardiovascular outcomes in overweight and obese subjects. N Engl J Med. 2010 Sep 2; 363 (10):905-17.

Table 117. Incidence of Hypertension, Phase 3 Trials Year 1 (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Total, Hypertension SMQ	111 (3.5)	27 (3.4)	117 (3.7)	15 (5.9)	7 (7.4)	9 (3.6)
Hypertension	70 (2.2)	19 (2.4)	78 (2.4)	13 (5.1)	6 (6.3)	8 (3.2)
Blood pressure increased	38 (1.2)	8 (1.0)	35 (1.1)	0	1 (1.1)	0
Blood pressure systolic increased	2 (0.1)	0	5 (0.2)	1 (0.4)	0	1 (0.4)
Blood pressure diastolic increased	1 (<0.1)	0	1 (<0.1)	1 (0.4)	0	0
Diastolic hypertension	1 (<0.1)	0	0	0	0	0
Orthostatic hypertension	1 (<0.1)	0	0	0	0	0

Source: Reviewer created from datasets

Hypotension adverse events were also explored. There is a slight imbalance with lorcaserin greater than placebo, although the overall incidence is low.

Table 118. Incidence of Hypotension, Phase 3 Trials Year 1 (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185	Lorc 10 BID N=256	Lorc 10 QD N=95	Pbo N=252
Total, Hypotension-related AEs	20 (0.6)	4 (0.5)	10 (0.3)	2 (0.8)	0	0
Blood pressure decreased	9 (0.3)	3 (0.4)	5 (0.2)	0	0	0
Hypotension	7 (0.2)	1 (0.1)	4 (0.1)	2 (0.8)	0	0
Orthostatic hypotension	4 (0.1)	0	1 (<0.1)	0	0	0

Source: Reviewer created from datasets

7.4.4 Electrocardiograms (ECGs)

This section includes findings from ECGs and related adverse events (heart rate-related).

Study APD356-007 (original NDA submission) was designed to evaluate the potential for lorcaserin to prolong QTc in healthy individuals at the proposed therapeutic dose of 15 mg and a supra-pharmacological dose (40 mg) compared to placebo. The study was a single-site, double-blind, randomized, placebo- and positive-controlled, parallel-designed, steady-state/multiple-dose trial. As discussed in the original EMDAC briefing document, the study was reviewed by the FDA Interdisciplinary Review Team for QT studies (IRT). Findings included:

- No significant QT prolongation effect of lorcaserin at either dose. The largest upper bounds of the 2-sided 90% CI for the mean difference between lorcaserin and placebo were below 10 ms.
- A small dose-related increase in PR interval and decrease in heart rate (HR) due to lorcaserin.

The PR interval increases and HR decreases seen in study APD356-007 were explored in the Phase 2 and 3 trials. In the Phase 2 trials APD356-003 and APD356-004, there was a dose-related increase in incidence of patients with PR interval changes > 15 msec. In the pooled non-diabetes Phase 3 trials, there was a greater mean decrease in HR and slightly greater mean increase in PR interval in the lorcaserin 10 mg BID group as compared to the placebo group.

Table 119. Selected ECG Findings, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID	Lorc 10 QD	Pbo	Lorc 10 BID	Lorc 10 QD	Pbo
Mean (SE) Δ in HR from BL at Week 52*	-1.9 (0.2)	-0.3 (0.4)	-0.3 (0.2)	-2.1 (0.8)	-3.3 (1.1)	0.1 (0.8)
Mean (SE) Δ in RR from BL at Week 52	29.9 (2.8)	6.4 (5.1)	4.1 (2.9)	31.2 (8.8)	26.3 (12.6)	6.8 (8.1)
Mean (SE) Δ in PR from BL at Week 52	2.9 (0.3)	1.9 (0.5)	2.1 (0.3)	2.5 (0.9)	4.0 (1.7)	1.3 (0.9)
% of patients with PR > 200 msec and PR Δ > 40 msec	0.2%	0	0.4%	0.5%	1.2%	0.5%
* Heart rate results for BLOOM-DM taken from vital signs; HR from ECG not reported						

Source: NDA 022529, ISS Tables 138, 139, 141, and 142; BLOOM-DM CSR, Tables 67, 14.3.48, 14.3.49, and 14.3.104

A search of the lorcaserin Phase 3 databases was conducted to determine whether these ECG changes were reported as adverse events and whether such changes might translate to adverse events of bradyarrhythmia such as bradycardia or heart block. As Table 120 shows, in the Phase 3 trials, events related to bradyarrhythmia were infrequent, but more than twice as common in lorcaserin 10 mg BID treated patients.

Table 120. Bradyarrhythmia Adverse Events, Phase 3 Trials

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID	Lorc 10 QD	Pbo	Lorc 10 BID	Lorc 10 QD	Pbo
Total, Bradyarrhythmia AEs	14 (0.4)	2 (0.2)	6 (0.2)	1 (0.4)	0	0
Sinus bradycardia	5 (0.2)	0	2 (0.1)	0	0	0
Bradycardia	4 (0.1)	1 (0.1)	1 (<0.1)	1 (0.4)	0	0
Atrioventricular block first degree	3 (0.1)	0	1 (<0.1)	0	0	0
Electrocardiogram PR prolongation	1 (<0.1)	0	2 (0.1)	0	0	0
Heart rate decreased	1 (<0.1)	0	0	0	0	0
Sick sinus syndrome	0	1 (0.1)	0	0	0	0

Source: Reviewer created from datasets

Analyses of HR in the non-diabetes pooled Phase 3 trials found that 1.2% lorcaserin 10 mg BID versus 0.8% placebo-treated patients had a HR less than 45 BPM during 52 weeks of treatment. By contrast, in the BLOOM-DM trial, 0.8% lorcaserin 10 mg BID versus 1.2% placebo-treated patients had a HR less than 45 BPM during 52 weeks of treatment. Of note, although infrequent, there were also more patients in the lorcaserin groups with tachycardia (HR > 100 BPM) than placebo in the BLOOM-DM trial. The converse was seen in the pooled non-diabetes trials.

Table 121. Assessment of Categorical Heart Rate (BPM) Values at Any Time During the Trial, Pooled Phase 3 and BLOOM-DM (Safety Population)

	BLOOM + BLOSSOM			BLOOM-DM		
	Lorc 10 BID N=3095	Lorc 10 QD N=771	Pbo N=3038	Lorc 10 BID N=251	Lorc 10 QD N=94	Pbo N=248
Heart Rate - Low						
50-54	574 (18.5)	126 (16.3)	421 (13.9)	26 (10.4)	12 (12.8)	17 (6.9)
45-49	176 (5.7)	35 (4.5)	101 (3.3)	8 (3.2)	3 (3.2)	4 (1.6)
<45	37 (1.2)	4 (0.5)	23 (0.8)	2 (0.8)	1 (1.1)	3 (1.2)
Heart Rate - High						
101-115	30 (1.0)	9 (1.2)	47 (1.5)	6 (2.4)	6 (6.4)	1 (0.4)
116-130	0	0	5 (0.2)	0	0	2 (0.8)
>130	0	0	0	0	0	0

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 75

7.4.5 Special Safety Studies/Clinical Trials

This section is unchanged from the original NDA review.

7.4.6 Immunogenicity

Not applicable. Lorcaserin is not a therapeutic protein.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

BLOSSOM and BLOOM-DM evaluated lorcaserin at two doses: 10 mg BID and QD. Adverse events considered to be lorcaserin related, such as headache, nausea, fatigue, and dizziness, were dose-related in non-diabetic patients. A less-consistent dose-relationship was seen in the BLOOM-DM trial, which is not surprising since there was not a dose-relationship for the weight loss efficacy outcome.

The original clinical review described the results of the Phase 1 and 2 dose-response trials that were conducted as part of the drug development program.

7.5.2 Time Dependency for Adverse Events

Time dependency for certain adverse events of interest was described in the original clinical review. The two pieces of new information available from the review of the BLOOM-DM trial are: 1) time to first event of hypoglycemia (type 2 diabetes patients only), which is shown graphically in Figure 6, and 2) time to first event of breast tumor/mass (pooled data from all three Phase 3 trials), which is shown graphically in Figure 7 and Figure 8.

7.5.3 Drug-Demographic Interactions

The relationship of selected safety findings to demographics (age, sex, and race) are presented in the relevant subsections in section 7.

7.5.4 Drug-Disease Interactions

BLOOM-DM evaluated the safety of lorcaserin in patients with type 2 diabetes mellitus, which allows for comparison with patients without diabetes (BLOOM and BLOSSOM trials). Those side-by-side comparisons are presented throughout section 7. The following safety issues are worth highlighting here:

- VHD: At Week 52 in BLOOM-DM, six patients on lorcaserin 10 mg BID, as compared with only one on placebo had echocardiographically-diagnosed FDA-defined VHD, which raises the question whether the diabetes population may be more vulnerable to lorcaserin-associated VHD. Importantly, the placebo rate was actually lower than has been seen previously in the non-diabetes trials, rather than the lorcaserin rate being considerably higher. One would have expected different results if, for example, there was differential 5HT2B expression in patients with type 2 diabetes. Furthermore, the imbalance was less pronounced at Week 24. I believe that the imbalance seen at Week 52 was likely due to chance in the diabetes trial.
- Hypoglycemia: Adverse events of hypoglycemia were relatively common in the BLOOM-DM trial in lorcaserin- and placebo-treated groups, whereas hypoglycemia was extremely rare in the non-diabetes trials. As discussed at the May 10, 2012 advisory committee meeting, HbA1c change was positively correlated with weight change in all treatment groups in BLOOM-DM, which suggests that weight loss is associated with improved glycemic control and therefore may predispose patients with diabetes to hypoglycemia. As noted in the safety summary, however, no action was taken for the majority of events, and all events resolved.

7.5.5 Drug-Drug Interactions

Unchanged from the original clinical review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In the original submission, concern arose over the results of two-year carcinogenicity studies in rats, in which lorcaserin was associated with mammary gland tumors in both sexes at clinically relevant exposures. Other tumor types (astrocytoma, schwannoma, hepatocellular carcinoma and adenoma, squamous cell carcinoma and benign fibroma of skin, and benign follicular cell adenoma of the thyroid) were also seen in male rats at

higher doses. As part of the activities for the complete response, all mammary and lung tissues from the female rat carcinogenicity study were re-adjudicated by a panel of five veterinary pathologists, who read the tissues in a blinded fashion. Please see Dr. Fred Alavi's review for details of the animal findings. It is noted that the re-adjudicated data showed a numerically lower incidence of mammary adenocarcinoma in low- and mid-dose female rats than had been shown previously; a significant increase in mammary adenocarcinoma was seen only at the high dose of 100 mg/kg/day, providing a 24-fold exposure margin for the dose at which no increase in mammary adenocarcinoma was observed (30 mg/kg/day). However, benign mammary fibroadenoma was increased by lorcaserin at all doses tested, and the sponsor believes that these findings are secondary to increased prolactin stimulation of the mammary tissue.

Overall, malignancies were seen infrequently in the Phase 3 program; see Table 122 for an updated table including the BLOOM-DM data (reviewer pooled with BLOOM and BLOSSOM); the second year data from the BLOOM trial is reproduced from the original briefing document. No formal cancer screening was conducted.

Table 122. Neoplasms (MedDRA Malignant or unspecified tumours SMQ), BLOOM, BLOSSOM, and BLOOM-DM

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

Source: Reviewer created from datasets

Table 123. Neoplasms (MedDRA Malignant or unspecified tumours SMQ), BLOOM Year 2

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

Source: Reviewer created from datasets

Breast Cancer and Prolactin

The sponsor suggests that the mammary neoplasm findings in rats can be attributed to lorcaserin-stimulated prolactin release. Prolactin has been shown to cause mammary gland tumors in rodents and promote growth of normal and malignant breast cells *in vitro*.⁶⁵ Dr. Alavi's review will address the sponsor's support for attributing lorcaserin-induced increases in mammary tumors to prolactin. The relationship of prolactin to human breast carcinogenesis is unknown. Because it was noted that lorcaserin increased prolactin concentrations after single doses in a Phase 1 trial, the sponsor was asked to conduct an evaluation of chronic prolactin release in the Phase 3 program.

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

Breast Neoplasms

Over the two years of the Phase 3 trials (BLOOM and BLOSSOM), seven women randomized to lorcaserin 10 mg BID, one woman randomized to lorcaserin 10 mg QD, and five women randomized to placebo were diagnosed with a breast neoplasm, as shown in Table 124. No patient in the BLOOM-DM trial had a diagnosis of breast cancer.

⁶⁵ Reviewed in: Hankinson SE, et al. Plasma prolactin levels and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Instit 1999 Apr; 91(7): 629-34.

Table 124. Breast Neoplasms, Phase 3 Trials, Years 1 and 2

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

Source: NDA 22529, ISS Table 60

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

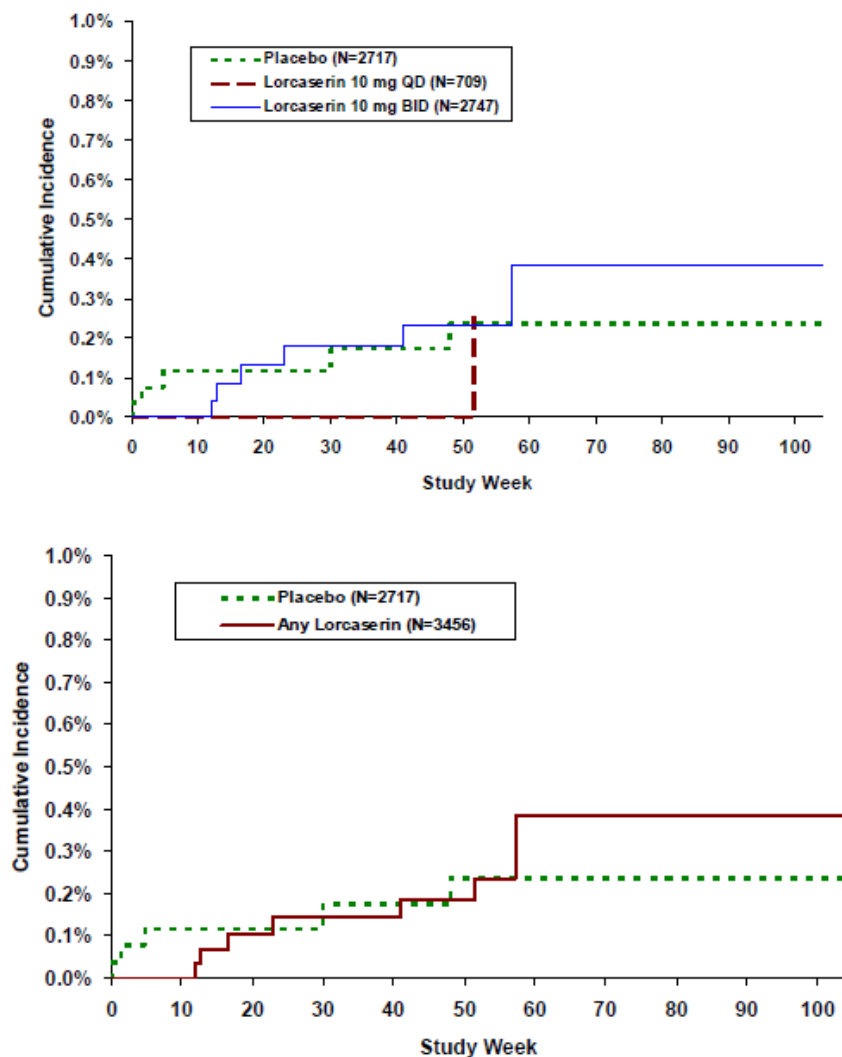
The sponsor conducted two searches: the first was based on the MedDRA SMQ, 'breast neoplasm', which is a list of preferred terms that fit into categories of malignant tumors of the breast (e.g., 'breast cancer', 'breast sarcoma', 'inflammatory carcinoma of the breast', 'mastectomy', etc.) and breast tumors of unspecified malignancy (e.g., 'breast lump removal', 'breast neoplasm', 'nipple neoplasm', etc.). The adverse event term in Table 124 above, 'atypical ductal hyperplasia', mapped to 'breast mass', so it was not included in this search. Table 125 and Figure 7 below demonstrate these findings.

Table 125. Analysis of Time to First Event of SMQ 'Breast Neoplasms' in All Women Enrolled in Phase 3 Trials

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

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

Figure 7. Kaplan-Meier Plot: Time to First Event of SMQ 'Breast Neoplasm' during Entire Study, All Women in Phase 3 Trials



Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52	Week 76	Week 104
Pooled Placebo	2717	1870	1298	467	218
Pooled Lorcaserin 10 mg QD	709	550	349	--	--
Pooled Lorcaserin 10 mg BID	2747	2062	1492	584	259
Any Locaserin Dose	3456	2613	1842	584	259

Source: NDA 022529 Breast Cancer Report Amendment 2, Figure 1

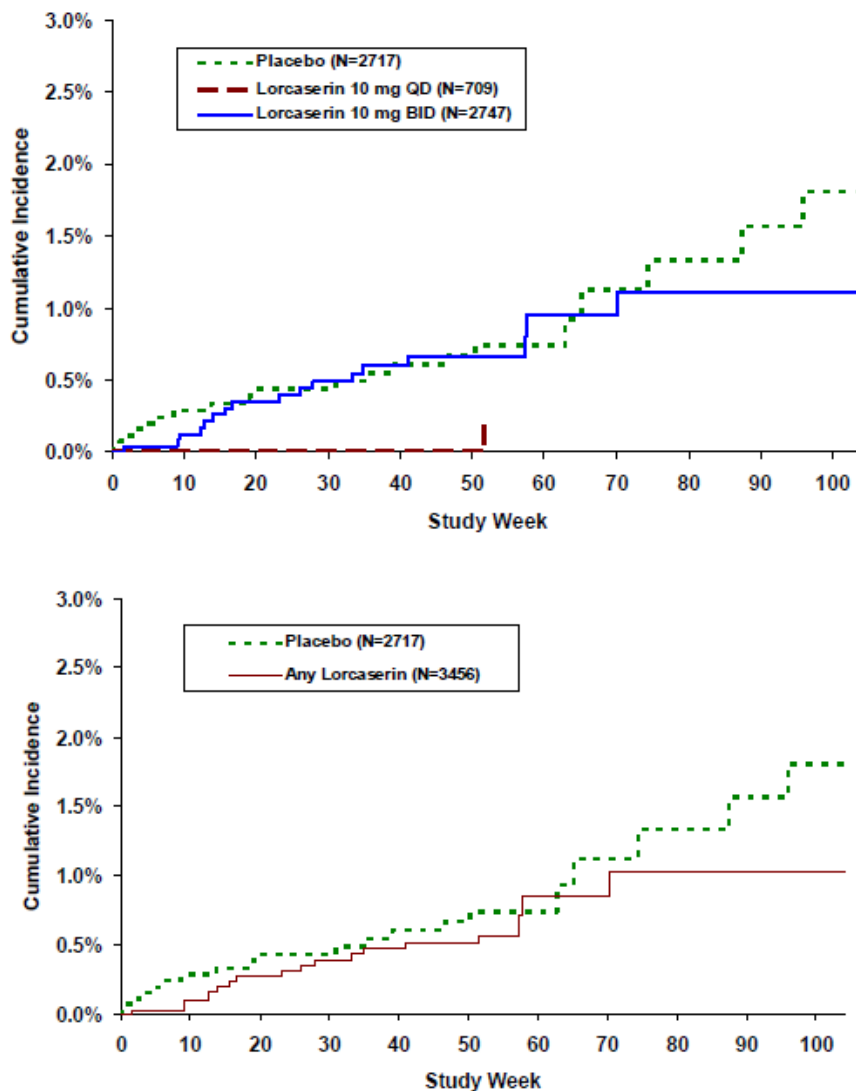
The sponsor also conducted a custom search in which they added the preferred term 'breast mass' to the original SMQ search. These results are presented in Table 126 and Figure 8, below.

Table 126. Analysis of Time to First Event of SMQ 'Breast Neoplasms' + Arena Custom Search 'Breast Mass' in All Women Enrolled in Phase 3 Trials

	Pooled Lorc 10 BID N=2747	Pooled Lorc 10 QD N=709	Any Lorc Dose N=3456	Pooled Pbo N=2717
Total Patient-years	2689	564	3252	2408
No. (%) of patients with event	17 (0.6)	1 (0.1)	18 (0.5)	20 (0.7)
Incidence per 100 patient-years (95% CI)	0.6 (0.4, 1.0)	0.2 (0.0, 1.0)	0.6 (0.3, 0.9)	0.8 (0.5, 1.3)
Hazard ratio (95% CI) relative to placebo	0.76 (0.40, 1.46)	0.26 (0.03, 2.02)	0.44 (0.15, 1.36)	--

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

Figure 8. Kaplan-Meier Plot: Time to First Breast Cancer or Mass Identified by Arena Custom Search during Entire Study, All Women in Phase 3 Studies



Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52	Week 76	Week 104
Pooled Placebo	2717	1863	1288	463	215
Pooled Lorcaserin 10 mg QD	709	550	349	--	--
Pooled Lorcaserin 10 mg BID	2747	2057	1484	580	256
Any Lorcaserin Dose	3456	2608	1834	580	256

Source: NDA 022529 Breast Cancer Report Amendment 2, Figure 2

Prolactin

Prolactin is a polypeptide hormone secreted from the anterior pituitary gland and is negatively regulated by dopamine release from the hypothalamus. Serotonin has been

shown to increase prolactin via a number of receptors, including 5HT_{2C}.⁶⁶ 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.⁶⁷

A comprehensive review of this topic suggests that epidemiological data support a modest association between prolactin concentrations in women and the risk of breast cancer.⁶⁸ 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.⁶⁷ With the exception of oral contraceptives, a relationship between these medications and breast cancer has not been definitely demonstrated to date.⁶⁸ However, studies have generally been limited by short duration and low risk populations. As stated in some antipsychotic drug labels, tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, which could be of importance in a patient with previously detected breast cancer.⁶⁹

Transient increases in plasma prolactin were observed after single-dose lorcaserin administration. Prolactin C_{max} increased approximately 1.5-fold over placebo after 10 mg and 2-fold after 20 and 40 mg doses. Prolactin AUC₀₋₆ increased approximately 1.2-, 1.6-, and 1.4-fold over placebo after lorcaserin 10, 20, and 40 mg dose administration, respectively.

Prolactin results from the BLOSSOM trial were presented in the original NDA submission and summarized for the 2010 advisory committee meeting. The following is an update of these data, incorporating the prolactin results from the BLOOM-DM trial.

In BLOSSOM, blood samples for prolactin measurement were collected from all patients at selected sites (n=20 sites, 1504 patients), constituting approximately 38% of randomized patients. In BLOOM-DM, blood samples for prolactin measurements were collected at all study sites that participated in the trial.

Samples were obtained in the morning prior to administration of study medication and 2 ± 0.5 hours after study drug administration at baseline and at Weeks 4 (BLOSSOM only), and 12, 24 and 52/exit (BLOSSOM + BLOOM-DM). Reproductive status and the

⁶⁶ Freeman ME, et al. Prolactin: structure, function, and regulation of secretion. *Physiol Rev* 2000; 80: 1523-631.

⁶⁷ Haddad PM and Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs* 2004; 64(20): 2291-314.

⁶⁸ Tworoger SS and Hankinson SE. Prolactin and breast cancer etiology: an epidemiologic perspective. *J Mammary Gland Biol Neoplasia* 2008 Mar; 13(1): 41-53.

⁶⁹ Risperdal (NDA 020272) package insert

start date of last menstrual period were documented at each of these visits in female patients. Baseline pre-dose prolactin data were divided into quartiles by subgroup (sex, menopausal status) and treatment group. The baseline characteristics were well-matched and reflected those of the lorcaserin Phase 3 program overall.

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 127. Baseline Prolactin Concentrations (Mean and Range), BLOSSOM Substudy + BLOOM-DM

	Lorc 10 BID N=875	Lorc 10 QD N=373	Pbo N=840
Mean (SD), ng/mL	8.8 (7.09)	8.7 (6.41)	9.0 (9.68)
Range, ng/mL	1.4-87.6	0.3-68.6	1.9-141.0

Source: NDA 022529 Prolactin Study Report, Table 1

At baseline, prolactin concentrations in quartiles were as follows:

Table 128. Baseline Prolactin Concentrations (Quartiles, ng/mL), BLOSSOM Substudy + BLOOM-DM

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Pre/perimenopausal Pbo	≤ 6.00	> 6.00-8.15	> 8.15-11.80	> 11.80
Pre/perimenopausal Lorc 10 QD	≤ 6.30	> 6.30-8.40	> 8.40-11.70	> 11.70
Pre/perimenopausal Lorc 10 BID	≤ 5.80	> 5.80-7.90	> 7.90-11.50	> 11.50
Postmenopausal Pbo	≤ 4.60	> 4.60-6.00	> 6.00-8.10	> 8.10
Postmenopausal Lorc 10 QD	≤ 4.00	> 4.00-5.75	> 5.75-8.30	> 8.30
Postmenopausal Lorc 10 BID	≤ 4.40	> 4.40-5.60	> 5.60-7.70	> 7.70
Men Pbo	≤ 5.20	> 5.20-7.30	> 7.30-10.70	> 10.70
Men Lorc 10 QD	≤ 5.60	> 5.60-7.70	> 7.70-11.40	> 11.40
Men Lorc 10 BID	≤ 5.10	> 5.10-7.30	> 7.30-10.70	> 10.70
Total Pbo	≤ 5.10	> 5.10-7.00	> 7.00-9.80	> 9.80
Total Lorc 10 QD	≤ 5.20	> 5.20-7.00	> 7.00-10.20	> 10.20
Total Lorc 10 BID	≤ 5.10	> 5.10-7.00	> 7.00-9.80	> 9.80

Source: NDA 022529 Prolactin Study Report, Table 34

By contrast, the Nurses' Health Study demonstrated higher quartile cutoffs of prolactin concentrations, with the 4th quartile in particular associated with an increase in risk of breast cancer (Table 129; RR top vs. bottom quartile in an analysis of pooled pre- and postmenopausal women = 1.3, 95% CI 1.1-1.6⁶⁸). It is unclear if the lower baseline prolactin concentrations in the BLOSSOM and BLOOM-DM trials reflect a true prolactin difference in the obese population, a lower baseline breast cancer risk than the general population, or an assay-related difference. Based on a National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool (BCRT) survey⁷⁰ analysis conducted by the

⁷⁰ <http://www.cancer.gov/bcrisktool> Accessed 10 July 2010.

sponsor, the population studied in the lorcaserin Phase 3 trials appears to be representative of the general population for background risk.

Table 129. 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 71 and 72

Lorcaserin was associated with small mean increases in prolactin from pre-dose to post-dose at all time points (Table 130) and the proportion of patients who increased in prolactin quartile from pre- to post-dose increased at all time points (Table 132).

Table 130. Serum Prolactin Baseline Values and Change from Pre- to Post-Dose in Pooled Trials BLOSSOM and BLOOM-DM

Visit	Treatment Group	N	Pre-Dose Mean (SD)	Mean (SD) Δ (post- minus pre-dose)	Min, Max
Day 1	Lorc 10 mg BID	796	8.57 (7.15)	0.24 (3.82)	-57.60, 22.00
	Lorc 10 mg QD	340	8.58 (6.25)	0.16 (3.35)	-15.00, 42.10
	Pbo	760	8.95 (10.03)	-1.17 (4.45)	-86.20, 21.70
Week 12	Lorc 10 mg BID	537	8.76 (6.50)	-0.38 (3.09)	-16.60, 21.00
	Lorc 10 mg QD	225	9.03 (6.63)	-0.53 (4.24)	-27.90, 24.50
	Pbo	494	8.28 (5.98)	-1.21 (3.09)	-30.00, 17.10
Week 24	Lorc 10 mg BID	482	8.49 (6.67)	-0.34 (3.50)	-20.70, 23.60
	Lorc 10 mg QD	214	9.29 (8.71)	-0.43 (3.91)	-34.00, 15.30
	Pbo	441	8.10 (5.94)	-1.15 (3.96)	-55.00, 23.00
Week 52	Lorc 10 mg BID	408	8.87 (7.51)	-0.47 (3.46)	-30.40, 17.10
	Lorc 10 mg QD	181	8.99 (6.77)	-0.67 (3.81)	-28.50, 9.60
	Pbo	357	8.08 (6.74)	-1.16 (4.19)	-62.90, 13.60

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 62

Lorcaserin was also associated with small increases in mean pre-dose prolactin from baseline to post-baseline visits (Table 131). However, lorcaserin was not associated with an increase in the proportion of patients with an increase in prolactin quartile baseline to post-baseline (Table 132).

⁷¹ 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.

⁷² Tworoger SS, et al. Plasma prolactin concentrations and risk of postmenopausal breast cancer. Cancer Res 2004 Sept; 64: 6814.

Table 131. Change from Baseline in the Pre-Dose Prolactin Measurements (ng/mL) by Visit, BLOSSOM Substudy and BLOOM-DM

Visit	Treatment	N	BL Pre-Dose Mean (SD)	Visit Pre-Dose Mean (SD)	Change from BL in Pre-Dose		
					Mean (SD)	Median	Min, Max
Week 12	Lorc 10 BID	599	8.33 (6.50)	8.97 (6.40)	0.64 (4.02)	0.50	-26.50, 19.50
	Lorc 10 QD	250	8.29 (6.43)	8.89 (6.43)	0.60 (4.07)	0.40	-20.80, 19.40
	Pbo	555	8.30 (7.56)	8.32 (5.76)	0.02 (6.97)	0.10	-112.70, 33.90
Week 24	Lorc 10 BID	503	8.10 (6.39)	8.59 (6.62)	0.49 (4.43)	0.20	-25.20, 24.20
	Lorc 10 QD	217	8.48 (6.82)	9.13 (8.62)	0.65 (4.70)	0.30	-27.50, 33.40
	Pbo	450	8.43 (8.64)	8.29 (6.72)	-0.15 (7.85)	0.00	-109.10, 62.80
Week 52	Lorc 10 BID	413	7.95 (6.27)	8.85 (7.37)	0.90 (5.29)	0.50	-26.30, 51.40
	Lorc 10 QD	181	8.11 (5.27)	9.03 (6.82)	0.91 (4.90)	0.30	-26.10, 23.20
	Pbo	377	8.30 (8.60)	8.10 (6.69)	-0.19 (8.75)	0.00	-112.80, 62.60

Source: NDA 022529 Prolactin Study Report, Table 16

Table 132. Percent of Patients with Increase in Prolactin Quartile, BLOSSOM Substudy + BLOOM-DM

		Pre- to Post-Dose			Baseline to Post-Baseline		
		Lorc 10 BID	Lorc 10 QD	Pbo	Lorc 10 BID	Lorc 10 QD	Pbo
Baseline	Pre/perimenopausal	27.6	27.3	7.5	-	-	-
	Postmenopausal	27.0	25.6	9.0	-	-	-
	Men	22.8	25.0	11.7	-	-	-
	Total	21.6	19.4	8.0	-	-	-
Week 12	Pre/perimenopausal	34.0	30.4	14.3	24.0	26.1	21.2
	Postmenopausal	24.1	21.7	14.8	26.0	18.1	26.2
	Men	22.7	46.4	24.7	23.9	31.1	25.3
	Total	27.8	28.0	17.8	29.4	26.4	26.5
Week 24	Pre/perimenopausal	33.9	33.9	25.7	25.0	23.4	25.9
	Postmenopausal	26.6	18.3	14.5	27.6	16.4	22.7
	Men	19.9	35.3	18.8	24.5	35.8	27.5
	Total	25.2	23.7	17.8	29.8	20.7	30.2
Week 52	Pre/perimenopausal	30.4	33.3	19.2	32.7	24.1	25.0
	Postmenopausal	32.6	22.6	14.6	33.6	17.5	22.9
	Men	24.1	30.4	12.3	29.4	27.7	27.3
	Total	30.7	25.0	16.3	33.7	28.7	30.5

Source: NDA 022529, Prolactin Study Report, Tables 5 and 6

Finally, an outlier analysis was conducted to determine if there was an imbalance of the number of patients with especially high values of prolactin that could be considered clinically meaningful. As Table 133 demonstrates, the proportion of patients in any treatment group with prolactin values greater than the upper limit of normal was small.

At Week 52 there was a slightly increased proportion of patents treated with lorcaserin with prolactin values > ULN, > 2x ULN, and visit pre-dose > 2x baseline pre-dose values. No lorcaserin-treated patient was found to have prolactin values > 10x ULN.

Table 133. Proportion of patients with Prolactin Outlier Values by Visit in Pooled Trials, BLOSSOM and BLOOM-DM

Visit	Prolactin Change Criterion	Lorc 10 mg BID	Lorc 10 mg QD	Pbo
Day 1 (Baseline)	Pre-dose > ULN	3.3%	2.4%	2.9%
	Pre-dose > 2x ULN	0.8%	0.5%	1.0%
	Pre-dose > 5x ULN	0.1%	0	0.1%
	Pre-dose > 10x ULN	0	0	0
	Pre- to post-dose Δ > 2x pre-dose	0.5%	0.3%	0.1%
	Pre- to post-dose Δ > 5x pre-dose	0	0.3%	0
	Pre- to post-dose Δ > 10x pre-dose	0	0	0
Week 12	Pre-dose > ULN	3.0%	3.9%	1.9%
	Pre-dose > 2x ULN	0.8%	0.4%	0.2%
	Pre-dose > 5x ULN	0	0	0
	Pre- to post-dose Δ > 2x pre-dose	0.4%	0.9%	0.2%
	Pre- to post-dose Δ > 5x pre-dose	0.2%	0	0
	Pre- to post-dose Δ > 10x pre-dose	0	0	0
	Pre-dose > 2x baseline pre-dose	0.7%	0.8%	1.1%
	Pre-dose > 5x baseline pre-dose	0.2%	0	0.2%
	Pre-dose > 10x baseline pre-dose	0	0	0
Week 24	Pre-dose > ULN	2.8%	3.4%	3.1%
	Pre-dose > 2x ULN	0.8%	0.4%	0.6%
	Pre-dose > 5x ULN	0	0	0
	Pre- to post-dose Δ > 2x pre-dose	1.2%	0.5%	0.5%
	Pre- to post-dose Δ > 5x pre-dose	0	0	0
	Pre-dose > 2x baseline pre-dose	1.4%	0.5%	1.3%
	Pre-dose > 5x baseline pre-dose	0.2%	0	0.2%
	Pre-dose > 10x baseline pre-dose	0	0	0.2%
Week 52	Pre-dose > ULN	3.7%	2.9%	1.9%
	Pre-dose > 2x ULN	1.3%	0	0.5%
	Pre-dose > 5x ULN	0	0	0
	Pre- to post-dose Δ > 2x pre-dose	0.5%	0	0.3%
	Pre- to post-dose Δ > 5x pre-dose	0	0	0.3%
	Pre- to post-dose Δ > 10x pre-dose	0	0	0.3%
	Pre-dose > 2x baseline pre-dose	2.4%	2.2%	0.5%
	Pre-dose > 5x baseline pre-dose	0	0	0

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 64

Adverse events that could potentially be associated with hyperprolactinemia are presented in the table below.

Table 134. Adverse Events that Could be Related to Hyperprolactinemia, Phase 3 Trials

	BLOOM		BLOSSOM		BLOOM-DM	
	Lorc 10 BID N=1593	Pbo N=1584	Lorc 10 BID N=1602	Pbo N=1601	Lorc 10 BID N=256	Pbo N=252
Galactorrhea	1 (0.1)	0	0	0	0	0
Gynecomastia	0	0	0	1 (0.1)	0	0
Amenorrhea	4 (0.3)	4 (0.3)	1 (0.1)	1 (0.1)	0	0
Oligomenorrhea	0	0	0	1 (0.1)	0	0
Hypomenorrhea	0	0	1 (0.1)	1 (0.1)	0	0
Erectile dysfunction	3 (0.2)	1 (0.1)	3 (0.2)	1 (0.1)	1 (0.4)	0
Infertility	0	0	0	0	0	0
Libido decreased	7 (0.4)	6 (0.4)	5 (0.3)	3 (0.2)	1 (0.4)	0
Libido disorder	0	0	0	0	0	0
Male sexual dysfunction	0	0	1 (0.1)	0	0	0
Female sexual dysfunction	0	0	0	0	0	0
Hypogonadism	0	0	0	0	0	0
Hyperprolactinemia	0	0	0	0	0	0
Prolactin increased	0	0	4 (0.2)	3 (0.2)	1 (0.4)	0
Other related terms						
Ejaculation delayed	0	0	0	0	0	0
Ejaculation failure	0	0	1 (0.1)	0	0	0
Anorgasmia (female)	0	0	1 (0.1)	0	0	0
Orgasm abnormal	0	1 (0.1)	0	0	0	
Disturbance in sexual arousal	1 (0.1)	0	0	0	0	0

Source: NDA 022529 Summary of Clinical Safety (resubmission), Table 30

The one patient (181-S001, lorcaserin 10 mg BID, BLOOM trial) who had an adverse event of 'galactorrhea' also had a prolactinoma diagnosed during the trial.

- Patient 181-S001 was a 45 year old female in the BLOOM trial who was screened on 16 October 2006 and randomized to lorcaserin 10 mg BID on 08 November 2006. She had a medical history of hypothyroidism, hypertension, dyslipidemia, seasonal allergies, and menorrhagia (5 year history). The following is a summary of relevant events for this patient:
 - (b) (6): Hysterectomy for menorrhagia. Prolactin 90 ng/mL. Reported galactorrhea (duration not specified), and an MRI showed evidence of a 5 mm microadenoma.
 - October 2007: Started bromocriptine.
 - February 2008: Changed to cabergoline due to poor toleration of bromocriptine.
 - (b) (6) Patient was evaluated by neurosurgeon; continued suppressive therapy with cabergoline; prolactin 51 ng/mL.
 - (b) (6): Patient remained symptomatic despite cabergoline and surgery was performed. Tissue diagnosis: pituitary adenoma. Signs and symptoms resolved post-operatively.

The symptom of galactorrhea was first recorded in February 2007, three months after beginning lorcaserin. The study site apparently informed Dr. Christen Anderson of Arena (no longer with the company) that in retrospect, the galactorrhea preceded enrollment to the study, but the site never provided documentation. Presently, due to closure of the site, this information cannot be confirmed. The primary investigator judged the prolactinoma to be not-related to study drug.

In the BLOOM-DM trial, there were two prolactin-adverse adverse events in the lorcaserin 10 mg QD arm that was not included in the table above: one patient with an adverse event of 'hypogonadism' and one patient with an adverse event of 'libido decreased'.

There was one adverse event of increased prolactin in the BLOOM-DM trial. Patient 1160-S012 was a 47-year-old black female with an adverse event of 'blood prolactin increased' treated with lorcaserin 10 mg BID. The event was asymptomatic and resolved spontaneously. No action was reported in response to this adverse event. Her laboratory values were as follows:

Table 135. Serum Prolactin Concentrations in Patient 1160-S012 with Adverse Event of 'Blood Prolactin Increased'

	Baseline	Week 12*	Unscheduled	Week 24	Week 52
Pre-dose prolactin (ng/mL)	24	35.6	13.5	8.6	19.5
Post-dose prolactin (ng/mL)	32.7	40.3	-	9.2	20.1
* Adverse event reported					

Source: NDA 022529 Response to FDA Request of 31 January 2012, Table 2

Relevant prolactin data were not acquired at the time of diagnosis for any of the patients diagnosed with breast cancer during the study (Table 124). Two of these patients had prolactin concentrations collected at other times during the BLOSSOM substudy (2203-S032 and 2141-S039); all values were within normal limits.

Cerebrospinal Fluid Concentrations and Safety Margin Calculations

In a carcinogenicity study in rats, astrocytoma was noted. As lorcaserin targets the central nervous system and brain concentrations in humans are unknown, it was of obvious concern that safety margins for this finding might be lower than what might be apparent from plasma concentrations.

Because a more consistent relationship was seen between cerebrospinal fluid (CSF) and brain concentrations of lorcaserin across species (rats and monkeys) versus the variable plasma:brain ratio in these species, it was thought that a more reliable estimation of brain drug concentrations in humans could be made based on measured CSF concentrations of lorcaserin. See section 4.4.3 for the human CSF PK data.

Non-clinical brain:CSF ratios were used to project human brain exposure, and brain exposure ratios were calculated. At the 10 mg/kg/day (no astrocytoma seen) and 30 mg/kg/day (astrocytoma seen) doses used in the two-year male rat carcinogenicity study, brain exposure margins relative to human brain at the maximum recommended dose were greater than or equal to 70 and 360, respectively. In the female rat, where astrocytoma was not increased even at the 100 mg/kg/day dose, the exposure margin was calculated to be > 1000.

7.6.2 Human Reproduction and Pregnancy Data

This section is unchanged from the original clinical review. No patients assigned to lorcaserin reported pregnancy during BLOOM-DM.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable. Lorcaserin has not been studied in individuals under the age of 18.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The mechanism of action of lorcaserin is identical to that of Schedule I hallucinogens (5HT_{2C} and 2A agonism). This issue was addressed in the original NDA review, and there are no new clinical findings to report regarding abuse potential (e.g., no euphoria was seen in the new clinical trials). The sponsor did submit two new nonclinical studies for review by the controlled substance staff (CSS). CSS has concluded that lorcaserin has abuse potential most similar to that of zolpidem (Schedule IV), and therefore, lorcaserin will be recommended for placement in Schedule IV of the Controlled Substances Act.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Not applicable. Lorcaserin has not been marketed in any country.

9 Appendices

9.1 Literature Review/References

Referenced literature is cited in the body of the review.

9.2 Labeling Recommendations

The label will be reviewed separately.

9.3 Advisory Committee Meeting

The Endocrinologic and Metabolic Advisory Committee meeting was held in Silver Spring, MD on May 10, 2012. The committee voted 18 to 4 (with 1 abstention) that the benefits of lorcaserin treatment outweigh its risks.

A summary of the discussion follows:

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

The committee agreed that there is an increase in mammary tumors both in females and males. There was some discussion regarding combining the fibroadenoma with the adenocarcinoma in the rats for the purposes of assessing human risk. Dr. Malarkey noted that the appropriateness of combining the fibroadenomas with the adenocarcinomas was unclear, and would be based on the site of origin of the tumor. Dr. McConnell and Dr. Hendricks agreed that it made sense not to combine fibroadenomas and adenocarcinomas in this case, and Dr. Hendricks thought the findings of the Pathology Working Group should be considered definitive.

- b. The potential clinical risk associated with lorcaserin-induced mammary adenocarcinoma in rats (e.g., a sufficient safety margin).

The committee agreed that adenocarcinomas are more concerning than fibroadenomas in the rat, and in general agreed that there is a sufficient safety margin for the drug when it is used at the concentrations intended for patients. However, it does fall below the relative risk of 25 times (i.e., 24 times), which has been considered a cut-off for acceptable risk in FDA guidance. The fact that the drug is not genotoxic was reassuring to the panel members. There was some concern that there may be an as-of-yet undefined vulnerable patient population who are more likely to develop a tumor due to lorcaserin.

- c. The mechanism of action (e.g., prolactin increase) for the mammary tumors observed in rats.

The committee for the most part agreed that the prolactin hypothesis was still just that, and while it may contribute to the tumors in rats, there are a multitude of potential mechanisms and prolactin may not be the major one. There remains a significant question about possible other growth promoting mechanisms in that tissue.

Dr. Bessesen commented that weight loss in and of itself may reduce the risk of cancer.

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

In general, the committee felt that the sponsor provided sufficient information related to the clinical risk associated with lorcaserin-induced astrocytomas in rats (i.e., CSF exposure in humans). Although it was reassuring that these tumors were only seen in one specie and one sex, a caveat is that the female rats (fewer astrocytomas) had toxicity and died for other reasons, such as the adenocarcinomas of the breast.

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

Committee members felt that despite the comprehensive echocardiographic evaluation in the Phase 3 program, there are probably not sufficient data at this time to rule out a clinically meaningful increase in the risk for valvular heart disease. There was some concern (Dr. Nelson) that lorcaserin had not been adequately studied with other serotonergic agents and therefore the impact on valvular disease in “the real world” was unknown. Nevertheless, most panel members felt that further assessment could be accomplished post-approval. Some of the members of the panel (including Dr. Connolly) felt that patients should have an echocardiogram done as part of the initiation of therapy and potentially be followed with echocardiography long-term. Dr. Goldfine thought that it was important for patients who did not benefit from the drug to be taken off it, since duration of use may impact the risk for valvular heart disease.

- 4) Taking into account the March 28 and 29, 2012 Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting on cardiovascular risk assessment of obesity drugs, discuss the available data to assess for excess risk for major adverse cardiovascular events in patients treated with lorcaserin.

The committee agreed that the available data are not adequate to make a full assessment regarding cardiovascular risk. In this low risk population, there were too few events in the Phase 3 program leading to a wide confidence interval. Nevertheless, the point estimate for MACE is actually reassuring. Furthermore, in this program, heart rate and blood pressure stayed the same or improved, which was also reassuring. The committee members agreed that should be a cardiovascular outcomes trial and most felt it should be conducted post-approval.

- 5) Do the available data demonstrate that the potential benefits of lorcaserin outweigh the potential risks when used long-term in a population of overweight and obese individuals?
- If you voted 'Yes' to question #5, please provide your rationale and comment on the need for and approach to patient monitoring and risk management.
 - If you voted 'No' to question #5, please provide your rationale and comment on what additional preclinical or clinical information should be required to potentially support approval.

Vote: 18 'yes', 4 'no', 1 'abstain'

The following are the members' votes with comments and recommendations summarized in bullet points:

William Hiatt – yes

- Non-clinical concerns around malignancies: risks have been defined and could be monitored post-marketing
- VHD: REMS program
- MACE: cardiovascular outcomes trial
- Modest efficacy: "I would hope that in that in the context of cardiovascular outcomes trial we'd learn whether that benefit is there or not beyond a net 3 percent weight loss"

Allison Goldfine – yes

- Non-clinical: no more can be done in the preapproval setting; will warrant monitoring
- VHD: cannot be evaluated further, given the intensive and extensive echocardiographic analysis that was already done

- MACE: post-approval CVOT

Sanjay Kaul – no

- Cancer and neuropsychiatric adverse events: no major concerns
- MACE: insufficient data to adjudicate cardiovascular risk, needs another trial in higher risk patients
- VHD: still a lingering uncertainty, needs more study
- Modest efficacy: not clear if mean placebo-subtracted weight loss of 3 percent is clinically meaningful

Daniel Bessesen – yes

- Concerned about lack of treatment options for obesity
- VHD: small signal, needs further study, clinical monitoring should be left up to providers

Jeanmarie Perrone – no

- Primary concern is serotonergic effects, potentially related to VHD and especially because lorcaserin has not been studied with other serotonergic drugs such as SSRIs

Eric Felner – yes

- VHD: frequent clinic monitoring (every 2-3 months) with echocardiogram at least 2-3 times a year

David Capuzzi – no

- Wants to see a CVOT

Lamont Weide – yes

- REMS: if the drug doesn't show meaningful weight loss by three months, it should be stopped
- VHD: monitor with echocardiography
- MACE: CVOT
- Lingering questions can be answered post-approval

Ida Spruill – yes

- Favors patient education

Abraham Thomas – yes

- Needs CVOT with echocardiography
- VHD: Until the definitive trial is done to show that it doesn't increase valvulopathy, everyone should get an echocardiogram at the beginning of treatment

- Clinicians and patients need to be aware of the VHD and CV uncertainty, as well as potential interaction with other serotonergic agents

Vera Bittner – yes

- Should not expect a single obesity agent to cure obesity
- Wants a post-marketing CVOT; perhaps with design to discontinue patients who have not lost certain amount of weight in the first three months

Erica Brittain – yes

- Placebo-controlled trial post-approval

Edward Gregg – yes

- CVOT, but also a trial to look at disability, QoL, sleep, diabetes incidence, etc., with good follow-up

Angelica Walden – yes

- Questions can be answered post-marketing

David Malarkey – yes

- Multiple tumors in multiple sites at high doses, but acceptable margin of safety and perhaps a prolactin mode-of-action
- Monitor VHD and cancer outcomes

Ed Hendricks – yes

- Enough responders that it could provide benefit to a substantial number of patients; prevention of weight gain might be beneficial
- Will be prescribed with phentermine, he is “sure” that we will see clinical trials being done with this combination
- Post-marketing CVOT – look for CV benefits
- REMS – not worried that patients will continue the drug if no benefit; focus on a REMS that’s educational and not overly onerous

Katherine Flegal – yes

- Surveillance and examining what the health benefits and adverse effects of the drug

McConnell – abstain (if had to choose between yes and no, would have chosen yes)

- Clear carcinogen, but notes the concept of “margin of safety”
- Not that impressed with weight loss and concerned that two years of data not enough for a long-term exposure

Robert Smith – yes

- Post-marketing CVOT
- VHD: post-marketing strategies to assess risk
- Concerns regarding the potential for producing tumors/growth-promoting effects that should be addressed post-marketing
- Post-marketing assessment of psychiatric effects

Peter Gross – yes

- Signals not strong enough to warrant a risk management program
- VHD: don't get echocardiograms on everyone, would like prospective observational study

Jack Yanovski – yes

- CVOT with evaluation for valvulopathy, neuropsychiatric effects, and breast tumors to be designed and approved prior to approval of the drug
- Longer, perhaps open-label trial
- State-of-the-art behavioral modification to target 5-10% weight loss in control group
- Study in patients with BMI > 45
- Study in adolescents
- Further animal studies to rule in or out [prolactin] hypothesis
- VHD: echocardiograms at baseline and at least once a year
- Warnings regarding VHD, breast abnormalities and risk of cancer

Heidi Connolly – yes

- CV testing post-marketing
- Clinical monitoring: assessment of CV risk factors, screening for VHD (both as part of a study and clinically – at baseline and annually thereafter)

Lewis Nelson – no

- Concerned about its use without diet and exercise, in less healthy people, for other indications, and with serotonergic (or amphetaminergic, catecholaminergic, etc.) drugs
- Only in infancy in understanding serotonergic receptor system; wary of extrapolating receptor-level data
- REMS with ETASU: echocardiography, prescriber training, patient education, better surveillance program (looking for cancer)

9.4 BLOOM-DM Study Design

Objectives

Primary

- To assess the weight loss effect of lorcaserin during one year of treatment

Secondary

- To assess the ongoing safety of lorcaserin
- To assess changes in glycemic control during one year of lorcaserin treatment
- To assess changes in body composition between Baseline and Week 52
- To assess changes in cardiovascular risk factors associated with obesity (i.e., dyslipidemia, hypertension) between Baseline and Week 52
- To assess echocardiographically-determined heart valve regurgitant scores and pulmonary artery pressure changes during one year of lorcaserin treatment
- To assess changes in Quality of Life measures during one year of lorcaserin treatment
- To assess population pharmacokinetics of lorcaserin

Design

This was a randomized, double-blind, placebo-controlled clinical trial of one year duration. Approximately 750 patients were originally planned for enrollment into the study, randomized in a 1:1:1 ratio to placebo, lorcaserin 10 mg QD or lorcaserin 10 mg BID. Due to slow enrollment, the total enrollment target was reduced to 600 by discontinuing randomization to the low dose group. After the implementation of protocol Amendment 3, patients were randomized in a 1:1 ratio to placebo or lorcaserin 10 mg BID. Patients randomized into the lorcaserin 10 mg QD group prior to the implementation of Amendment 3 remained enrolled in the trial to complete all planned study procedures.

Each patient completed screening procedures within six weeks of dosing on Day 1. Eligible patients were randomized to receive study medication for 52 weeks, with periodic follow-up visits to assess efficacy and safety parameters.

Randomization was stratified by:

- HbA1c: < 9% and ≥ 9%
- Medication used to treat diabetes: patients taking a sulfonylurea (alone or in combination) or patients taking metformin (alone or in combination). Patients taking both metformin and a sulfonylurea were included in the sulfonylurea group.

Patients were required to participate in the Arena Healthy Lifestyle Program® diet and exercise program. The prescribed diet consisted of approximately 600 calories less per day than the patient's calculated Estimated Energy Requirement (EER). The EER was calculated using WHO criteria with a fixed activity factor of 1.3 for most patients; however, for patients who engage in ≥ 1 hour /day aerobic exercise, an activity factor of 1.4 was used.

With respect to adjustment of medications for the treatment of diabetes:

- The increase or addition of anti-hyperglycemic medications was not recommended prior to the Week 12 visit because weight loss could obviate the need for increased medication.
- It was recommended that anti-hyperglycemic medication dose be reduced in the event of one documented and otherwise unexplained hypoglycemic event [blood glucose (BG) < 65 mg/dL] or two undocumented and otherwise unexplained suspected hypoglycemic events between two scheduled visits. For patients on more than one anti-hyperglycemic medication, the recommended order in which to reduce medication dose was:
 - Decrease/discontinue sulfonylurea
 - Decrease/discontinue anti-hyperglycemic medications other than metformin (e.g., TZD, DPP-IV inhibitor, metiglinide)
 - Decrease/discontinue metformin
- If the majority of fasting plasma glucose (FPG) self-monitoring readings for a patient were ≥ 10 mg/dL at the 12-week or subsequent study visit, or several self-monitored fasting BG measurements between scheduled visits at 12 weeks or later were > 240 mg/dL, increasing the anti-hyperglycemic medication dose was considered, in the following order:
 - If on a single agent, increase the dose of that agent
 - If on more than one agent:
 - Increase metformin to maximum tolerated or recommended dose
 - Increase or add another agent (TZD, DPP-IV inhibitor, etc.)
- Any patient with (1) HbA1c increase of $\geq 1.5\%$ from baseline at any scheduled measurement, or (2) HbA1c $\geq 11\%$ at any scheduled measurement, or (3) FPG > 270 mg/dL on two consecutive study visits was withdrawn from the study and referred to his/her primary care physician for management of uncontrolled diabetes.
- To avoid confounding effects on weight:
 - Patients must not have initiated use of insulin in any form during the study

- Patients must not have initiated use of exenatide or pramlintide during the study

Other concomitant medication guidelines/restrictions included the following:

- Medications for the treatment of hypertension may have been started, discontinued or adjusted during the study if, in the judgment of the PI or the patient's physician, such a change was medically indicated
- Medications for the treatment of dyslipidemia may have been started, discontinued or adjusted during the study if, in the judgment of the PI or the patient's physician, such a change was medically indicated
- Patients must not have initiated use of prescription weight loss drugs (e.g., phentermine, sibutramine, orlistat) or OTC medication (including herbal supplements) for the treatment of obesity for the duration of the study
- Patients must not have initiated the use of topiramate at any time during the study
- Patients must not have initiated use of agents that have documented correlation with increased incidence of valvulopathy and/or pulmonary hypertension (e.g., cyproheptadine, trazodone, nefazodone, amoxapine, tricyclic antidepressants, mirtazapine, pergolide, ergotamine, methysergide) during the study
- Patients must not have initiated use of prescribed medication for the treatment of depression, anxiety, or other psychiatric disease (e.g., bupropion, SSRIs, SNRIs, tricyclics, MAOIs) during the study
- Patients must not have initiated the use of prescribed SSRIs, SNRIs or bupropion for treatment of other indications (e.g., migraine, weight loss, smoking cessation) during the study
- Patients must not have initiated use of St. John's Wort during the study

Investigational product dispensed was recorded on the Drug Accountability Form. Patients were instructed to bring their study drug (blister cards) with them to each visit. Compliance was assessed by the number of remaining tablets. Patients were instructed not take more than the prescribed amount of one tablet in the morning and one tablet in the evening. If a dose was missed, this was recorded in the CRF as part of the compliance assessment. Continued noncompliance (< 80%) was a valid reason for removal from the study.

Table 136. Schedule of Events

Evaluation	Screening ^a	Randomization	Dosing Period (Study Week)														F/U
	-42 to -1	Day 1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/Exit ^b	56
Informed Consent	X																
Medical History	X	X ^c															
Physical Exam	X	X ^c		X					X							X	
BDI-II	X			X					X							X	
Binge Eating Scale	X																
Echocardiogram	X ^d								X							X	
12-Lead ECG	X															X	
Clinical Labs	X	X		X		X			X			X				X	
Drugs of Abuse Screen	X																
Thyroid Function Tests (T4, TSH)	X															X	
Hemoglobin A1c	X	X				X			X			X				X	
Fasting Insulin, CRP		X	X						X							X	
Prolactin ^e		X				X			X							X	
Pregnancy Test ^f	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Virology Screen (HIV, Hep C, and HBsAg)	X																
Vital Signs ^g	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Waist and Hip Circumference ^h		X							X							X	
DEXA ⁱ		X							X							X	
PK Blood Collection						X			X							X	
Quality of Life Assessment		X							X							X	
Diet and Exercise Counseling		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Compliance Check			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication Assessments		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IVRS Call ^j		X				X			X			X			X	X	
Drug Administration ^k																	
Adverse Event Monitoring																	

a All screening activities are to be completed within 42 days, or sooner, prior to dosing on Day 1.

b At the completion of the study or upon early termination from the study, all procedures should be performed as indicated. For patients who prematurely

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Golden, J.
NDA 022529
Belviq (lorcaserin hydrochloride)

Evaluation	Screening ^a	Randomization	Dosing Period (Study Week)														F/U
	-42 to -1	Day 1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/Exit ^b	56
<p>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.</p> <p>c Partial examination and medical history to update findings from that performed at screening.</p> <p>d Baseline echocardiogram must be acquired before randomization; randomization may occur as soon as echo core lab determines that the echo is technically adequate; interpretation need not be completed prior to randomization.</p> <p>e Blood samples for prolactin measurement will be collected prior to administration of study medication and 2 ± 0.5 hours after study drug administration.</p> <p>f Serum hCG pregnancy test required at Screening and Week 52/Exit. Urine pregnancy test will be done at other study visits as indicated.</p> <p>g 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 hours after the first dose. Height will be measured at screening only.</p> <p>h Hip and waist circumference to be measured in triplicate. Final result will be the average of the 3 measurements.</p> <p>i DEXA scan to be performed Day 1/Randomization (+ 2 weeks), Week 24 (± 2 weeks), and Week 52/Exit (± 2 weeks) at designated sites.</p> <p>j Sites will call the IVRS at Day 1 and Weeks 12, 24, 36, and 48. The IVRS will be used to track each patient's progress through the study to ensure that adequate drug supply is at the site. In addition, sites will call the IVRS at Screening and study completion or early termination.</p> <p>k Randomized patients will be instructed to administer one dose in the morning (about 60 minutes prior to breakfast) and one dose in the evening (about 60 minutes prior to dinner).</p>																	

Source: NDA 022529 BLOOM-DM CSR, Table 4

Patient Population

Inclusion Criteria

- Male or female, 18 - 65 years
- Ambulatory and able to perform exercise program
- Non-pregnant, non-lactating, non childbearing potential or used an accepted method of birth control (females)
- Surgically sterile or used an accepted method of birth control (males)
- BMI 27 - 45 kg/m²
- Type 2 diabetes mellitus
- Treated with metformin, sulfonylurea, or either agent in combination with other oral medications (e.g., TZDs, DPP-IV inhibitors, metiglinides, or acarbose) at a stable dose (TZD had to be stable for at least 6 months, for all other medications, 3 months)
- HbA1c 7 - 10%
- Fasting glucose ≤ 240 mg/dL
- No history of ketoacidosis or hypoglycemic unawareness
- Considered to be in stable health in the opinion of the Investigator

Exclusion Criteria

- Prior participation in any study of lorcaserin
- Clinically significant new illness in past month
- Not suitable to participate in the study in the opinion of the Investigator
- Recent history (within one year before entering the study) of major depression, anxiety, or other psychiatric disease requiring treatment with prescription medication
- Beck Depression Inventory-II (BDI-II) total score ≥ 20 or > 0 on Question 9 (pertaining to suicidal thoughts)
- History of a binge eating disorder (score >17 on the Binge Eating Scale)
- History of seizure disorder
- Surgical treatment of obesity
- Uncontrolled hypertension (≥ 150/95 on two different days)
- History of any of the following cardiovascular conditions:
- Valve replacement surgery
- Myocardial infarction (MI), cerebrovascular accident (CVA), transient ischemic attack (TIA), or reversible ischemic neurological deficit (RIND) within six months of screening; cardiac arrhythmia requiring medical or surgical treatment within six months of screening
- Unstable angina
- History of congestive heart failure caused by insufficiency, damage, or stenosis of any heart valve
- History of pulmonary artery hypertension
- History of organ transplantation

- TSH > 1.5x ULN
- Hyperthyroidism, T4 > ULN, TSH < LLN, taking methimazole or PTU and/or beta-blockers for hyperthyroidism
- AST or ALT > 2.5x ULN or total bilirubin > 1.5x ULN
- Serum creatinine > 1.5x ULN
- Fasting triglycerides > 499 mg/dL on two days
- LDL-cholesterol \geq 160 mg/dL
- Positive HIV, hepatitis B, or hepatitis C screens
- Malignancy within five years of the screening visit (except basal cell or squamous cell carcinoma with clean surgical margins)
- Use of insulin within three months
- Use of exenatide (Byetta) or pramlintide (Symlin) within three months
- Use of one or more of the following:
 - fenfluramine or related derivatives (i.e., dexfenfluramine, norfenfluramine) agents that have documented correlation with increased incidence of valvulopathy and/or primary pulmonary hypertension (e.g., cyproheptadine, trazodone, nefazodone, amoxapine, mirtazapine, pergolide, ergotamine, methysergide)
- Recent over-the-counter weight loss products, appetite suppressants, or prescription anti-obesity drugs
- Recent history of alcohol or drug abuse
- Significant change in smoking habits
- Change in weight of > 5 kg within three months of screening
- Use of very-low calorie liquid weight loss diet within six months
- Recent major surgical procedure

Treatment Groups

Prior to the implementation of Amendment 3, treatment groups were as follows:
lorcaserin 10 mg QD: lorcaserin 10 mg BID: placebo; 1:1:1

After implementation of Amendment 3, randomization changed to:
lorcaserin 10 mg BID: placebo; 1:1

Endpoints

Efficacy Measurements

Body Weight

Each patient was weighed throughout the study at designated times to assess changes in body weight. All efforts were made to schedule study visits prior to 10:00 AM to capture the fasting body weight and to reduce the variability in body weight normally observed throughout the day. All weights were measured in kilograms (kg). Patients

were weighed at each study visit using a digital scale provided by Arena, or by a similar scale already at the site as approved by Arena. All scales met NTEP standards, had a precision to the nearest 100 g, and were approved for providing certifiable weights.

Waist and Hip Measurements

For a given patient, all attempts were made to have the same site personnel measure the waist and hips throughout the study to avoid variability in the method of measurement. Waist measurements were done according to the NHLBI Guideline in the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (September 1998). Hip measurements were performed using a tape measure to comfortably measure the distance around the largest extension of the buttocks. All measurements were reported in centimeters (cm). Each measurement was made and recorded 3 times at baseline, Week 24, and Week 52; the average of the 3 values at each time point was reported.

Changes in Use of Oral Hypoglycemic Medications

Changes in the use of hypoglycemic medications at each visit were recorded as follows:

- Start new hypoglycemic medication
- Increase dose of existing hypoglycemic medication
- No change
- Decrease dose of existing hypoglycemic medication
- Discontinue hypoglycemic medication

Body Composition

Body composition, including total body fat mass and total body lean mass was determined using Dual Energy X-ray Absorptiometry (DEXA) in a subset of randomized patients at selected Radiant Research, Inc. sites. BioClinica, Inc. (formerly Bio-Imaging Technologies, Inc.) of Newtown, PA provided all administration and project management services for DEXA scanning. This included site and image data management services, as well as site training and certification.

DEXA scans were performed on baseline (+ 2 weeks), Week 24 (\pm 2 weeks), and Week 52/Exit (\pm 2 weeks).

Quality of Life Assessment

The Impact of Weight on Quality of Life-Lite® (IWQOL-Lite) is a 31-item self-report measure of obesity-specific quality of life. The IWQOL-Lite provides an overall total score as well as scores on five domains: 1) physical function, 2) self esteem, 3) sexual life, 4) public distress, and 5) work.

The assessments were given at Day 1, Week 24, and Week 52 visits.

Metabolic Parameters and Markers of Cardiovascular Risk

Plasma lipids (total cholesterol, LDL-C, HDL-C, triglycerides, apolipoprotein B, apolipoprotein A1), hemoglobin A1c, and change in blood pressure (systolic and diastolic) were measured periodically during the study.

Pharmacokinetic Parameters

Blood samples were collected at Week 12, Week 24 and Week 52 for assessment of lorcaserin concentrations for use in the population pharmacokinetic analysis. Blood samples were collected at three time points during each of the three visits: 15 minutes prior to study drug administration, 1.5-2.5 hours post-dose, and 3.5-6 hours post-dose.

Safety Measurements

- Vital signs: blood pressure, heart rate, oral temperature
- Clinical laboratory tests: serum chemistry, hematology, urinalysis, virology screens, drugs of abuse screens, urine pregnancy testing
- Physical and neurological examination
- 12-lead electrocardiograms (ECGs) were performed at Screening and Week 52/Exit and sent to a central reading laboratory for evaluation
- Adverse events
- Glycemic monitoring: Patients were asked to perform glucose self-monitoring at least twice daily and in the event of a suspected hypoglycemic event. Patients were asked to call the IVRS system to answer a series of questions at each suspected hypoglycemic event. The call was to be made after treatment for the event was completed. The patient was asked to provide the date and time of the event, self-monitored glucose value, action(s) taken, whether the assistance of another person was required, and whether hospitalization was required.
- Blood samples for prolactin measurement were collected in the morning prior to administration of study medication, and 2 ± 0.5 hours after study drug administration on Day 1 and on the same days that PK samples were collected (Week 12, 24 and 52/exit).
- Depression assessment: Symptoms of depression were assessed at screening and at Weeks 4, 12, 24, 36, and 52 (or early termination) by the Beck Depression Inventory Second Edition (BDI-II), in part to proactively provide evaluation or intervention if indicated. BDI-II is a 21-item self-report instrument intended to assess the presence and severity of symptoms of depression as listed in the American

Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV).

- Echocardiography was performed at screening, Week 24, and Week 52/Exit

Protocol Amendments and Changes to the Planned Analyses

Table 137. Changes to the Conduct of BLOOM-DM

Amendment	Date	Changes
1	12 Nov 2007	Removed screening echocardiogram requirement and added baseline echocardiogram requirement in relevant sections Changed window for DEXA scan from " ± 4 weeks" to "+ 2 weeks" (Day 1/Randomization) and " ± 2 weeks" (Week 24) Changed method of assigning patients to treatment groups to delete "7" from "HbA1c: 7-9%" and replace with "< 9%" Added "Binge Eating Scale" to list of screening/enrollment procedures Added clarifications to Exit Procedures/Early Termination and Exit echocardiogram procedures.
2	27 Nov 2007	Revised prolactin and pharmacokinetic schedule as follows: "For females, reproductive status and the start date of last menstrual period will be documented at each visit for prolactin measurement" Deleted text in Echocardiography Procedures as follows: "In these cases, a patient will qualify on the basis that the pulmonary valve flow acceleration time will be ≥ 120 msec, indicating the pulmonary artery pressure is not elevated"
3	01 Aug 2008	Revised text in relevant sections to indicate discontinuation of patient randomization into lorcaserin 10 mg QD dose group Adjusted sample size to accommodate discontinuation of lorcaserin 10 mg QD dose group Revised hypothesis, efficacy assessments, and data analysis sections to accommodate inclusion of 10% weight reduction group in overall analyses Added exclusion of topiramate to avoid confounding effects on weight

9.5 Appendices to the May 10, 2012 Advisory Committee Briefing Document Addendum

1. Cerebrovascular Disorders SMQ

Adverse Events in Cerebrovascular Disorders SMQ

Adverse Events in Cerebrovascular Disorders (CVD)								
		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	2	1.26	0.99 (0.14, 7.07)	0.99 (0.14, 7.07)	0.75 (0.26, 2.15)	0.84 (0.32, 2.18)
	Lorc 10 BID	1593	2	1.26				
BLOOM-DM	Pbo	252	1	3.97	0.98 (0.06, 15.82)	2.16 (0.22, 20.92)		
	Lorc 10 BID	256	1	3.91				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	5	3.12	0.60 (0.14, 2.51)	0.53 (0.14, 1.99)		
	Lorc 10 BID	1602	3	1.87				
	Lorc 10 QD	801	1	1.25				

¹Lorcaserin 10mg BID vs placebo

²All lorcaserin vs placebo

Serious Adverse Events in Cerebrovascular Disorders SMQ

Serious Adverse Events in Cerebrovascular Disorders Only								
		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	1	0.63	0.99 (0.06, 15.91)	0.99 (0.06, 15.91)	0.25 (0.03, 2.23)	0.75 (0.19, 2.99)
	Lorc 10 BID	1593	1	0.63				
BLOOM-DM	Pbo	252	0	0.00	-	-		
	Lorc 10 BID	256	0	0.00				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	3	1.87	-	0.22 (0.02, 2.13)		
	Lorc 10 BID	1602	0	0.00				
	Lorc 10 QD	801	1	1.25				

¹Lorcaserin 10mg BID vs placebo

²All lorcaserin vs placebo

2. Ischaemic cerebrovascular conditions SMQ

Adverse Events in Ischaemic cerebrovascular conditions SMQ

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	2	1.26	-	-	0.14 (0.02, 1.16)	0.41 (0.12, 1.42)
	Lorc 10 BID	1593	0	0.00				
BLOOM-DM	Pbo	252	1	3.97	-	1.44 (0.13, 15.95)		
	Lorc 10 BID	256	0	0.00				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	4	2.50	0.25 (0.03, 2.23)	0.33 (0.06, 1.82)		
	Lorc 10 BID	1602	1	0.62				
	Lorc 10 QD	801	1	1.25				

¹Lorcaserin 10mg BID vs placebo

²All lorcaserin vs placebo

Serious Adverse Events in Ischaemic cerebrovascular conditions SMQ

		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	1	0.63	-	-	-	0.73 (0.14, 3.66)
	Lorc 10 BID	1593	0	0.00				
BLOOM-DM	Pbo	252	0	0.00	-	-		
	Lorc 10 BID	256	0	0.00				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	2	1.25	-	0.33 (0.03, 3.67)		
	Lorc 10 BID	1602	0	0.00				
	Lorc 10 QD	801	1	1.25				

¹Lorcaserin 10mg BID vs placebo

²All lorcaserin vs placebo

3. Ischaemic heart disease SMQ

Adverse Events in Ischaemic heart disease SMQ

Adverse Events in Ischaemic heart disease GMD								
		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	6	3.79	1.66 (0.60, 4.58)	1.66 (0.60, 4.58)	1.53 (0.79, 2.94)	1.45 (0.77, 2.73)
	Lorc 10 BID	1593	10	6.28				
BLOOM-DM	Pbo	252	7	27.78	0.7 (0.22, 2.23)	0.82 (0.29, 2.28)		
	Lorc 10 BID	256	5	19.53				
	Lorc 10 QD	95	3	31.58				
BLOSSOM	Pbo	1601	2	1.25	4.01 (0.85, 18.92)	3.01 (0.65, 13.93)		
	Lorc 10 BID	1602	8	4.99				
	Lorc 10 QD	801	1	1.25				

¹Lorcaserin 10mg BID vs placebo

²All lorcaserin vs placebo

Serious Adverse Events in Ischaemic heart disease SMQ

Serious Adverse Events in Ischaemic heart disease (MI)								
		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	2	1.26	0.99 (0.14, 7.07)	0.99 (0.14, 7.07)	1.79 (0.60, 5.35)	1.68 (0.58, 4.92)
	Lorc 10 BID	1593	2	1.26				
BLOOM-DM	Pbo	252	2	7.94	0.49 (0.04, 5.44)	1.08 (0.18, 6.50)		
	Lorc 10 BID	256	1	3.91				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	1	0.62	6.02 (0.72, 50.02)	4.01 (0.48, 33.30)		
	Lorc 10 BID	1602	6	3.75				
	Lorc 10 QD	801	0	0.00				

¹Lorcaserin 10mg BID vs placebo

²All lorcaserin vs placebo

4. Myocardial infarction SMQ

Adverse Events in Myocardial infarction SMQ

Adverse Events in Myocardial Infarction (MI)								
		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	5	3.16	0.80 (0.21, 2.97)	0.80 (0.21, 2.97)	1.16 (0.53, 2.51)	0.98 (0.46, 2.13)
	Lorc 10 BID	1593	4	2.51				
BLOOM-DM	Pbo	252	6	23.81	0.82 (0.25, 2.71)	0.71 (0.23, 2.24)		
	Lorc 10 BID	256	5	19.53				
	Lorc 10 QD	95	1	10.53				
BLOSSOM	Pbo	1601	1	0.62	5.01 (0.58, 42.93)	3.34 (0.39, 28.58)		
	Lorc 10 BID	1602	5	3.12				
	Lorc 10 QD	801	0	0.00				

¹Lorcaserin 10mg BID vs placebo

²All lorcaserin vs placebo

Serious Adverse Events in Myocardial infarction SMQ

Serious Adverse Events in Myocardial Infarction Arm								
		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio ¹ (95% CI)	Odds Ratio ² (95% CI)	Mantel-Haenszel OR ¹	Mantel-Haenszel OR ²
BLOOM	Pbo	1584	2	1.26	0.50 (0.05, 5.49)	0.50 (0.05, 5.49)	1.74 (0.51, 5.94)	1.35 (0.38, 4.72)
	Lorc 10 BID	1593	1	0.63				
BLOOM-DM	Pbo	252	2	7.94	0.49 (0.04, 5.44)	0.36 (0.03, 3.96)		
	Lorc 10 BID	256	1	3.91				
	Lorc 10 QD	95	0	0.00				
BLOSSOM	Pbo	1601	0	0.00	-	-		
	Lorc 10 BID	1602	5	3.12				
	Lorc 10 QD	801	0	0.00				

¹Lorcaserin 10mg BID vs placebo

²All lorcaserin vs placebo

5. Lorcaserin 10 mg QD Analyses: Broad and Narrow Searches

Adverse Events in Broad² CV Search. Lorcaserin 10mg QD vs Placebo

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio (95% CI)	Mantel- Haenszel OR
BLOOM-DM	Pbo ¹	80	6	75.00	0.69 (0.20, 2.33)	0.64 (0.24, 1.67)
	Lorc 10 QD	95	5	52.63		
BLOSSOM	Pbo	1601	7	4.37	0.57 (0.12, 2.75)	
	Lorc 10 QD	801	2	2.50		

¹Randomized before amendment 3

²Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ and Ischaemic heart disease SMQ

Serious Adverse Events in Broad² CV Search. Lorcaserin 10mg QD vs Placebo

Serious Adverse Events in Broom - QV Search: Efficacy in Tumor QD vs Placebo						
		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio (95% CI)	Mantel-Haenszel OR
BLOOM-DM	Pbo ¹	80	0	0.00	-	1.87 (0.44, 7.92)
	Lorc 10 QD	95	4	42.11		
BLOSSOM	Pbo	1601	4	2.50	0.50 (0.06, 4.47)	
	Lorc 10 QD	801	1	1.25		

¹Randomized before amendment 3

²Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ and Ischaemic heart disease SMQ

Adverse Events in Narrow² CV Search. Lorcaserin 10mg QD vs Placebo

Adverse Events in Narrow QV Search: Efficacy Testing QD vs Pbo						
		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio (95% CI)	Mantel-Haenszel OR
BLOOM-DM	Pbo ¹	80	5	62.50	0.49 (0.11, 2.11)	0.45 (0.14, 1.52)
	Lorc 10 QD	95	3	31.58		
BLOSSOM	Pbo	1601	5	3.12	0.40 (0.05, 3.42)	
	Lorc 10 QD	801	1	1.25		

¹Randomized before amendment 3

²Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ and Ischaemic heart disease SMQ

Serious Adverse Events in Narrow² CV Search

Serious Adverse Events in Narrow QV Search						
		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio (95% CI)	Mantel-Haenszel OR†
BLOOM-DM	Pbo ¹	80	0	0.00	-	2.37 (0.34, 16.39)
	Lorc 10 QD	95	2	21.05		
BLOSSOM	Pbo	1601	2	1.25	1.00 (0.09, 11.04)	
	Lorc 10 QD	801	1	1.25		

¹Randomized before amendment 3

²Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ and Ischaemic heart disease SMQ

6. Preferred terms from SMQ search in Phase 3 trials

STUDY	SUBJID	ARM	PT	SAE	Broad	Narrow
BLOOM	101013	Lorcaserin	Electrocardiogram T wave abnormal	0	1	0
	106048	Lorcaserin	Electrocardiogram ST segment abnormal	0	1	1
	106048	Lorcaserin	Troponin increased	0	1	1
	107147	Lorcaserin	Arteriosclerosis coronary artery	0	1	0
	119084	Lorcaserin	Angina unstable	1	1	0
	119084	Lorcaserin	Coronary artery disease	0	1	0
	122212	Lorcaserin	Electrocardiogram T wave abnormal	0	1	0
	122274	Lorcaserin	Myocardial infarction	0	1	1
	126037	Lorcaserin	Subarachnoid haemorrhage	1	1	0
	126037	Lorcaserin	Subdural haemorrhage	1	1	0
	158036	Lorcaserin	Myocardial infarction	0	1	1
	180003	Lorcaserin	Electrocardiogram T wave abnormal	0	1	0
	180080	Lorcaserin	Coronary artery occlusion	1	1	1
	189070	Lorcaserin	Dysarthria		0	0
	210025	Lorcaserin	Cardiac stress test abnormal	0	1	0
	106036	Placebo	Blood creatine phosphokinase increased	0	1	1
	109022	Placebo	Carotid artery stenosis	0	1	1
	154030	Placebo	Blood creatine phosphokinase increased	0	1	1
	156006	Placebo	Myocardial infarction	1	1	1
	163017	Placebo	Coronary artery disease	0	1	0
	177074	Placebo	Transient ischaemic attack	1	1	1
	188048	Placebo	Coronary artery occlusion	1	1	1
	205109	Placebo	Blood creatine phosphokinase increased	0	1	1
BLOOM-DM	1130-0494	Lorcaserin 10 mg BID	Dysarthria	0	0	0
	1146-0423	Lorcaserin 10 mg BID	Angina unstable	0	1	0
	1146-0423	Lorcaserin 10 mg BID	Coronary artery occlusion	1	1	1
	1146-0423	Lorcaserin 10 mg BID	Coronary artery occlusion	0	1	1
	1159-0041	Lorcaserin 10 mg BID	Blood creatine phosphokinase increased	0	1	1
	1205-0192	Lorcaserin 10 mg BID	Blood creatine phosphokinase increased	0	1	1

Clinical Review
Golden, J.
NDA 022529
Belviq (lorcaserin hydrochloride)

STUDY	SUBJID	ARM	PT	SAE	Broad	Narrow
	1219-0587	Lorcaserin 10 mg BID	Blood creatine phosphokinase increased	0	1	1
	1226-0289	Lorcaserin 10 mg BID	Blood creatine phosphokinase increased	0	1	1
	1131-0021	Lorcaserin 10 mg QD	Blood creatine phosphokinase increased	0	1	1
	1131-0061	Lorcaserin 10 mg QD	Coronary artery disease	1	1	0
	1131-0061	Lorcaserin 10 mg QD	Coronary artery disease	0	1	0
	1174-0188	Lorcaserin 10 mg QD	Angina pectoris	1	1	0
	1227-0127	Lorcaserin 10 mg QD	Cerebrovascular accident	1	1	1
	1275-0276	Lorcaserin 10 mg QD	Cerebrovascular accident	1	1	1
	1105-0129	Placebo	Angina pectoris	0	1	0
	1105-0129	Placebo	Angina pectoris	0	1	0
	1130-0114	Placebo	Transient ischaemic attack	0	1	1
	1130-0497	Placebo	Myocardial infarction	1	1	1
	1149-0045	Placebo	Blood creatine phosphokinase increased	0	1	1
	1159-0024	Placebo	Blood creatine phosphokinase increased	0	1	1
	1162-0026	Placebo	Blood creatine phosphokinase increased	0	1	1
	1165-0155	Placebo	Blood creatine phosphokinase increased	0	1	1
	1243-0304	Placebo	Myocardial infarction	1	1	1
BLOSSOM	2106-0982	Lorcaserin 10 mg BID	Angina pectoris	0	1	0
	2128-0886	Lorcaserin 10 mg BID	Acute myocardial infarction	1	1	1
	2137-3797	Lorcaserin 10 mg BID	Angina pectoris	1	1	0
	2137-3797	Lorcaserin 10 mg BID	Dysarthria	0	0	0
	2160-1094	Lorcaserin 10 mg BID	Dysarthria	0	0	0
	2196-0343	Lorcaserin 10 mg BID	Acute coronary syndrome	1	1	1
	2203-3369	Lorcaserin 10 mg BID	Myocardial infarction	1	1	1
	2222-1382	Lorcaserin 10 mg BID	Myocardial ischaemia	0	1	0
	2236-0400	Lorcaserin 10 mg BID	Myocardial infarction	1	1	1
	2236-2802	Lorcaserin 10 mg BID	Cerebrovascular accident	0	1	1
	2250-0033	Lorcaserin 10 mg BID	Myocardial infarction	1	1	1
	2267-1001	Lorcaserin 10 mg QD	Transient ischaemic attack	1	1	1
	2270-2970	Lorcaserin 10 mg QD	Angina pectoris	0	1	0
	2133-1095	Placebo	Carotid arteriosclerosis	0	1	1
	2140-3835	Placebo	Haemorrhage intracranial	1	1	0
	2146-1669	Placebo	Angina unstable	0	1	0
	2146-1669	Placebo	Coronary artery disease	1	1	0
	2167-0962	Placebo	Troponin increased	0	1	1
	2180-3035	Placebo	Transient ischaemic attack	1	1	1
	2182-2834	Placebo	Carotid artery occlusion	0	1	1
	2223-1109	Placebo	Cerebral ischaemia	1	1	1

7. Endpoint Definitions for Sponsor's CV Event Adjudication

A. DEATH CLASSIFICATION

Death will be classified into Cardiovascular, Non-Cardiovascular, or Undetermined

Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Sudden Cardiac Death:** refers to death that occurs unexpectedly and includes the following deaths:
 - a. Death witnessed and instantaneous without new or worsening symptoms
 - b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
 - c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
 - d. Death after unsuccessful resuscitation from cardiac arrest
 - e. Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)
 - f. Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)
2. **Death due to Acute Myocardial Infarction** refers to a death within 30 days after a myocardial infarction (MI) related to consequences seen immediately after the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period), they should be designated by the immediate cause.
3. **Death due to Heart Failure* or Cardiogenic Shock** refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death.

4. **Death due to Stroke:** refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.
5. **Death due to Other Cardiovascular Causes:** refers to death due to a cardiovascular cause not included in the above categories (e.g. dysrhythmia, pulmonary embolism, cardiovascular intervention, aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularization, even if “non-cardiovascular” in nature, should be classified as cardiovascular deaths

Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death. Suggested categories* include:

- Pulmonary causes
- Renal causes
- Gastrointestinal causes
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Malignancy (i.e., new malignancy, worsening of prior malignancy)
- Accidental/Trauma
- Hemorrhage, not intracranial
- Suicide
- Non-cardiovascular system organ failure (e.g., hepatic failure)
- Non-cardiovascular surgery
- Other non-cardiovascular, specify: _____

Undetermined Cause of Death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause.

B. MYOCARDIAL INFARCTION

1. Criteria for Acute Myocardial Infarction

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction.

For each MI type, one must consider the totality of clinical, electrocardiographic, and cardiac biomarker information to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis.

a. Spontaneous MI

Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99th percentile of the upper reference limit (URL)* together with evidence of myocardial ischemia with at least one of the following:

- o Symptoms of ischemia
- o ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]**
- o Development of pathological Q waves in the ECG
- o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

*For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. Total CK may be used only in the absence of troponin and CK-MB data. In the absence of available biomarker data, the CCEC may use other available clinical information (e.g., new thrombotic occlusion of a coronary artery at coronary angiogram in a patient with new acute ST elevation in the distribution of the occluded artery) to determine whether an MI has occurred.

****ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):**

- ST elevation
New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
- ST depression and T-wave changes
New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

*****Definition of a pathological Q-wave**

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)^a

^aThe same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

Percutaneous Coronary Intervention-Related Myocardial Infarction

For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL* within 48 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than $3 \times 99^{\text{th}}$ percentile URL* (Troponin or CK-MB $> 3 \times 99^{\text{th}}$ percentile URL*) are consistent with PCI-related myocardial infarction. MB is the preferred biomarker. Symptoms are not required.

If the cardiac biomarker is elevated prior to PCI, a $\geq 50\%$ increase of the value in the second cardiac biomarker sample within 48 hours of the PCI (and Troponin or CK-MB $> 3 \times 99^{\text{th}}$ percentile URL*) and documentation that cardiac biomarker values were decreasing (two samples 3-6 hours apart) prior to the suspected recurrent MI is also consistent with PCI-related myocardial infarction.

c. Coronary Artery Bypass Grafting-Related Myocardial Infarction

For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99th percentile URL within 72 hours of the procedure is indicative of peri-procedural myocardial necrosis. By convention, an increase of biomarkers greater than 5 x 99th percentile URL (Troponin or CK-MB > 5 x 99th percentile URL) plus

- either new pathological Q waves in at least 2 contiguous leads that persist through 30 days or new persistent non-rate related LBBB *or*
- angiographically documented new graft or native coronary artery occlusion or other complication in the operating room resulting in loss of myocardium *or*
- imaging evidence of new loss of viable myocardium

is consistent with CABG-related myocardial infarction. MB is the preferred biomarker.

If the cardiac biomarker is elevated prior to CABG, a $\geq 50\%$ increase of the value in the second cardiac biomarker sample within 72 hours of CABG (and Troponin or CK-MB > 5 x 99th percentile URL) and documentation that cardiac biomarker values were decreasing (two samples 3-6 hours apart) prior to the suspected recurrent MI plus any of the three bullets above is consistent with a periprocedural myocardial infarction after CABG.

Symptoms of cardiac ischemia are not required.

d. Pathological findings of an acute myocardial infarction

Criteria for Silent Myocardial Infarction or Prior Myocardial Infarction (with or without Symptoms)

No evidence of acute myocardial infarction AND any one of the following criteria:

- Appearance of new persistent pathological Q waves. A confirmatory ECG is recommended if there have been no clinical symptoms or history of myocardial infarction.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a healed or healing myocardial infarction

ECG Changes associated with prior myocardial infarction:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)^a
- R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

^aThe same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

3. Criteria for Reinfarction

In patients where recurrent myocardial infarction is suspected from clinical signs or symptoms following the initial infarction, recurrent infarction should be diagnosed if there is a $\geq 20\%$ increase of the value between a measurement (cardiac biomarker) made at the time of the initial presentation and a further sample taken 3-6 hours later. This value should also exceed the 99th percentile URL.*). This scenario applies to patients enrolled in a clinical trial with an acute myocardial infarction who experience a recurrent myocardial infarction post-enrollment or in patients enrolled in a clinical trial without an acute myocardial infarction but who subsequently experience a myocardial infarction during the course of the trial and a recurrent myocardial infarction.

If cardiac biomarkers are elevated prior to the suspected new MI, there must be decreasing cardiac biomarker values on two samples at least 3 hours apart prior to the suspected new MI in combination with other criteria for reinfarction (ECG, imaging).

If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible.

4. General Considerations

- For a diagnosis of acute myocardial infarction, elevation of cardiac biomarkers should be present. However, myocardial infarction may be adjudicated for an event that has characteristics (i.e., ischemic symptoms) of a myocardial infarction but which does not meet the strict definition because biomarker or electrocardiographic results are not available (e.g. not measured) or are non-contributory (e.g. may have normalized).
- For procedure-related myocardial infarction, all available biomarker information will be taken into account. Furthermore, in cases where the cardiac biomarker is elevated prior to PCI or CABG.
- Not infrequently, patients with renal disease or congestive heart failure may have elevated cardiac biomarkers. In these circumstances, the Clinical Endpoints Committee must use the totality of the evidence to determine whether the cardiac biomarker elevation or underlying condition represents the primary process or endpoint event.

C. HOSPITALIZATION FOR UNSTABLE ANGINA

Unstable angina requiring hospitalization is defined as

1. Symptoms of myocardial ischemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity

AND

2. Prompting an unscheduled visit to a healthcare facility and hospitalization (including chest pain observation units) within 24 hours of the most recent symptoms

AND

3. At least one of the following:

- a. New or worsening ST or T wave changes on resting ECG

- ST elevation

New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

- ST depression and T-wave changes

New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. It is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- b. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs
- c. Angiographic evidence of $\geq 70\%$ lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs
- d. Need for coronary revascularization procedure (PCI or CABG) during the same hospital stay. This criterion would be fulfilled if the admission for myocardial ischemia led to transfer to another institution for the revascularization procedure without interceding home discharge

AND

4. No evidence of acute myocardial infarction

5. General Considerations

- Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β -blockers, should be considered supportive of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient alone to support classification as hospitalization for unstable angina.
- If subjects are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina.
- Planned rehospitalization for performance of an elective revascularization in the absence of symptoms at rest prompting admission should not be considered a hospitalization for unstable angina. For example, a patient with stable exertional angina whose admission for coronary angiography and PCI is prompted by a positive outpatient stress test should not be considered a hospitalization for unstable angina.
- A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina endpoint.

D. TRANSIENT ISCHEMIC ATTACK AND STROKE

1. Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

2. Stroke

Stroke is an acute symptomatic episode of neurological dysfunction attributed to a vascular cause.

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A or B.

3. General Considerations

- In general a stroke is associated with either symptoms greater than 24 hours in duration, death prior to 24 hours, or imaging evidence of infarction of central nervous tissue
- Intracerebral microhemorrhages will not be considered evidence of a primary hemorrhagic stroke
- For the purpose of adjudication, a stroke known to be ischemic in nature with subsequent transformation to hemorrhagic will be considered an ischemic stroke.

**8. Cardiovascular Clinical Endpoints Committee Results Summary (Post-hoc Adjudication),
BLOOM and BLOSSOM**

Subject ID	Verbatim Term	Preferred Term	Result	Treatment Assignment (Added by Arena)
119084	UNSTABLE ANGINA	Angina unstable	Hosp for UA	Lorc 10 BID
2128-S010	ACUTE MI	Acute myocardial infarction	MI-Spontaneous	Lorc 10 BID
2203-S058	NON Q WAVE MYOCARDIAL INFARCTION	Myocardial infarction	MI-Spontaneous	Lorc 10 BID
2236-S032	MYOCARDIAL INFARCTION	Myocardial infarction	MI-Spontaneous	Lorc 10 BID
2250-S008	MYOCARDIAL INFARCTION	Myocardial infarction	MI-Spontaneous	Lorc 10 BID
192006	ATYPICAL CHEST PAIN	Chest pain	No MI/UA	Lorc 10 BID
2102-S039	CHEST PAIN-MUSCULOSKELETAL	Musculoskeletal chest pain	No MI/UA	Lorc 10 BID
2137-S050	CHEST PAIN OF UNKNOWN ETIOLOGY	Chest pain	No MI/UA	Lorc 10 BID
2137-S083	ANGINA	Angina pectoris	No MI/UA	Lorc 10 BID
2196-S002	PROBABLY ACUTE CORONARY SYNDROME	Acute coronary syndrome	No MI/UA	Lorc 10 BID
2213-S076	NON CARDIAC CHEST PAIN	Non-cardiac chest pain	No MI/UA	Lorc 10 BID
2255-S073	CHEST PRESSURE	Chest discomfort	No MI/UA	Lorc 10 BID
2202-S062	CHEST PAIN NON-CARDIAC	Non-cardiac chest pain	No MI/UA	Lorc 10 QD
2267-S007	TRANSIENT ISCHEMIC ATTACK	Transient ischaemic attack	No Stroke/TIA	Lorc 10 QD
180080	CORONARY ARTERY DISEASE	Coronary artery occlusion	Hosp for UA	Lorc / Pbo
188048	CORONARY ARTERY 95% BLOCK	Coronary artery occlusion	Hosp for UA	Pbo
2146-S090	CORONARY ARTERY DISEASE	Coronary artery disease	Hosp for UA	Pbo
156006	REMOTE LATERAL MYOCARDIAL INFARCTION	Myocardial infarction	MI-Silent	Pbo
146067	CHEST PAIN	Chest pain	No MI/UA	Pbo
2125-S001	CHEST PAIN	Chest pain	No MI/UA	Pbo
2223-S009	CEREBRAL GLOBAL ANOXIA	Cerebral ischaemia	Non CV Death – Pulmonary Stroke Ischaemic	Pbo
132023		Road traffic accident	Non CV Death – Accident/Trauma	Pbo

Clinical Review
Golden, J.
NDA 022529
Belviq (lorcaserin hydrochloride)

Subject ID	Verbatim Term	Preferred Term	Result	Treatment Assignment (Added by Arena)
177074	TRANSIENT ISCHEMIC ATTACK	Transient ischaemic attack	TIA	Pbo
2180-S078	TRNSIENT ISCHEMIC ATTACK	Transient ischaemic attack	TIA	Pbo

Source: NDA 022529 CV Study Report, pg 25 of 54

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/s/

JULIE K GOLDEN
06/19/2012

ERIC C COLMAN
06/19/2012

Summary Basis for Regulatory Action

Date	October 22, 2010
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	NDA 22529
Applicant Name	Arena Pharmaceuticals, Inc.
Proprietary / Established (USAN) Names	Lorqess Lorcaserin hydrochloride
Dosage Forms / Strength	Tablet 10 mg BID
Proposed Indication(s)	Weight management
Action:	<i>Complete Response</i>

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding lorcaserin and I refer the reader to the reviews in the action package for a more detailed discussion. Lorcaserin is a new molecular entity that is a 5-hydroxytryptamine 2C (5HT_{2c}) receptor agonist designed to have effects at that receptor in the appetite center of the brain. The proposed indication as specified in Dr. Golden's review is:

- Lorqess 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. Lorqess is indicated for obese patients with an initial body mass index ≥ 30 kg/m², or overweight patients with a body mass index ≥ 27 kg/m² in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea).

Obesity is a growing epidemic in the United States and epidemiologic data indicate it is associated with a myriad of adverse health outcomes that greatly impact obese people's lives and are very costly to the health care system. When discussing the poor outcomes associated with obesity, most attention is paid to the development of diabetes and cardiovascular disease, but other associated diseases that are important include sleep apnea, osteoarthritis and some cancers. The goal of weight management, therefore, is to affect weight loss in obese patients with the goal of decreasing these adverse outcomes and improving quality of life. Since there are epidemiologic data that indicate that as weight increases so do the poor outcomes mentioned above, it would seem intuitive that weight loss will reverse these poor outcomes and can be used as a surrogate to indicate probable decreases in obesity-related diseases. This may be true for weight loss that is achieved through non-pharmacologic means; however, history has taught us that many marketed weight-loss drugs (and some reviewed for possible marketing), also had 'off-target' activity that could adversely affect the outcomes above, or may even cause other unforeseen adverse effects not associated with obesity, such that an unfavorable risk:benefit ratio has not allowed initial, or continued, marketing. Such was the case for fenfluramine ('fen-phen') and dexfenfluramine where there were unexpected cases of primary pulmonary hypertension and valvular regurgitation associated with drug use thought to be due to effects on serotonin receptors.¹ This adverse event profile, in the context of fairly marginal weight loss and inability to identify those that may be at risk, was deemed too unsafe to allow continued marketing. Sibutramine is also an example of a medication having an off-site activity as the SCOUT trial demonstrated that the cardiovascular benefit of weight loss was not realized due to increases in blood pressure and heart rate.² Just as in the case of fen-phen, no population could be identified where weight loss with sibutramine was significant enough to overcome the risk caused from off-site activity. The best that could be demonstrated from the SCOUT trial (and that was from sub-group analysis which should always be viewed with caution) was that sibutramine may not increase cardiovascular risk in some, but at the same time it never demonstrated that it provided any benefit on cardiovascular, or any other outcome, to justify what could be considered fairly modest amounts of weight loss.

Other applications, such as rimonabant, have not received approval (and was removed from foreign markets) because of suicidality concerns. Recently Qnexa (phentermine/topiramate) was presented at an advisory committee where the panel voted 10 to 6 against approval, mainly because of teratogenicity concerns, despite robust weight loss. As such, while we have a great desire to try to find effective medications for sustained weight management, there is little tolerance for potential devastating adverse effects, even if rare, in the environment of modest weight loss.

¹ Cufman GD. Diet pills redux. *N Engl J Med* 1997; 337:629-30.

² James WPT, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010; 363:905-17.

Into this environment have come several new agents, (Qnexa mentioned above and others), and also lorcaserin, which is the subject of this NDA. Several areas of safety concern have been identified with this application.

There are pre-clinical concerns regarding the results of rat carcinogenicity studies. In 2-year carcinogenicity studies, lorcaserin caused mammary gland tumors (as well as many other malignant tumor types albeit with a safety margin) in both genders at clinically relevant exposures. To date, the sponsor has not been able to demonstrate a mechanism that is assuring that this is rodent specific and not applicable to humans. Given that the presumed target population for lorcaserin use is mainly in females, this is very concerning. Additionally, astrocytomas have been demonstrated, and, due to selective partitioning of lorcaserin in the central nervous system (CNS) we have not been able to apply a no adverse affect level (NOAEL) in animals to human exposure.

Another concern is that, while the sponsor claims that lorcaserin is a specific 5HT_{2C} receptor agonist which should avoid the valvular problems seen with fenfluramine and dexfenfluramine (which affected a wide array of serotonin receptors-the main one being 5HT_{2B}), lorcaserin is still somewhat permissive at other serotonin receptors, and there is some uncertainty regarding the true functional potency at different serotonin receptors as there is conflicting data submitted with this NDA. Because the reported severe valvular problems with fenfluramine were somewhat rare, it becomes a problem of how to evaluate (what degree of certainty is acceptable) whether lorcaserin really will not have adverse effects to cardiac valves. While no overt valvular damage was demonstrated during the development program, echocardiography evaluation revealed that a 50% increase for the development of FDA-defined valvular heart disease (VHD) could not be ruled out. It is important to emphasize that ruling out a 50% increase is not agency policy, or even an agreement we had made, rather it was a starting point in the sponsor's development program as we were involved in uncharted territory, did not want to stall drug development, but at the same time could not determine what an appropriate margin may be without some initial data.

The above concerns must be viewed in the context of efficacy, which was marginal at best for lorcaserin. Placebo-subtracted mean differences in weight loss associated with lorcaserin treatment were 3.7% for one trial and 3.0 % for another. While there may be a small proportion of patients that achieve impressive and probably quite important weight loss, meager population weight changes of this percentage do not allow for a lot of lee way in regard to important risk uncertainties.

As such, I believe that this application should receive a complete response (CR) action. The sponsor will need at a minimum to define that the rodent carcinogenicity findings are not applicable to humans in order to allow marketing. Further consideration also needs to be given regarding whether lorcaserin has demonstrated that it will not have adverse valvular effects. I will expand on the above assessment below.

Efficacy

Efficacy is based on two pivotal trials. The results italicized below are extracted verbatim from Dr. Golden's review (page 33).

In the first year of the BLOOM trial:

- *47.5% of patients treated with lorcaserin 10 mg BID lost $\geq 5\%$ 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 $\geq 10\%$ 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 $\geq 5\%$ 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 $\geq 10\%$ 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 $\geq 5\%$ 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 $\geq 5\%$ 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 above demonstrates that lorcaserin 10 mg BID treatment on average resulted in 3.25 kg (about 7 lbs.) greater weight loss than placebo. This is in line with previous weight loss drugs, but is not very impressive and is also about the amount of weight loss demonstrated for weight maintenance drugs that have been removed from the market, or not allowed to have marketing, for rare severe adverse events. To put this into further perspective Dr. Golden has a table (Table 3, Page 34) which demonstrates that about half of subjects that started the study actually completed, and about 20% of the completers had greater than or equal to a 10% wt loss above and beyond placebo. So, if everyone starting the study was considered, only about 10% of subjects could have expected to have a 10% wt loss above and beyond placebo, the rest having no change, or changes less than this. It should also be noted that neither of the pivotal efficacy trials included subjects with diabetes. This is important because most (all?) other applications have demonstrated that drug therapy in subjects with diabetes have attenuated efficacy compared to obese subjects without diabetes. Therefore, in the diabetic population, we would expect even lower amounts of weight loss than that demonstrated in the two efficacy trials above. Most the secondary endpoints trended in the correct direction commensurate with the amount of weight loss demonstrated.

In summary, only one of the two efficacy benchmarks identified in our draft guidance was achieved (categorical-proportion of subjects losing 5% or more of body weight in drug group is at least 35% and approximately double the proportion in the placebo-treated group), and that was only in one trial, with the second trial narrowly missing.³ The other criteria that are evaluated are whether the mean weight loss between drug and placebo-treated groups is at least 5%. The two lorcaserin trials had mean weight loss placebo subtraction loss of 3.7% and 3.0%. While these efficacy results are in line with other weight loss drugs that have been approved, it is disappointing and must be considered in light of any potential safety concerns.

Safety

³ FDA Guidance for Industry: Developing Products for Weight Management. February 2007.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf>

The main concerns with safety are pre-clinical carcinogenicity findings in rats, and evaluation of the potential for clinically important valvular heart disease (VHD).

Regarding the pre-clinical findings, lorcaserin has been associated with non-genotoxic carcinogenic findings of multiple tumor types (multiple carcinogenic tumor types for drugs active at the serotonin receptor seem unique for lorcaserin). Among the multiple tumor types, mammary and brain tumors are the most concerning as the others could potentially be monitored for clinically (i.e. squamous cell cancer of the skin) or have adequate safety margins. A safety margin has not been identified for mammary tumors, and remains incompletely defined for brain tumors. These results were presented at the executive carcinogenicity assessment committee (execCAC) which agreed with the divisional primary reviewer and team leader's assessments.

In evaluating rodent mammary tumors, it is standard practice to combine fibroadenoma and adenocarcinoma mammary tissues in study analysis. As Dr. Brown points out in his review, this has been done historically for over 20 years without challenge to its validity. It is felt this is appropriate in part because distinguishing these tumor types can be challenging, (in fact the sponsor changed several cases of adenocarcinoma to fibroadenoma), they can both be present in the same animal, and the relationship to whether fibroadenomas may progress to adenocarcinomas in animals is still an open question. There has been criticism from e-mails sent to the agency from investors of Arena about the validity of the pre-clinical evaluation and in particular combining these two tumor types. While it is true these tumors were combined to look for signals, the agency pre-clinical scientists also review each tumor type individually looking for trends of increases in benign and malignant tumors and mortality that may indicate dose-related increases of malignancy and decreased latency for disease expression. When testing for statistical significance however, both types are combined together for the reasons discussed above, and studies have been powered for the number of animals required with this in mind.

As mentioned above, each component tumor type is separately evaluated to determine if there are numerical imbalances and to determine if those imbalances seem to be dose related. Such is the case here. Statistically significant mammary tumors (fibroadenomas and adenocarcinomas combined) were noted at the lowest dose tested (7-fold human exposure) in female rats and at 17-fold human exposures in the male rats (historic rates in control male rats 0.3% on average based on 11 studies). This necessitated closer inspection of the individual tumor types. There was a statistically significant increase in fibroadenomas alone at all doses in female rats and for adenocarcinoma at the highest dose. Also concerning, for both sexes there were numerical increases in adenocarcinomas above historical and control animal values that seemed to be dose related and did not provide a no-observed-adverse-effect-level (NOAEL). Lorcaserin also caused a dose-dependent increase in the number of deaths, and decreased the survival time (latency) in female rats, due to mammary tumors with nearly twice as many dead female rats at the low dose than in control

animals. As well as being associated with a dose-dependent reduced latency, lorcaserin is also associated with adenocarcinomas of increased aggressiveness that appeared in the low and mid-doses as demonstrated by metastasis and multiple tumors not found in control animals. Some of these results are summarized below in a table from Dr. Alavi's review (Page 5).

Lorcaserin Dose, mg/kg	0	10	30	100
Mammary Tumors in Male Rats				
AUC Exposure Multiples	-	5x	17x	55x
Adenocarcinoma @ (historical range 0 - 2%)	0	0	2/65 (3%)	2/75 (3%)
Fibroadenoma @ (historical range 0 - 3.3%)	0	1/65 (1.5%)	4/65 (6%)	6/75 * (8%)
Combined	0	1	6 *	8 **
Mammary Tumors in Female SD Rats				
Exposure multiples	--	7x	24x	82x
Adenocarcinoma @ (historical range 8.3 - 37%)	28/65 (43%)	34/65 (52%)	35/65 (54%)	60/75 ** (80%)
Fibroadenoma @ (historical range 22 - 54%)	20/65 (31%)	47/65 ** (72%)	53/65 ** (82%)	45/75 ** (60%)
Combined	40	56 **	61 **	70 **

The reviewers have also been concerned regarding data integrity. While it can be challenging to distinguish these types of tumors, it is concerning that several adenocarcinomas determined at week 96, were downgraded to fibroadenomas with the NDA submission. A good explanation for this change has not been received from the sponsor. See the table below from Dr. Alavi's review (page 6).

Mammary Adenocarcinoma Incidence over time in Female Rats (main study)				
Data Update (Week)	Control	10 mg/kg	30 mg/kg	100 mg/kg
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

Mammary Fibroadenoma Incidence over time in Female Rats (main study)				
Data Update (Week)	Control	10 mg/kg	30 mg/kg	100 mg/kg
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

This would seem to have been done in an unblinded fashion, and for the most part, tumor downgrade from malignant to benign was unbalanced in favor of drug therapy. Also, as Dr. Bourcier points out, there seem to have been gross errors in the pathology reports where on physical exam masses were noted, yet the tissues were identified as normal. The types of inconsistencies has eroded confidence in the accuracy of the data we have been supplied. It would seem reasonable for such a high stakes decision, As Dr. Brown notes that this and other irregularities noted by the reviewers and the execCAC would further support combining these tumors for analysis.

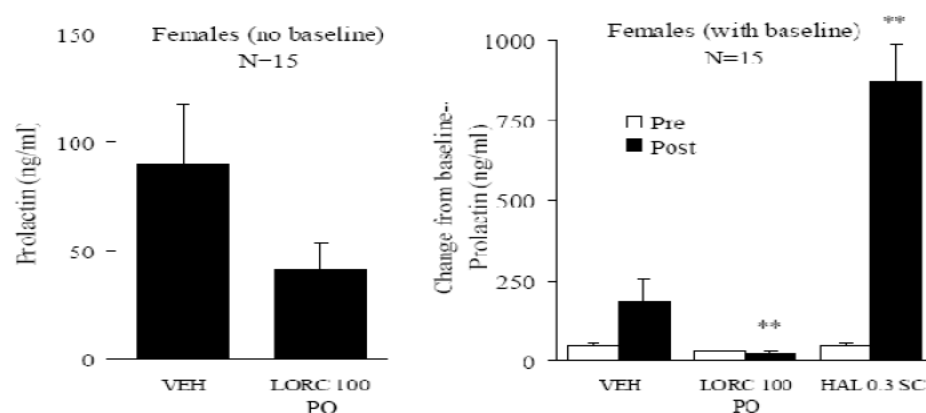
The sponsor has made the counter argument that we have approved other drugs that have been associated with mammary tumors. To determine if this is a valid argument, one must consider the environment and reasoning behind these decisions. There is an accepted explanation that mammary tumors found in animals do not translate into human risk, if the drug being tested results in increased

prolactin levels in animals, which is known to cause mammary tumors in animals. This is the theory that the sponsor had put forth, but our review of the data indicated that lorcaserin had no robust or sustained effect on serum prolactin in female or male rats, and actually reduced prolactin levels in male rats by 50% after multiple doses. This is demonstrated in the following table from Dr. Alavi's review (page 7).

Serum Prolactin at week 55 and 56 in TK rats in the carcinogenicity study		
Lorcaserin, mg/kg	Serum prolactin at WK 55 in male rats	Serum prolactin at WK 56 in female rats, ng/ml
0	57.8 ± 32 *	115 ± 80
10	28.2 ± 12	130 ± 56
30	29.9 ± 11	106 ± 68
100	23.6 ± 16	117 ± 63

This is in contra-distinction to what has been demonstrated for the antipsychotic agents that the sponsor cites as demonstrated in the following table from Dr. Alavi's review where rats were given single dose lorcaserin compared to haloperidol and serum prolactin levels were assessed (page 197).

Effects of lorcaserin and haloperidol on serum prolactin levels in female Sprague Dawley rats **p<0.01 compared to vehicle controls



So, for the most part in other drugs that we have approved that had pre-clinical findings of mammary tumors there was a plausible mechanism for why this would only occur in the animal species (prolactin effects). It is worth also pointing out that these drugs were approved for a condition that may warrant more risk tolerance (schizophrenia). Perhaps if we were able to feel comfortable that there was accurate differentiation of true fibroadenomas from adenocarcinomas such that there is an acceptable margin of safety for the adenocarcinomas, this issue may be resolved. Barring that however, the sponsor would need to provide a suitable explanation as to why this finding is species-specific and not relevant to humans.

The other pre-clinical tumor of concern is astrocytomas of the brain. There seemed to be an increase with the mid-dose (non-significant) and a statistically significant increase with the high dose in male rats. This signal emerged at 17-fold higher than clinical exposures with no effect seen at a 5-fold safety margin based on plasma drug levels. This is demonstrated in the table below from Dr. Alavi's review (page 7).

Lorcaserin dose, mg/kg	0 n=65	10 n=65	30 n=65	100 n=75
AUC Exposure Multiples	-	5x	17x	55x

Nervous System Tumors in Male Rats				
Astrocytoma @ (historical range 0 to 5%)	1 (1.5%)	0	4 (6%)	8 ** (10.7%)
Malignant Schwannoma @ (historical range, 0-3.3%)	0	0	2 (3%)	9** (12%)

These changes were not seen in female rats, but the death rate from mammary tumors was very high and therefore exposures in female rats were truncated. While there may be a 5-fold safety margin based on serum levels, lorcaserin is selectively partitioned into brain tissue (35x plasma levels in rats and 10x plasma levels in monkeys) so a safety margin cannot be reliably based on plasma levels. If one were to use rat brain partitioning, there would be a 5-fold safety margin, whereas based on monkey brain partitioning there would be 14-fold safety margin. Since brain partitioning is different in different species and we do not know the partitioning coefficient in humans compared to other animals, we cannot make an accurate assessment of the safety margin. As such, we will either need data defining partitioning ratios, or data that this tumor is species- specific and not relevant to humans.

It also bears mentioning (as noted above) that there were other tumors noted including carcinoma of the skin, malignant schwannoma, liver and thyroid follicular neoplasms. As Dr. Bourcier notes, it is uncommon for non-genotoxic compounds to display such a wide array of tumor types affecting multiple tissues and this type of finding has not been seen with other dopaminergic or serotonergic drugs.

It should be noted, that concerns regarding these tumor findings in animals were discussed, and our concerns expressed, during the development program, but we weren't made aware of these findings until later in develop as carcinogenicity studies are frequently performed concurrent with clinical testing. Without having access to all the data, the sponsor had presented to us that they felt the mammary tumors had an adequate explanation as to why they were species specific (prolactin effect) and that there were adequate margins for the astrocytomas. We had the sponsor include these animal findings in the informed consent for subjects, but upon review of the NDA and the actual data, we have concluded that we do not agree with their assessment that the mammary tumor has a good species specific reason for occurring, or that there have been adequate safety margins defined for the astrocytomas, that would alleviate concerns for humans. While one might question whether clinical trials can continue without further evaluation of these concerns, as Dr. Brown points out, the risk of tumor development with short term use of lorcaserin, or any nongenotoxic carcinogen, is likely to be small.

The clinical safety assessment of lorcaserin focused on concerns related to potential valvular heart disease. Echocardiographic assessments were designed to rule out a 50% or greater increase in the relative risk for FDA-defined valvular heart disease (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation). This 50% increase was arbitrarily chosen as a starting point, with the concept that more data may be needed depending on the results. The sponsor performed echocardiography in approximately 4800 subjects and at week 52 had a RR of 1.07 (95% C.I.: 0.74, 1.55). The greatest proportion of lorcaserin-treated VHD occurred at Week 24 and seemed to attenuate somewhat by Week 52. This is highlighted in the table below from Dr. Golden's review (page 80).

Table 1. 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

	BLOOM		BLOSSOM			POOLED	
	Pbo	Lorc 10 BID	Pbo	Lorc 10 QD	Lorc 10 BID	Pbo	Lorc 10 BID
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

There is probably a great deal of imprecision inherent in echocardiographic evaluation. Evidence to support this are that a total of 48 subjects who were diagnosed with VHD at Week 24 ‘reverted’ back to non-VHD at Week 52 and the Kappa statistic between readers ranged from 0.32 to 0.38 depending on the valve evaluated, which is only fair agreement.⁴ We may be able to derive some comfort that the completers, which are those that continued to take the drug, had a RR of 0.9 (95% C.I.:0.59-1.38). When looking at safety issues, both the ITT and completers results should be evaluated, because for non-inferiority, using ITT may actually dilute a signal if continued drug exposure is required for the adverse events, and therefore, some advocate that the most important group to evaluate is completers. As well, it may also be somewhat reassuring that no cases of severe left-sided VHD were noted, but it still does not rule-out that rare cases might occur as the result of drug therapy.

However, as noted above, there is confusion regarding the permissiveness of lorcaserin binding to other serotonin receptors. It would be helpful to reassure us if we had further data (if possible) on the time course of severe valvular disease and number needed to harm with use of fen-phen to determine if the lorcaserin safety program would have been expected to have enough exposures (and for long enough) to actually see any cases of significant valvular disease. Most case reports indicate that severe valvular disease associated with fenfluramine occurred within several months and the above data would seem to indicate that lorcaserin, if it does cause valvular disease, does not do it to the level that fenfluramine or dexfenfluramine does (at least not FDA defined VHD as evaluate by echocardiography), so while we may not have certainty, we may have some comfort that this is not as concerning as has been demonstrated by previous drugs.⁵

Advisory Committee Meeting

An advisory committee meeting was held on September 16, 2010. The committee voted 9 to 5 against approval of lorcaserin. Major concerns expressed were regarding the pre-clinical data, and marginal efficacy results that may compensate for theoretical risks.

Conclusions and Recommendations

Obesity can be a devastating disease, has become an epidemic in this country and is a burden on our healthcare system. Obesity’s causes are multi-factorial however, and it always strikes me that during my childhood a standard soft drink was 12 ounces or less. Now, it is difficult to obtain a 12 ounce soft drink with the standard size being 20 ounces and many fountains allowing the purchase of 48 ounces or more. This is a simplistic but illustrative example that environmental factors are overwhelmingly responsible for obesity, consisting of easy and cheap access to high calorie foods and drinks (and consumer pressure to get a ‘better deal’ by supersizing), less physical activity as our population demographics have switched from a rural to urban setting combined with our natural instinct to obtain calories for survival. In this type of setting, it may be impractical that any medication by itself will be a solution and thought

⁴ Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*, March 1977;159-174

⁵ Sachdev M, Miller WC, Ryan T, Jollis JG. Effect of fenfluramine-derivative diet pills on cardiac valves: A meta-analysis of observational studies. *Am Heart J*. 2002 Dec; 144(6):1065-73

needs to be given to wider interventions that can help to combat this epidemic. However, within the agency we feel the urgency to try to provide aid and appropriate treatments. This urgency however has to be weighed against any potential medication induced adverse effects. Lorcaserin has many concerning pre-clinical signals, and, while there has not been any demonstrated VHD, the risk has not been entirely ruled-out either. This is in the backdrop of fairly marginal efficacy findings.

As such, this application should receive a CR action. The sponsor will need to demonstrate that either there is an adequate margin (which may include readjudication of tissue slides or reexamination of stored tissue) for the pre-clinical concerns, or that they are rat specific and not applicable to humans. Regarding potential VHD, the sponsor will need to clarify potential discrepancies in the receptor binding studies, and then justify that the present database is adequate to put this concern to rest. This may be achieved (if receptor binding discrepancies can be clarified) if they can convince us that their database has an adequate number and length of exposures to identify rates of severe valvular heart disease (leading to replacement) as those seen with fen-phen. If not, it may require further echocardiography study. These studies may need to be done pre-marketing, or perhaps post-marketing depending on the information that the sponsor is able to provide.

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/s/

CURTIS J ROSEBRAUGH
10/22/2010

Summary Review for Regulatory Action

Date	
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	22529
Applicant Name	Arena Pharmaceuticals
Date of Submission	December 22, 2009
PDUFA Goal Date	October 22, 2010
Proprietary Name /Established Name	Lorcaserin/Lorqess
Dosage Forms / Strength	Tablet/10 mg BID
Proposed Indication(s)	Weight Management
Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Julie Golden, MD
Statistical Review	Janice Derr, PhD/Xiao Ding, PhD
Pharmacology/Toxicology Review	Fred Alavi, PhD/Todd Bourcier, PhD
CMC Review/OBP Review	Olen Stephens, PhD/John Duan, PhD/Raanan Bloom, PhD
Microbiology Review	NA
Clinical Pharmacology Review	Immo Zdrojewski, PhD/Sally Choe, PhD
DDMAC	Sam Skariah, PharmD
DSI	Kassa Ayalew, MD
CDTL Review	See Deputy Division Director Summary Memorandum
OSE/DMEPA	Lubna Najam, MS, PharmD
DRISK	NA
Thorough QT Consult	Christine Garnett, PhD
Controlled Substance Staff	Katherine Bonson, PhD

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations

DRISK=Division of Risk Management

CDTL=Cross-Discipline Team Leader

1. Introduction

This memorandum summarizes the conclusions and regulatory recommendations of the review disciplines assigned to this application. I am not aware of any significant disagreements within or between the review disciplines regarding final regulatory recommendations. A sizable portion of this memorandum deals with nonclinical carcinogenicity data – specifically mammary and brain tumors in rats – and issues of clinical efficacy and safety – in particular evaluations for valvular heart disease.

2. Background

Lorcaserin is a first-in-class, relatively selective oral agonist of the 5HT_{2c} receptor, which as of this writing, has not been approved by any regulatory body in the world. The sponsor is seeking approval of lorcaserin 10 mg BID for the treatment of obesity in obese (BMI ≥ 30 kg/m²) or overweight (BMI 25 – 29.9 kg/m²) individuals with at least one weight-related comorbidity. Activation of 5HT_{2c} receptors, which densely populate areas of the brain controlling appetite, has been shown in animal models to reduce caloric intake and decrease body weight. There is sufficient justification to study the weight-loss efficacy and safety of a 5HT_{2c} receptor agonist in humans.

Activation of the 5HT_{2b} receptor is believed to account for the association between dexfenfluramine and fenfluramine with left-sided valvular heart disease (VHD). These two weight-loss drugs were removed from the United States market following identification of this adverse effect in 1997. A detailed discussion of cardiac valve evaluation during the phase 3 lorcaserin clinical trials is provided in the reviews of Drs. Julie Golden and Xiao Ding and in the Clinical Safety section of this memorandum.

As discussed in detail in the reviews by Drs. Alavi and Bourcier and in the Nonclinical Pharmacology/Toxicology section of this memorandum, the Division was notified by the sponsor in late spring of 2007 that some rats in the then ongoing 2-year carcinogenicity had died and upon necropsy were found to have malignant tumors of the mammary gland and brain. These findings led to a series of interactions between the sponsor and the Division and the Agency's Executive Carcinogenicity Committee, as outlined below.

3. CMC

The CMC reviewer states that there are no pending deficiencies to resolve and recommends that the application be approved. I agree that there are no outstanding CMC issues at this time. Dr. Bloom from the Office of Pharmaceutical Science recommends a finding of no significant impact (FONSI).

4. Nonclinical Pharmacology/Toxicology

Nonclinical Carcinogenicity

Drs. Alavi and Bourcier recommend against approval of lorcaserin due to its characterization as a non-genotoxic carcinogen. Following review of the two-year rat carcinogenicity study of lorcaserin at low-dose (LD), mid-dose (MD), and high-dose (HD), the Agency's Executive Carcinogenicity Assessment Committee concluded that the following tumors were lorcaserin-related: Male: hepatocellular adenoma and carcinoma combined (HD), mammary adenocarcinoma and fibroadenoma combined (MD and HD), skin/subcutis squamous carcinoma and fibroma (MD and HD), schwannoma (MD and HD) and thyroid adenoma (HD); Female: mammary adenocarcinoma and fibroadenoma combined (LD, MD, and HD). Of particular concern are the mammary and brain tumors.

As shown in the table on pages 5-6 of Dr. Alavi's review, in female rats, the incidence rates of mammary adenocarcinoma as reported in the NDA were 43%, 52%, 54%, and 80% in the control, LD, MD, and HD groups, respectively. The incidence rates of mammary fibroadenoma in female rats were 31%, 72%, 82%, and 60% in the control, LD, MD, and HD groups, respectively. The test of trend was statistically significant for adenocarcinoma, fibroadenoma, and adenocarcinoma combined with fibroadenoma. Compared with the control group, the incidence of adenocarcinoma alone and fibroadenoma alone in the HD lorcaserin groups were statistically significantly greater. When adenocarcinoma and fibroadenoma are combined, the incidence rates in the individual active-treatment groups were statistically significantly greater versus control. The exposure margins were 7X the proposed clinical dose for the LD group, 24X for the MD group, and 82X for the HD group.

The incidence rates of mammary tumors in male rats exposed to lorcaserin was much lower than the rates observed in female rats. The tests of trend were statistically significant for fibroadenoma and for adenocarcinoma combined with fibroadenoma. There were no male rats in the control or LD groups that developed mammary adenocarcinoma; two rats in each of the MD and HD groups developed adenocarcinomas. The exposure margins were 5X the proposed clinical dose for the LD group, 17X for the MD group, and 55X for the HD group.

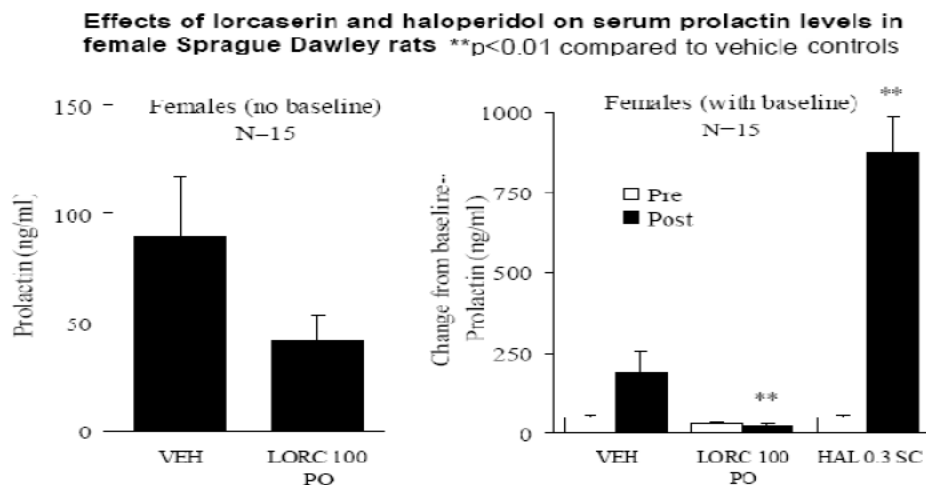
As pointed out by Drs. Alavi and Bourcier and shown in the table on pages 5-6 of Dr. Alavi's review, it appears that a number of female rats in the MD and HD groups identified as having mammary adenocarcinoma at the Week 96 time point were no longer classified as having adenocarcinoma in the final analysis. The incidence rates of adenocarcinoma decreased by 8%, 16%, 21%, and 16% in the control, LD, MD, and HD groups, respectively, from Week 96 to the final evaluation. Likewise, a number of female rats in the MD and HD groups classified as having mammary fibroadenomas at Week 104 were not classified as having fibroadenomas in the final analysis. In numerous cases, an initial classification of adenocarcinoma was subsequently changed to fibroadenoma. While there may be a logical explanation for these patterns of change, the sponsor has not provided one and they raise concern about the validity of the histological evaluations and diagnostic accuracy of the tumor data. That Dr. Alavi noted inconsistencies in the reporting of mammary tumor-related findings in some female rats adds to this concern.

If tumors were reclassified due to difficulty distinguishing benign versus malignant masses, this supports combining adenocarcinoma with fibroadenomas for statistical analysis. As noted above, the incidence rates of mammary adenocarcinoma plus fibroadenoma in female rats were statistically significantly greater in each of the lorcaserin groups versus control.

I would mention that while fibroadenomas may not represent a life-threatening risk to humans, a drug that increased the incidence of these breast tumors would add at least a temporary emotional burden to women following detection of a breast mass of unknown histology. This is admittedly a softer safety concern than adenocarcinoma.

The sponsor claims that the mammary tumor findings are not relevant to humans because they are due to lorcaserin-mediated increases in serum prolactin, a rodent-specific mechanism according to their consultant (b) (4). While drugs such as haloperidol have been shown to increase the risk for mammary tumors in rodents through increases in serum prolactin levels, Drs. Alavi and Bourcier do not believe that the totality of data provided by the sponsor support the hypothesis that lorcaserin increases prolactin levels in rats to an extent commensurate with the increase in the incidence of mammary tumors observed in the 2-year carcinogenicity study.

For example, as discussed in Dr. Alavi's review and shown in the figure below, following administration of a single oral doses of 100 mg/kg lorcaserin and a single subcutaneous dose of 0.3 mg/kg of haloperidol to female rats, compared with vehicle-treated animals, serum prolactin levels 30 minutes post-dosing were significantly lower in the lorcaserin-treated animals and significantly higher in haloperidol-treated animals.



In another study, following 28 days of treatment of female rats with 100 mg/kg lorcaserin or vehicle, serum prolactin levels were 569 ng/ml in the vehicle group and 167 in the lorcaserin group 2-hours post-dose; 409 ng/ml in the vehicle group and 882 ng/ml in the lorcaserin group 6-hours post-dose; and 294 ng/ml in the vehicle group and 205 ng/ml in the lorcaserin group 24-hours post-dose.

Following standard histological sampling and detection methods, one rat was identified with malignant astrocytomas in the control group compared with 2, 5 and 12 mostly male animals in the LD, MD, and HD groups, respectively. The concentration of lorcaserin in plasma is much lower than the concentration in the central nervous system (CNS). The CNS-to-plasma ratio is 35X in rats and 10X in monkeys. Hence, as pointed out by Dr. Alavi, if the CNS-to-plasma ratio of lorcaserin in humans is similar to rats, the safety margin for astrocytomas is only 5X the proposed clinical dose of lorcaserin; if the CNS-to-plasma ratio in humans is similar to monkeys, the safety margin is 14X the proposed clinical dose.

There were no notable tumor findings in the 2-year mouse carcinogenicity study of lorcaserin. However, drug exposure in female mice did not exceed 4X the proposed clinical dose and did not exceed 7X the proposed clinical dose in male mice. Thus, the mouse carcinogenicity data do not provide reassurance regarding the rat carcinogenicity findings.

Before lorcaserin is considered for approval, I agree with Drs. Alavi and Bourcier that all slides of mammary tissue need to be re-evaluated by an independent pathologist or pathologists. Ideally, the evaluations should be conducted blinded to treatment allocation. Particular attention should be paid to the tissue samples initially classified as adenocarcinoma and then re-read as fibroadenoma. The sponsor should also provide an explanation for the changes in the number of mammary tumors in female rats between the Week 96 and the final histological evaluation. In addition, the sponsor may need to explore mechanistic explanations other than prolactin for the mammary tumor findings as they relate to human risk.

Regarding astrocytomas, Dr. Bourcier recommends that additional CNS tissue samples from all experimental rat groups be evaluated to verify the dose-response relationship for astrocytomas. He believes that a more extensive evaluation of brain tissue is warranted because the standard carcinogenicity evaluation of brain tissue is limited and may have missed tumors. I do not disagree with this recommendation. However, given that lorcaserin levels are significantly higher in brain tissue, but not cerebrospinal fluid, than the plasma, it may prove difficult if not impossible to obtain an accurate measure of CNS levels of lorcaserin in humans to determine if an adequate margin of safety exists for this tumor. Our concern would be lessened if the sponsor provided data to support their assertion that the astrocytoma findings in rats are not relevant to humans.

Chronology of Events Related to the Nonclinical Carcinogenicity Assessments

Following the September 16, 2010, advisory committee meeting on lorcaserin, the Agency received numerous public emails raising the question of why the lorcaserin development program was allowed to proceed if FDA scientist were “so concerned” about the breast tumor findings in the 2-year rat carcinogenicity study. A chronology of interactions among the sponsor, the Division, and the Executive Carcinogenicity Committee related to nonclinical carcinogenicity information follows.

For point of reference, one of the pivotal phase 3 clinical trials was initiated in November of 2006, and was completed in February of 2009. A second pivotal phase 3 trial was initiated in January of 2008 and was completed in July of 2009. The third pivotal trial was initiated in

December of 2007 and was completed in mid-2010 (data not included in the NDA submission).



During discussions within the Division on and around June 20, 2007, Dr. Fred Alavi notified the clinical team that interim histological examination of rats that died prematurely during 2-year carcinogenicity study revealed the development of astrocytomas in 2 MD animals and 3 HD animals.

On June 28, 2007, the Division sent an advice letter to the sponsor acknowledging their plans to revise the investigator brochure and patient informed consent forms to include the rat mammary and brain tumor findings.

On August 29, 2007, the Division sent an advice letter to the sponsor requesting revisions to language in the patient informed consent form related to the rat mammary and brain tumor data.

At this time, the sponsor hypothesized that the mammary tumors were due to lorcaserin-induced increases in serum prolactin levels. It is well known that antipsychotics, for example, cause rat mammary tumors through elevations in serum prolactin levels – a mechanism that some believe does not pertain to humans. The sponsor's hypothesis was reasonable, but it needed to be substantiated with data on prolactin levels in animals and humans exposed to lorcaserin.

In September of 2007, the Division requested that Arena provide bi-monthly updates on the status of the ongoing carcinogenicity studies in rats and mice

From September 2007, through March 2008, the Division and the sponsor exchanged numerous communications related to the nonclinical tumor data and the assessment of serum prolactin levels, adverse events related to hyperprolactinemia, and breast cancer risk in subjects taking part in the ongoing clinical trials.

The bi-monthly updates on the ongoing carcinogenicity studies indicated a strengthening of the mammary adenocarcinoma and astrocytoma dose-response relationship with continued dosing of lorcaserin in rats. On April 1, 2008, The Agency's Executive Carcinogenicity Assessment Committee was briefed on the information, and stated that while conclusions must await completion of the studies, the interim data indicated that lorcaserin increases mammary adenocarcinoma at all dose levels in female rats and astrocytoma at the MD and HD levels.

Prior to meeting with the Executive Carcinogenicity Assessment Committee on April 1, 2008, the Division discussed internally whether the lorcaserin IND should be placed on clinical hold due to the nonclinical tumor/cancer data. The sponsor was made aware of our concerns and was asked to meet with us to defend continuation of their clinical development program. The sponsor provided a background package containing information not included in prior updates.

A face-to-face meeting with the sponsor was held on April 9, 2008.

Our decision to allow the clinical program to proceed following our meeting with the sponsor was based on the following: 1) the updated informed consent forms included the nonclinical breast and brain cancer findings; 2) we learned that drug exposure in rats was nearly twice as high as predicted, which increased the safety margin to clinical exposure; 3) preliminary data showed a modest increase in serum prolactin levels after a single dose in male rats, lending support to the hypothesis that prolactin was responsible for the rat mammary findings; 4) we acknowledged that the interim tumor incidence data would change (e.g., might be less worrisome) as full histopathology assessments became available after completion of the study, particularly for astrocytoma; 5) only with continued clinical study was it possible to assess whether long-term dosing with lorcaserin increased serum prolactin levels in humans; 6) only with continuation of clinical dosing would we obtain an accurate assessment of lorcaserin's weight-loss efficacy and safety in diabetics; and 7) given that lorcaserin is non-genotoxic, we believed that cancer risk was low under the conditions of use in the ongoing clinical trials (not the case with chronic or indefinite use).

Receptor Binding Affinity and Activation and Cardiac Valvulopathy

As stated by Dr. Bourcier in his briefing document for the September 16, 2010 advisory committee meeting, "lorcaserin preferentially activates 5HT_{2C} with 8 to 15-fold greater potency compared to 5HT_{2A}, and 45 to 90-fold greater potency compared to 5HT_{2B}. Depending on the studies one considers, off-target activation of 5HT_{2A} 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." Data on the relative binding and activation of serotonin receptors by lorcaserin are shown in the below table from excerpted from Dr. Bourcier's briefing document.

Lorcaserin's Relative Receptor Binding and Activation Profile

	5HT2A	5HT2B	5HT2C
Receptor Binding (K _i , nM)	92	147	13
PI Hydrolysis (EC ₅₀ , nM)	133	811	9
Calcium release (EC ₅₀ , nM)	52	350	6

These *in-vitro* data provide a modest degree of comfort regarding lorcaserin's potential to activate the 5HT2b receptor and promote cardiac valvular abnormalities.

I am also somewhat reassured by the fact that there were no notable imbalances in cardiac valve abnormalities (e.g., hypertrophy) reported in rats treated long-term with lorcaserin versus control.

5. Clinical Pharmacology

The clinical pharmacology reviewer concludes that the data submitted in support of the NDA are acceptable and recommends that the application be approved. I agree with the reviewer that there are no outstanding clinical pharmacology issues.

Based on review of the data from a thorough QT study, the Agency's interdisciplinary review team for QT studies concluded that lorcaserin does not significantly prolong the QT interval. The largest upper bounds of the 2-sided 90% CI for the mean difference between lorcaserin (10 mg and 50 mg) and placebo was below 10 ms.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Dr. Golden is recommending that the lorcaserin application not be approved at this time due to an unfavorable benefit-to-risk profile: marginal weight-loss efficacy, coupled with the inability of the sponsor to rule out an increase of 50% in the risk for valvulopathy, and unclear relevance of the rat tumor findings, particularly of breast and brain tissue, to humans.

Phase 3 Clinical Trials

The long-term efficacy of lorcaserin was examined in two phase 3 clinical trials.

BLOOM was a placebo-controlled two-year trial that randomized approximately 3000 overweight and obese male and female subjects to placebo or lorcaserin 10 mg BID in a 1:1 manner. After one year of treatment, the lorcaserin group was re-randomized 2:1 to lorcaserin

10 mg BID or placebo, stratified by 5% weight loss responder status. The subjects originally randomized to placebo remained on placebo during the second year. The primary endpoints were weight loss following one year of treatment and maintenance of weight loss during a second year of treatment.

BLOSSOM was a placebo-controlled one-year trial that randomized approximately 4000 overweight and obese male and female subjects to placebo, lorcaserin 10 mg QD, or lorcaserin 10 mg BID in a 2:1:2 fashion. The primary endpoint was weight loss following one year of treatment.

As shown in the below table from Dr. Golden's review, the baseline demographic characteristics were well-matched for the three treatment groups. The mean age of the study participants was about 44 years, 82% were women, and 67% were Caucasian and 20% African-American. The average BMI was 36 kg/m². Approximately 42% of the subjects had at least one weight-related comorbidity, primarily hypertension and/or dyslipidemia. There were no overweight or obese type 2 diabetic subjects in BLOOM or BLOSSOM.

Baseline Subject Demographics - Pooled Data from BLOOM and BLOSSOM

	Lorcaserin 10 BID N=3195	Lorcaserin 10 QD N=801	Placebo 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, %	67.7	67.2	66.2
Black, %	18.9	20.0	19.4
Hispanic, %	11.1	10.7	12.4
BMI, kg/m ² 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			

In BLOOM, 55% of subjects randomized to lorcaserin and 45% of subjects randomized to placebo completed the first year of the study. Approximately 73% of subjects who entered the second year of the study completed that phase of the trial. In BLOSSOM, 57% of subjects randomized to lorcaserin 10 mg BID, 59% of subjects randomized to lorcaserin 10 mg QD, and 52% of subjects randomized to placebo completed the one-year trial. These drop-out rates are consistent with those from other weight-loss drug trials. The most commonly-reported reason for premature withdrawal from the two lorcaserin phase 3 studies was "patient decision" followed by "lost to follow-up". Adverse events accounted for approximately 6-7% of the drop-outs in the lorcaserin groups and about 5% in the placebo groups.

The primary efficacy analyses were performed on the modified intent-to-treat (MITT) population, defined as all randomized subjects who had a baseline weight measurement, took at least one dose of study drug, and had at least one post-baseline weight measurement. Unless indicated otherwise, the below efficacy data are from the MITT population with the last observation carried forward (LOCF).

In BLOOM, the mean adjusted placebo-subtracted weight loss following up to one year of treatment with lorcaserin 10 mg BID was -3.7% ($p < 0.0001$). In BLOSSOM, mean adjusted placebo-subtracted weight loss following up to one year of treatment with lorcaserin 10 mg BID was -3.0% and -1.9% with lorcaserin 10 mg QD ($p < 0.0001$ for both groups). In an analysis of data pooled from BLOOM and BLOSSOM, the mean adjusted placebo-subtracted weight loss following up to one year of treatment with lorcaserin 10 mg BID was approximately -3.0% ($p < 0.001$).

In BLOOM, the percentages of subjects achieving $\geq 5\%$ weight loss following up to one year of treatment were 48% in the lorcaserin 10 mg BID group and 20% in the placebo group ($p < 0.001$). In BLOSSOM, the percentages of subjects achieving $> 5\%$ weight loss following up to one year of treatment were 47% in the lorcaserin 10 mg BID group, 40% in the lorcaserin 10 mg QD group, and 25% in the placebo group ($p < 0.0001$ for both groups vs. placebo). In an analysis of data pooled from BLOOM and BLOSSOM, the percentages of subjects achieving $\geq 5\%$ weight loss following up to one year of treatment were 47% in the lorcaserin 10 mg BID group and 23% in the placebo group ($p < 0.001$).

As stated in the Agency's 2007 Draft Guidance for Developing Products for Weight Management, in general, a product can be considered effective for weight management if after one year of treatment either of the following occurs:

- 1. 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*
- 2. 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*

Lorcaserin 10 mg BID failed to satisfy the mean efficacy criterion but did, by a slim margin, satisfy the categorical efficacy criterion when data from the BLOOM and BLOSSOM trials were pooled.

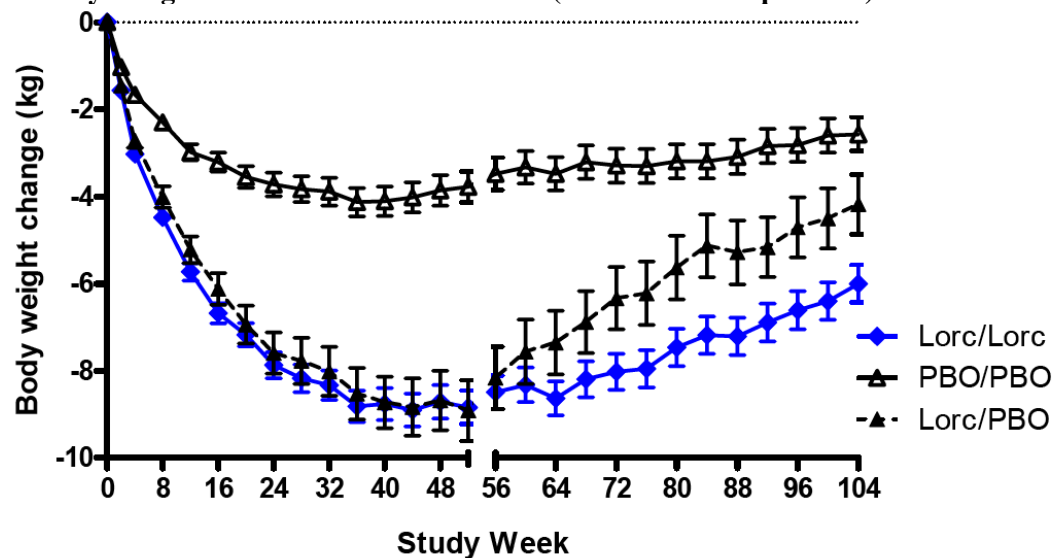
In general, lorcaserin-associated weight loss was associated with improvements in blood pressure, levels of high-density lipoprotein lipid and triglycerides, and fasting glucose and insulin concentrations commensurate with the degree of weight loss.

Other efficacy endpoints of interest include the percentage of subjects achieving $\geq 10\%$ weight loss and the durability of lorcaserin-induced weight loss.

In an analysis of data pooled from BLOOM and BLOSSOM, 22% of subjects treated with lorcaserin 10 mg BID versus 9% of subjects treated with placebo lost $\geq 10\%$ of baseline weight following up to one year of treatment.

As shown in the figure below, compared with placebo, treatment with lorcaserin 10 mg BID attenuated weight regain during a second year of treatment. Of note, however, the slope of the line depicting the change in mean body weight in the subjects treated with lorcaserin is more positive during the second year of treatment than the line depicting the mean change in body weight in the placebo group (similar patterns of change were shown for the Completers population). This raises the question of whether body weight in lorcaserin-treated subjects would reach that of placebo-treated subjects with treatment beyond 2 years.

Change in Body Weight from Baseline to Week 104 (Per-Protocol Population)



The BLOSSOM and BLOOM trials did not include subjects with type 2 diabetes. To the best of my knowledge, the efficacy of all weight-loss drugs tends to be less in overweight and obese type 2 diabetics compared with overweight or obese nondiabetics. It will therefore be important to review the data from a recently-completed study of lorcaserin in overweight and obese type 2 diabetics. The sponsor stated that data from the study in diabetics should be available by the end of 2010. The data from type 2 diabetics take on greater significance given that the efficacy of lorcaserin in nondiabetics is marginal.

8. Safety

Valvular Heart Disease

The weight-loss drugs dexfenfluramine and fenfluramine were removed from the United States market in 1997 due to reports implicating their involvement in the development of left-sided VHD. Research conducted subsequent to this discovery suggested that dexfenfluramine and fenfluramine's activation of the 5HT_{2b} receptor on valvular tissue was the mechanism

responsible for the VHD. In a 2002 meta-analysis of nine cross-sectional studies, the incidence of FDA-defined VHD (at least mild aortic regurgitation or at least moderate mitral regurgitation) in subjects exposed to fenfluramine or dexfenfluramine for more than 3 months was calculated to be 12% versus 6% in unexposed or control subjects [OR = 2.2 (95% CI 1.7, 2.7)].¹ Subjects exposed to fenfluramine or dexfenfluramine for less than 3 months did not appear to have an increased risk for FDA-defined VHD.

Given that lorcaserin targets the serotonergic system, VHD was identified as a leading safety concern requiring extensive evaluation during the drug's clinical development. Although the results of *in-vitro* studies indicate that lorcaserin's binding affinity for and activation of the 5HT2b receptor are lower than those of dexfenfluramine and fenfluramine, the Division requested that the sponsor conduct echocardiographic evaluation of heart valves in all subjects participating in long-term lorcaserin clinical trials.

Arena proposed that the phase 3 clinical development program be powered to rule out a doubling of the risk for FDA-defined VHD. The Division believed that a doubling was too permissive and requested that the program be powered to rule out at least a 50% increase in risk (i.e., upper bound of the 95% CI 1.5 or less). This necessitated increasing the sample size of the phase 3 program from approximately 4000 to 7000 subjects. It was made clear to the sponsor that ruling out at least a 50% increase in the risk for FDA-defined VHD was an arbitrary benchmark and that the adequacy of the valvulopathy data would be determined by not only the data themselves, but lorcaserin's efficacy and overall safety profile as well.

All echocardiograms obtained in the BLOOM and BLOSSOM trials were over-read by 2 blinded central readers. Any discrepant readings between the two primary readers were adjudicated by a third reader. In BLOOM, echocardiograms were obtained at screening and at Weeks 24, 52, 76, and 104/exit. In BLOSSOM, echocardiograms were obtained at screening and at Weeks 24 and 52/exit. The primary endpoint of the echocardiographic evaluations was the incidence of FDA-defined valvulopathy at Week 52.

The incidence rates and relative risks for FDA-defined VHD at Week 52 are shown below in a table modified from Dr. Golden's review. In BLOOM, the incidence rates for VHD in the safety population were 2.4% for placebo and 2.7% for lorcaserin 10 mg BID [RR 1.13 (95% CI 0.69, 1.85)]. In BLOSSOM, the incidence rates for VHD were 2.0% for placebo and 2.0% for lorcaserin 10 mg BID [RR 1.0 (95% CI 0.57, 1.75)]. In the analysis of pooled data, the RR for FDA-defined VHD was 1.07 (95% CI 0.74, 1.55). The kappa statistic was 0.32 for reading of the mitral valve and 0.38 for reading of the aortic valve. These values indicate that the echocardiographic readings from the two primary readers were in fair agreement.

Given that the upper bound of the 95% confidence interval for the relative risk for FDA-defined VHD with lorcaserin exceeded 1.5, albeit by a small amount, one cannot conclude that the lorcaserin is non-inferior to placebo. When the valvulopathy analysis is restricted to subjects who completed 52 weeks of treatment, the RR for FDA-defined valvulopathy was

¹ Sachdev M, et al. Effect of fenfluramine-derivative diet pills on cardiac valves: A meta-analysis of observational studies. *Am Heart J* 2002; 144:1065-73.

0.90 (95% CI 0.59, 1.38). It should be noted, however, that the RR estimates for VHD in BLOSSOM are considerably different for the safety and completers populations. The reason for the discrepancy is unclear, but it was not observed in BLOOM.

The lorcaserin development program provides the largest amount of controlled data on the prevalence of FDA-defined VHD in overweight and obese individuals and I believe the only data on the incidence of VHD in this target population. It bears mentioning that the prevalence of FDA-defined VHD in subjects screened for participation in the BLOSSOM trial was approximately 4.5%, similar to the 6% prevalence rate for FDA-defined VHD reported in control subjects from the 2002 meta-analysis of observational studies by Sachdev, et al.

Incidence of FDA-Defined Valvulopathy at Week 52

	BLOOM		BLOSSOM			POOLED	
	Pbo	Lorc 10 BID	Pbo	Lorc 10 QD	Lorc 10 BID	Pbo	Lorc 10 BID
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 (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 (95% CI)		1.12 (0.65, 1.95)			0.63 (0.32, 1.27)		0.90 (0.59, 1.38)

Although the VHD associated with dexfenfluramine and fenfluramine was predominately left-sided, use of other 5HT2b agonists has been associated with abnormalities of the right-sided heart valves. It is therefore of interest to examine the proportion of subjects who experienced any increase from baseline in valvular regurgitation of any cardiac valve at Week 52 (excluding absent to trace) was 33% in the lorcaserin 10 mg BID group and 28% in the placebo group (see following table from Dr. Golden's review).

Proportion of Subjects with an Increase from Baseline in Valvular Regurgitation at Week 52 Excluding Absent to Trace

	Lorcaserin 10 BID	Placebo	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

The increases in the proportion of subjects exposed to lorcaserin 10 mg BID versus placebo that had increases in regurgitation of the pulmonic and tricuspid valves were of nominal statistical significance. The clinical significance of these findings is unknown.

Importantly, there were no cases of moderate or severe aortic regurgitation or severe mitral regurgitation observed in the BLOSSOM or BLOOM trials.

The echocardiographic data from the lorcaserin program provide reasonable assurance that this drug is not associated with the degree of risk for VHD observed with dexfenfluramine or fenfluramine. Taking into account the *in-vitro*, nonclinical, and clinical data, I do not believe that lorcaserin is associated with a prohibitive risk for FDA-defined VHD. However, I do believe serious thought should be given to obtaining additional echocardiographic data to provide a more precise estimate (i.e., tighter confidence interval) of lorcaserin's effect on valvular morphology and function. This could perhaps be done post-approval, assuming that the sponsor adequately addresses all other outstanding safety concerns and deficiencies.

Primary Pulmonary Hypertension

Some anorexigens, including dexfenfluramine and fenfluramine, have been associated with an increased risk for the development of primary pulmonary hypertension (PPH), a rare but usually fatal disease. As Dr. Golden discusses in her review, it is estimated that no more than 1 in 1000 individuals exposed for more than 3 months to fenfluramine or dexfenfluramine developed PPH. The mechanism(s) responsible for fenfluramine and dexfenfluramine-associated PPH are not well defined. Yet, some evidence suggests that activation of the 5HT_{2a} or 5HT_{2b} receptors may play a causative role. Although cardiac catheterization is required to definitively diagnose of PPH, pulmonary artery systolic pressure (PASP) of 27-50 mmHg suggest *possible* PPH and values greater than 50 mmHg suggest *likely* PPH.

As shown in the following table extracted from Dr. Golden's review, there was a slightly higher percentage of lorcaserin- compared with placebo-treated subjects who developed elevated PASP values during BLOOM and BLOSSOM.

Subjects with Elevated PASP Values during BLOOM and BLOSSOM

	Lorc 10 BID	Pbo
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

On pages 95-96 of Dr. Golden's review case narratives are provided for the two lorcaserin-exposed subjects who developed PASPs > 50 mmHg. Based on this information, it is difficult to conclude that lorcaserin was a probable or even possible cause of the increased PASP readings.

No subject treated with lorcaserin was reported to have been diagnosed with PPH. Given the size and duration of the clinical development program, it is safe to assume that lorcaserin is not associated with an increase in the risk of PPH to a degree observed with fenfluramine and dexfenfluramine. But given the rarity of PPH, it would take wide-spread use of lorcaserin before one could determine if the drug is associated with a small or modest increase in risk for PPH. At this point, PPH remains a theoretical risk for lorcaserin.

Other Relevant Safety Considerations

There were two deaths reported during the development program; both in subjects randomized to placebo. The incidence rates for serious adverse events from the phase 3 clinical trials were 2.3% in placebo-treated subjects and 2.7% in subjects randomized to lorcaserin 10 mg BID.

A total of 0.8% of subjects randomized to lorcaserin 10 mg BID and 1.0% of subjects randomized to placebo from BLOOM and BLOSSOM were diagnosed with any type of cancer.

Four subjects (0.1%) randomized to lorcaserin 10 mg BID and four subjects (0.1%) randomized to placebo in BLOOM and BLOSSOM were diagnosed with breast cancer. The lack of an increase in the number of breast cancer cases in lorcaserin-treated subjects does not indicate that the drug is without risk for this cancer. The size and duration of the phase 3 trials and the average age of the study participants were inadequate to assess the question.

There was an imbalance in cognitive-related adverse events in subjects from the lorcaserin 10 mg BID groups (2.4%) compared with subjects from the placebo groups (0.8%). “Memory impairment,” “disturbance in attention,” and “amnesia” were the terms with the largest imbalances between active drug and placebo. These effects may be mediated through activation of the 5HT_{2a} receptor in the CNS.

There were no notable imbalances between treatment groups in adverse events related to suicidality in the phase 3 clinical trials. Suicidality has been a concern with some centrally-acting weight-loss drugs.

Given lorcaserin’s mechanism of action, serotonin syndrome is a potential risk for this compound. As noted on pages 117-118 of Dr. Golden’s review, there were 2 cases from the lorcaserin development program that investigators considered to fall within the spectrum of serotonin toxicity. Both subjects were randomized to lorcaserin 10 mg BID. When all potential clinical signs or symptoms of serotonin toxicity – chills, tremor, confusional state, disorientation, and hyperhidrosis – were assessed, 1.7% of subjects from the lorcaserin 10 mg BID groups versus 0.6% of subjects from the placebo groups reported at least one of these signs or symptoms during the phase 3 clinical trials.

Dr. Alavi raises some concern in his review of nonclinical data about adverse renal findings in monkeys, but not rats, treated with lorcaserin. The adverse effects in monkeys included renal tubular regeneration and degeneration at lorcaserin doses \geq 10 mg/kg and 125 mg/kg, respectively. There was no evidence from the phase 3 clinical trials that lorcaserin 10 mg BID increased risk for renal toxicity.

9. Advisory Committee Meeting

An advisory committee meeting was held on September 16, 2010, to discuss the efficacy and safety of lorcaserin. In response to the question of whether the potential benefits of lorcaserin

outweighed the potential risks, the committee voted 9 “no” and 5 “yes”. The marginal weight-loss efficacy combined with uncertainty regarding the clinical relevance of the nonclinical tumor data and the “healthy” status of the subjects studies in the phase 3 clinical trials were principal reasons for the “no” votes.

10. Pediatrics

(b) (4)
Since the application is not being approved this review cycle, details of the proposed pediatric plan will be addressed in consultation with PeRC at a later date.

11. Other Relevant Regulatory Issues

Dr. Golden notes in her review that the sponsor has certified that no investigator from the phase 3 pivotal trials has entered into a financial agreement with the sponsor.

Routine inspection of four clinical sites by the Division of Scientific Investigation did not uncover any significant deficiencies or irregularities in reporting of clinical data.

The Controlled Substance Staff believe that lorcaserin has abuse potential and recommend that it be placed in Schedule IV of the Controlled Substance Act.

12. Labeling

Because the application will receive a Complete Response, there were no labeling reviews or negotiations with the sponsor.

13. Decision/Action/Risk Benefit Assessment

The clinical and pharmacology/toxicology reviewers recommend that the lorcaserin application not be approved at this time. I agree that the currently-available data do not support a favorable benefit-risk profile for lorcaserin. I support issuing a Complete Response on the PDUFA goal date of October 22, 2010.

The mean placebo-subtracted change in body weight in subjects treated with lorcaserin 10 mg BID for up to one year was approximately -3.0%. The proportion of subjects who lost $\geq 5\%$ of baseline body weight was 47% in the lorcaserin 10 mg BID group and 23% in the placebo group. It is safe to assume that lorcaserin’s efficacy in overweight and obese type 2 diabetics will be less than that demonstrated in the overweight and obese nondiabetics. Before re-considering approval of lorcaserin, the sponsor needs to submit the final study report for the recently-completed study in type 2 diabetics.

Although the Agency’s draft obesity drug guidance states that efficacy will be assessed following one year of treatment, the sponsor voluntarily conducted a two-year trial. Data from

this trial raise concern that lorcaserin's efficacy wanes considerably with treatment beyond one year.

Against this marginal and perhaps transient efficacy, one must weigh the following potential risks:

1). Nonclinical tumorigenicity: In a two-year rat carcinogenicity study lorcaserin was associated with an increased number of benign and malignant tumors. Of greatest concern are malignant tumors of breast and brain tissue. Given irregularities in the diagnosing and reporting of breast adenocarcinomas and fibroadenomas during and following completion of the rat carcinogenicity study, I support pharmacology/toxicology's recommendation that *all* of the rat breast tissue slides be re-adjudicated by an independent pathologist(s). It is vital that we are confident in the histological diagnoses of all of the rat breast tumors, given that the target population for weight-loss drugs tends to be overweight and obese middle-aged women, individuals at heightened risk for breast cancer due to their body weight.

Regarding astrocytomas, I do not disagree with the recommendation to have the sponsor conduct a more detailed evaluation of rat brain tissue, but suspect that we will be left with some degree of uncertainty regarding the clinical relevance of the rat findings regardless of the outcome of the additional evaluations. Given that astrocytoma is a relatively uncommon tumor in humans (7-10 cases per 100,000 people), it is possible that a post-approval registry would be an acceptable approach to studying the clinical relevance of the rat data.

2). Valvular heart disease: Based on echocardiographic evaluation of approximately 7000 subjects, the sponsor provided evidence that rules out a 55% or greater increase in the risk for FDA-defined VHD. I believe additional echocardiographic data should be obtained to improve the precision of the risk estimate. However, depending on the sponsor's response to the deficiencies included in the Complete Response letter, it may be appropriate to obtain the additional echocardiographic data as a post-marketing requirement.

3). Cognitive-related adverse events: There was a notable imbalance in cognitive-related adverse event in subjects treated with lorcaserin versus placebo. When viewed in isolation, I do not believe that these adverse events would prevent approval of the drug.

4). Serotonin syndrome: There was a weak signal for serotonin toxicity from the phase 3 clinical data. This is not surprising given lorcaserin's mechanism of action. When viewed in isolation, I do not believe that this potential toxicity would prevent approval of the drug.

5). Primary pulmonary hypertension: There was perhaps a very weak signal for increased pulmonary artery pressure in lorcaserin-treated subjects. Given the rarity of PPH (~ 500 cases per year in the U.S.), the only realistic means to determine if lorcaserin increases the risk for the disease would be by conducting a case-control study post-approval.

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/s/

ERIC C COLMAN
10/21/2010

CLINICAL REVIEW

Application Type	NDA
Application Number	22529
Priority or Standard	Standard

Submit Date	December 22, 2009
Received Date	December 22, 2009
PDUFA Goal Date	October 22, 2010
Division / Office	DMEP / ODE 2

Reviewer Name	Julie K. Golden
Review Completion Date	October 21, 2010

Established Name	Lorcaserin hydrochloride
Proposed Trade Name	Lorqess
Therapeutic Class	Obesity
Applicant	Arena Pharmaceuticals, Inc.

Formulation	Tablet
Dosing Regimen	10 mg BID
Indication	Weight management
Intended Population	BMI \geq 30 kg/m ² or \geq 27 kg/m ² with co-morbidities

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that this application receive a complete response action for failure to establish that the benefits of lorcaserin treatment outweigh the potential risks.

Specifically:

- Only one of the 2 efficacy benchmarks was marginally achieved
- Non-inferiority (i.e., RR 95% C.I. upper bound < 1.5) to placebo for the risk of developing FDA-defined valvular heart disease at 52 weeks was not established
- The clinical relevance of the carcinogenicity signal observed in rats, particularly for tumors of the breast and brain, cannot be dismissed

1.2 Risk Benefit Assessment

Obesity is associated with a myriad of adverse health outcomes, including diabetes mellitus/insulin resistance, cardiovascular disease (including related biomarkers such as dyslipidemia and hypertension), sleep apnea, venous stasis, gallbladder disease, osteoarthritis, depression, and some forms of cancer. Weight loss beneficially impacts many of these conditions. FDA, in concert with the NIH overweight and obesity guidelines,¹ has defined clinically important weight loss as 5 percent: in effect, the amount of weight loss that generally provides demonstrable improvement in cardiovascular and metabolic biomarkers for disease.²

Lorcaserin meets one of the two standards for achievement of the 5 percent benchmark: 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. Strict doubling of the placebo incidence was achieved in one trial but not achieved in another trial. The other standard – the difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is

¹ Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. NIH Publication Number 98-4083; September 1998. U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute.

² FDA Draft Guidance for Industry: Developing Products for Weight Management. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf> Accessed 27 July 2010.

statistically significant – was not achieved by lorcaserin (the mean difference was 3.7% for one trial and 3.0% for another trial).

Other obesity drugs have been approved in the United States by meeting only the categorical 5 percent endpoint. Nevertheless, given the following safety concerns, I believe that achieving the minimal requirements for weight loss cannot be considered sufficient for approval of lorcaserin at this time. In other words, the small potential benefit of lorcaserin treatment for obesity does not outweigh the potential risks.

- Valvular heart disease. Lorcaserin is a 5HT_{2C} receptor agonist. The 5HT_{2C} receptor is a member of the family of serotonin receptors that includes 5HT_{2B} – agonism of which has identified as the likely culprit for fenfluramine-, dexfenfluramine-, and ergotamine-associated valvular heart disease (VHD). Given this potential relationship, the primary safety concern during lorcaserin development was VHD. During development, FDA stressed to the sponsor that ruling out a 50% increase for the development of FDA-defined VHD (greater than mild mitral or greater than trace aortic regurgitation) was a key safety endpoint of the phase 3 program. The clinical data as collected up to this point do not exonerate the drug for this potential risk, as the noninferiority margin prespecified by FDA was not achieved. Notably, patients who developed fenfluramine-associated valvular regurgitation had a spectrum of valvular-related morbidity, including in some cases, valve replacement surgery. Despite the theoretical nature of this risk, the potential for harm, particularly in the absence of demonstrated cardiovascular benefit is high. Additional echocardiogram data generated in the ongoing diabetes trial may be supportive, but are unlikely to be definitive given the relatively small number of patients randomized (n=604).
- Rat carcinogenicity. In 2-year carcinogenicity studies in rats, lorcaserin caused mammary gland tumors in both genders at clinically relevant exposures, with no safety margin identified for female rats. Although the sponsor claims that this is a prolactin-mediated phenomenon, a clear relationship between prolactin elevation and tumorigenesis was not established. 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. Astrocytoma is particularly concerning, given that lorcaserin targets the central nervous system. The concentration of lorcaserin in human brain is unknown, thus safety margins are only estimates. As members of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) articulated, the clinical relevance of these tumors cannot be dismissed. In my opinion, if additional nonclinical evaluation cannot clearly

mitigate this risk, a demonstrable clinical benefit of lorcaserin in a higher-risk population may be the only way to offset this concern.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I believe that the development of Postmarket Risk Evaluation and Mitigation Strategies (REMS) is not currently warranted, given the regulatory recommendation.

1.4 Recommendations for Postmarket Requirements and Commitments

I believe that the development of Postmarket Requirements (PMRs) and Commitments (PMCs) is not currently warranted, given the regulatory recommendation.

2 Introduction and Regulatory Background

2.1 Product Information

Lorcaserin hydrochloride (proposed tradename: Lorqess) is a new molecular entity (NME) developed for weight management. It is a first-in-class 5-hydroxytryptamine 2C (5HT_{2C}) receptor agonist; the 5HT_{2C} receptor resides in appetite centers in the brain and regulates energy intake.

The proposed indication is as follows:

- Lorqess 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. Lorqess is indicated for obese patients with an initial body mass index ≥ 30 kg/m², or overweight patients with a body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea).

The proposed dose for marketing is 10 mg twice-a-day (BID).

2.2 Currently Available Treatments for Proposed Indication

The only currently approved drug with a weight management indication for the same patient population (BMI ≥ 30 kg/m² or ≥ 27 kg/m² with of at least one

weight related comorbid condition) is orlistat (Xenical). While this review was being completed, sibutramine (Meridia), the other obesity drug approved for the chronic treatment of obesity, was removed from the market (8 October 2010) due to adverse cardiovascular risk identified in the Sibutramine Cardiovascular Outcome Trial (SCOUT). See section 2.4 for further discussion.

2.3 Availability of Proposed Active Ingredient in the United States

Lorcaserin hydrochloride is not available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

In the mid-1990s, fenfluramine as one component of the fenfluramine-phentermine (“fen-phen”) sensation and dexfenfluramine were ushering in a new era of chronic pharmacological treatment of obesity. Reports of valvular heart disease associated with fenfluramine and dexfenfluramine led to their withdrawal from the U.S. market in 1997. Lorcaserin notably targets the same serotonin receptors as fenfluramine and dexfenfluramine, albeit more selectively.

Sibutramine and orlistat were approved for chronic obesity treatment shortly after the withdrawal of fenfluramine and dexfenfluramine. The publication of SCOUT^{3,4} earlier this year demonstrated that sibutramine treatment in patients at high risk for cardiovascular disease resulted in 11.4% of patients developing a major adverse cardiovascular event as compared to 10% of placebo-treated patients. Sibutramine was recently removed from the U.S. market due to these findings. Orlistat, the only currently FDA-approved obesity drug, has 4-year weight loss data (45% of orlistat-treated patients lost 5% or more of body weight as compared to 28% of placebo-treated patients). Additionally, orlistat was shown to delay the onset of type 2 diabetes in obese patients with impaired glucose tolerance over this 4-year trial period. Nevertheless, orlistat is now used most often in its lower dose in a nonprescription setting, a setting in which long-term benefit has not been evaluated. Additionally, orlistat has been associated with rare events of serious liver toxicity.

Despite meeting the efficacy requirements for chronic weight loss established in the newly published FDA draft guidance for weight management products, the development program for rimonabant, the first in a wave of cannabinoid-1

³ James WPT, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010; 363:905-17.

⁴ FDA Early Communication about an Ongoing Safety Review of Meridia (sibutramine hydrochloride). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm191650.htm> Accessed 19 July 2010.

receptor antagonists for obesity, was dismantled after suicidality concerns emerged.

Most recently, EMDAC voted 10 to 6 that the benefits of Qnexa (phentermine/topiramate) were not adequately shown to outweigh its potential risks (primarily teratogenicity), despite robust weight loss at the high dose.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The lorcaserin program was designed to conform to the February 2007 FDA draft guidance for developing weight management drugs.² 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 7.3.5.

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 benchmarks⁵) 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)

⁵ 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.

echocardiogram, and use of a third reader in case of non-agreement (see section 7.3.5 and 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. Alavi, and clinical findings are presented in section 7.6.1. The sponsor did submit a revised informed consent and investigator's brochure under IND 69,888 serial number 54 that included the information known at that time about the astrocytoma and breast carcinoma findings in the rat carcinogenicity study. 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 also presented in section 7.6.1.

Finally, it should 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. The sponsor was informed that in the event that lorcaserin is approved prior to the completion of BLOOM-DM, 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.

Milestone meetings were the end-of-phase 2 (EOP2) meeting held on May 1, 2006 and the preNDA meeting held on August 12, 2009.

The following clinical issues and requests were discussed at the EOP2 meeting:

- The sponsor may want to be more conservative in drop-out estimate of 40% and increase this to 50%, in order to ensure adequate exposures after one year.
- The primary endpoint should include the categorical 5% response as well as the difference between groups in mean change from baseline to the end of Year 1.
- No regulatory definition of weight maintenance is available, but any proposal should be tied to the 5% weight loss criterion.
- A program designed to exclude a requirement for echocardiographic monitoring post-approval would take into account the following: 1) the FDA-defined criteria of drug-induced valvulopathy, 2) the consideration of prevalence data from the Framingham Heart Study or other large database, and 3) the need to rule out a small increase in the risk for development of FDA-defined drug-induced valvulopathy (e.g., $RR < 1.5$). FDA additionally noted that it is unlikely that we could commit to a lack of need for post-

approval echocardiographic monitoring until after we have reviewed all of the Phase 3 efficacy and safety data.

- The clinical development program should be designed to assess safety and efficacy in adults ≥ 18 years old who are obese (that is, a BMI ≥ 30 kg/m²), or in those who have a BMI ≥ 27 kg/m² with at least one co-morbid condition.
- Echocardiograms will need to be conducted at screening and exclude individuals with echocardiographic evidence of clinically significant valvular abnormalities.
- A plan for detailed evaluation and long-term follow-up of any valvulopathy cases as well as increased PA pressure + RV enlargement cases that are found in the trial should be implemented.
- Echocardiograms will need to be conducted in all trials lasting longer than 3 months in duration and should be performed every 6 months.
- Because the maximum tolerated dose (MTD) differently in males (40 mg) and females (20 mg) was defined differently, based on CNS findings, pharmacokinetic analysis by gender, in addition to other subject characteristics of interest, such as BMI, should be performed.
- Detailed assessments of mood, suicidality, cognitive function, and the potential for psychosis using validated instruments will need to be performed. There should be a plan to have a predefined algorithm for psychiatric and/or neurological referral.
- The issue of the safety of studying APD356 and SSRIs concomitantly will need to be discussed further.
- Body composition (e.g., by DEXA) should be assessed in at least one phase 3 trial.
- FDA recommended a two-week 'run-in' period of diet and exercise in order to enrich the study population and thus minimize non-compliance and reduce the number of subjects that dropout during the course of the trial.

The following clinical issues and requests were discussed at the preNDA meeting:

- FDA will not necessarily approve a (b) (4)
- The valvulopathy endpoint is considered as critical as the weight endpoint for approvability. As was previously conveyed, at a minimum the echocardiographic data must be robust enough to rule out a relative risk of 1.5 for FDA-defined valvulopathy.
- Source documents (written interpretations) of echocardiography should be provided for all cases of FDA-defined valvulopathy and in those situations that required third reader adjudication for AR and MR readings with ≥ 2 grades discordance.
- Echocardiographic results should be presented by study separately and combined.

- The sponsor was provided a list of items from the clinical review template that should be included as analyses in the NDA.
- Discontinuations due to “other” reasons need to be identified.
- AEs of special interest should be analyzed: cardiac valve disorders, pulmonary hypertension, depression and suicide, psychosis, serotonin syndrome, breast neoplasms, and priapism (male and female).
- A retrospective suicidality analysis should be conducted. Certain aspects of the scoring were asked to be clarified and the work process document was asked to be included.
- Liver laboratory cut-points of interest were requested to be analyzed.
- Key ISS tables (deaths, SAEs, and AEs leading to discontinuation) should hyperlink to the relevant CRFs.
- Narratives should be provided for deaths and SAEs.
- The sponsor should consider returning to demonstrate the electronic submission for the primary reviewers.

2.6 Other Relevant Background Information

The 5HT₂ receptor is a member of the G-protein-coupled family of serotonin receptors, and is the target for a variety of centrally-acting drugs, including those to treat depression, migraine, and obesity. The three sub-classes, 5HT_{2A}, 5HT_{2B}, and 5HT_{2C} 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.

Lorcaserin is a 5HT_{2C} receptor agonist with 8- to 15-fold selectivity over the 5HT_{2A} receptor and 45- to 90-fold selectivity over the 5HT_{2B} receptor (Table 1). Lorcaserin is considered a full agonist at the 2C and 2B receptors, and a partial agonist at the 2A receptor.

Table 1. 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)
5HT _{2A}	133 (113, 157)	14 (7, 30)
5HT _{2B}	811 (678, 969)	82 (62, 110)
5HT _{2C}	9 (8, 10)	1.85 (1, 3)
CI=confidence interval		

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

The 5HT_{2A} 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.⁶ The 5HT_{2A} receptor is thought to be the target for hallucinogens such as d-lysergic acid diethylamide (LSD).⁷

The 5HT_{2B} receptor is distributed in the brain in low concentrations, and at higher concentrations in the lung, kidney, heart, intestine, and stomach.⁶ 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.⁸

The 5HT_{2C} 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.⁷ The 5HT_{2C} receptor has high homology to the 5HT_{2A} receptor, and therefore has similar pharmacological binding profiles.⁹ The agonism of the 5HT_{2C} receptor is thought to induce hypophagia, hyperthermia, penile erections, and anxiety, and decrease locomotor activity in rats.^{10,11,12}

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.^{13,14}

⁶ Hoyer D, et al. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). *Pharmacol Rev* 1994 Jun; 46(2): 157-203.

⁷ Roth BL, et al. 5-Hydroxytryptamine₂-family receptors (5-Hydroxytryptamine_{2A}, 5-Hydroxytryptamine_{2B}, 5-Hydroxytryptamine_{2C}): where structure meets function. *Pharmacol Ther* 1998; 79(3): 231-57.

⁸ 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.

⁹ Giorgetti M and Tecott LH. Contributions of 5HT_{2C} receptors to multiple actions of central serotonin systems. *Eur J Pharmacol* 2004; 488: 1-9.

¹⁰ Kimura Y, et al. Pharmacological profile of YM348, a novel, potent and orally active 5-HT_{2C} receptor agonist. *Eur J Pharmacol* 1 Jan 2004; 483(1): 37-43.

¹¹ 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.

¹² Kimura A, et al. Overexpression of 5-HT_{2C} receptors in forebrain leads to elevated anxiety and hypoactivity. *Eur J Neurosci* 2009; 30: 299-306.

¹³ Connolly HM, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997 Aug 28;337(9): 581-8.

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

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the submission was fair. Some of the information in the clinical sections of this application was difficult to find. There were a number of omissions and errors in the submission that did not impact the integrity of the submission. The sponsor was responsive in responding to requests for clarification.

I have 2 major complaints with this submission:

1) I thought the use of electronic case report forms (eCRF) was problematic. While certainly the advantages from a data management point of view are clear, the eCRF did not capture those informative contextual details that are often found in paper CRFs. All of the data generated from the eCRF was found in the datasets, so there was not additional information to be gained from their review. Sponsor narratives were similarly fairly uninformative. Upon request, the sponsor did provide MedWatch forms for serious adverse events, but they were often difficult to review.

2) I also had difficulty with the ISS/ISE datasets. First, there were no ISE datasets, so it was difficult for me as a medical officer (without programming expertise) to conduct exploratory analyses on the efficacy data. Second, the Year 2 data from BLOOM were included in the ISS datasets, but only with the Year 1 randomization. Therefore, analyses of second year data could only be conducted from the BLOOM datasets. Third, visit identifiers were inconsistent from dataset to dataset, making longitudinal analyses difficult, particularly in those cases where datasets needed to be merged. Fourth, the BLOSSOM trial utilized screening identifiers for some datasets and trial identifiers for others, making merging (particularly for echocardiogram data), as well as finding data from individual patients across datasets, difficult.

3.2 Compliance with Good Clinical Practices

The sponsor attested that clinical trials were conducted in compliance with the Declaration of Helsinki on biomedical research involving human volunteers and regulatory guidance, and that clinical investigators obtained and documented volunteer informed consent for each patient screened for this study (see below for the exception).

Dr. Leslie Moldauer's investigative site in the BLOSSOM trial was audited and received a No Action Indicated (NAI) letter. At this site, 126 patients were screened and 81 enrolled into the study. Other investigative site inspection

reports from the FDA Division of Scientific Investigation (DSI) are pending, with interim Voluntary Action Indicated (VAI) classifications for the 3 sites. I am not aware that any violations were identified in these routine inspections that would materially affect the reliability of the data.

One investigator site (BLOOM site 189, P.I.: Dr. Ivan Goldsmith) was inspected for cause in October 2008 due to a report of protocol violations from its Institutional Review Board (IRB). In addition to protocol deviations, this investigator was cited for deficiencies in recordkeeping, obtaining informed consent in accordance with 21 CFR Part 50, and notifying the IRB of changes. A total of 56 patients were randomized at this site and were prematurely discontinued when the investigator resigned from the trial.

In total, the BLOOM trial had 98 sites. A total of 3182 subjects were randomized. The BLOSSOM trial had 97 sites. A total of 4008 subjects were randomized. It is unlikely that any one site drove the efficacy or safety results.

3.3 Financial Disclosures

The sponsor has certified that no investigator from the Phase 3 pivotal trials has entered into a financial agreement with the sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no chemistry issues that impact the efficacy or safety assessment of lorcaserin.

4.2 Clinical Microbiology

Not applicable. Lorcaserin is not an injectable.

4.3 Preclinical Pharmacology/Toxicology

Preclinical data are relevant to the safety assessment of lorcaserin and some of these findings are touched on in other sections of this review. Please refer to Dr. Alavi's review for a full discussion of these issues. I will briefly address the key findings here, with the source presented above.

Source: Dr. Bourcier's pharmacology memorandum for the EMDAC briefing package:

- The neurobehavioral studies conducted with lorcaserin in rats and monkeys did not identify any major adverse neurological effect, although limitations of these studies preclude definitive conclusions regarding elicitation of 5HT_{2A}-related behaviors by lorcaserin.
- No adverse cardiac lesions were observed at ~100-times the clinical dose of lorcaserin; however, given the experimental limitations, FDA has not definitively concluded that lorcaserin is devoid of valvulopathy-related cardiac effects in animals.

Source: Dr. Alavi's carcinogenicity assessment for the EMDAC briefing package:

- 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.
 - No safety margin was identified in female rats for mammary tumors, which emerged within 7-fold of the proposed clinical dose of 10 mg BID. 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.
 - Lorcaserin increased the incidence of brain astrocytoma in male rats by an unidentified mechanism of action. 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. Safety margins based on plasma drug concentrations yields a safety margin to the non-tumorigenic dose in rats of 5x.
- Lorcaserin did not increase tumors in mice, but this is considered a reflection of lower drug exposure achieved in mice compared to rats.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

As described in section 2.6, lorcaserin is a 5HT_{2C} receptor agonist. The 5HT_{2C} receptor is concentrated in the central nervous system (CNS) where it regulates feeding behavior. The endogenous ligand is serotonin.

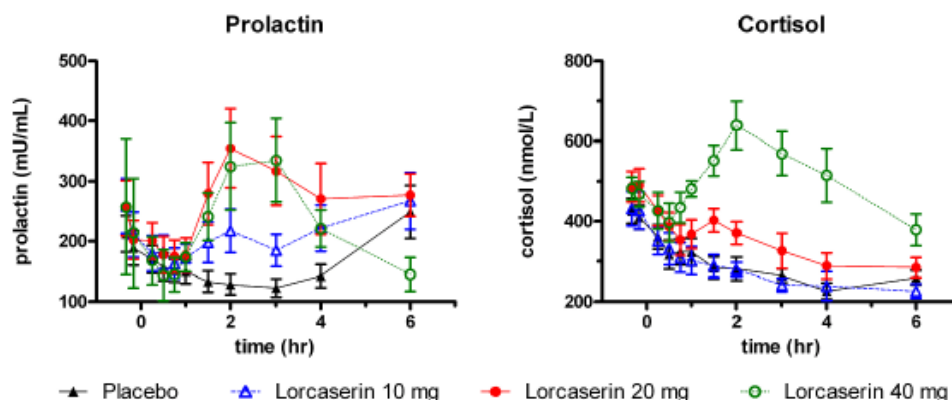
4.4.2 Pharmacodynamics

The intended pharmacological effect of lorcaserin is decreased food intake due to activation of 5HT_{2C} 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 5HT_{2C}, promote the secretion of prolactin and cortisol due to pituitary stimulation in rodents and humans.¹⁵ 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 681 nmol/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 7.6.1.

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.

¹⁵ Meltzer HY and Maes M. Pindolol pretreatment blocks stimulation by meta-chlorophenylpiperazine of prolactin but not cortisol secretion in normal men. Psych Res 1995; 58: 89-98.

4.4.3 Pharmacokinetics

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 2). 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 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 2. 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 7.5.3).

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 Cockcroft-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*-carbamoyle-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 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Type of Study	Study Identifier	Primary Objective	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK	APD356-001A	Define the MTD of lorcaserin following a single oral dose	Double-blind, placebo-controlled, randomized, dose-escalation study	Lorcaserin: 10, 20, and 40 mg; single dose, oral	45	Healthy subjects	Single dose
PK (Extrinsic Factor)	APD356-001B	Determine the PK characteristics of a single oral dose of lorcaserin in the fed versus fasted state	Open-label, 2 period crossover study	Lorcaserin: 10 mg, single dose, oral	12	Healthy subjects	Single dose
PD/PK	APD356-001C	Assess the effect of a single oral dose of lorcaserin on appetite and food intake	Double-blind, placebo-controlled, randomized, four period crossover study	Lorcaserin: 0.1, 1, and 10 mg; single dose, oral	20	Healthy subjects	Single dose
PK	APD356-002	Define the MTD of lorcaserin following multiple oral doses	Double-blind, placebo-controlled, randomized, dose-escalated study	Lorcaserin: 3, 10, and 20 mg; Placebo; QD/14 days, oral	27	Healthy subjects	14 days
Safety and Efficacy	APD356-003	Assess the effect of lorcaserin on body weight in uncomplicated obese patients	Double-blind, placebo-controlled, randomized, parallel group study	Lorcaserin: 1, 5, and 15 mg; Placebo; QD/28 days, oral	352	Obese and overweight patients	28 days
Safety and Efficacy	APD356-004	Assess the effect of lorcaserin on body weight after 12 weeks of administration in obese patients	Double-blind, placebo-controlled, randomized, dose ranging, parallel group study	Lorcaserin: 10 mg QD/3 mo; 10 mg BID/3 mo; 15 mg QD/3 mo; Placebo BID/3 mo, oral	469	Obese and overweight patients	3 mo
BA	APD356-005	Assess the single-dose relative bioavailability of 10 mg tablets compared to 10 mg lorcaserin hard gelatin capsules,	Open-label, randomized, 2-way crossover, 2-sequence, comparative bioavailability	Lorcaserin: 10 mg single dose tablet form and 10 mg single dose capsule form after 14 days, oral	28	Healthy subjects	14 days

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Lorcless (lorcaserin hydrochloride)

Type of Study	Study Identifier	Primary Objective	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
		under fasting conditions	study under fasting conditions				
PK	APD356-006	Assess the mass balance of lorcaserin following a single oral dose of ¹⁴ C-labeled lorcaserin	Open-label, single-dose, mass balance study	Lorcaserin: 10 mg single dose, oral	6	Healthy subjects	Single dose
Thorough ECG	APD356-007	Determine the effects of lorcaserin on ECG parameters	Double-blind (with exception of moxifloxacin), randomized, placebo- and positive-controlled, parallel arm, steady state, multiple dose study	Lorcaserin: 15 mg or 40 mg or placebo, QD/7 days; and moxifloxacin: 400 mg single dose, oral	244	Healthy Subjects	7 days
PK (Extrinsic Factor)	APD356-008	Evaluate the impact of multiple doses of lorcaserin on the plasma levels of a single dose of dextromethorphan	Open-label, single- and multiple-dose, 1-sequence, drug-drug interaction study under fasted conditions	Lorcaserin: 20 mg QD/4 days; dextromethorphan 30 mg/20 mL, 2 single doses separated by 9 days, oral	24	Healthy Subjects	11 days
Safety and Efficacy	APD356-009	Assess the weight loss effect of lorcaserin at the end of 52 weeks in overweight and obese patients; and the ability of lorcaserin to maintain body weight loss at the end of 104 weeks	Randomized, double-blind, placebo-controlled, parallel group study	Lorcaserin: 10 mg and matching placebo, BID/104 weeks, oral	3182	Obese and overweight patients	104 weeks
Safety and Efficacy	APD356-010	Assess the weight loss effect of lorcaserin at the end of 52 weeks in overweight and obese patients with type 2 diabetes mellitus managed with oral hypoglycemic agent(s)	Randomized, double-blind, placebo-controlled, parallel group study	Lorcaserin 10 mg and matching placebo, QD and BID/52 weeks, oral	604	Obese and overweight patients with Type II diabetes mellitus	52 weeks

Clinical Review
Golden, JK
NDA 22529
Lorqess (lorcaserin hydrochloride)

Type of Study	Study Identifier	Primary Objective	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety and Efficacy	APD356-011	Assess the weight loss effect of lorcaserin at the end of 52 weeks in overweight and obese patients	Randomized, double-blind, placebo-controlled, parallel group study	Lorcaserin: 10 mg QD and BID and matching placebo/52 weeks, oral	4008	Obese and overweight patients	52 weeks
PK (Extrinsic Factor)	APD356-012	Determine the impact of multiple doses of lorcaserin on the plasma levels of dextromethorphan	Open-label, single-and multiple-dose, randomized, 1-sequence, drug-drug interaction study under fasting conditions	Lorcaserin: 10 mg, BID/4 days; dextromethorphan 60 mg/20 mL, 2 single doses separated by 9 days, oral	24	Healthy Subjects	11 days
Abuse Liability	APD356-013	Evaluate the abuse potential of lorcaserin as measured by Drug Liking Visual Analog Scale	Randomized, double-blind, double-dummy, placebo- and active-controlled, 7-way crossover study	Zolpidem: 15 and 30 mg Ketamine: 100 mg Locaserin: 20, 40, and 60 mg, matching placebo, oral	35	Healthy subjects who are recreational polydrug users	5 day 3-dose visit; followed by seven 3-day, single dose visits, each with a 7-day washout
Energy Expenditure/Metabolism	APD356-014	To assess the effect of lorcaserin on 24h energy metabolism after 56 days of treatment	Double-blind, randomized, placebo-controlled, parallel group study	Lorcaserin 10 mg and matching placebo, BID/56 days, oral	~56	Overweight and obese patients	56 days
PK (Extrinsic Factor)	APD356-015	Evaluate the PK properties of lorcaserin in fed versus fasted state	Open-label, 2-period, crossover study	Lorcaserin 10 mg, single dose fed and single dose fasted separated by a 7+/-1 day washout period, oral	12	Obese and overweight patients	11 days
PK (Intrinsic Factor)	APD356-016	Assess PK properties of lorcaserin in subjects with mild, moderate, or severe renal impairment as compared to subjects with normal renal function	Open-label, parallel group study	Group 1-4: 10 mg lorcaserin Group 5: 10 mg lorcaserin Day 1 (non-dialysis) and 10 mg lorcaserin Day 8 (dialysis period), oral	40	32 Renally Impaired Subjects, 8 Healthy Subjects	Groups 1-4: Single dose; Group 5: 8 days
PK (Intrinsic Factor)	APD356-017	Evaluate PK properties of	Open-label, parallel group	Lorcaserin: 10 mg single dose, oral	24	16 Hepatically	Single dose

Type of Study	Study Identifier	Primary Objective	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
		lorcaserin in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function	study			Impaired Subjects, 8 Healthy Subjects	
PK (Intrinsic Factor)	APD356-018	Compare the PK parameters of lorcaserin in obese or overweight elderly to those of obese or overweight adults	Open-label, parallel group study	Lorcaserin: 10 mg single dose, oral	24	12 Elderly Subjects, 12 Healthy Subjects	Single dose

Source: NDA 22529, Tabular listing

5.2 Review Strategy

I am the primary reviewer for the clinical review and am responsible for its content. I referred to Dr. Derr's statistical efficacy review and Dr. Ding's statistical safety review for those respective sections. The statistical reviewers provided some of the statistical analyses presented in this review and to the EMDAC meeting. The clinical pharmacology section and nonclinical pharmacology information presented in the clinical EMDAC briefing document were both edited by the respective reviewers in those disciplines. That information is generally presented similarly in this review. I referred to the pharmacology/toxicology and controlled substance staff (CSS) reviews for any additional information I included in this final review, and those sections are referenced to those reviews.

5.3 Discussion of Individual Studies/Clinical Trials

Phase 1 Program

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 μ Ci 14 C-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).

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.

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.

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.

Phase 2 Program

- 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).

Phase 3 Program

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/m² with or without a co-morbid condition or 27-29.9 kg/m² 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/m² with or without a co-morbid condition or 27-29.9 kg/m² 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 Review of Efficacy

Efficacy Summary

In the first year of the BLOOM trial:

- 47.5% of patients treated with lorcaserin 10 mg BID lost $\geq 5\%$ 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 $\geq 10\%$ 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 $\geq 5\%$ 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 $\geq 10\%$ 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 $\geq 5\%$ 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 $\geq 5\%$ 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 3. 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.

6.1 Indication: Weight management

6.1.1 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 4.4.2), 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. Derr's statistical review for a comprehensive analysis of the efficacy data.

6.1.2 Demographics

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/m² 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 4. 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, %	67.7	67.2	66.2
Black, %	18.9	20.0	19.4
Hispanic, %	11.1	10.7	12.4
BMI, kg/m ² 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			

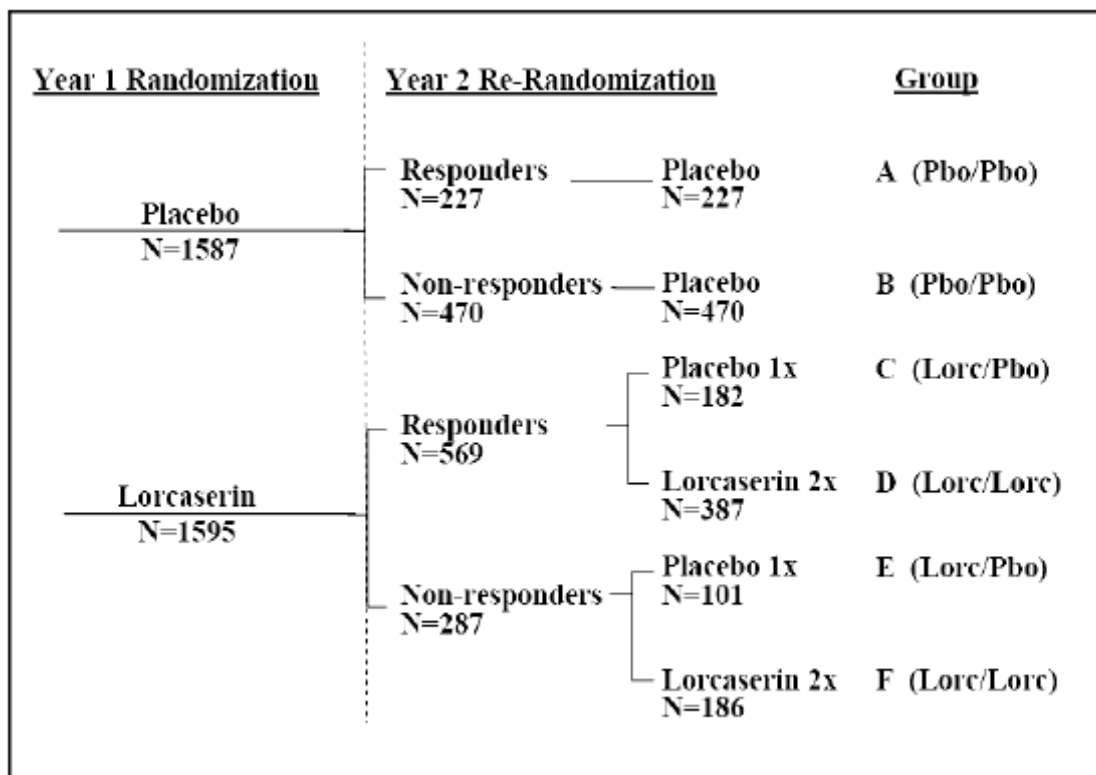
Source: NDA 22529, ISE Table 3 and Reviewer created from datasets

6.1.3 Subject Disposition

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 2. Patient Disposition, BLOOM Trial



Source: NDA 22529, APD356-009 CSR Figure 1

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.

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 5. 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.*¹⁶

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).

6.1.4 Analysis of Primary Endpoints

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.

¹⁶ 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.

Table 6. 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) (95% CI)	p-value
Lorc 10 BID vs. Pbo	27.2 (24.0, 30.5)	< 0.0001

Source: NDA 22529, APD356-009 CSR Table 10

Table 7. 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) (95% CI)	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 8. 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) (95% CI)	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 9. Pooled Phase 3 Trials 5% Responder, Other Analysis Populations

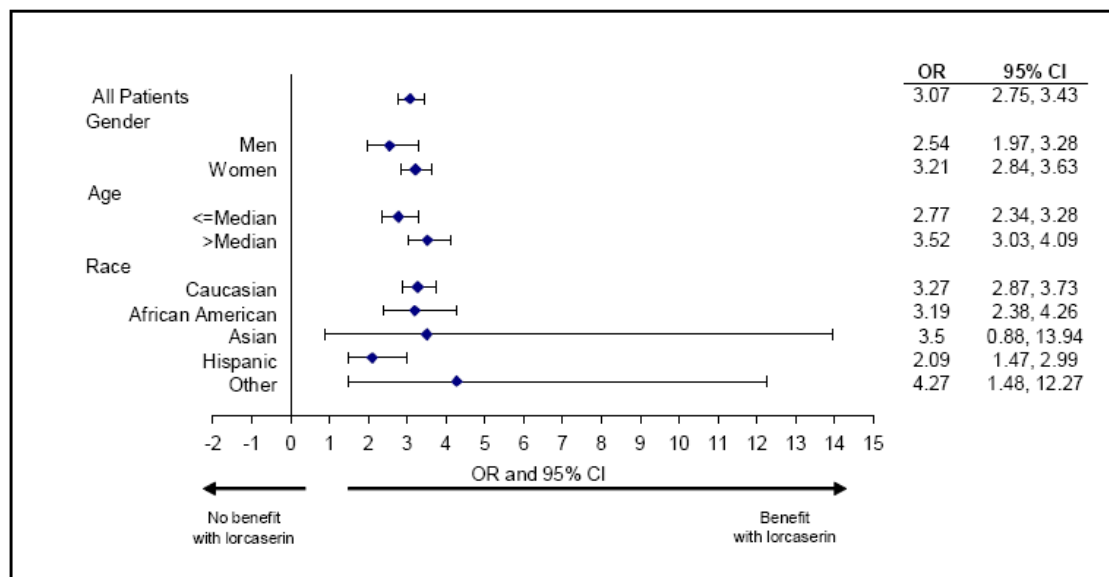
Treatment	Completer		RDP	
	N	n (%)	N	n (%)
Lorc 10 mg BID	1775	1135 (63.94)	2043	1197 (58.59)
Pbo	1529	512 (33.49)	1839	584 (31.76)
Between Treatment Comparison	Difference in Proportion (percentage) (95% CI)	p-value	Difference in Proportion (percentage) (95% CI)	p-value
Lorc 10 BID vs. Pbo	30.44 (27.18, 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.¹⁷ In this program, the RDP is still considered a select group of patients.

Figure 3 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.

Figure 3. Odds Ratios for the Proportion of Patients Achieving 5% Weight Loss at Week 52 by Subgroup



Source: NDA 22529, ISE Figure 17

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.

¹⁷ Simons-Morton DG, et al. Obesity research – limitations of methods, measurements, and medications. JAMA 2006; 295(7): 826-8.

Table 10. 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

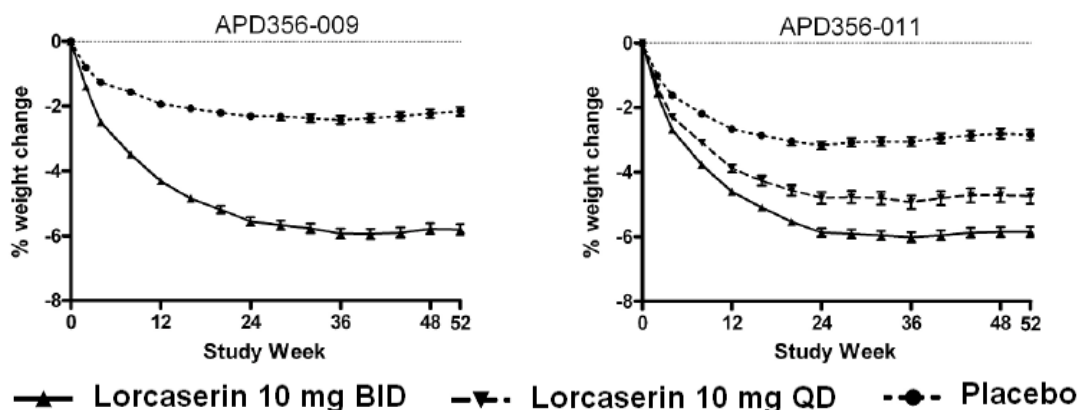
^a Results from the BLOSSOM trial

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 4 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.

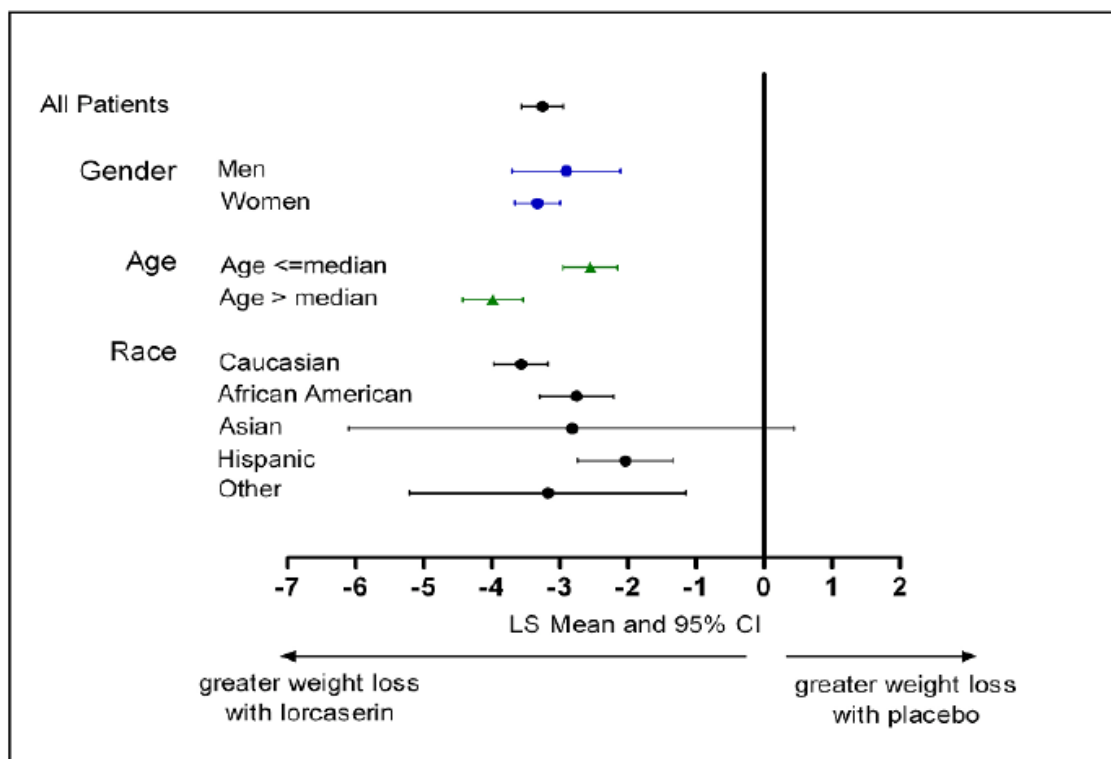
Figure 4. Mean Percent Weight Loss, BLOOM (APD356-009) and BLOSSOM (APD356-011), MITT LOCF



Source: NDA 22529, ISE Figure 5

Subgroup analyses of mean weight loss are fairly consistent with the subgroups of responder analyses (see Figure 3 and Figure 6), in that women, older individuals, and Caucasians/Whites appear to benefit from lorcaserin more so than others. As described in section 4.4.3, sex, age, and race did not significantly impact lorcaserin PK.

Figure 5. Difference in Mean Change from Baseline in Body Weight (kg) at Week 52 by Subgroup, MITT



Source: NDA 22529, ISE Figure 18

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 11. 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) (95% CI)	p-value
Lorc 10 BID vs. Pbo	14.9 (12.4, 17.4)	< 0.0001

Source: NDA 22529, APD356-009 CSR Table 12

Table 12. 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) (95% CI)	p-value
Lorc 10 BID vs. Pbo	12.88 (10.33, 15.43)	< 0.0001
Lorc 10 QD vs. Pbo	7.63 (4.58, 10.69)	< 0.0001
Lorc 10 QD vs. Lorc 10 BID	-5.25 (-8.63, -1.86)	0.0031

Source: NDA 22529, APD356-011 CSR Table 12

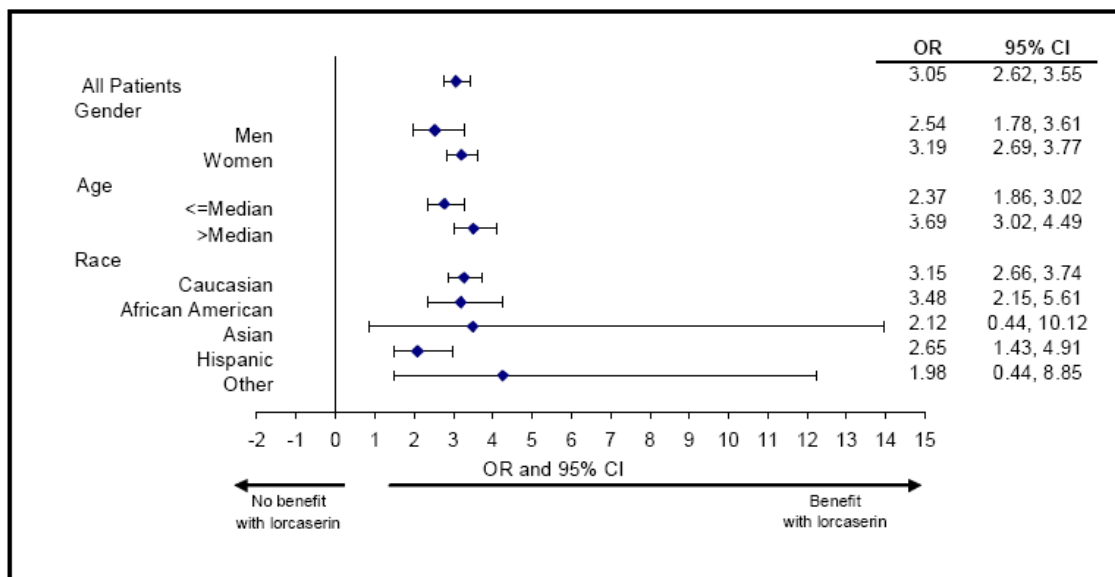
Table 13. Pooled Phase 3 Trials 10% Responder, MITT LOCF

Treatment	N	n (%)
Lorc 10 BID	3098	695 (22.43)
Pbo	3038	264 (8.69)
Between Treatment Comparison	Difference in Proportion (percentage) (95% CI)	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 6, 10% responders by subgroup demonstrated a similar pattern to the 5% responders by subgroup.

Figure 6. Odds Ratios for the Proportion of Patients Achieving 10% Weight Loss at Week 52 by Subgroup



Source: NDA 22529, ISE Figure 19

6.1.5 Analysis of Secondary Endpoints

Anthropometric measures

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 14. 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/m², suggesting that a significant proportion of treated patients remained obese (Table 15).

Table 15. Change from Baseline in Body Mass Index (kg/m²) 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

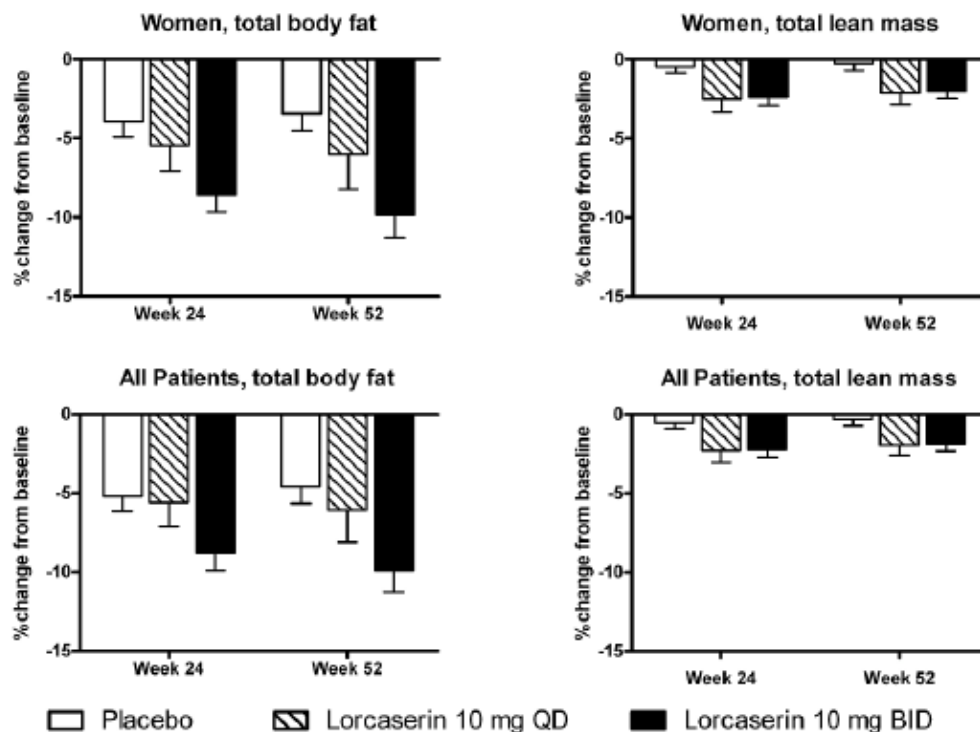
DEXA

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 7. 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

Metabolic- and Cardiovascular-related Endpoints

Additional secondary efficacy endpoints of interest to FDA include blood pressure, lipids, and fasting glucose and insulin measures.²

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 16. 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 $\geq 5\%$ 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 17. 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 18. 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

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}

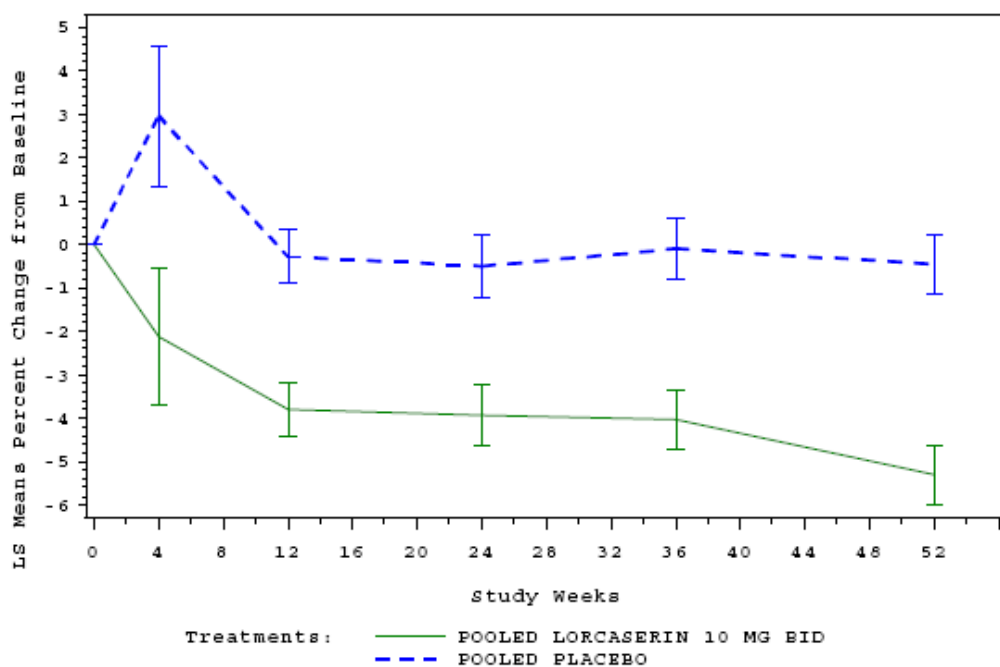
The lowest mean LDL cholesterol and total cholesterol values were observed after 4 weeks of treatment with lorcaserin 10 mg BID, and values increased from baseline during the remaining study period in both the lorcaserin- and placebo-treated groups.

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.

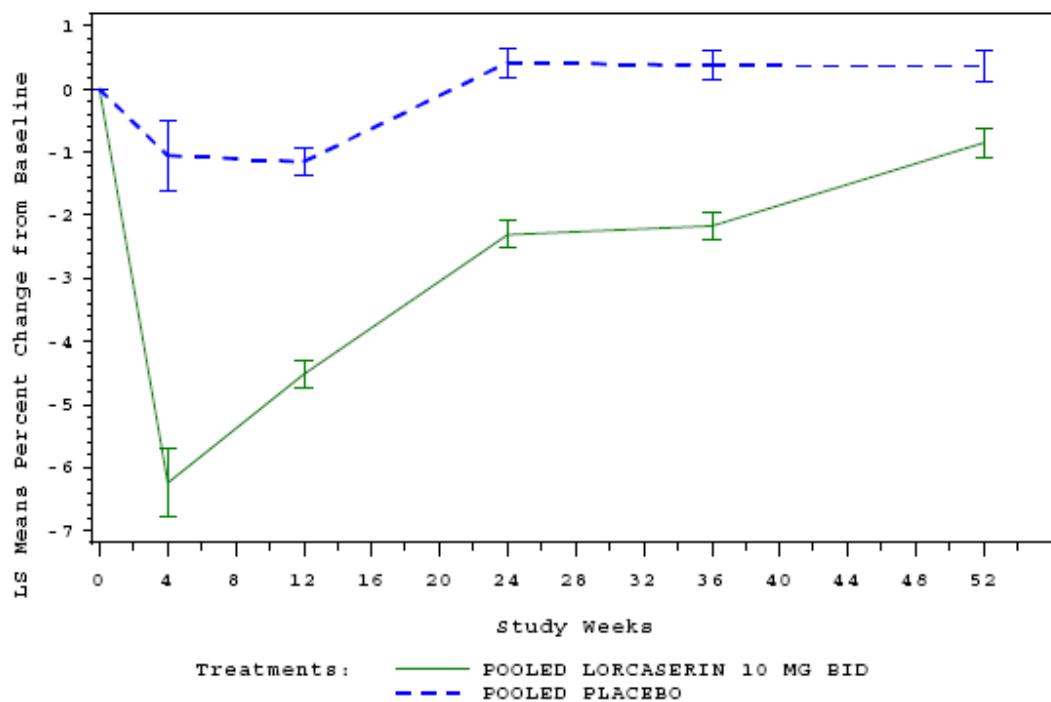
¹⁹ Thompson PD, et al. Unexpected decrease in plasma high density lipoprotein cholesterol with weight loss. *Am J Clin Nutr* 1979; 32: 2016-21.

Figure 8. Mean Percent Change from Baseline in Triglycerides, MITT LOCF



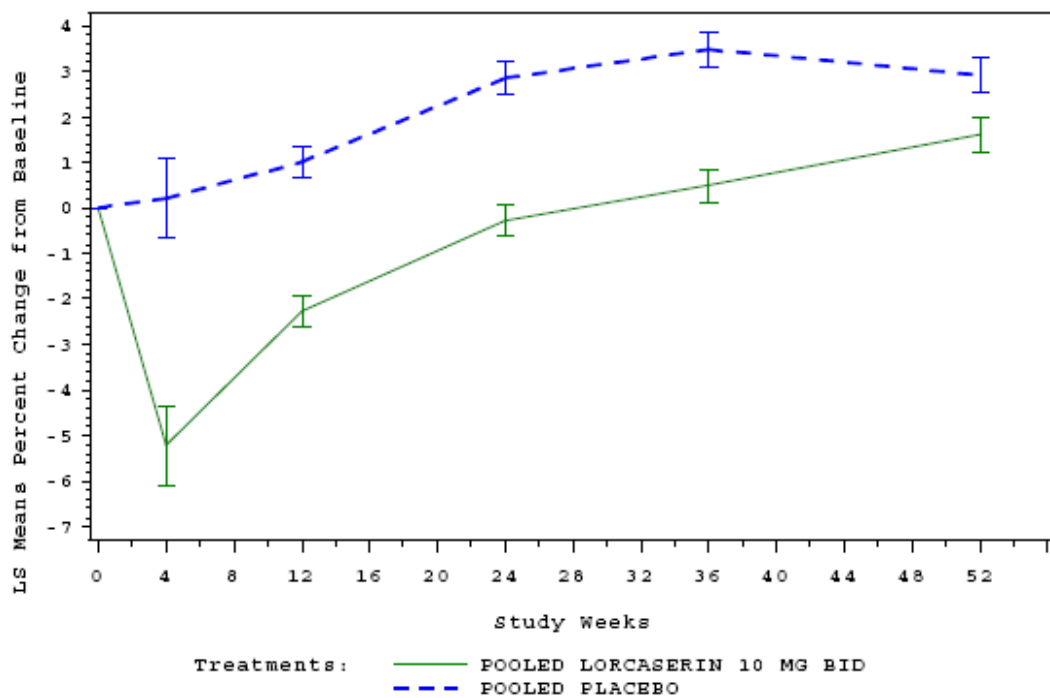
Source: NDA 22529, ISE Statistical Report Figure 7

Figure 9. Mean Percent Change from Baseline in Total Cholesterol, MITT LOCF



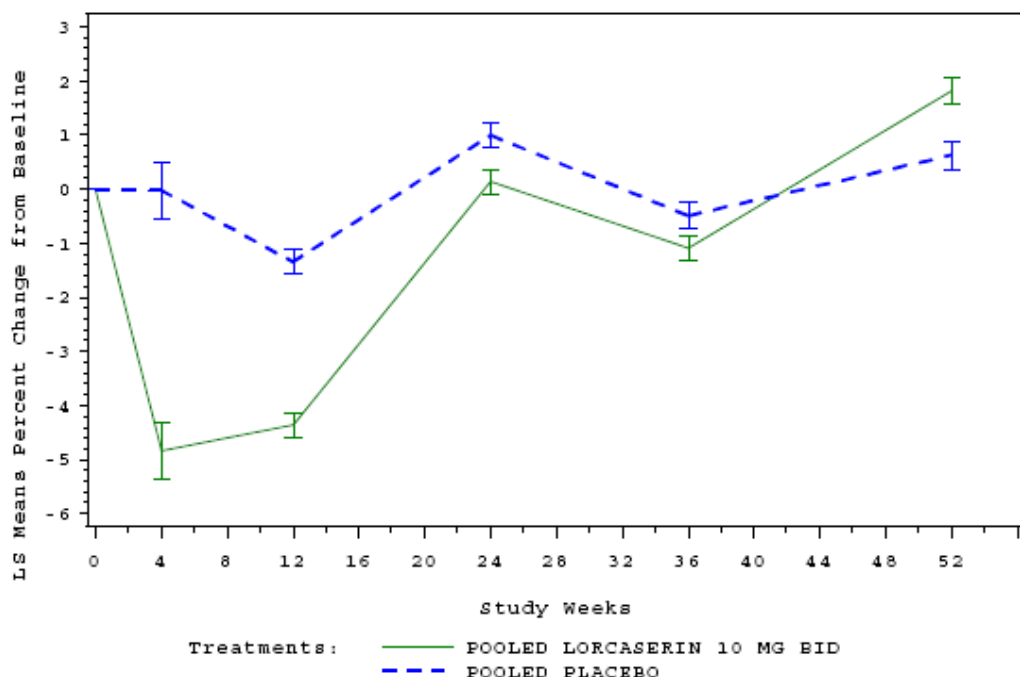
Source: NDA 22529, ISE Statistical Report Figure 8

Figure 10. Mean Percent Change from Baseline in LDL-C, MITT LOCF



Source: NDA 22529, ISE Statistical Report Figure 9

Figure 11. Mean Percent Change from Baseline in HDL-C, MITT LOCF



Source: NDA 22529, ISE Statistical Report Figure 10

Table 19 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 19. 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 20. 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

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 21. 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 22. 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 23. 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 24. 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 25. 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

6.1.6 Other Endpoints

The sponsor evaluated quality of life (QOL) using the Impact of Weight on Quality of Life (IWQOL)-Lite questionnaire. (b) (4)

The overall difference in mean change (1.9) was statistically significant in favor of lorcaserin, but the clinical significance of this difference is uncertain.

6.1.7 Subpopulations

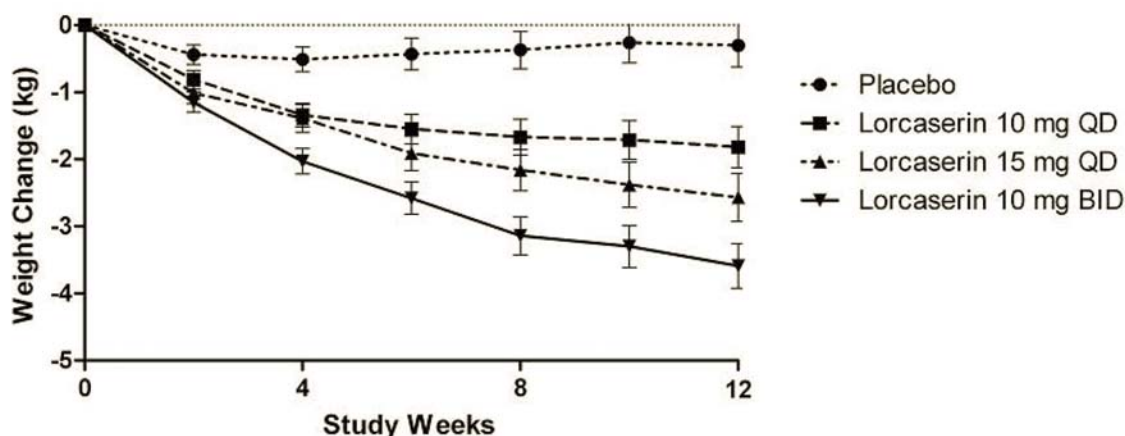
Primary efficacy findings for the subpopulations of sex, age, and race/ethnicity are discussed within section 6.1.4.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

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 12).

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



Source: NDA 22529, Summary of Clinical Efficacy Figure 3

As noted in section 7.3.3, the lorcaserin 15 mg QD treatment in study APD356-004 was less well-tolerated (i.e., patients experienced more adverse events leading to discontinuation) than the lorcaserin 10 mg QD or BID treatments, primarily due to headache, dizziness, and nausea.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy is best described by the BLOOM Year 2 results, despite the fact that only half of Year 1 randomized patients were re-randomized into Year 2, thus limiting the generalizability to the target population.

Table 26 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,²⁰ 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, $p < 0.0001$).

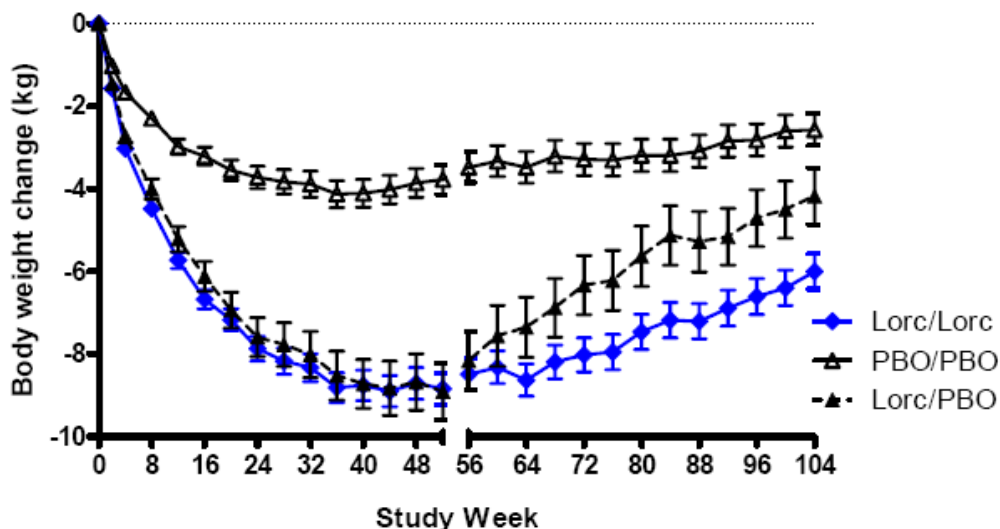
²⁰ Davidson MH, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. JAMA. 1999 Jan 20;281(3):235-42.

Table 26. Change in Body Weight to Week 104, MITT2, BLOOM trial

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

Source: NDA 22529, APD356-009 CSR Table 20

Figure 13. Change in Body Weight from Baseline to Week 104, PP2, BLOOM trial



Source: NDA 22529, APD356-009 CSR Figure 7

Patients who were 5% weight loss responders on lorcaserin in Year 1 of BLOOM were more likely to maintain a \geq 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%).

6.1.10 Additional Efficacy Issues/Analyses

As described in the FDA draft guidance for developing weight management drugs,² 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.²¹

²¹ 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.

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 EMDAC meeting (Qnexa, 15 July 2010) and in the literature (naltrexone/bupropion).²² Table 27 presents the weight changes in active drug (high dose) and placebo groups from various Phase 3 trials that are available for comparison.

Table 27. 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 22
Lorcaserin 10 mg BID	-5.8 kg	-2.5 kg	NDA 22529, ISE Table 13

7 Review of Safety

Safety Summary

The safety assessment of lorcaserin was focused on concerns related to 5HT_{2C} receptor activation and the potential for off-target effects (i.e., activation of the 5HT_{2A} and 5HT_{2B} 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 5HT_{2B} receptor. Lorcaserin activates the 5HT_{2C} receptor with 45- to 90-fold selectivity over the 5HT_{2B} 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.

²² Greenway FL, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. www.thelancet.com Published online 30 July 2010.

- **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 trials 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.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The entire clinical program was reviewed for serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation.

The rest of this review primarily focuses on the Phase 3 trials; the results of which 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.

7.1.2 Categorization of Adverse Events

Adverse event coding utilized MedDRA Dictionary Version 12.0. For the most part, coding and preferred term mapping was appropriate. However, I did identify one clearly misclassified event. The verbatim term was “psychiatric crisis”, which mapped to the preferred term “acute psychosis”. This was a serious adverse event of depression and anxiety, but not, in fact, psychosis.

In addition, EMDAC members highlighted a limitation of MedDRA, in that several members were concerned that the preferred term “amnesia” represented a more serious event than the actual event of short term memory loss as reported by the investigator.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The following table describes demographics and baseline comorbidities by trial; the following variables are similar and generally support data pooling for safety.

Table 28. 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, %	66.9	67.0
Black, %	18.8	19.6
Hispanic, %	12.4	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

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

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.

Table 29. 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

7.2.2 Explorations for Dose Response

Dose response in the Phase 3 trials was evaluated in the BLOSSOM trial, which included a lorcaserin 10 mg QD arm. See section 7.5.1 for more details.

7.2.3 Special Animal and/or *In Vitro* Testing

The preclinical program for *in vivo* neuropsychiatric and valvular effects, as well as carcinogenicity in mice had limitations that were touched on in section 4.3.

In addition, our IRT colleagues noted in their review of the thorough QT study that lorcaserin caused small, but clinically insignificant increases in the PR interval and decreases in HR. They recommended that the sponsor study the effect of lorcaserin on sodium and calcium channels and determine if there are any adrenergic or cholinergic receptor interactions.

7.2.4 Routine Clinical Testing

Limitations to testing within the clinical database include:

- Potentially inadequate power to rule out a 50% increase in cardiac valvulopathy with echocardiography
- Depression and suicidality measurements were not conducted at every visit; the Columbia-Suicide Severity Rating Scale was not used for prospective monitoring
- No prospective questioning regarding priapism-related symptoms

- An evaluation on the effect of ACTH and urinary free cortisol was not performed (should have been considered given the pharmacodynamic effect of lorcaserin on cortisol)

Despite the above power limitations, the sponsor did conduct a large program evaluating echocardiograms. Additionally, prolactin was measured in the BLOSSOM trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic, clearance, and interaction workup in this program was sufficient. See section 4.4 for details.

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.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other drugs from this class to consider for evaluation. As discussed elsewhere, the sponsor conducted a comprehensive program to evaluate the valvular safety of lorcaserin, given the known safety concern with 5HT2B receptor agonists. The psychiatric monitoring is considered somewhat incomplete, given the new recommendations for depression and suicidality monitoring for centrally-acting obesity drugs as outlined in the FDA draft weight management guidance.

7.3 Major Safety Results

7.3.1 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.

7.3.2 Nonfatal Serious Adverse Events

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.

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 section 7.3.5.

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 7.3.5.

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/Hispanic	> Q3	Myocardial infarction	Myocardial infarction	Mild	Yes	Yes

Source: Reviewer created from NDA 22529 datasets

Ischemic cardiac events are addressed in section 7.3.5.

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 section 7.3.5 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

7.3.3 Dropouts and/or Discontinuations

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 7.3.5.

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.

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 7.4.4).

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 number (%) patients with 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 number (%) patients with 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 7.3.2).

- 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 7.3.5.
- 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 7.4.4.
- 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.

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 7.3.5), 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.

7.3.4 Significant Adverse Events

Significant adverse events are primarily addressed in section 7.3.5.

The Year 1 Phase 3 database was searched for terms that could be related to a hypersensitivity reaction (e.g., anaphylaxis, wheezing, rash, angioedema). No strong signal emerged.

Table 40. Potential Hypersensitivity-Related AEs

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Cough	136 (4.3)	31 (3.9)	109 (3.4)
Rash	67 (2.1)	10 (1.2)	58 (1.8)
Hypersensitivity	28 (0.9)	3 (0.4)	32 (1.0)
Pruritus	27 (0.8)	8 (1.0)	20 (0.6)
Dyspnoea	18 (0.6)	6 (0.7)	22 (0.7)
Urticaria	12 (0.4)	7 (0.9)	21 (0.7)
Eczema	6 (0.2)	1 (0.1)	11 (0.3)
Dermatitis allergic	6 (0.2)	1 (0.1)	2 (0.1)
Drug hypersensitivity	6 (0.2)	0	6 (0.2)
Rash pruritic	6 (0.2)	0	3 (0.1)
Photosensitivity reaction	5 (0.2)	1 (0.1)	5 (0.2)
Pruritus generalised	5 (0.2)	1 (0.1)	1 (<0.1)
Wheezing	3 (0.1)	1 (0.1)	7 (0.2)
Rash generalised	3 (0.1)	0	3 (0.1)
Rash papular	2 (0.1)	3 (0.4)	5 (0.2)
Dermatitis atopic	2 (0.1)	1 (0.1)	1 (<0.1)
Allergic cough	2 (0.1)	0	1 (<0.1)
Skin exfoliation	2 (0.1)	0	1 (<0.1)
Swelling face	1 (<0.1)	1 (0.1)	2 (0.1)
Angioedema	1 (<0.1)	1 (0.1)	1 (<0.1)
Periorbital oedema	1 (<0.1)	0	0
Photosensitivity allergic reaction	1 (<0.1)	0	0
Stridor	1 (<0.1)	0	0
Rash macular	0	1 (0.1)	4 (0.1)
Anaphylactic reaction	0	1 (0.1)	3 (0.1)
Rash erythematous	0	1 (0.1)	1 (<0.1)
Lichen planus	0	1 (0.1)	0
Pruritus allergic	0	1 (0.1)	0
Drug eruption	0	0	1 (<0.1)
Stevens-Johnson syndrome	0	0	1 (<0.1)

Source: Reviewer created from NDA 22529 datasets

7.3.5 Submission Specific Primary Safety Concerns

This section presents safety issues in a targeted format, primarily by compiling preferred terms of interest that addressed an individual question. This section also includes the results of echocardiographic testing that was conducted in the clinical program in order to rule out FDA-defined valvular heart disease (VHD) and assess pulmonary artery systolic pressure (PASP). VHD was the primary clinical safety concern with lorcaserin development, and the results of the assessment are provided first. Additional targeted safety issues of interest then follow.

Heart Valve Assessment

As described in section 2.6, 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.²³

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.¹⁴ Mild or less mitral regurgitation (MR), and trace or less aortic regurgitation (AR), are relatively common conditions in the general population and 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).¹⁴ 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;²⁴ 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,

²³ Bhattacharyya S, et al. Drug-induced fibrotic valvular heart disease. *Lancet* 2009; 374: 577–85.

²⁴ Smith SR, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010; 363: 245-56.

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.

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)
- LVEF: absolute value from secondary reader was within $\pm 10\%$ 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 \geq 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.

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 that follows. The relative risk for FDA-defined VHD in this analysis was 1.07 (95% CI: 0.74, 1.55).

Table 41. 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 42. 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 43. 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.

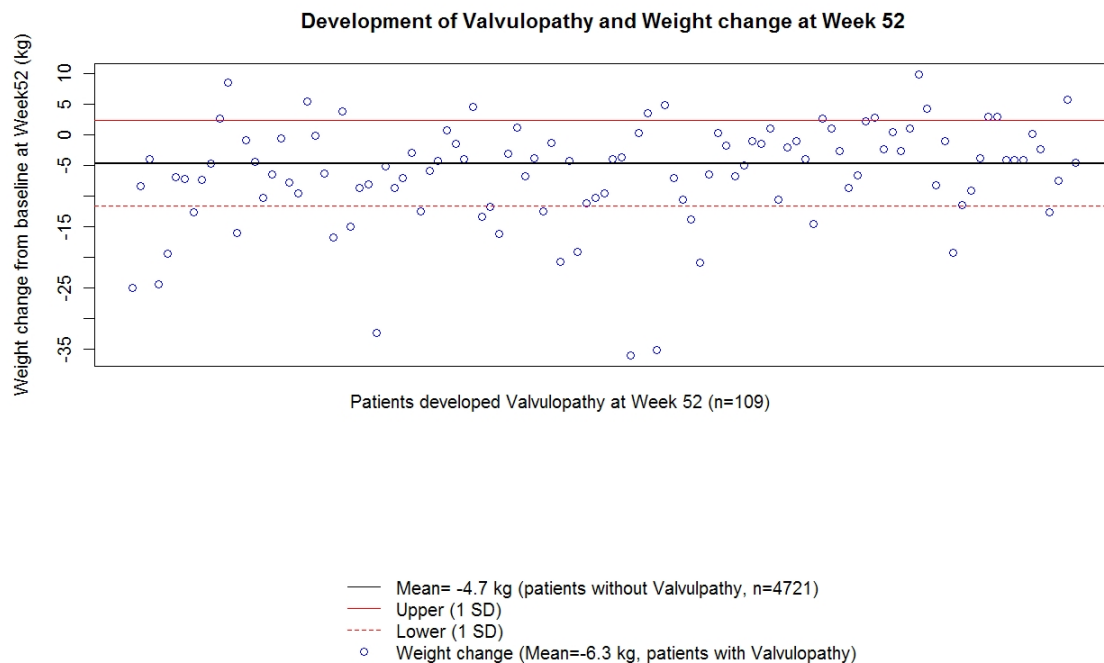
Table 44. Mean (SD) Age of Patients with and without FDA-Defined VHD at Week 52

	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

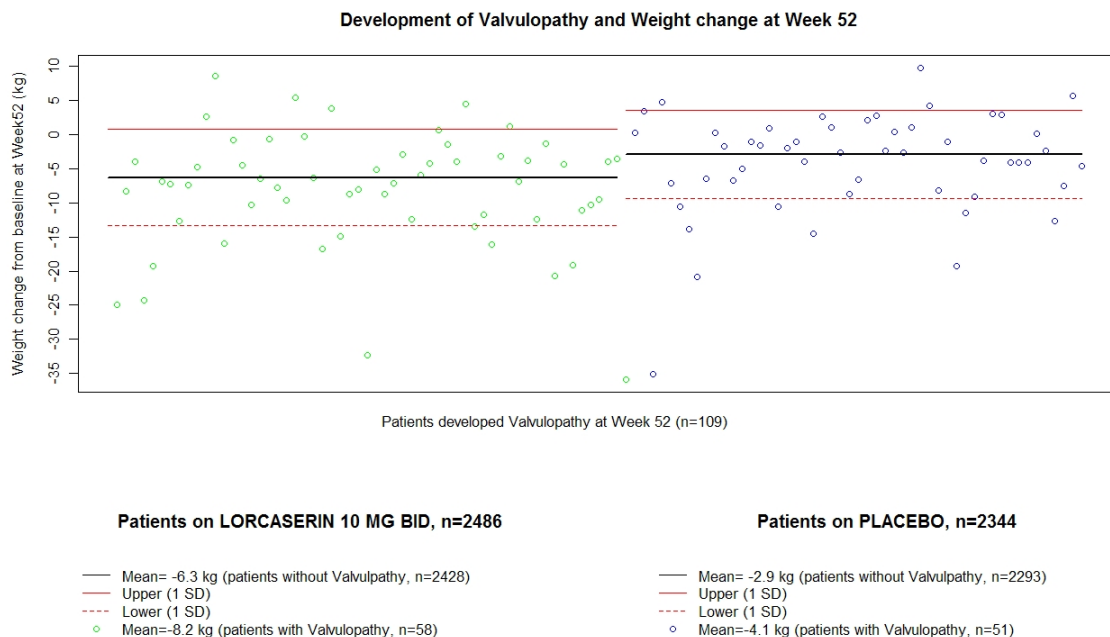
The mean weight loss in patients without FDA-defined VHD was -4.7 kg; the mean weight loss in those patients with FDA-defined VHD at Week 52 was -6.3 kg (Figure 14). However, when 5 FDA-defined VHD outliers are removed, the mean change – and difference between groups – is attenuated (mean weight loss 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 45. 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.

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.²⁵ 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.

²⁵ 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 46. 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 (3.1%)	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 (2.2%)	19 (1.7%)
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

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 47. 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 48. 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 49. 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 50. 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 51. 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 52. 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 53. 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 54. 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 47 to Table 50 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.^{13,14} Carcinoid- and ergot-related VHD have also been described as involving the tricuspid valve.^{26,27} 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 56.

Table 55. 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

²⁶ 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.

²⁷ Redfield MM, et al. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. *Ann Intern Med* July 1992; 117(1): 50-52.

- 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.

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 56. 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,²⁸ 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.

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

²⁸ 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.

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:

Table 57. 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 58. 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 59. 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%).

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.²⁹ 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

²⁹ 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.

increase when used for more than 3 months).³⁰ It has been estimated that 1 in 1000 or fewer patients who are exposed to such agents ultimately develop PPH.³¹

Anorexigens associated with PPH are thought to act by increasing serotonin release via the serotonin transporter.³² Other potential serotonin mediators may include the 5HT1B, 5HT2A, and 5HT2B receptors.^{33,34}

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.³⁵

PASP positively correlates with age and BMI and is higher in men than women.³⁶ Higher PASP may in fact be physiological in very obese patients.³⁵ 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”.³⁷ 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.

³⁰ Abenham L, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med.* 1996 Aug 29; 335(9): 609-16.

³¹ 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>

³² Rothman RB and Baumann MH. Serotonin releasing agents. *Neurochemical, therapeutic and adverse effects.* *Pharmacol Biochem Behav.* 2002 Apr;71(4): 825-36.

³³ Dempsey Y and MacLean MR. Pulmonary hypertension: therapeutic targets within the serotonin system. *Br J Pharmacol* 2008; 155: 455-62.

³⁴ Launay, J-M, et al. Function of the serotonin 5-hydroxytryptamine 2B receptor in pulmonary hypertension. *Nature Med* 2002 Oct; 8(10): 1129-35.

³⁵ Milan A, et al. Echocardiographic indexes for the non-invasive evaluation of pulmonary hemodynamics. *J Am Soc Echocardiogr* 2010; 23: 225-39.

³⁶ 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.

³⁷ Galie N, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. The task force for the diagnosis and treatment of pulmonary hypertension of the European Society for Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; 30 (20): 2493-2537.

The 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.

Table 60. 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 61. 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 62. 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 \geq 40 mmHg. No patients had PASP \geq 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.

Depression and Suicidality

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).³⁸ 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:

1. Sadness
2. Pessimism
3. Past failure
4. Loss of pleasure
5. Guilty feelings
6. Punishment feelings

³⁸ Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory (BDI-II). 2nd ed. San Antonio, TX: The Psychological Association; 1996.

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,³⁹ pharmacotherapy,³⁹ and bariatric surgery.⁴⁰

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 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.

³⁹ Faulconbridge LF, et al. Changes in symptoms of depression with weight loss: results of a randomized trial. *Obesity* 2009 May; 17(5): 1009-16.

⁴⁰ Hayden MJ, et al. Characterization of the improvement in depressive symptoms following bariatric surgery. [Obes Surg](#). 2010 Jun 18. [Epub ahead of print]

We looked at the BDI-II total score results by mean and categorical changes, and by visit and highest value.

As Table 63 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.^{39,40}

Table 63. 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.³⁸ 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 64. 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 65. 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 66. 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 67 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 67. 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 68. 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.⁴¹ The following preferred terms were used in the search; the bolded items were those found in the lorcaserin database:

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

Table 69. Standardized MedDRA Queries (Narrow and Broad) for Depression

Narrow PTs	Broad PTs
Activation syndrome Adjustment disorder with depressed mood Adjustment disorder with mixed anxiety and depressed mood Agitated depression Anhedonia Antidepressant therapy Childhood depression Decreased interest Depressed mood Depression Depression postoperative Depressive symptom Dysphoria Dysthymic disorder Electroconvulsive therapy Feeling guilty Feeling of despair Feelings of worthlessness Major depression Menopausal depression Postpartum depression	Affect lability Alcohol abuse Alcohol problem Alcohol rehabilitation Alcoholism Apathy Blunted affect Constricted affect Crying Disturbance in attention Drug abuse Drug abuser Drug dependence Drug dependence, antepartum Drug dependence, postpartum Dyssomnia Emotional distress Hypersomnia Hyposomnia Impaired self-care 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 70 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 below).

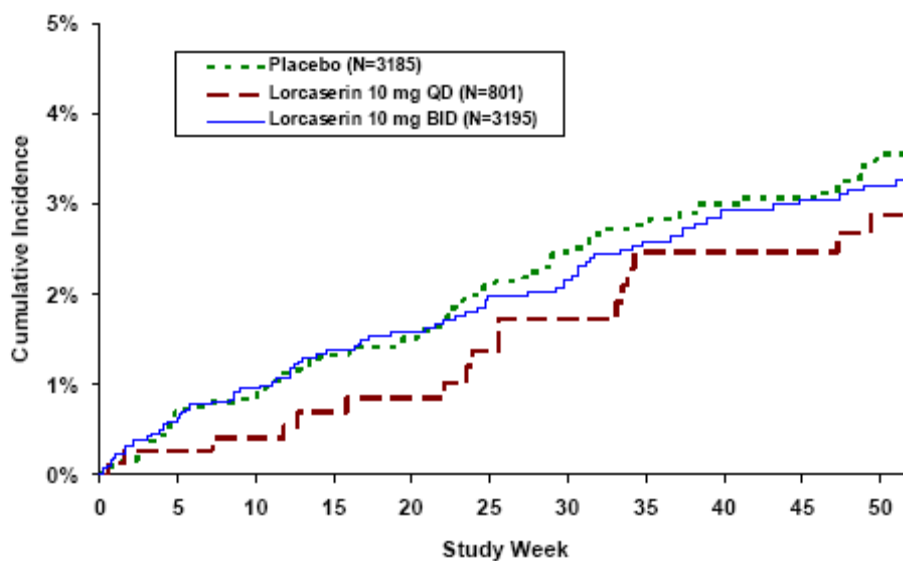
Table 70. Incidence of Depression, Phase 3 Trials, Pooled

	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

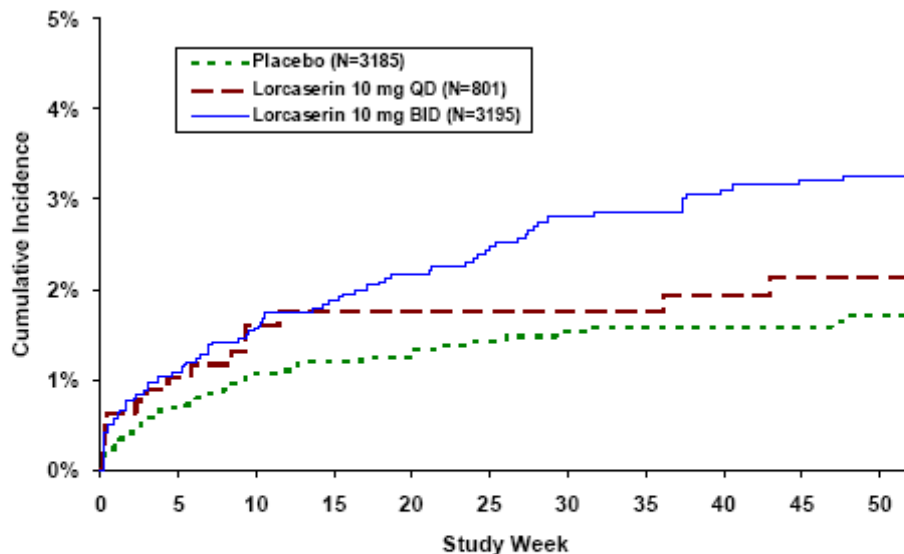


Number of patients at risk:

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 71 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 71. 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,⁴² with a particularly consistent relationship in women.^{43,44} (This is supported by the baseline incidence of depression in the Phase 3 database: 8.6% of women and 4.7% of men 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 72), although the results do suggest 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 4.4.3).

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.

⁴² Simon GE, Von Korff M, Saunders K, et al. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry*. 2006; 63(7): 824–30.

⁴³ Carpenter KM, Hasin DS, Allison DB, et al. Relationships between obesity and DSM-IV major depressive disorder, suicide ideation, and suicide attempts: results from a general population study. *Am J Public Health*. 2000; 90(2): 251–7.

⁴⁴ Heo M, Pietrobelli A, Fontaine KR, et al. Depressive mood and obesity in US adults: comparison and moderation by sex, age, and race. *Int J Obes (Lond)*. 2006; 30(3): 513–9.

Table 72. 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 7.3.3, patients in the lorcaserin 10 mg BID group were slightly more likely to discontinue due to depression AEs.

Table 73. 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:

Table 74. 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 75. 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

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

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

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

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

⁴⁷ Developed by K. Posner, et al.

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

- 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.⁴⁹ 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.

Table 76. 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

⁴⁹ 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 77. 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 78).

Table 78. 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 79. 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 80. 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

Cognitive Effects

Centrally-acting obesity drugs of a variety of mechanisms have been found to possess neuropsychiatric effects, including adverse effects on cognition.⁵⁰ The 5HT_{2A} receptor is thought to play a role in cognition and memory, and alterations in 5HT_{2A} receptor signaling are implicated in the cognitive dysfunction seen in disorders such as schizophrenia and depression.^{51,52}

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.

⁵⁰ Nathan PJ, et al. Neuropsychiatric adverse effects of centrally acting obesity drugs. CNS Neurosci Ther 2010 Jul 7. [Epub ahead of print]

⁵¹ Nichols DE. Hallucinogens. Pharmacol Ther 2004 Feb; 101(2): 131-81.

⁵² Williams GV, et al. The physiological role of 5-HT_{2A} receptors in working memory. J Neurosci 1 Apr 2002; 22: 2843-2854.

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 5HT_{2A} activation.⁵²

Cognitive AEs from the single dose (healthy individuals) and Phase 2 trials, respectively, are as follows:

Table 81. 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 82. 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 83. MedDRA Preferred Terms of Interest Related to Cognitive Function

Modified Dementia SMQ	Additional Cognitive Preferred Terms of Interest
Activities of daily living impaired Agnosia Amnesia Amnesic 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	Disturbance in attention Dysphasia Psychomotor retardation

Source: Reviewer generated from MedDRA 13.0 Browser version 3.0.1

Table 84 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 84. 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 85 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 85. 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.

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 7.3.2 (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.

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.^{53,54} Recent work in this area suggests that agonism at the 5HT2A receptor contributes to serotonin syndrome.^{53,55}

There were 2 cases within the lorcaserin development program that the investigators considered to fall within the spectrum of serotonin toxicity:

⁵³ Boyer EW and Shannon M. The serotonin syndrome. N Engl J Med 2005; 352 (11): 1112-20.

⁵⁴ Wappler F, et al. Pathological role of serotonin system in malignant hyperthermia. Br J Anaesth 2001; 87: 794-8.

⁵⁵ Isbister GK and Whyte IM. Serotonin toxicity and malignant hyperthermia: role of 5HT2 receptors. Br J Anaesth 2002; 88(4): 603.

- Phase 2 patient 25/007 from study APD356-004 (lorcaserin 10 mg BID) was mentioned in section 7.3.3.
- 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 guaifenesin 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.⁵³ Supratherapeutic doses of dextromethorphan have been described as pro-serotonergic in combination with a SSRI.⁵⁶ 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.

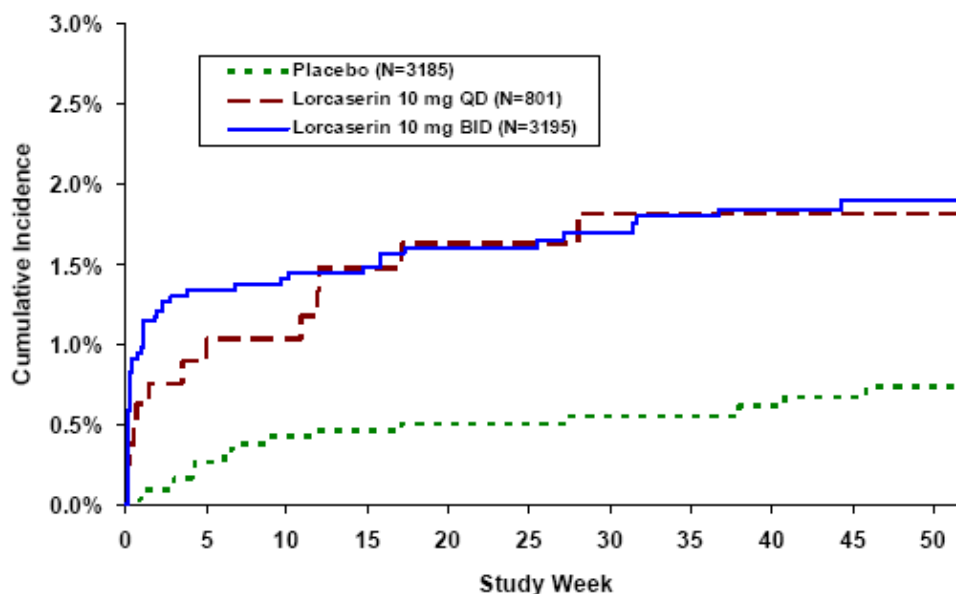
Table 86. MedDRA Preferred Terms Potentially Related to Serotonin Toxicity

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

⁵⁶ Schwartz AR, et al. Dextromethorphan-induced serotonin syndrome. Clin Toxicol 2008 Sep; 46(8): 771-3.

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 87. 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

Gallbladder Events

Aside from liver-related events (see section 7.4.2), 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.⁵⁷

As discussed in section 7.3.2, 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 88. 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.

⁵⁷ Stinton LM, et al. Epidemiology of gallstones. Gastroenterol Clin North Am 2010 Jun; 39(2): 157-69, vii.

Table 89. 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

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 5HT_{2A} receptor is involved in vasoconstriction and platelet aggregation and 5HT_{2A} antagonists have been evaluated for treatment of vascular disease.⁵⁸ Any potential relevance of these 5HT_{2A} 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 6.1.2.

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.

⁵⁸ 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 90. Ischemic Heart Disease-Related Preferred Terms

Myocardial infarction SMQ	Other ischemic heart disease SMQ
Acute coronary syndrome Acute myocardial infarction Blood creatine phosphokinase MB abnormal Blood creatine phosphokinase MB increased Coronary artery embolism Coronary artery occlusion Coronary artery reocclusion Coronary bypass thrombosis Kounis syndrome Myocardial infarction Myocardial reperfusion injury Papillary muscle infarction Post procedural myocardial infarction Postinfarction angina Silent myocardial infarction Postinfarction angina Silent myocardial infarction Troponin I increased Troponin increased Troponin T increased Blood creatine phosphokinase abnormal Blood creatine phosphokinase increased Cardiac enzymes increased Coronary artery restenosis Electrocardiogram Q wave abnormal Electrocardiogram ST segment abnormal Electrocardiogram ST segment elevation Electrocardiogram ST-T segment elevation Infarction In-stent coronary artery restenosis Scan myocardial perfusion abnormal Vascular graft occlusion	Angina pectoris Angina unstable Arteriosclerosis coronary artery Arteriospasm coronary Coronary angioplasty Coronary arterial stent insertion Coronary artery bypass Coronary artery disease Coronary artery dissection Coronary artery insufficiency Coronary artery restenosis Coronary artery stenosis Coronary endarterectomy Coronary no-flow phenomenon Coronary ostial stenosis Coronary revascularization Dissecting coronary artery aneurysm ECG signs of myocardial ischaemia External counterpulsation Haemorrhage coronary artery In-stent coronary artery restenosis Ischaemic cardiomyopathy Microvascular angina Myocardial ischaemia Percutaneous coronary intervention Prinzmetal angina Stress cardiomyopathy Subclavian coronary steal syndrome Subendocardial ischaemia Arteriogram coronary abnormal Cardiac stress test abnormal 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 7.3.2, 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 91. 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 7.3.1).

Table 92. 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 93). Furthermore, there were no events of stroke or cardiovascular death in Year 2.

Table 93. 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

Priapism

Serotonin activation at the 5HT_{2C} receptor has been implicated in priapism seen in animals.⁵⁹ 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 95 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.

Table 94. 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

⁵⁹ Millan MJ, et al. 5-HT_{2C} receptors mediate penile erections in rats: actions of novel and selective agonists and antagonists. Eur J Pharmacol 1997; 325: 9–12.

Table 95. 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.

Ophthalmological Adverse Events

Several preferred terms in the Eye Disorders SOC were seen more frequently in the lorcaserin 10 mg BID treatment group.

Table 96. Ophthalmological AEs, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Vision blurred	34 (1.1)	4 (0.5)	14 (0.4)
Dry eye	18 (0.6)	5 (0.6)	8 (0.3)
Visual impairment	7 (0.2)	0	1 (<0.1)

Source: Reviewer created from NDA 22529 datasets

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following table of common adverse events was taken from the sponsor's proposed package insert. Individual adverse events are discussed in more detail below.

Table 97. Adverse Events Reported by $\geq 5\%$ of Lorcaserin-treated Patients and More Commonly than with Placebo in BLOOM and BLOSSOM

	Lorc 10 BID N = 3195	Placebo N = 3185
Headache	537 (16.8)	321 (10.1)
Upper respiratory tract infection	439 (13.7)	391 (12.3)
Nasopharyngitis	414 (13.0)	381 (12.0)
Dizziness	270 (8.5)	122 (3.8)
Nausea	264 (8.3)	170 (5.3)
Fatigue	229 (7.2)	114 (3.6)
Urinary tract infection	207 (6.5)	171 (5.4)
Diarrhea	207 (6.5)	179 (5.6)
Back pain	201 (6.3)	178 (5.6)
Constipation	186 (5.8)	125 (3.9)
Dry mouth	169 (5.3)	74 (2.3)

Source: NDA 22529, Draft Labeling

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 7.3.3, 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 98. 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 99. 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 100. 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

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 7.3.3, 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 101. 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 102. 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

Nausea and Vomiting

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 103. 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

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 104. 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

7.4.2 Laboratory Findings

This section will include hepatic, renal, and hematological laboratory findings. I have also included adverse events that could be related to the relevant organ systems or to the abnormal laboratory data.

Hepatic Laboratory Data and Related Adverse 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 105. 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 injury⁶⁰ 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.

⁶⁰ 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 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 106). No patients in the lorcaserin treatment groups and 1 (< 0.1%) patient in the placebo group met the > 20x ULN criteria.

Table 106. 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.
- 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 107. 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

Renal Laboratory Data and Related Adverse Events

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 108). 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 108. 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
	Tubulointerstitial nephritis
	Urea renal clearance decreased
	Urine output decreased

Source: NDA 22529, 2 Apr 2010 Response to 74-day filing letter requests Table 7

Table 109. 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 110. Renal Failure SMQ, BLOOM Year 2

	Lorc/Lorc N=573	Lorc/Pbo N=283	Pbo/Pbo 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 111).

Table 111. 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

Hematology Laboratory Data and Related Adverse Events

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 112. 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 113). Adverse events related to decreases in WBCs were infrequent, but greater in lorcaserin-treated patients than those who were placebo-treated (Table 114).

Table 113. 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%
< $1.5 \times 10^9/L$	2.8%	2.7%	2.2%
< $1 \times 10^9/L$	0.6%	0.4%	0.3%
< $0.5 \times 10^9/L$	<0.1%	0.1%	0

Source: NDA 22529, 2 Apr 2010 Response to 74-day filing letter requests Table S14.2.1

Table 114. 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 $75 \times 10^9/L$. No patients treated with lorcaserin 10 mg BID had platelet counts less than $50 \times 10^9/L$ 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.

7.4.3 Vital Signs

Heart rate is discussed in section 7.4.4. Blood pressure is discussed in section 6.1.5 with respect to efficacy. A discussion of the potential for significantly decreased blood pressure is included here.

Slightly more patients treated with lorcaserin developed low blood pressure during the first year as compared to placebo:

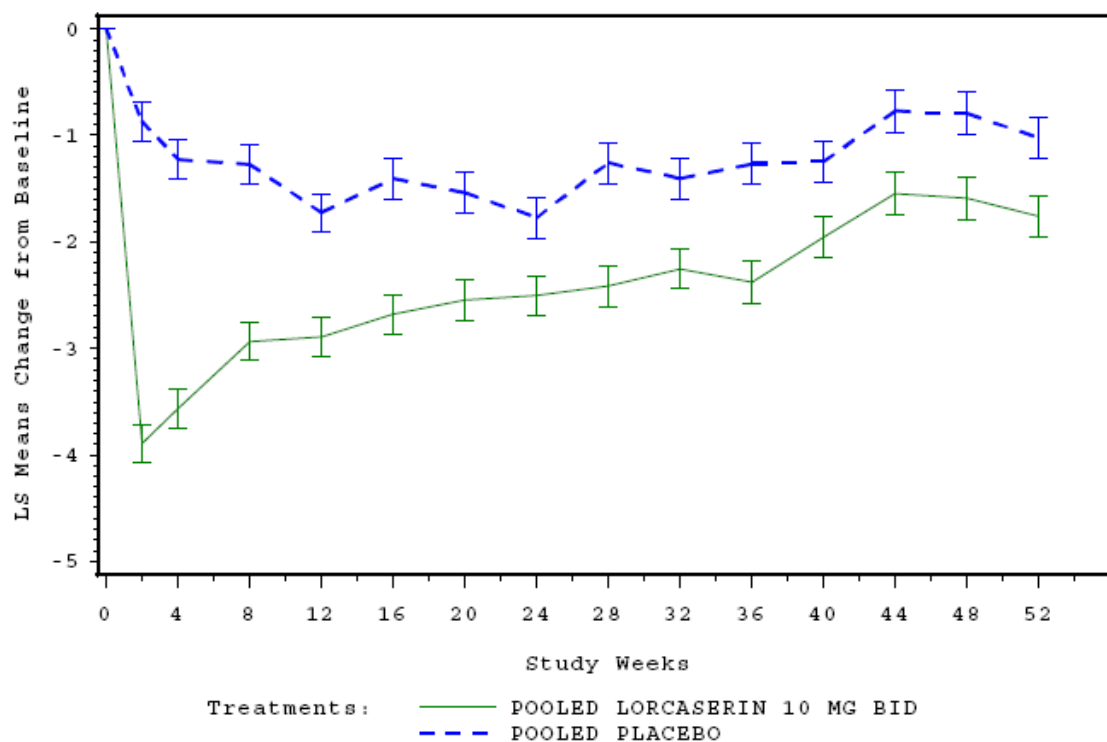
Table 115. Incidence of Blood Pressure Exceeding Predefined Limits of Change During 52 Weeks of Study

	Lorc 10 BID N=3095	Lorc 10 QD N=771	Pbo N=3038
Systolic blood pressure, mmHg			
85-89	56 (1.8)	12 (1.6)	42 (1.4)
80-84	17 (0.5)	4 (0.5)	15 (0.5)
< 80	14 (0.5)	5 (0.6)	9 (0.3)
Diastolic blood pressure, mmHg			
< 60	393 (12.7)	78 (10.1)	292 (9.6)

Source: NDA 22529, Response to NDA Questions Dated 24 Feb 2010 Table 42.1

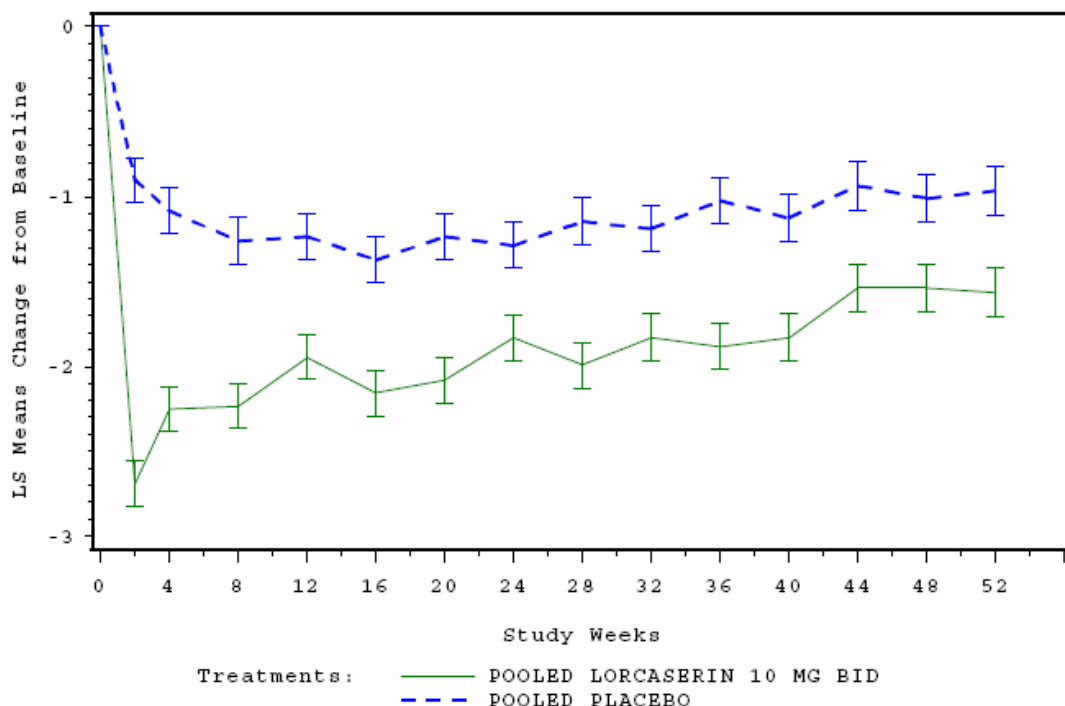
Evaluation of the longitudinal data demonstrates that lorcaserin-treated patients experienced larger drops in blood pressure in the first few weeks of treatment:

Figure 19. Mean Change from Baseline in Systolic Blood Pressure across Time: MITT LOCF



Source: NDA 22529, ISE Statistical Report Figure 13

Figure 20. Mean Change from Baseline in Diastolic Blood Pressure across Time: MITT LOCF



Source: NDA 22529, ISE Statistical Report Figure 14

The AE datasets were explored to determine if there was any imbalance in hypotension or low blood pressure AEs between groups; approximately twice as many patients on lorcaserin 10 mg BID experienced low blood pressure/hypotension-related AEs as compared to those on placebo.

Table 116. Low Blood Pressure or Hypotension-related AEs, Pooled Phase 3 Trials

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
Low blood pressure/hypotension-related AEs	20 (0.6)	4 (0.5)	10 (0.3)
Blood pressure decreased	9 (0.3)	3 (0.5)	5 (0.2)
Hypotension	7 (0.2)	1 (0.1)	4 (0.1)
Orthostatic hypotension	4 (0.1)	0	1 (<0.1)

Source: Reviewer created from NDA 22529 datasets

7.4.4 Electrocardiograms (ECGs)

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 117. 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 118. 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 119. 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 120 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 120. 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.

7.4.5 Special Safety Studies/Clinical Trials

The results of the thorough QT study are summarized in section 7.4.4.

The results of the abuse liability study are summarized in section 7.6.4.

7.4.6 Immunogenicity

Not applicable. Lorcaserin is not a therapeutic protein.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The BLOSSOM trial did include an arm evaluating the lorcaserin 10 mg QD dose. Because the randomization was not equal and the trials were frequently pooled for the safety analyses, this dose should be viewed as an informal dose exploration. Nevertheless, for frequent, clearly drug-related adverse events (e.g., headache, dizziness), a dose-response is evident.

Lorcaserin dose response was also evident in the Phase 1 trials that evaluated a supratherapeutic dose (primarily psychiatric events) and the Phase 2 trial, APD356-004, that demonstrated that the 15 mg QD dose was less effective and less well-tolerated as compared to the 10 mg BID dose.

7.5.2 Time Dependency for Adverse Events

Time to selected lorcaserin-related common adverse events are described in section 7.4.1.

7.5.3 Drug-Demographic Interactions

The relationship of selected safety findings to demographics (age, sex, and race) are presented in the relevant subsections in section 7.

7.5.4 Drug-Disease Interactions

Patients with disease states of relevance to the safety of lorcaserin, such as diabetes mellitus and cardiovascular disease were generally not included in the clinical trials.

An increase in the worsening of FDA-defined VHD in those patients with valvular regurgitation at baseline meeting that definition was not evident from the data presented.

7.5.5 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 7.3.5).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

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. 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 121. 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 122. 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

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*.⁶¹ 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 4.4.2), 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 5HT_{2C}.⁶² 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.⁶³

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.⁶⁴ 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.⁶³ With the exception of oral contraceptives, a relationship between these medications and breast cancer has not been definitely demonstrated to date.⁶⁴ 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

⁶¹ Reviewed in: Hankinson SE, et al. Plasma prolactin levels and subsequent risk of breast cancer in postmenopausal women. *J Natl Cancer Inst* 1999 Apr; 91(7): 629-34.

⁶² Freeman ME, et al. Prolactin: structure, function, and regulation of secretion. *Physiol Rev* 2000; 80: 1523-631.

⁶³ Haddad PM and Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs* 2004; 64(20): 2291-314.

⁶⁴ Tworoger SS and Hankinson SE. Prolactin and breast cancer etiology: an epidemiologic perspective. *J Mammary Gland Biol Neoplasia* 2008 Mar; 13(1): 41-53.

randomized to placebo (0.2%) were diagnosed with a breast neoplasm, as shown in Table 123. 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).

Table 123. 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 124. 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 125. 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 126). 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) survey⁶⁵ 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 126. 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 66 and 67

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 127).

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

⁶⁵ <http://www.cancer.gov/bcrisktool> Accessed 10 July 2010.

⁶⁶ 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.

⁶⁷ Tworoger SS, et al. Plasma prolactin concentrations and risk of postmenopausal breast cancer. Cancer Res 2004 Sept; 64: 6814.

increase in the proportion of patients with an increase in prolactin quartile (Table 127) or pre-dose prolactin above the upper limit of normal.

Table 127. 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 comments: Based on the quartile analysis, I would generally 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. However, it is noted that on Week 52 6 (2%) patients on lorcaserin 10 mg BID experienced a predose prolactin concentration > 2x ULN as compared with no patients on placebo or lorcaserin 10 mg QD experiencing such increases.

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 123). Two of these patients had prolactin concentrations collected during the BLOSSOM substudy (2203-S032 and 2141-S039); all values were within normal limits.

7.6.2 Human Reproduction and Pregnancy Data

No subjects or subject partners became pregnant during participation in Phase 1 studies. One woman assigned to lorcaserin 10 mg BID discovered that she was pregnant following participation in the APD356-012 (drug-drug interaction study); she underwent an elective abortion.

Two women became pregnant during Phase 2 trials; one was assigned to lorcaserin 5 mg QD in the APD356-003 study and was lost to follow-up, and the other was assigned to placebo in the APD356-004 study.

In Phase 3 trials, 54 female patients and 5 female partners of male patients became pregnant (Table 128).

Table 128. Summary of Pregnancies in Pooled Phase 3 Trials

	Lorc (any dose) N=3996	Pbo N=3185
Patient pregnancies	30	24
Partner pregnancies	4	1
Outcomes (for patient pregnancies)		
Healthy baby	6	3
Miscarriage/spontaneous abortion	2	4
Elective abortion	5	7
Unknown	4	4 ^a
Contraception used		
Hormonal	5	8
Barrier	14	9
Intrauterine device	2	0
Unknown	9	8
Duration of exposure ^b (days)		
Mean (SD)	203 (126)	195 (197)
Range	12-453	2-737
Median	207	114
a Includes 1 SAE of multiple congenital anomalies diagnosed <i>in utero</i> ; patient lost to follow-up		
b Number of days from Randomization to pregnancy notification		

Source: NDA 22529, ISS Table 95

7.6.3 Pediatrics and Assessment of Effects on Growth

Lorcaserin has not been studied in individuals under the age of 18.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Lorcaserin is known to possess activity at the 5HT_{2A} receptor (see section 2.6). An adverse event profile consistent with 5HT_{2A} activity could include hallucinations, euphoria, and other perceptual or dissociative symptoms.⁵¹ Such adverse events were seen predominantly in the studies in healthy (lower weight) individuals at supratherapeutic doses.

The potential for abuse liability has been fully assessed by the Controlled Substances Staff (CSS) and the reader is referred to the CSS review for details. In brief, CSS recommends that lorcaserin be listed as a Schedule IV drug based on the following (taken from the summary section of Drs. Bonson and Gong's CSS review):

- Lorcaserin is a high-affinity agonist at 5HT2A and 5HT2C receptors.
- A rat study evaluating overt serotonin behaviors lacks validity because the positive control in the study failed to produce both 5HT2A and 5HT2C behaviors.
- A rat drug discrimination study conducted in rats lacks validity because of numerous procedural discrepancies, including the inability of rats to maintain adequate recognition of the training drug over the course of the study.
- The overall incidence of euphoria in Phase 1 and Phase 2/3 clinical efficacy and safety studies following administration of lorcaserin (0.7%) is more than 10 times higher than that reported following administration of placebo (0.06%). The ability of lorcaserin to produce euphoria is dose-dependent, with supratherapeutic doses producing the highest incidence of the AE. Individuals treated with lorcaserin showed a higher incidence of other prominent safety or abuse-related AEs (such as feeling jittery, psychomotor hyperactivity, paresthesia, abnormal dreams, and confusional state) than subjects treated with placebo.
- Although the overall incidence of the AE euphoria in Phase 1, 2 and 3 studies is relatively low, lorcaserin produced a high incidence of the AE euphoria (6-19%) in a human abuse potential study with drug abusers. The incidence of euphoria in this study resulting from lorcaserin administration is similar to that reported following zolpidem administration (13-16%), lower than that reported following ketamine administration (50%), and higher than that reported following placebo administration (0%).
- In the human abuse potential study in recreational abusers of psychedelic drugs and CNS depressants (n = 28), lorcaserin (20-60 mg) and the positive control drugs zolpidem and ketamine produced statistically significant increases on certain positive subjective measures ("High", "Good Drug Effects" (unipolar scale) and "Good Drug Effects" (bipolar scale)), as well as a numerical increase in "Hallucinations" compared to placebo. Lorcaserin, as well as zolpidem and ketamine, produced statistically significant increases in "Sedation" compared to placebo. The subjective response data suggest that lorcaserin produces effects that are similar to those of ketamine and zolpidem, drugs with hallucinogenic and euphorogenic properties. However, lorcaserin did not produce statistically significant increases in ratings on other positive control drugs compared to placebo ("Drug Liking", "Overall Drug Liking", "Euphoria", "Take Drug Again"), although zolpidem and ketamine did. Additionally, lorcaserin produced statistically significant increases in certain negative subjective effects ("Overall Dislike Drug", "Bad Effects"). On the VAS-Drug Similarity scale, subjects identified the two highest doses of lorcaserin as similar to "LSD" and "MDMA," while subjects identified ketamine as "ketamine" and zolpidem as "benzodiazepine." However, since zolpidem and ketamine have different

mechanisms of action from that of lorcaserin, they are not ideal comparators for determining the hallucinogenic profile of lorcaserin.

- The ability of lorcaserin to produce hallucinations, euphoria, and positive subjective responses, in healthy individuals and in obese patients, at doses greater than the proposed therapeutic dose of 20 mg suggests that lorcaserin can produce psychic dependence similar to that of other 5HT2 agonist hallucinogens.

I also conducted a review of adverse events that might be associated with drug abuse potential.

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 CSS. 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 7.4.1.

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.

Table 129. 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 130. 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 131. 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 132. 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 133. 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, muzy, 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 134. 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

	Lorc 10 BID N=3195	Lorc 10 QD N=801	Pbo N=3185
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
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 7.3.2, 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 7.3.2 and 7.3.5.

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, 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).

7.7 Additional Submissions / Safety Issues

Summaries of 2 trials were included in the 120-day safety update: unblinded data from the TULIP trial and still blinded data from BLOOM-DM.

The TULIP trial was a 56-day, double-blind, randomized, placebo-controlled, parallel-group study designed to assess the effect of lorcaserin on 24h energy metabolism and on a panel of measures related to hunger, satiety, and eating behaviors. Study participants were overweight and obese male and female patients, aged 18 to 65 years. There were no deaths, SAEs, or premature discontinuations in this trial.

The BLOOM-DM trial was conducted as a double-blind, randomized, placebo-controlled, parallel-group study to assess the effects of lorcaserin during 52 weeks of administration to overweight and obese male and female patients, aged 18 to 65 years, with type 2 diabetes mellitus managed with oral hypoglycemic agent(s). The objectives include assessment of the safety and efficacy of lorcaserin for weight reduction, and improvement in glycemic control. Echocardiograms were conducted. No patients were reported to have died in BLOOM-DM. Two seizures occurred in one patient, and this narrative is included in Appendix C. No further assessment of safety was conducted given that the trial is still blinded.

8 Postmarket Experience

Not applicable. Lorcaserin is not marketed anywhere in the world.

9 Appendices

9.1 Literature Review/References

References are embedded as footnotes throughout the document.

9.2 Labeling Recommendations

I believe that labeling recommendations are not currently warranted, given the regulatory recommendation.

9.3 Advisory Committee Meeting

An advisory committee meeting was held on September 16, 2010. The following questions were asked; a summary of committee members' comments follow (taken from my own notes):

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. Are there additional studies that you would recommend pre- or post-approval to further evaluate lorcaserin's efficacy?

The committee discussed the need to study a broader patient population, given that achievable results are typically never as good in actual clinical practice. Dr. Kaul commented that the use of such a filtered patient population tends to overestimate efficacy and underestimate risk.

Some committee members felt that missing data make the interpretation of efficacy somewhat difficult; however, the company still met the 'burden of proof' in that efficacy was small in magnitude but could be important to a select few.

Others felt the ongoing diabetes study (n=604) would provide an important contribution to the efficacy assessment; it is expected to be completed at the end of 2010. Prior to this study being completed, it is unclear what language a label would include regarding patients with diabetes.

Finally, with respect to efficacy, the panel acknowledged that the effect on morbidity and mortality is unknown.

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.

The committee felt that further animal studies likely would not be helpful to further characterize the risk, although receptor transfection studies and additional studies with use in combination with other agents might provide additional information.

Dr. Proschan noted that although the company did not meet the strict 1.5 threshold, the only way that one would be confident that there is no increased risk is if the drug in fact decreased risk. He went on to say that such studies cannot rule out harm but he was not sure the sponsor can be asked to do a whole lot more than they have already done in the pre-approval phase.

With respect to post-marketing strategies to mitigate risk, Dr. Connolly felt that follow-up echocardiography would be useful. Another committee member suggested a reporting mechanism in which “alarm bells” go off after 10 to 15 cases leading to further follow-up.

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.

Dr. Henderson stated that the risk for neoplasm was her number 1 concern. Other committee members echoed her concern but noted that they did not know how to suggest studies to assess the risk. Several members asked about the utility of further animal mechanistic studies and others wondered about a cancer registry. Dr. Segal asked FDA about the feasibility of approving a drug now, with the possibility of withdrawing it later.

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.

The committee did not provide much in the way of discussion for this concern. Dr. Thomas noted that baseline psychiatric history in clinical trials was limited and given the exclusion for SSRIs, it was difficult to extrapolate the risk to the likely patient population.

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.

Some committee members were worried by these events; particularly those characterized as ‘amnesia’. Others were reassured that the events were mostly reversible and patients tended to stay on the drug. It was noted that many approved drugs have this effect. Dr. Henderson found the quality of life data reassuring in that those data might reflect that patients were not bothered by these events.

In terms of post-marketing strategies, the committee stated that this was a safety issue worth monitoring because older people may be more susceptible. Ongoing or post-marketing studies with a formal analysis of cognition might be additionally helpful.

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.

The final vote was: 5 yes, 9 no, 0 abstain.

Individual comments made by the committee members and the (paraphrased) rationale for their votes are as follows:

Segal (yes). Dr. Segal felt that the clinical program met the efficacy requirements and the requirements for VHD. She did feel that the cancer risk was unsettled. She did not believe that depression/dissociation was an issue. She suggested active surveillance, large post-approval studies, and claim studies.

Goldfine (yes). Dr. Goldfine found this to be a very difficult decision given that the efficacy was of small magnitude and a limited patient population was studied. Nevertheless, she was encouraged that the clinical endpoints looked favorable. She felt that women could be counseled for the potential breast cancer risk. She recommended a post-marketing study, reviewing the diabetes study, and evaluating potential mechanisms of breast cancer in rats.

Gregg (no). Dr. Gregg also found this decision very difficult. He believes that lorcaserin is a promising drug with acceptable weight loss and an encouraging risk factor profile, with no clear evidence for danger. However, he also believes that there is enough uncertainty that the magnitude of efficacy did not pass bar. He thinks the drug is “not quite there yet”.

Proschan (yes). This was also a close vote for Dr. Proschan. He noted that the efficacy is of small margin, but benefit on some surrogates was demonstrated. He continues to have doubts stemming from the restricted population that was studied. He feels that although there were troubling results in some animals, he did not know how to translate that concern to humans. There was no “huge safety flag” raised in the clinical trials.

Thomas (yes). Dr. Thomas stated he was vacillating because of small actual efficacy. He suggested that FDA may have to set a higher efficacy bar. He also worried that the clinical trials may be not representative of what occurs in actual clinical practice. Nevertheless, he was glad to see that the benefits with weight loss correlate with the secondary endpoints. He believes that the goal with weight loss was prevention, not just treatment of weight-related disease. With respect to the rat tumors, he wondered if there would be utility in further animal study. Such endeavors should get underway soon, given that it might take awhile to sort out.

Flegal (no). Dr. Flegal felt that lorcaserin was a promising drug that could fill a niche. She noted that weight loss was small but was encouraged that biomarkers tracked in the right direction. Nevertheless, she still had unanswered concerns about the risks and who will benefit.

Weide (no). Dr. Weide was most concerned about tumors while reading through the materials, but after hearing the discussion stated that he was really bothered by the limited patient population and the very small weight loss. He was also disturbed that the ongoing diabetes trial has only 600 patients, which he feels is too small. He suggested that a broader study was needed that demonstrates “more bang for the buck”. The mechanism of breast tumors should be further elucidated.

Felner (no). Dr. Felner thinks the sponsor did “a great job” but the risks versus the benefits were just not obvious. He was additionally concerned by the second year weight data. He thinks more pre-marketing studies are needed and probably more than 600 patients in the diabetes trial.

Henderson (no). Dr. Henderson agreed that lorcaserin is a promising drug and would encourage the sponsor to reapply. She “loves the quality of life data”, but feels there is too much uncertainty surrounding cancer risk and the limited patient population studied.

Douglas (no). Dr. Douglas expressed concern about the margins for efficacy in a limited patient population. She felt that the “urgent public need” for an obesity drug does not mitigate lingering concerns about lorcaserin.

Kaul (no). Dr. Kaul believes that the current portfolio is not sufficient to assess risk/benefit. He noted that the patient population studied was highly selected with important disease conditions excluded. He reiterated that this translated to an overestimation of benefit and an underestimation of risk. He also felt that despite the public’s appetite for the availability of an obesity drug, one should not lower the bar in order to bring a drug to market.

Coffin (yes). Ms. Coffin applauded the sponsor for including a diverse racial and ethnic patient population, although she wished the patients were “sicker”. She felt that lorcaserin met the criteria for approval.

Gardener (no). Dr. Gardener also applauded the clinical program for its diversity and the achievement of other endpoints. However, she did have concern regarding the rat tumors, and hoped that there might be a way to shed light on this going forward. She felt that approval should await the diabetes data. She considered what could be done in a post-marketing environment to mitigate risk, but was not confident about the ability to do it right in that setting.

Connolly (no). Dr. Connolly felt the potential risks outweighed the benefits. She paid particular attention to the “long-term” part of the question.

9.4 Additional 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/m² (obese) with or without co-morbid conditions or 27 to 29.9 kg/m² (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 bupropion], tricyclics, antipsychotics, lithium). Use of SSRI's and SNRI's (including bupropion) 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) ≥ 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 ≥ 140 or diastolic blood pressure ≥ 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 $> 1.5\times$ ULN. Patients with slightly higher TSH ($\sim 2\times$ 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 $> 2.5\times$ ULN, or total bilirubin $> 1.5\times$ ULN) or renal function lab tests (e.g., creatinine $> 1.25\times$ 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 cm²)
 - 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 msec 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/m² with or without a comorbid condition (e.g., hypertension, dyslipidemia, CV disease, glucose intolerance, sleep apnea), or 27 to 29.9 kg/m² 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 bupropion) 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.

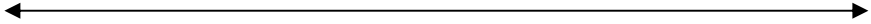
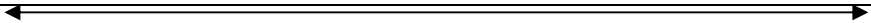
Patients participated in the Arena Healthy Lifestyle Program, designed by the Behavioral Health Solutions (BHS) division of Johnson & Johnson Health Care Systems, Inc. The objectives of the program were to: develop a moderate-intensity weight management program for all APD356 study participants, standardize 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 135. 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							X
Beck Depression Inventory-II	X			X		X			X			X				X
Binge Eating Scale	X															
Echocardiogram	X ³								X							X
12-Lead ECG	X			X					X							X
Clinical Labs	X	X		X		X			X			X				X
Drugs of Abuse Screen	X															
Thyroid Function Tests (i.e., T4, TSH)	X								X							X
Hemoglobin A1c	X								X							X
CV Risk Markers (i.e., CRP, fibrinogen)		X							X							X
Markers of Glucose Intolerance (i.e., fasting glucose and insulin)		X				X			X			X				X
Pharmacokinetic Sample ⁴						X ⁴										
Plasma Sample for Banking ⁵		X							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															
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							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

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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
Concomitant Medication Assessments (including antihypertensives and lipid agents)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IVRS Call ⁹	X	X				X			X			X			X	X
Drug Administration ⁹																
Adverse Event Monitoring																
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.																
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 136. Schedule of Events and Procedures, Year 2

[illegible]

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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.
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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/m², or with a BMI of 27 to 29.9 kg/m² 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” ($\geq 5\%$ 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 137. 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 $\geq 5\%$ 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 (EMA), the protocol was subsequently amended to provide for three hierarchically ordered Week 52

endpoints: the proportion of patients achieving $\geq 5\%$ reduction in body weight from baseline, absolute weight change from baseline, and the proportion of patients achieving $\geq 10\%$ 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 ($\mu\text{IU/mL}$)
- 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.

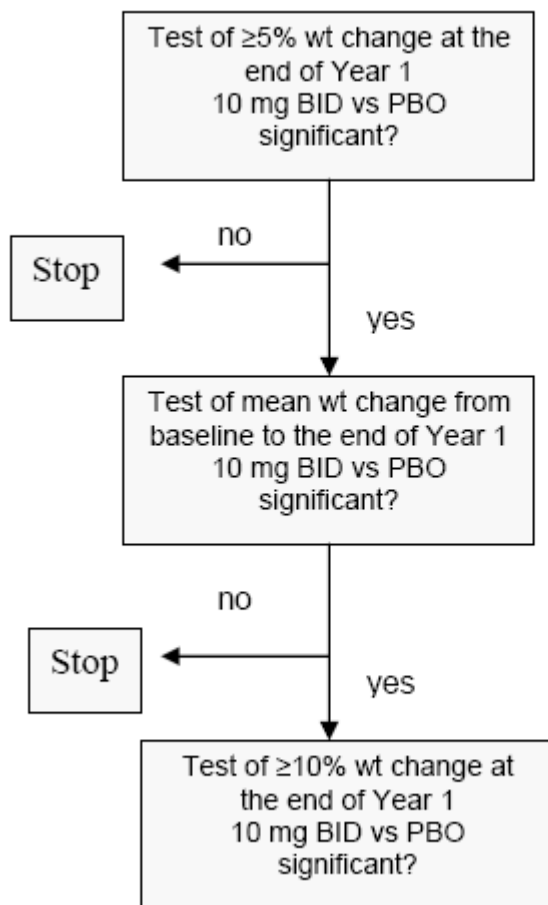
Deviations that were considered to be important during Year 2 included the following:

- 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.

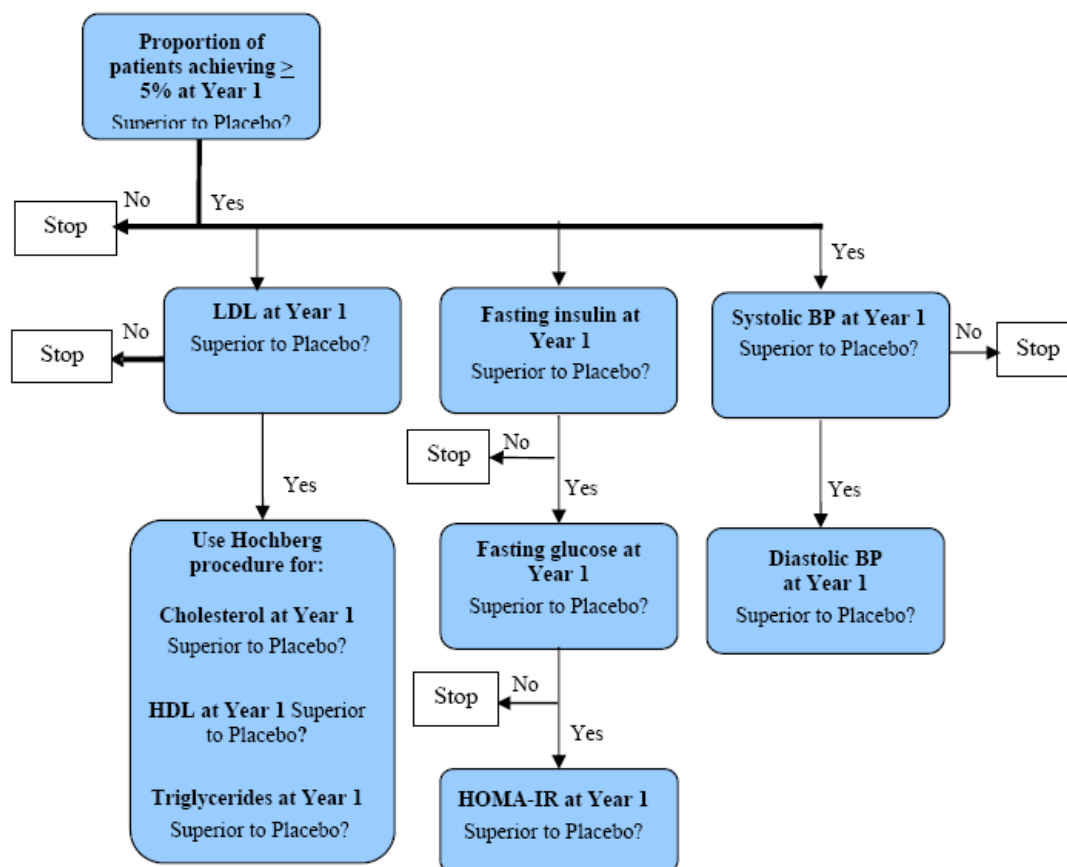
Figure 21. Testing Procedure for the Primary Efficacy Endpoints



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 22. 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 138. 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:

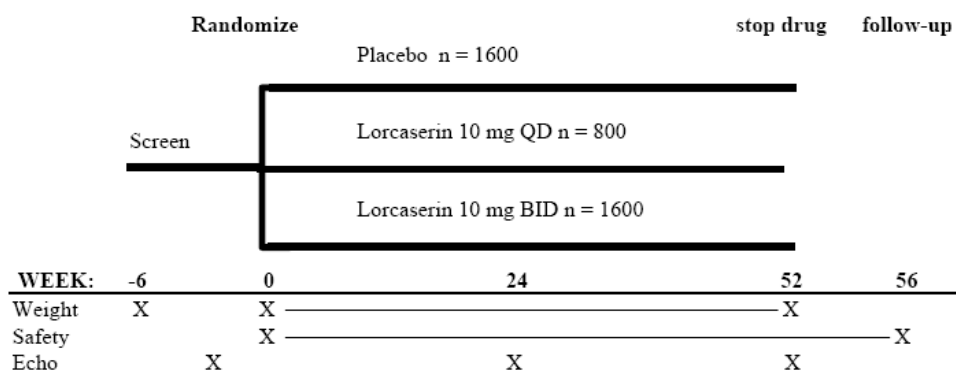
- To assess the safety of lorcaserin
- To assess changes in cardiovascular risk factors associated with obesity (i.e., dyslipidemia, hypertension) between Baseline and Week 52
- To assess changes in mood between Baseline and Week 52
- To assess echocardiographically-determined heart valve and pulmonary 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 23. BLOSSOM Study Design



Source: NDA 22529, APD356-011 CSR Figure 1

As in BLOOM, patients participated in the Arena Healthy Lifestyle Program.

Table 139. 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					X							X		
Beck Depression Inventory-II	X				X					X							X		
Binge Eating Scale	X																		
Echocardiogram	X ⁴									X							X		
12-Lead ECG	X																X		
Clinical Labs	X	X			X		X			X			X				X		
Drugs of Abuse Screen	X																		
Thyroid Function Tests (T4, TSH) and HbA1c	X																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																		
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								X							X		
PK Blood Collection ⁹							X			X							X		
Prolactin ¹⁰		X			X		X			X							X		
Apolipoprotein A1 ¹¹		X															X		
Apolipoprotein B ¹¹		X															X		
Quality of Life Assessment		X								X							X		
IVRS Call ¹²	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		

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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	
Collect Study Medication and Perform Drug Accountability and Compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug Administration ¹³																			
Adverse Event Monitoring																			
<p>1 All screening activities are to be completed within 42 days, or sooner, prior to dosing on Day 1.</p> <p>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.</p> <p>3 Partial examination to update findings from the examination performed at screening.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>7 Hip and waist circumference to be measured in triplicate. Final result will be the average of the 3 measurements.</p> <p>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.</p> <p>9 PK samples will be collected from approximately 1/3 of randomized patients.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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).</p>																			

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 $\geq 5\%$ weight loss
- Change from baseline in body weight
- Percent of patients achieving $\geq 10\%$ 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

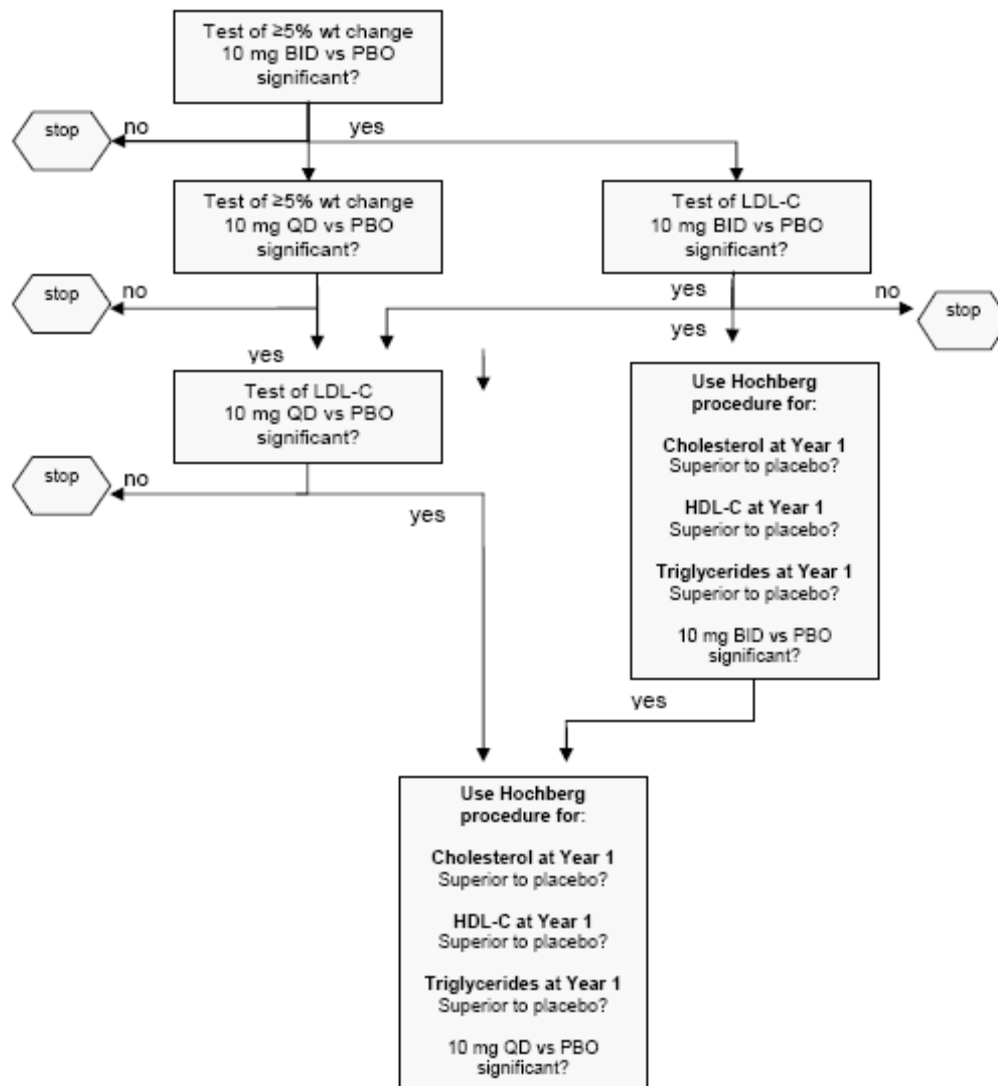
Statistical Considerations:

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 24 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 24. 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.

APPEARS THIS WAY ON ORIGINAL



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

Lorcaserin 10 mg BID

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 (guaifenesin 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 was 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/m² 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 140), which would indicate a “moderate” strength of agreement (Table 141).

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 140), which would indicate a “fair” strength of agreement (Table 141), and the kappa result for MR was 0.41 (Table 140), which would indicate a “moderate” strength of agreement (Table 141).

Table 140. 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 141. 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 ⁶⁸

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

⁶⁸ Landis JR and Koch GG. The measurement of observer agreement. Biometrics 1977; 33: 159-74.

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.

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 142. 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 143. 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.

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/s/

JULIE K GOLDEN
10/21/2010

ERIC C COLMAN
10/21/2010